SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion and scientific discussion on procedures which have been finalised before 1 September 2004. For scientific information on procedures after this date please refer to module 8B.

1. Introduction

Bondronat contains the active substance ibandronic acid, a new bisphosphonate agent, which inhibits bone resorption. Ibandronic acid is an enzyme-resistant analogue of pyrophosphate, the naturally occurring inhibitor of mineralisation in bone, the P-O-P structure of pyrophosphate being replaced by P-C-P. It is concentrated in areas of high bone turnover, is taken up by and impedes the bone-resorbing activity of osteoclasts in a dose-dependent manner. It thus reduces the turnover of bone.

The detailed mechanism of action of bisphosphonates is not well understood. They may alter proton pump function or impair the release of acid hydrolases into the extracellular lysosomes contiguous with mineralised bone. They also may inhibit the differentiation of monocyte-macrophage precursors into osteoclasts.

Bondronat is presented as an ampoule in two strengths (1 mg/1 ml and 2 mg/2 ml) containing a concentrate for solution for infusion. Ibandronic acid, like most bisphosphonates, is poorly absorbed orally.

The therapeutic indication of Bondronat is the treatment of tumour-induced hypercalcaemia with or without metastases. Other bisphosphonates are already licensed for the proposed indication, among which differences appear between onset and duration of action, predictability of activity, inhibition of normal bone mineralisation and potency. Efficacy as measured by clinical endpoints has been shown for ibandronic acid: between 2 and 4 mg, given as a single intravenous dose, it returns serum calcium to normal within 7 days in 75 percent of patients.

2. Part II: Chemical, pharmaceutical and biological aspects

Dosage form

Bondronat is presented as an isotonic infusion concentrate in colourless glass ampoules type I, Ph. Eur. The formulation contains 1.125 mg/ml of the monohydrate of the monosodium salt of ibandronic acid (equivalent to 1 mg/ml of ibandronic acid) and sodium chloride in an aqueous acetate buffer. The contents of each ampoule of Bondronat concentrate for solution for infusion are intended to be diluted in 500 ml of either isotonic sodium chloride or 5% dextrose and infused intravenously over 2 hours.

Method of preparation

The manufacturing process for Bondronat concentrate for solution for infusion consists of seven steps. A second sterile filtration step has been introduced between the manufacture and the filling. Process validation has been carried out and included sterile filtrations, precision of filling, absence of adsorption of drug substance onto equipment and efficacy of the terminal sterilisation step. This demonstrated that the product consistently meets its specification.

Control of starting materials

The synthesis of the drug substance consists of seven stages, for which the potential impurities have been identified. The specifications and the routine release tests are adequate to control the quality of the active substance.

The applicant has provided data in addition to that included in the application on the interpretation of the Infra Red spectrum, tests and limits for heavy metals, Thin Layer Chromatography (TLC) test for phosphate and phosphite impurities, content of impurities expressed as % weight by using High Performance Liquid Chromatography (HPLC) and validation of complexometric titration.

Limits for individual unidentified impurities, for the total unidentified impurities and for total related impurities have been set as requested.

Control of the finished medicinal product

The specifications and release tests for the finished product are in compliance with the European Pharmacopoeia (general monograph on Parenteralia). During the assessment procedure of the application, the company was requested to change the finished product specification requirements on content of one specified impurity and to present the structure of three other potential impurities. Adequate responses were provided. Additional satisfactory data on equations for calculation of the results and validation of the HPLC-purity test were supplied by the company.

The data submitted for the validation of the assay method and the Relative Standard Deviation for both the analytical method used to analyse the drug substance and the finished product were satisfactory. Limits of detection and quantification of the HPLC-purity method have been lowered due to further validation and referred to the amount of ibandronic acid, monosodium salt, monohydrate injected. Calculation formula and mass factors have been introduced in the HPLC-purity test.

Stability

Stability test results supplied with the application and in response to the consolidated list of questions were satisfactory for both the concentrate for solution for infusion and the product when diluted for use. The initial shelf life at the time of the Marketing Authorisation was 24 months. The Marketing Authorisation Holder applied for an extension of the shelf life to 5 years through a Type I variation. The stability data provided demonstrated that the specifications are all met and that a shelf life of 5 years is acceptable.

After dilution, the in-use shelf-life is 24 hours when the solution is stored under refrigeration (2°C to 8°C).

3. Part III: Toxico-pharmacological aspects

Bisphosphonates exhibit a role in bone mineralisation. They slow *in vitro* the formation and the dissolution of crystals of hydroxyapatite. The physicochemical interaction of bisphosphonates with the crystal of hydroxyapatite draw out their high affinity for bone but the cellular mechanisms of their action on the dynamics of crystal formation and dissolution have not yet been fully elucidated. *In vivo* they inhibit osteoclast-mediated bone resorption.

The primary effects of ibandronic acid on bone resorption have been adequately investigated and demonstrated in relevant animal models. Ibandronic acid is a very potent inactivator of osteoclasts, which translates into inhibition of bone resorption and inhibition of hypercalcaemia.

Intravenous as well as peroral administration routes were investigated, but for treatment of tumour-induced hypercalcaemia in man, only intravenous administration is relevant.

Pharmacodynamics

Studies on pharmacodynamic effects with respect to the proposed indication were conducted using three animal models. Studies on bone resorption and hypercalcaemia induced by vitamin A analogues (retinoids) in thyroparathyroidectomized (TPTX) rodents demonstrated a linear dose response relation for an interval from 0.0015 mg/kg to 0.15 mg/kg. This range includes the intended maximal human therapeutic dosage, which is 0.07-0.1 mg/kg.

The investigations on tumour-related bone loss via direct tumour osteolysis or humoral factors (parathyroid hormone-related peptide, PTHrP) were the most relevant studies. PTHrP induces hypercalcaemia and hypercalciuria via two mechanisms: osteolysis and increased renal calcium reabsorption. Ibandronic acid as other bisphosphonates only inhibits osteolysis but has no influence on the renal mechanism. Ibandronic acid is more potent than pamidronate (about 50 times) and clodronate (300-1000 times) with regard to antiosteolytic activity in these animal models.

Studies intended to investigate potential secondary pharmacological effects were performed, mainly on central nervous, renal, gastrointestinal and cardiovascular systems. Most safety pharmacological studies did not provide any evidence for special organ or systemic risks. However, some *in vitro* tests using isolated organs revealed that only renal function could be eventually affected. Further investigation to elucidate this effect was conducted during the toxicity studies.

No **interactions studies** in animals have been performed.

Pharmacokinetics

The pharmacokinetic profile was determined in rodents and non-rodents with ^{14}C-ibandronic acid. Only one i.v. dose level was used (0.1 mg/kg) and only single dose pharmacokinetics have been investigated. Like other bisphosphonates, the oral bioavailability of ibandronic acid is very low (1%). Therefore, intravenous administration is preferred for the treatment of malignancy-related hypercalcaemia. Concerning the distribution of ibandronic acid, autoradiography in entire animals of ^{14}C-ibandronic acid 0.1 mg/kg i.v. has been performed in rodents. The maximum amount of the substance was found in bone, followed by the kidneys.

In both rodents and non-rodents, renal excretion was the predominant route of elimination, and no metabolite was detected in the urine after i.v. administration. Ibandronic acid is similar to other bisphosphonates with respect to a substantial bone uptake and a very slow elimination from this compartment.

Toxicology

Single dose toxicity

Single i.v. doses of ibandronic acid were tested in rodents. Up to 17.4 mg/kg single i.v. doses did not reveal severe toxicity. At higher doses mortality occurred 8-14 days after dosing. The LD_{50} values in rodents after single i.v. dose are 200-400 times higher than the proposed maximum human dose. Toxicity symptoms were rough pelt, sedation and ptosis, and paralysis. Dead animals showed pulmonary oedema, organ congestion and intestinal dilatation suggesting cardiac failure as the ultimate cause of death after a single i.v. dose of ibandronic acid.

Repeated dose toxicity

The repeated dose toxicity studies consisted of 4-week i.v. administration studies and of oral administration studies lasting from 4 weeks to 6 months, in both rodents and non-rodents.

None of the animals in these studies died during the 4-week period of treatment with ibandronic acid. Two effects of long term administration of ibandronic acid (mid and high doses), proximal tubular kidney damage and hepatic injury, with elevation of ALAT and ASAT, degeneration and necrosis of liver cells in individual cases, were indicated in non-rodents after multiple daily doses of 3 to 10 times above the intended human dose to be given as a single dose.

As the renal and the hepatic function appeared to be target organ for toxicity, human safety studies particularly monitored these functions.

Reproduction studies

Embryotoxicity, teratology and fertility studies have not been presented. For the claimed indication, conduction of these studies is not required. Ibandronic acid should not be used during pregnancy and lactation.

Mutagenic potential

Mutagenic potential has been investigated through *in vitro* tests: gene mutation assay on bacteria (Ames Test), gene mutation assay in mammalian cells, cytogenetic tests in human lymphocytes, and through an *in vivo* test (mouse micronucleus test). There was no evidence of mutagenic potential in any of these tests.

Carcinogenic potential

Carcinogenicity studies have not been performed given the proposed indication. Carcinogenicity studies would be required for further indications such as Paget's disease or prevention of osteoporosis, which imply the chronic use of this drug.

In addition, there is no evidence at present that the other bisphosphonate therapeutic agents currently available have carcinogenic potential.

Local tolerance

There were no signs of local irritation after a single i.v. dose in non-rodents. Paravenous dosing caused moderate to severe inflammatory oedema.

Subcutaneous administration elicits tissue irritation in rodents and in non-rodents.

Environmental risk

Environmental toxicity has been investigated. Under the worst assumptions the predicted environmental concentration in water (PEC_{water}) is 10^3 times lower than the lowest proposed action limit for further ecotoxicological evaluation and testing. With respect to soil the ratio between PEC_{soil} and the proposed action limit is even smaller. Accordingly, for the indication of tumour-induced hypercalcaemia, ibandronic acid has no potential risk for the environment.

It was considered that for a drug that should be used as short-term treatment for tumour-induced hypercalcaemia with or without metastases, the toxicological studies were adequate both qualitatively and quantitatively.

4. Part IV: Clinical aspects

Hypercalcaemia due to malignancy is common, often severe and confusing as to aetiology. Traditionally it was thought to be related mainly to a local invasion and destruction of bone in tumour cells; it is now known to possibly result from the elaboration by the malignant cells of humoral mediators of hypercalcaemia. The treatment of tumour-induced hypercalcaemia must be considered in the perspective of the control of the tumour and guided by the understanding of the particular pathogenesis of hypercalcaemia.

The acute treatment of this metabolic dysfunction in cancer patients includes restoration of normal hydratation and the use of calcium lowering agents. Bisphosphonates have been used successfully in the management of hypercalcaemia associated with malignancy for many years. The evaluation of the data submitted to support the use of ibandronic acid in the treatment of tumour-induced hypercalcaemia with or without metastases, concluded that this drug is highly potent and has a favourable ratio of blocking resorption over inhibiting bone formation.

The clinical dossier consisted of two randomised double-blind placebo-controlled studies in healthy volunteers aimed to evaluate pharmacodynamic effects and pharmacokinetic profile and three studies in patients with hypercalcaemia of malignancy to assess clinical efficacy.

Pharmacodynamics/pharmacokinetics

The pharmacodynamic/pharmacokinetic studies consisted of two randomised double-blind placebo-controlled trials, assessing pharmacokinetics and pharmacodynamic parameters, as well as safety with special emphasis on the renal function, in healthy volunteers. The first study was primarily designed to detect possible signs of renal tubular damage or influences on parameters of kidney function as this organ appeared to be target for toxicity in the animal studies. At the dose administered (2 mg), no definite rise of markers of early tubular lesions was observed. The second study compared the pharmacodynamic effects of ibandronic acid with placebo and assessed the pharmacokinetic profile of this new medicinal product. The effects on bone metabolism using serum calcium, sodium, and potassium were within normal limits and showed no differences between the treatment groups.

As it could be considered unethical to carry out a conventional pharmacokinetic study in patients with terminal hypercalcaemia in malignancy, the dossier submitted only contains pharmacokinetic data established in healthy volunteers and in postmenopausal population.

The pharmacokinetic data were investigated after single injection of 0.5, 1.0 and 2.0-mg ibandronic acid in healthy volunteers as well as after a single infusion of 2.0, 4.0 or 6.0-mg ibandronic acid in 20 postmenopausal women.

The results of this study are summarised in Table 1. Both Area Under the Curve (AUC) and peak-plasma concentration (C_{max}) are dose-proportional, indicating pharmacokinetic linearity, and comparable with those seen in healthy volunteers.

Table 1: Main pharmacokinetic parameters after i.v. administration of different doses of ibandronic acid

	2 mg	4 mg	6 mg
AUC [ng x h/ml]	318	577	960
C_{max} [ng/ml]	89	159	328
$t_{1/2}$ [h]	10.2	15.6	15.8
Cl [ml/min]	113	130	108

Distribution studies have not been performed for ethical reasons; it is assumed that ibandronic acid will be bound to bone.

After a 2 hours infusion of 2, 4 and 6 mg ibandronic acid pharmacokinetic parameters are dose proportional. The highest serum concentration achieved after a single 2 hours infusion of 6 mg was 328 ng/ml and after single i.v. injection of 2 mg 246 ng/ml.

Plasma protein binding of ibandronic acid is independent from serum concentration. Up to the concentration of 2000 ng/ml protein binding is 99%. This level is never achieved with therapeutic dosages.

The binding to erythrocytes and platelets is very low.

The kidney is the predominant route of excretion and patients with severe renal insufficiency were excluded from the clinical trials. This raised concerns about the use of ibandronic acid in patients with such severe renal impairment. The information in the Summary of Product Characteristics (SPC) was modified accordingly to address this issue, the use of ibandronic acid being contra-indicated in patients with severe renal insufficiency (serum creatinine > 5 mg/dl or 442 μmol/l).

Although no formal drug-drug interaction studies have been performed, caution is advised when this new bisphosphonate is administered with aminoglycosides agents since both agents can lower serum calcium levels for prolonged periods. Attention should also be paid to the possible existence of simultaneous hypomagnesaemia.

Therapeutic efficacy

In order to assess the therapeutic efficacy of ibandronic acid, three clinical trials were performed, involving a total of 343 patients with hypercalcaemia of malignancy. All patients were designed to receive a single dose but in one study (P3) 50 patients were treated with a second dose. The observation period was 4 weeks. More than 250 patients received 2 mg or less as first active dose.

The primary efficacy parameter was changes in albumin-corrected serum calcium after standardised hydration therapy prior to exposure with ibandronic acid. The complete response rate was defined as per cent of hypercalcaemic patients whose albumin-corrected serum calcium values normalised (to 2.70 mmol/l or less) and fell at least by more than 0.3 mmol/l compared with baseline. The partial response rate was defined by a decrease of albumin-corrected serum calcium levels by at least 0.3 mmol/l.

Secondary efficacy parameters included urinary calcium excretion measured by calcium/creatinine ratio, time to onset of calcium lowering effect, and duration of this effect. Other parameters were hydroxyproline/creatinine ratio, and alkaline phosphatase in serum.

A **dose-finding study** in relation to the proposed indication was a German-Swiss multicenter phase-II pilot trial. The primary objective was the effect on serum calcium and tolerability of different doses of ibandronic acid. Calcium excretion in the urine was used as a further parameter of efficacy. Thirty-two patients were evaluable for efficacy. This descriptive phase II trial has documented the calcium lowering effect of ibandronic acid but has not revealed a clear dose-response relation. The lowest efficacy dose level was established (0.4 mg) but the optimal dosage in relation to efficacy and safety was less well defined. A fall in the urinary calcium/creatinine ratio in the majority of the patients indicated that ibandronic acid decreases osteoclast-mediated bone resorption.

The **first therapeutical study** (P3 study) was a European open phase II multicenter (40 centers) dose-finding study comparing 0.6 mg with 1.1 mg and 2 mg as a single 2-hour i.v. infusion, following a randomised, dose-controlled and parallel group design. Exclusion criteria were primary hyperparathyroidism, serum creatininine > 5 mg/100 ml, treatment with other calcium-lowering agents, chemotherapy one week before or during start of the study.

Response was defined as normalised serum calcium (≤ 2.70 mmol/l) for at least one visit and reduction of the serum calcium ≥ 0.3 mmol/l on day 3 after administration.

A total of 172 patients were evaluated for safety and 151 patients were evaluated for clinical efficacy. The main outcome of this study is summarised in Table 2.

Table 2: Overall efficacy from P3 study

	Dose of Ibandronic acid (mg)					
	0.6 mg		1.1 mg		2.0 mg	
	N	%	N	%	N	%
Response	22	44.00	24	52.17	37	67.27[3]
withdrawal prior to response[1]	26	52.00	20	43.48	17	30.91
no response[2]	2	4.00	2	4.35	1	1.82
All	50	100.0	46	100.0	55	100.0
Intent to treat resp/N	26/56	46.4	30/56	53.5	39/60	65

[1] Other treatment required before day 7 or need for a second infusion of ibandronic acid, death before day 7.

[2] No lowering of se-calcium to ≤ 2.70 mmol/l 7 days after ibandronic acid or no change of se-calcium for more than 3 days after initial lowering effect.

[3] P=0.019 for 0.6 mg vs 2.0 mg

Results indicate a dose-dependent normalisation of serum calcium levels by ibandronic acid in patients with underlying malignant disease and show a response rate related to baseline serum calcium level. The response rate did not depend on the tumour type humoral/local osteolytic. This trial did not define the optimal dose and schedule for patients with very high levels of calcium (i.e > 3.5 mmol/l) but a logistic regression analysis predicted that the response rate in these patients could be increased with a higher dose than 2 mg as single dose infusion. Patients with only documented bone metastases appeared to benefit also from higher doses of ibandronic acid (0.6 mg vs ≥ 1.1 mg). Response in relation to time after first infusion was studied and in 67.5% of cases studied the response was seen between days 2 and 7. There was a clear trend towards faster response with higher dosage.

Regarding re-treatment with ibandronic acid, 50 patients received a second infusion of ibandronic acid between days 2 and 30 after the first infusion. The reasons for re-treatment were insufficient efficacy in 40 patients (first dose between 0.6 mg and 2 mg) and recurrent hypercalcaemia in 10 patients. The maximum dose for both first and second administrations of ibandronic acid was 2 mg (except one patient who received 4 mg as a second dose).

There were some concerns about the fact that the trial did not allow to establish conclusions on the efficacy after multiple doses of ibandronic acid, since most patients who received a second infusion showed an unsatisfactory response to the first administered dose. The courses of 50 patients who received a second infusion clearly showed in general the benefit a patient can expect from a retreatment with ibandronic acid. Therefore, it was considered that patients should have the possibility of a second course of treatment, especially if the first dose chosen was inadequate. This consideration leads to a modification in the posology and method of administration section of the SPC.

The **second therapeutical study** (P6 study) was a phase II multicenter double-blind comparative trial, to investigate the efficacy of 2 mg, 4 mg or 6 mg as a single i.v. infusion over 2 hours. Only patients with serum calcium levels ≥ 3 mmol/l were included. Prior to randomisation patients were stratified into 4 strata with regard to serum calcium level (< 3.4 mmol/l vs ≥ 3.4 mmol/l) and tumour type (humoral tumour vs osteolytic tumour).

Response was defined as normalisation of serum calcium (≤ 2.7 mmol/l) on at least one visit. Of the 132 patients included in the study (P6), 125 patients were evaluable for efficacy. The main outcome of this study is summarised in Table 3.

Table 3: Overall efficacy from P6 study

	Dose of Ibandronic acid (mg)					
	2.0 mg		4.0 mg		6.0 mg	
	N	%	N	%	N	%
response[1]	22	50.00	31	75.61	31	77.50
withdrawal prior to response	20	45.45	7	17.07	9	22.50
no response	2	4.55	3	7.32	0	0.00
All	44	100.0	41	100.0	40	100.0
Intent to treat resp/N	23/46	50.00	32/44	72.72	32/42	76.19

[1]P=0.013 for 2 mg vs 4 mg, and P=0.024 for 2 mg vs 6 mg. The difference between 4 and 6 mg was not significant.

Results indicated that the tumour type (humoral vs local osteolytic) influences the response rate. Local osteolytic tumours display a higher response trend when compared with humoral tumours.

A logistic regression analysis identified three factors that significantly affect the predictability of the response: dose of ibandronic acid, baseline serum calcium and tumour class.

A dose response relation was confirmed, 4 mg being more effective than 2 mg in patients with serum calcium ≥ 3 mmol/l, whereas a dose of 6 mg did not add any further benefit in terms of efficacy.

The posology regimen was defined from results of these two studies. It was concluded that the appropriate dose for a single administration in patients with severe hypercalcaemia is 4 mg, whereas 2 mg is established as an efficient dosage for patients with moderate hypercalcaemia.

There was some concern that the recommended single i.v. dose proposed initially in relation to level of serum calcium or to tumoural mechanism of hypercalcaemia was not fully justified based on the submitted clinical data. There was a clear dose-response relationship from 0.6 mg to 4 mg i.v. but there was a minimal additional benefit from the highest administrated dose in terms of response rate, faster response, and non-responder patients. The dosage recommendation has been modified in the pharmacodynamic section of the SPC.

The time to response (reduction of serum calcium levels to normal range) was found to be within 7 days in most cases. The median duration of action after achieving the normal range (time to relapse = re-increase of albumin-corrected serum calcium above 3.0 mmol/l) was 18-26 days. The observed time to relapse was up to 37 days.

The absence of phase III confirmatory placebo or comparator trials was considered acceptable because of the ethical concerns in the use of placebo for this medical condition and because establishing therapeutic equivalence with existing effective comparators, such as pamidronate, would require firstly to demonstrate equipotent dosage between both bisphosphonates and secondly to conduct a large scale phase III study which, in turn, will not generate important new clinical knowledge in view of the high objective activity of ibandronic acid.

Safety

The safety profile of ibandronic acid was established based on the reports from the P3 and P6 studies.

The mortality was high but none of the death cases were related to ibandronic acid. Deaths were mostly due to the progression of the underlying malignant disease. All the serious adverse events were also clearly related to the neoplastic disease and none appeared to be drug- or dose-related. There was an equal distribution of non-serious adverse events among all dosage groups, and almost all of these events were considered not to be drug-related.

Toxicity of ibandronic acid includes low-grade fever in as many as 9 percent of patients, and possibility of reversible hepatocellular injury (liver enzyme increase). The increase of body temperature is likely to be related to release of cytokines from osteoclasts, monocytes and macrophages. This effect can be combined with flu-like symptoms, i.e. myalgia, bone pain, headache, pain in the extremities, hot flushes and increased sweating, and occurred within the first three days after treatment.

Other adverse reactions related to ibandronic acid were changes in serum electrolytes composition (hypocalcaemia, hypophosphatemia, hypomagnesaemia). Hypocalcaemia and hypophosphatemia are adverse effects that can be attributed to the pharmacological effect of ibandronic acid. These changes are mentioned in the SPC, and continuous monitoring is recommended. Hypertension, hypercalciuria, diarrhoea, vomiting have been reported in isolated cases.

Since the kidney and to a lesser extent the liver were the toxicological target organs in animal experiments, special attention has been paid to renal and hepatic function in the clinical studies. Single i.v. dosing (2 mg) in healthy volunteers did not cause any sign of early renal tubule lesions. Serious renal side effects have not been reported in the clinical studies. Although no signs of renal or hepatic dysfunction have been observed, close monitoring of the kidney and liver function is recommended.

No local intolerance after intravenous administration was seen in man. Given that inadvertent intra-arterial administration as well as paravenous administration can lead to tissue damage, it was required that the SPC mentions the necessity to ensure that ibandronic acid is administered strictly intravenously.

The company has agreed to perform a Post Marketing Surveillance study in order to describe the safety of a single intravenous infusion of ibandronic acid (2 - 4 mg) in patients with hypercalcaemia of malignancy. This would be an open multinational multicenter programme aimed at monitoring the incidence of adverse events.

5. Overall conclusions and benefit/risk assessment

Ibandronic acid, a new therapeutic agent that belongs to the class of bisphosphonates, inhibits osteoclast-related bone resorption and is effective in reducing elevated serum calcium in patients with malignant diseases. With dose ranging from 2 to 4 mg intravenous administration over a 2-hour infusion, 75% of the patients will achieve serum calcium within the normal range. The normalisation of this biochemical marker is considered to be of clear clinical benefit for patients affected by malignancy-related hypercalcaemia.

The starting dose should be chosen on the basis of the severity of the hypercalcaemia and the tumour type because those two factors have been shown to influence the therapeutic response of the ibandronic acid treatment.

Although there is limited experience with patients who received a second administration of ibandronic acid, patients who either experience a recurrent hypercalcaemia episode or fail to show efficacy after the first administration could benefit from a second infusion.

Ibandronic acid associated adverse events were few and mild in relation to the severity of the underlying disease, the most frequent being fever and changes in serum electrolytes composition such as hypocalcaemia, hypomagnesemia and hypophosphatemia. They were similar to those observed with other bisphosphonate compounds. Additional clinical safety data based on proper Post Marketing Surveillance study have been submitted in order to better define the overall safety profile of this medicinal product.

In the light of the current scientific data the CPMP agreed to grant a positive opinion for this medicinal product for the following indication: tumour-induced hypercalcaemia with or without metastases.

6. New presentation: 6 mg/ 6ml

The MAH now applied to add a new presentation: 6mg/6ml of the strength of 1mg/ml.

6. 1 Chemical, pharmaceutical and biological aspects

The additional dosage presentation 6 mg/6 ml has been developed in addition to and on the basis of the existing IV formulations. The already approved dosage strengths are: 1 mg/1 ml, 2mg/2 ml and 4mg/4 ml, for the treatment of hypercalcaemia of malignancy.

Composition
The compositions are identical on a mg/ml basis. Bondronat concentrate for solution for infusion 6 mg/6ml ibandronic acid contains 6.75 mg ibandronic acid, monosodium salt, monohydrate – equivalent to 6 mg ibandronic acid.
During the clinical development 1 mg/1 ml was used.

Drug substance
The drug substance is well characterised and is already marketed in the European Union in the form of Bondronat concentrate for infusion 1 mg/1 ml, 2mg/2ml and 4 mg/4ml
The synthesis of Ibandronic acid has been described sufficiently and the in-process control is considered adequate. The specification set to control the active substance is acceptable with regard to chosen requirements.
The test procedures used for the release of the drug substance have been validated extensively. Analytical results of 57 batches produced since 1992 are presented. All within the set limits in the specification.

Excipients
No excipients are derived from ruminants. Furthermore, neither starting material nor reagents used in the synthesis are derived from ruminants.
However, CoA for all excipients should be submitted.

Product development and finished product
The pharmaceutical development has been satisfactorily addressed. The critical manufacturing steps have been identified and evaluated. Appropriate IPC's are carried out. Validation data have been submitted for 2 pilot and 3 production scale batches, and the results indicate consistency of product quality. The 30 hours holding time is the same as approved for the other dosage strengths.
The manufacturing processes are adequately described and validated.

1. Manufacturing process

The manufacturing site is Roche Diagnostics GmbH, Mannheim, Germany, where conventional equipment and validated manufacturing procedures are used to ensure a safe and reproducable quality.
The product contains standard excipients, and standard packaging materials are used.
The specifications and control tests for the finished product comply with the requirements of the Ph. Eur. and are in line with the relevant guidelines (ICH Topic Q6A and Q3B). All methods are sufficiently described and validated. The limits and parameters in specifications have been justified and are considered adequate.
Batch analysis data consists of 5 batches. All results are within the set specifications.

Stability
The stability data provided support the proposed shelf-life of 60 months, after reconstitution 24 hours at 2-8°C. No storage remark is required.

<u>Discussion on chemical, pharmaceutical and biological aspects</u>

This is a standard formulation of a conventional dosage form, and the manfacturing process is validated. The specifications set to control the finished product are in compliance with ICH requirements for impurities and the control of the finished product is satisfactory, and should ensure a product with uniform and reliable performance in the clinic.
This presentation will be more convenient for administration to breast cancer patients with bone metastases as the recommended dose for metastatic bone disease is 6 mg IV given every 3-4 weeks. The dose should be infused over 1 hour.

1 Introduction

Bondronat concentrate for solution for infusion 1 mg/1 ml and 2 mg/2 ml and 4 mg/4ml ibandronic acid have already been approved in the EU Centralised Procedure for the treatment of malignancy-associated hypercalcaemia in patients with or without bone metastases. More than 350,000 patients have been treated with i.v. ibandronate since it has been on the market.
The MAH now applied to add a new presentation (6mg/6ml) of the strength.

2 Chemical, pharmaceutical and biological aspects

The additional dosage presentation 6 mg/6 ml has been developed in addition to and on the basis of the existing IV formulations. The already approved dosage strengths are: 1 mg/1 ml, 2mg/2 ml and 4mg/4 ml, for the treatment of hypercalcaemia of malignancy.

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Batch analysis data consists of 5 batches. All results are within the set specifications.

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Discussion on chemical, pharmaceutical and biological aspects

This is a standard formulation of a conventional dosage form, and the manfacturing process is validated. The specifications set to control the finished product are in compliance with ICH requirements for impurities and the control of the finished product is satisfactory, and should ensure a product with uniform and reliable performance in the clinic.

Conclusion

There are no unresolved quality aspects which could have a negative impact on the benefit/risk balance. Furthermore, this presentation will be more convenient for administration to breast cancer patients with bone metastases (indication discussed under section 8 of this EPAR) as the recommended dose for metastatic bone disease is 6 mg IV given every 3-4 weeks. The dose should be infused over 1 hour.

7. Line extension: Bondronat 50 mg, film coated tablet

The MAH applied to introduce oral ibandronate as film coated tablets of 50 mg. This formulation is intended to be used for a new indication: Prevention of skeletal events (pathological fractures, bone complications requiring radiotherapy or surgery) in patients with breast cancer and bone metastases, which was applied in parallel also for all licensed presentations and is discussed under section 8 of this EPAR.
The recommended oral dose is one 50 mg tablet daily.

7. 1. Chemical, Pharmaceutical and Biological aspects

Bondronat exists in the EU market as a concentrate for solution for infusion, 1mg/ml in various volumes. This line extension extends the pharmaceutical form to include a film-coated tablet, 50mg.

Composition
Bondronat 50 mg film-coated tablets contain 50 mg ibandronic acid (corresponding to 56.25 mg monosodium salt, monohydrate) and are packaged in a PVC thermoforming film which is sealed with a heat-seal coated aluminium lidding foil.
The composition is standard for a tablet, and all excipients comply with the relevant PhEur monographs and are listed in the SPC (q.v.).

Drug substance
Information on the drug substance supplements the information supplied when the solution for infusion was first authorised, and has been updated by approved variations.

Manufacture
The synthesis comprises seven steps. In-process controls are performed via validated GC methods (purity, content) as well as at the level of the purified active ingredient before milling (content of water and residual solvents). The manufacturing process as well as the in-process controls are sufficiently described.
No catalysts are used. As solvents acetone, ethanol, methanol, diethylcarbonate, diisopropylether and methylethylketone are used. Specifications of all starting materials, reagents and solvents used are presented. As confirmed by release data homogeneous batches are produced and the manufacturing process can be considered as robust.

Structure elucidation was performed sufficiently, interpretation of all spectra is included.
Residual solvents (acetone, methanol, ethanol, diisopropylether, methylethylketone and diethylcarbonate) are controlled adequately. Catalysts are not used, however, a heavy metal test is included within the specification.

The substance is a very stable compound as demonstrated by long-term studies. Only under extreme conditions in stress studies (i.e. oxidative conditions), a small increase of phosphate and phosphite was observed.

Drug Substance Specification
The specification includes tests with relevant limits for identification, assay (HPLC), related impurities, water content, residual solvents, heavy metals, bacterial endotoxins, and particle size distribution via granulometry (laser diffraction).
A large number of batch analytical profiles has been accumulated over the years, and these reveal a reproducible manufacturing process leading to homogeneous batches.

Stability of the Drug Substance
This is well-known from the first authorisation of the solution for infusion.
Several stress tests were undertaken to induce degradation of the active ingredient. Only in the presence of hydrogen peroxide decomposition occurred, indicated by slightly increasing contents of phosphate, phosphite and two unknown impurities.
Three batches were stored as recommended in the ICH guideline on "Stability Testing of New Drug Substances and Products" (25°C/60 r.h. and 30°C for five years, 40°C and 40°C/75% r.h. for six months). Additionally, results of four batches are included in the stability report as supportive data. All results comply with the specification.
Though the titration performed for assay can not be regarded as a stability-indicating method itself, in combination with the various purity tests to investigate degradation products (TLC and HPLC) the overall stability-indicating capacity of the testing system can be assured.
Furthermore, it has to be noted that no catalysts are used within the production of the active ingredient, traces of which could exhibit a negative influence on the stability by inducing degradation.
As demonstrated by the stability data a re-test period has been justified when packaged in polyethylene liners in fiber drums or cardboard boxes and stored below 30°C.

Other Ingredients

All excipients contained in Bondronat 50 mg film-coated tablets comply with the relevant PhEur monographs. For the commercial mixture opadry 00A28646 a specification, method descriptions and a certificate of analysis are supplied. All ingredients correspond to relevant PhEur monographs and certificates of analyses of all excipients have been provided.

Product Development and Finished Product

The development of this tablet is standard. The active substance is very stable. It is used as a fine crystalline powder and is freely soluble in water, so the tablets dissolve very rapidly in aqueous media: Dissolution >85% after 15 minutes. The film-coating has no effect on the dissolution rate.

A second polymorfic form (B) has been identified, but it has similar solubility and intrinsic dissolution properties to polymorph A and is not expected to affect the tablet performance, if present in the tablets. The manufacturing processes are expected to produce tablets containing exclusively polymorph A.

Compatibility studies of the active ingredient with a number of excipients have been performed and based on these results the excipients mentioned above have been selected for the composition of the medicinal product. All excipients used are of PhEur quality and commonly used within pharmaceutical solid dosage forms.
No overages are used except for the film-coating, which is acceptable due to losses characteristic for this production step.

Manufacture
Povidone is dissolved in purified water. A mixture of ibandronic acid, lactose monohydrate and part of the microcrystalline cellulose is spray-granulated with the granulation solution and dried. After sieving, the remaining excipients are added to the granulate. The described manufacturing steps may

be performed in subbatches, which are combined at this stage. After mixing the granulate is compressed to tablet cores using a rotary press. Finally, the coating suspension is prepared from opadry, macrogol and water and sprayed onto the tablet kernels. Thus, the manufacturing process is described sufficiently by the applicant.
The following in-process controls are performed: the granulate is checked for loss on drying, the tablet cores are controlled for weight (individual and average) and hardness and, finally, the film-coated tablets are tested for weight (individual and average).
No critical steps are observed. The homogeneous distribution of the active ingredient has been demonstrated.

Product Specification
The same specification is applied for release and for shelf life concerning the assay of the active substance. The identity of the active ingredient is determined by means of two independent methods as recommended in the ICH guideline Q6A.
The impurity limits set are in accordance with ICH guideline Q3B, which requires identification above 0.2% and qualification above 200 µg (corresponding to 0.4%) for the proposed maximum daily intake of ibandronic acid.
Limits set for the disintegration test are tighter than supposed within the PhEur.

The microbiological purity is tested on the first five production batches and thereafter twice a year. A test for the identity of the colouring agent is described and is integrated in the specification. The methods are validated according to relevant EU/ICH guidelines.
Batch analysis data at release prove the homogeneity of the production process.

Stability of the Product

The active ingredient has been proven to be a very stable compound and this is also reflected in the stability of the product, which has been demonstrated by studies under ICH conditions. Furthermore, during development several batches have been monitored using three different TLC systems and one HPLC method. No significant increase in any degradation product was observed. The limits applied for unspecified impurities also are in line with ICH topic Q3B.
All methods used during analytical development are discussed and described sufficiently.

The results of the stability investigations by validated stability-indicating methods confirm the shelf life and storage conditions as defined in the SPC.

Discussion on chemical, pharmaceutical and biological aspects

This is a standard formulation of a conventional dosage form, and the manufacturing process is validated. The specifications set to control the finished product are in compliance with ICH requirements for impurities and the control of the finished product is satisfactory, and should ensure a product with uniform and reliable performance in the clinic. At the time of the CPMP opinion, there were a number of unresolved minor quality issues having no impact on the benefit/risk balance. The applicant agreed to resolve these as post-opinion follow up measures within a defined timeframe.

Conclusion

The physicochemical characteristics, manufacture and control of the active substance is unchanged and the evaluation of the pharmaceutical dossier has focused on the dosage form. The manufacture, control and stability of the tablet indicates compliance with current EU norms, and indicates satisfactory uniformity and clinical performance from batch to batch. There are no unresolved quality aspects which could have a negative impact on the benefit/risk balance.

8. Additional indication: Bone metastases due to breast cancer

The MAH applied to extend the licensed indication to include "**Prevention of skeletal events (pathological fractures, bone complications requiring radiotherapy or surgery) in patients with**

breast cancer and bone metastases". In parallel the MAH applied to introduce oral ibandronate as film coated tablets of 50 mg to be used for the above indication and to add a new presentation (6mg/6ml) of the existing liquid formulation.
The recommended dose for metastatic bone disease is 6 mg IV given every 3-4 weeks. The dose should be infused over 1 hour.
Bondronat concentrate for solution for infusion 1 mg/1 ml and 2 mg/2 ml and 4 mg/4ml ibandronic acid have already been approved in the EU Centralised Procedure for the treatment of malignancy-associated hypercalcaemia in patients with or without bone metastases. More than 350,000 patients have been treated with i.v. ibandronate since it has been on the market.

1 Introduction

Breast cancer is the most common carcinoma in women. Of those with recurrent disease, 30% will develop their first metastases in bone, and skeletal disease will be present in approximately 80% at death. The most common skeletal complications are bone pain, spinal cord compression and pathological fractures at both axial and appendicular sites that might require palliative radiotherapy, surgery and analgesics. A systemic consequence is hypercalcaemia, which can be life threatening. Symptoms include confusion, dehydration and weakness. These complications impair markedly the quality of life of affected patients.

Two mechanisms are considered to be involved in the pathogenesis of metastatic bone disease. Firstly, direct tumour osteolysis resulting from the local invasion of the bone and marrow by tumour cells, and secondly, production by the tumour itself of humoral factors such as parathyroid hormone-related peptide (PTHrP) which directly increase osteoclastic bone resorption and/or the renal tubular re-absorption of calcium.

Bisphosphonates are analogues of pyrophosphate containing a P-C-P bond, which allows tight binding of the compound to hydroxyapatite crystals (the mineral component of bone). Although their mode of action is complex, bisphosphonates have been shown to localise preferentially to sites of active bone remodelling and inhibit the action of mature osteoclasts (the cells effecting bone resorption), probably via an effect on enzymes of the mevalonate pathway. Recent findings also suggest that bisphosphonates can induce osteoclast apoptosis as well as indirectly inhibiting the recruitment of osteoclasts by inducing the release of inhibitory factors from osteoblasts and inhibiting farnesyl pyrophosphate synthetase in the mevalonate pathway and the prenylation of proteins, leading to 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. The net effect is a reduction in the excessive bone resorption and progressive destruction of the bone seen in these disease states.

The bisphosphonates have been extensively investigated in the treatment and prevention of skeletal complications due to malignant disease. Clodronate (oral) and pamidronate (i.v.) have both been shown to be effective in reducing bone pain and excessive bone resorption from osteolytic metastases as well as in the treatment of hypercalcaemia of malignancy. Zometa (zoledronic acid) has recently been approved through the centralised procedure for the prevention of skeletal complications in patients with various malignant diseases. In an active control study in patients with metastatic bone disease due to multiple myeloma or breast cancer, zoledronic acid (4 mg i.v. infusion over 15 minutes) demonstrated similar efficacy and safety to pamidronate (90 mg i.v. over two hours).

Ibandronate, [3-(N-methyl-N-pentyl) amino-1-hydoxypropane-1,1-diphosphonic acid, monosodium, monohydrate] (INN Ibandronic acid) is a nitrogen-containing bisphosphonate. It is a 'third generation' bisphosphonate with a nitrogen containing side chain, which has been investigated in the treatment of metastatic bone disease due to breast cancer.

2 Toxico-pharmacological aspects

Pharmacodynamics

The non-clinical development programme comprised primary pharmacodynamic studies in in-vitro and in-vivo models of metastatic bone disease. These were conducted to provide proof of concept for the proposed indication, but were too limited to guide the selection of human dose levels. The secondary pharmacodynamic, safety pharmacology, pharmacokinetic and toxicology studies submitted in support of the extension are identical to those included in the recent application (EMEA/H/C/501-502) proposing the use of ibandronate 2.5 mg/day p.o. to treat and prevent osteoporosis in postmenopausal women.

In vitro studies

Pre-incubation of cortical and trabecular bone slices with ibandronate 10^{-6}-10^{-4} M in vitro caused a dose-dependent inhibition of the adhesion of MDA-MB-231 cells to the calcified matrix, with ID_{50}s just below 10^{-6} M (≈ 0.4 μg/ml). Pre-incubation of a non-mineralised bone matrix with ibandronate did not inhibit the attachment of MDA-MB-231, MCF-7 and prostate (PC3 and PmPC3) cell lines. However, when the cancer cells were pre-treated with ibandronate, concentrations of 1-5 x 10^{-12} M ≈ 0.4-2 pg/ml markedly inhibited their attachment to both cortical bone and the non-mineralised matrix as well as tumour-cell invasion through an artificial basement membrane. The mechanism of action of the inhibition of tumour-cell adhesion and invasion are unknown, as there was no effect on tumour-cell viability or expression of integrins (matrix receptors) or matrix metalloproteinases (MMP), although MMP activity was reduced due to zinc chelation. Higher concentrations (10^{-6}- 2.5 x 10^{-4} M ≈ 0.4-100 μg/ml) induced apoptosis or necrosis in human mammary cancer cell lines (T47D > MCF-7 >> MDA-MB-231).

In vivo studies

Primary pharmacodynamics investigated the effect on bone lesions in in-vivo models of metastatic bone disease and on tumour-cell adhesion, invasion and growth in vitro. In rodents inoculated with human or syngeneic tumour cells with affinity for bone, ibandronate 15-160 μg/kg/day s.c. consistently reduced the take and growth of osteolytic bone metastases. As none of the studies included more than one dose level, a dose-response curve could not be established. Early intervention was more effective than late. Treatment did not prolong survival and had inconsistent effects on non-bone lesions. In vitro, exposure to picomolar concentrations of ibandronate inhibited tumour-cell invasion and adhesion to bone matrices (mineralised or not), whereas levels from 1-250 μM were required to kill the tumour cells. By comparison, ibandronate inhibits osteoclastic bone resorption at low nanomolar concentrations. The proposed human dose is expected to produce blood levels ranging 3-140 nM (10-500 ng/ml), whereas a local concentration of several hundred μM may occur in bone resorption lacunae. As such, both inhibitions of invasion/adhesion and cytotoxicity may contribute to the effect on bone metastases, whereas toxic effects on tumour cells in other organs would be negligible.

Secondary pharmacodynamics showed ibandronate to be a potent inhibitor of osteoclast activity that increases bone mass and calcium balance in growing animals, but not in full-grown, intact adults. In models of tumour-induced bone resorption and hypercalcaemia, it demonstrated a linear dose-response relationship with respect to osteolysis, whereas there was no effect on the increase in renal tubular absorption of calcium induced by parathyroid-hormone-related protein. In spayed rats, dogs and Cynomolgus monkeys, which are well-established models of postmenopausal osteoporosis, ibandronate caused a consistent, dose-dependent inhibition or reversal of ovariectomy-induced decreases in bone mass and strength in cancellous bone, with less pronounced effects on cortical bone. These effects were evident at dose levels below or around the proposed human dose of 6 mg i.v. every 3-4 weeks ≈ 3-6 μg/kg/day in a 50- to 70-kg person. Ibandronate had no adverse effects on bone quality in intact dogs and rats given oral doses of up to 10 and 15 mg/kg/day corresponding to 10-15 times the proposed human dose for 1 and 2 years, respectively. However, there was a trend towards

impairment of bone formation and mineralisation in ovariectomised dogs administered ≥ 4.1 µg/kg/day s.c., which is close to the projected human exposure.

Pharmacodynamic drug interactions

Limited pharmacodynamic drug interaction studies indicate that ibandronate may reduce or enhance the effect of anticancer agents, depending on their mode of action.

General and safety pharmacology programme

The 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 Na^+ /K^+ ratio. Likewise, there was an increase in serum creatinine in all treatment groups in an osteoporosis study in ovariectomised dogs administered 0.8, 1.2, 4.1 or 14 µg/kg/day s.c. 5 days a week for 12 months. Further investigation to elucidate this effect was conducted during the toxicity studies.

Pharmacokinetics

Around 50% of a single dose of ibandronate were taken up by calcified tissue and 1-3% by non-calcified tissue. The primary pharmacological effect on bone is not directly related to blood levels, but rather to the amount taken up by bone. Therefore, it is acceptable that the pharmacokinetic studies focus on the measurement of drug concentrations in bone and on tissue distribution studies.

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. Ibandronate is not metabolised anywhere in the body, except possibly for a very small fraction in the duodenum.

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 ovariectomised 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.

In rats given 0.1 mg/kg ^{14}C-ibandronate i.v., 50% of the dose was found in calcified tissue after 2 and 24 hours. Radioactivity was 17-38 times higher in calcified tissue than in non-calcified tissue. There was a large, unexplained variation between studies in the labelling of calcified tissues. Relative distribution of radioactivity was bone >> liver > kidneys > spleen. Autoradiography in rats given 0.1 mg/kg ^{14}C-ibandronate i.v. for 7 days clearly showed that bone tissue is the main target for accumulation. The tissues ranked in order of amount of radioactivity were bone >>> kidney (renal cortex) > liver, faeces and spleen. Radioactivity in the kidney (renal cortex) was higher after repeated dosing than after single dosing. Distribution studies in rats given ^{14}C-ibandronate i.v. for 7 days showed that radioactivity increased 4-7 fold in calcified tissues and kidneys during repeated administration, whereas other organs showed only little (… 2-fold) or no accumulation. Accumulation in the kidneys may explain the nephrotoxicity observed in chronic toxicity studies.

Ibandronate concentration in bone was determined in intact rats after 2 years' daily oral dosing of 3, 7 or 15 mg/kg ibandronate. The uptake of ibandronate was dose-dependent and linear, with no evidence of skeletal saturation. This indicates a normal bone physiology after lifelong administration of 15 times the proposed human dose. Bone uptake was also linear with dose in aged ovariectomised rats treated for 12 months with up to 25 µg/kg/day s.c. However, rats do not have Haversian canals and may not be reliable models of bone remodelling in humans. Indeed, in ovariectomised Cynomolgus monkeys treated for 16 months, bone concentrations appeared to be dose-dependent in a non-linear fashion. The non-linearity was explained by the suppression of bone turnover secondary to ovariectomy. However, there were signs of saturation at a dose level that was practically identical to the expected human exposure. Therefore, it cannot be excluded that the proposed dose regimens will result in "frozen bone" in postmenopausal patients.

The average binding of ibandronate to plasma proteins determined in vitro was around 83-87%.

In rats, excretion in the faeces after i.v. administration was 5-20% and biliary excretion was practically zero. In dogs, elimination via the faeces after i.v. administration was negligible (0.4%). Ibandronate was excreted in the milk and crossed the placental barrier.

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 interactions are unlikely to occur in man.

Toxicology

The acute toxicity was low by oral, but relatively high by i.v. administration. A single i.v. dose of 1 mg/kg caused degeneration and single-cell necrosis in the proximal part of the convoluted tubules in rats, and 5 mg/kg was associated with a reversible reduction in kidney function in dogs. The pathogenesis of the kidney damage is unknown.

Studies not previously submitted comprised a 12-month oral rat study with 6 months' recovery, a 6-month dog study with 13 weeks' recovery (gelatine capsule), a 12-month dog study with 6 months' recovery (tablet) and 6-month i.v. studies in the rat and dog.

Expected pharmacodynamic effects included slight hypocalcaemia, increases in endochondral ossification and trabecular bone mass and haematological changes secondary to the decrease in bone marrow space. In dogs there was a dose-related occurrence of adverse bone effects such as focal necrosis of endochondral zones and focal inflammatory changes (oedema, haemorrhage, infiltration, fibrosis) in the bone marrow. The NOAEL for these effects was 5 mg/kg/day p.o. and 0.15 mg/kg once weekly or 0.3 mg/kg twice a month, i.v. administration, corresponding to a safety margin of 4-5.

In all repeat-dose studies, the key target organ was the kidney. In the 12-month oral studies, reversible degeneration, hypertrophy and/or hyperplasia of the tubules occurred in rats at 10 mg/kg/day and in dogs at 5 mg/kg/day. In the 26-week i.v. studies, 0.3 mg/kg caused kidney lesions in both species when administered once a week, but not when given twice a month. Safety margins calculated from AUC or C_{max} values at the highest dose without kidney abnormalities ranged from less than 1 to 9, Toxic effects on the liver, gastro-intestinal tract and the airways were only seen at clinically irrelevant dose levels.

Genotoxicity was studied with respect to gene mutations in bacteria and mammalian cells and chromosomal aberrations in vitro and vivo. There was no evidence of genotoxic potential in any of these tests.

Carcinogenicity studies were conducted by oral gavage in rats and mice and by administration in drinking water in mice. An increased incidence of benign histiocytomas of the skin in male rats and of C-cell adenomas in female rats was incidental and unrelated to treatment. Likewise, there were no treatment-related tumours in mice. Whereas reasonable exposure multiples were achieved in mice, a comparison of measured AUC values in rats and humans raises doubt about the adequacy of the exposure attained in the female sex. Nevertheless, the rat carcinogenicity study is considered acceptable for the following reasons:

- The highest dose was equal to the maximum tolerated oral dose, hence a higher exposure may not be feasible.
- There were unequivocal pharmacodynamic and toxic effects in the high-dose group.
- Bondronat is indicated for the symptomatic treatment of metastatic bone disease due to breast cancer, that is, in severely ill cancer patients with a poor prognosis.

In p.o. and i.v. fertility studies in the rat, ibandronate was found to reduce sperm concentration and decrease the number of corpora lutea and increase pre-implantation losses. When given by oral gavage, 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 the 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. The effects on fertility and development occurred at exposures equal to or below the proposed human dose (up to 1 mg/kg/day by mouth or 0.12 mg/kg every 3-4 weeks by i.v. infusion). Given the proposed indication, they do not give cause for concern, particularly as the SPCs contain appropriate warnings against use during pregnancy and lactation.

In local tolerance studies in rats and rabbits, solutions of ibandronate were well tolerated when administered i.v., but severely irritant when given paravenously or s.c. As such, the solution should only be administered by the i.v. route. The corrosiveness of the drug substance indicates that the tablets may cause irritation or burns to the oesophagus and gastric mucosa. Appropriate warnings to this effect are included in the SPCs for the tablets.

There was no evidence of antigenicity or immunotoxicity. The expected risk to the aquatic environment is very low.

Discussion on toxico-pharmacological aspects

The primary pharmacodynamic studies provided satisfactory proof of concept for the proposed indication, but were too limited to guide the selection of human dose levels. The secondary pharmacodynamic, safety pharmacology, pharmacokinetic and toxicology studies submitted in support of the extension are identical to those included in the recent application for Bonviva proposing the use of ibandronate 2.5 mg/day p.o. to treat and prevent osteoporosis in postmenopausal women.

The pharmacokinetic studies focus on the measurement of drug concentrations in bone and on tissue distribution studies. 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.
Clearance parameters in dogs given showed distribution volume of 7.3 l/kg, indicating penetration into a deep compartment (bone, liver and kidney) and excretion almost exclusively through urine. Serum kinetics in ovariectomised Cynomolgus monkeys showed a linear exposure in relation to dose, thus clearance mechanisms were not saturated. Tissue distribution studies in rats showed that the bone is the main target in bone, but also accumulation in kidney (renal cortex) and less in liver, faeces and spleen. Accumulation in the kidneys may explain the nephrotoxicity observed in chronic toxicity studies.

Ibandronate did not inhibit any of the major cytochrome P450 iso-enzymes in human liver microsomes, suggesting that hepatic drug-drug interactions are unlikely to occur in man.
In both acute toxicity and repeat-dose studies, the main target organ was the kidney. The pathogenesis of the kidney damage is unknown. Toxic effects on the liver, gastro-intestinal tract and the airways were only seen at clinically irrelevant dose levels.
The conduct of carcinogenicity studies is considered satisfactory in the context of the symptomatic treatment of metastatic bone disease due to breast cancer, that is, in severely ill cancer patients with a poor prognosis. There was no evidence of genotoxic potential.
Findings from fertility studies, they do not give cause for concern, given the proposed indication and particularly as the SPCs contain appropriate warnings against use during pregnancy and lactation.
Local tolerance studies have revealed that ibandronate solution may be severely irritant if given paravenously or s.c. it should only be administered by the i.v. route. The tablets may cause irritation or burns to the oesophagus and gastric mucosa. These findings are reflected in the SPC by appropriate warnings.

3. Clinical aspects

The clinical studies in this application were undertaken in accordance with GCP practices in place at the time of starting each study. There is a minor deviation in one study, MF 4265, in that Ethics Committee approval could not be sought by a centre in Kuwait (no committee constituted) but was approved by the Director of the cancer centre, as was normal practice at that time. In addition, the GCP status of a number of additional studies cited from the literature cannot be validated.

Clinical pharmacology

Pharmacodynamics

The rationale for using bisphosphonates in disorders associated with increased bone resorption is well established. These compounds, which are pyrophosphate analogues, are selective inhibitors of osteoclast mediated bone resorption. Phase II studies in patients with MBD indicated that i.v. and p.o. ibandronate is effective in reducing urinary excretion of calcium as well as lowering urinary excretion of the bone turnover markers in an apparent dose dependent manner.

Pharmacokinetics

The pharmacokinetic database is extensive. i.v. and oral ibandronate was studied in 24 clinical pharmacology studies, involving 593 subjects (healthy male volunteers, healthy postmenopausal women, osteopenic postmenopausal women, patients with varying degrees of renal impairment and patients with MBD). The pharmacokinetics of ibandronate is generally well described.
Following intravenous and oral administration of 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 patients with osteoporosis 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. There was no systemic accumulation when ibandronate was administered i.v. once every 4 weeks for 48 weeks to patients with MBD.

Pharmacokinetics has not been investigated in subjects below 18 years of age or in patient suffering from hepatic impairment. 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.

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.
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 present. In subjects with severe renal impairment (CLcr <30mL/min) dose adjustment is recommended. In patients with severe renal impairment, it is recommended that the oral dose is reduced from 50mg once daily to 50mg once weekly and for the i.v. therapy, it is proposed that the infusion dose is reduced from 6 mg to 2 mg at a rate of 60 minutes. As the pharmacokinetics of ibandronate was not assessed in patients with end-stage renal disease managed by other than haemodialysis, the pharmacokinetics of ibandronate in these patients are unknown. An appropriate warning of the use under these circumstances is made in the SPC.

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 is not of clinical relevance.

Clinical efficacy

The dose selection was based on 4 phase II pharmacodynamic studies, one with i.v. ibandronate and three investigating the efficacy of oral ibandronate in the treatment of MBD of cancer (including breast cancer).
Study **MF 4328** was an open, non-controlled, single dose study to investigate the efficacy and safety of 6 different i.v. doses of ibandronate (0.5, 1, 2, 3 mg ibandronate single i.v. injections and 4 and

6 mg ibandronate single i.v. infusions) in normocalcemic patients with MBD due to breast cancer. The study period was limited to 28 days. Treatment resulted in a dose dependent decrease in calcium/creatinine ratio, urinary hydroxyproline and urinary deoxypyridinoline. The dynamic range was greatest for the calcium creatinine ratio. Effects were observed on day 2 and, at the end of observation (day 28), values were significantly lower than pre-treatment values. These markers of bone resorption reached a nadir and thereafter tended to increase, though not to pre-treatment values. The extent of relapse appeared to be dose dependent, for example, with both the 4 mg and 6 mg dose, calcium/creatinine decreased by 76% and 77% at day 2, but at day 28 suppression was by 37% and 57%, respectively. The corresponding values for the 2 mg dose were 59% and 31%.

Study **MF 4218** was a single centre, open-label, dose-finding study designed to investigate the efficacy and safety of 5 different oral doses of ibandronate (10 mg, 20 mg, 40 mg, 50 mg and 80 mg/day; 3-5 patients per group) during one week's oral treatment in 23 normocalcemic patients with tumour-induced osteolysis. All doses with the exception of 10 mg ibandronate demonstrated distinct effects in terms of reducing elevated urinary calcium excretion, although a high degree of intra-individual variation was observed within the treatment groups. No obvious differences were identified between doses of ibandronate ranging from 20 mg to 80 mg daily for 7 days.

Study **MF 4269** was a double blind, multicentre, randomised, multiple dose study designed to investigate the efficacy and safety of oral doses of ibandronate during a four-week treatment in female patients with tumour-mediated osteolysis due to breast cancer. A significant dose response was observed on fasting calcium excretion (the primary endpoint) as well as on urinary deoxypyridinoline. No dose response was observed in urinary hydroxyproline. By week four, the median decrease in urinary calcium excretion was 22.9%, 62.2% and 61.9% for patients treated daily with 10, 20 and 50 mg ibandronate, respectively. Urinary calcium excretion returned to baseline levels after 3-4 weeks in patients who had received orally either 10 mg or 20 mg ibandronate daily, but remained below baseline values even after 8 weeks in patients who had received 50 mg daily.

Study **MF 4346** was a double blind, randomised, dose-finding study designed to investigate the efficacy and safety of four different oral doses of ibandronate (5 mg, 10 mg, 20 mg, 50 mg) versus placebo during a four-week treatment in patients with MBD from various cancers. The primary endpoint was again a reduction in fasting urinary calcium/creatinine, an index of net bone resorption.

The pivotal clinical programme comprised three double-blind, randomised, placebo controlled studies, all in women with recurrent breast cancer and skeletal metastases with an adequate performance status, as judged by a WHO grade of 0, 1 or 2. Two studies (**MF 4414** and **4434**) examined the effects of oral daily treatment of 20 mg and 50 mg ibandronate compared with placebo. Both were multicentre trials. Both studies recruited extensively from Russia and Europe, but one, MF 4434 also included centres from the United States, Australia, South Africa and New Zealand.Study **MF4265** compared the effects of 2 mg and 6 mg of the intravenous formulation administered every 3-4 weeks with placebo, for 96 weeks.

The primary efficacy measurement for each study was an index of the combined skeletal morbidity, as judged by new bone complications. These comprised: 1. Pathological vertebral fractures, 2. Pathological non-vertebral fractures, 3.Bone complications requiring radiotherapy, 4.Bone complications requiring surgery. The composite primary endpoint was to determine the effect of treatment on the **'skeletal morbidity period rate'** (SMPR). For the purposes of analysis, the applicants have considered a 12-week interval as a period. The primary endpoint is the number of 12-week periods with a new bone complication (PNBC) adjusted for observation time (i.e. the number of periods during which the patient was on study). In order to decrease the effect of early drop-outs in a study with a duration of 96 week the ratio is given as: **PNBC + 0.5 / periods of observation + 1**. The addition of the numerator and denominator constants differentiates patients who withdrew early with no skeletal event from those who withdrew late in the study with no events. This approach was considered by the CPMP in Scientific Advice Letter CPMP/1878/00 of 21 September 2000 to be problematic because this is not an intuitive statistic to employ. The analysis and interpretation could become quite complex unless all patients provide complete data. The CPMP recommended that the method should be supported by appropriate sensitivity analyses. The advice was given prior to the

unblinding of the oral phase III studies. The company was advised to follow up all patients in MF 4414 and MF 4434 who withdrew prematurely and to collect additional primary efficacy endpoint data (fractures, surgery, radiotherapy events) and safety data (serious adverse events). This post-withdrawal follow-up (PWFU) data were captured between the date of withdrawal of the patient (prior to week 92) and either the date of death of the patient or the date of the last scheduled study visit, whichever was earlier. Such data, if collected in an unbiased manner, would lead to a more balanced 'information time' between the treatment groups and would represent a true 'Intent to Treat' situation for the study population. For the evaluation of the primary endpoint in studies MF 4414 and MF 4434, the results have been analysed according to the SMPR procedure including the PWFU dataset. Sensitivity analyses excluding the PWFU dataset have also been performed and are presented.
Secondary efficacy variables included: 1. Bone pain score 2. Analgesic consumption 3. Quality of life 3. Survival 4. WHO performance status 5. Efficacy related adverse events 5. Urinary markers of bone turnover (pyridinoline and deoxypyridinoline).

Results

Study populations/accountability of patients

In **MF4265** a total of 251 patients (54% of all randomised patients) completed 60 weeks treatment and 189 patients (40.5%) completed the entire 96 week treatment period. A total of 277 patients (59.4%) prematurely withdrew from the study i.e. prior to week 96 (visit 26). The percentage of patients completing 96 weeks of treatment was higher in the 2 mg (47.4%) and 6 mg (42.9%) ibandronate treatment groups compared with placebo (31.6%). Median time on study was markedly longer for patients receiving 6 mg ibandronate (72.3 weeks) and 2 mg ibandronate (72.3 weeks) compared with those receiving placebo (52.3 weeks). The differences, although not statistically significant at the 5% level indicated a greater overall time of exposure to treatment for the patients in the ibandronate groups.

MF 4414 and **MF 4434** were similar in design with the same patient populations recruited. The primary and secondary efficacy endpoints were virtually identical as were the objectives of each study: To investigate the efficacy and safety of oral ibandronate in the treatment of bone complications of MBD in breast cancer patients. Eight hundred and forty six patients were randomised to treatment with oral ibandronate (20 mg or 50 mg) or placebo. A total of 344 patients (40.7% of all randomised patients) completed the studies while 502 patients (59.3%) were withdrawn prematurely. A total of 172 patients (41.8 %) completed study **MF 4414**, while 239 patients (58.2 %) prematurely withdrew (i.e. prior to week 96 (visit 26)). The percentage of patients completing the study was higher in the 20 mg (44.9 %) and 50 mg (44.6 %) active treatment groups compared with placebo (35.8 %). This demonstrates that MF 4414 was affected by unbalanced selective dropout, with a higher proportion of patient dropouts in the placebo arm. A total of 172 patients (39.5 % of randomised patients) completed study **MF 4434**, while 263 patients (60.5 %) prematurely withdrew prior to week 96 (visit 26). The percentage of patients completing **MF 4434** was similar in the placebo (37.8 %), 20 mg ibandronate (38.2 %) and 50 mg ibandronate (42.6 %) treatment groups.
Although most demographic and baseline characteristics were similar across the three treatment groups, in study **MF 4414** , the three groups do not appear to have been well balanced at baseline with respect to a number of important prognostic factors. In particular, patients in the two active treatment groups may have had more advanced and/or more aggressive disease than the placebo group at the time they entered the study (with the ibandronate 50 mg group having the greatest difference from placebo in some key parameters). In study MF 4414, a greater proportion of patients in the active treatment groups had a WHO performance status of '2', were currently receiving cytotoxic drugs, had pre-existing fractures and exhibited anaemia. These differences were generally more prominent in the 50 mg dose group.

Efficacy results

The main results for the **primary endpoints** in the pivotal trials are shown in tables 1 and 2 below.

Mean SMPR at Last Available Efficacy Date Per Patient Year (ITT Population) MF 4265

	Placebo N=158	2 mg Ibandronate N=154	6 mg Ibandronate N=154	global p-value
All New Bone Events	1.48	1.31 p=0.152[2]	1.19 **p=0.004**[2]	**0.004**[1]
Vertebral Fractures	0.82	0.70 **p=0.028**[2]	0.71 **p=0.023**[2]	**0.023**[1]
Non Vertebral Fractures	0.81	0.70 p=0.235[2]	0.72 p=0.396[2]	0.421[1]
Bone Events Requiring Radiotherapy	1.09	0.95 p=0.062[2]	0.91 p=**0.011**[2]	**0.012**[1]
Bone Events Requiring Surgery	0.62	0.50 p=**0.013**[2]	0.56 p=0.075[2]	0.060[1]

[1] global comparison between treatments using Jonckheere-Terpstra test
[2] pairwise comparisons versus placebo using Wilcoxon rank sum test. Unadjusted for multiplicity

Table 2 Mean SMPR in MF 4434 and MF 4414

	Mean SMPR			
MF 4434	**Placebo (N=143)**	**20 mg Ibandronate (N=144)**	**50 mg Ibandronate (N=148)**	**p-value[1]**
All New Bone Events	1.20	0.97 p=**0.024**[2]	0.98 p=**0.037**[2]	**0.044**
Vertebral Fractures	0.51	0.52 p=0.315[2]	0.52 p=0.739[2]	0.730
Non-Vertebral Fractures	0.52	0.54 p=0.596[2]	0.54 p=0.890[2]	0.887
Events Requiring Radiotherapy	0.99	0.81 p=0.082[2]	0.77 p=**0.005**[2]	**0.004**
Events Requiring Surgery	0.44	0.50 p=0.738[2]	0.43 p=0.644[2]	0.643

MF 4414	**Placebo (N=134)**	**20 mg Ibandronate (N=138)**	**50 mg Ibandronate (N=139)**	**p-value[1]**
All New Bone Events	1.10	0.95 p=0.200[2]	1.00 p=0.442[2]	0.423
Vertebral Fractures	0.53	0.51	0.47	-
Non-Vertebral Fractures	0.51	0.47	0.49	-
Events Requiring Radiotherapy	0.96	0.80	0.84	-
Events Requiring Surgery	0.45	0.41	0.38	-

[1] global comparison between treatments using Jonckheere-Terpstra test
[2] p-value for active treatment versus placebo calculated using Wilcoxon Rank sum test

N.B. Interpretation of statistical significance for pairwise comparisons is dependent on a global p-value; $p \leq 0.05$.

Compared with placebo, both doses of ibandronate were able to prevent or reduce deterioration in physical and role functions, but not emotional, cognitive or social functioning in the Quality of Life Evaluation. The global assessment of function was, however, statistically significantly improved by 50 mg ibandronate (p=0.030). (Details in Table 31 of the EU Written Summary).
Mean bone pain scores from baseline to last assessment increased in the placebo group but decreased in the two active treatment groups. The difference was statistically significant for both doses of

ibandronate. This reduction in bone pain was not achieved through increased use of analgesics in the ibandronate groups. Whereas the mean analgesic score increased by 87% in the placebo group, the score increased by only 49% in the 20 mg ibandronate group and 54% in the 50 mg group. These differences were also statistically significant.
In the pooled dataset, the WHO performance status deteriorates (i.e. the score increases) in all three treatment groups. However, the increase in WHO score in the two ibandronate dose groups is significantly less than that in the placebo group.

Table 3 Secondary Efficacy Results

	Placebo n=277	Bondronat 50 mg n=287	p-value
Bone pain *	0.20	-0.10	p=0.001
Analgesic use *	0.85	0.60	p=0.019
Quality of Life *	-26.8	-8.3	p=0.032
WHO performance score *	0.54	0.33	p=0.008
Urinary CTx **	10.95	-77.32	p=0.001

* Mean change from baseline to last assessment.
** Median change from baseline to last assessment

Both doses of ibandronate caused a marked reduction in the biochemical marker of bone destruction compared with the placebo group, where urinary CTx levels increased from baseline (up to week 72). A statistically significant reduction was seen between baseline and last assessment for both the 20 mg ($p<0.001$) and 50 mg ($p<0.001$) treatment groups. As in the phase II studies, the reductions in bone markers with 50 mg ibandronate were greater than those with 20 mg ibandronate ($p<0.001$). The reduction in urinary CTx was significantly correlated with the primary efficacy endpoint, SMPR.

Exploratory analysis performed across trials.

The three treatment groups in the oral phase III studies were not well balanced at baseline with respect to a number of important prognostic factors. These imbalances may have influenced the outcome of study MF4414. In order to determine more precisely which baseline factors had the most influence on the primary endpoint outcome, and to compensate for the difference between treatment groups, multivariate analyses were carried out for the primary efficacy variable in the oral studies. In addition for consistency, these exploratory analyses were performed on data from the i.v. phase III study and for the pooled MF 4414/MF 4434 dataset as well as for a pooled dataset from all phase III studies. Cox multivariate and Poisson multivariate analyses were performed to identify confounders and to set up adjusted models. The results of one important analysis is shown in table 4 below:

Table 4. Poisson Regression Analyses: Number of New Bone Events (ITT Population) Risk vs Placebo

	Risk estimate	**lower 95% CI**	**upper 95% CI**	**p-value**
MF 4265*				
2 mg	1.13	0.83	1.52	0.44
6 mg	0.60	0.43	0.85	**0.0033**
MF 4434**				
20 mg	0.62	0.43	0.89	**0.009**
50 mg	0.61	0.43	0.86	**0.005**
MF 4414**				
20 mg	0.68	0.48	0.95	**0.026**
50 mg	0.61	0.43	0.86	**0.0044**
MF 4414/MF 4434 Pooled Dataset**				
20 mg	0.64	0.50	0.82	**0.0004**
50 mg	0.62	0.48	0.79	**0.0001**
MF 4414/ MF 4434/ MF 4265 Pooled Dataset***				
2 mg i.v.	1.19	0.93	1.53	0.165
6 mg i.v., 20 mg and 50 mg oral ibandronate	0.62	0.51	0.74	**<0.0001**

Note: Offset variable is log of total number of events in study (ITT analysis); over dispersion corrected with Pearson scale.
*Covariates in final model: bone pain, fracture and Russian center; for periods: bone pain, fracture, at least one lesion > 1 cm, and alkaline phosphatase.
**Covariates in final model: bone pain, fracture, WHO, WHO grade 2, alkaline phosphatase, hepatic disease, analgesic consumption, at least one lesion>1cm and no previous chemotherapy.
***Covariates in final model: oral study, bone pain, fracture, analgesic consumption, Russian center, WHO, and alkaline phosphatase.

Discussion on clinical efficacy

The dose-finding programme is problematic. The effects on bone markers might not translate into clinical efficacy in the target population. It is desirable that dose-finding studies utilise the same clinical endpoints that are to be investigated in the pivotal phase III trials. Secondly, the dataset is limited both in terms of number of patients and as regards duration of exposure (1-4 weeks). This is probably the main reason for including two doses in both the i.v. phase III programme (2 and 6 mg ibandronate) and the oral phase III programme (20 and 50 mg ibandronate).
As the 20 mg film-coated tablet is no longer a part of the dosage regimen in the treatment of the metastatic bone-disease, the application for this strength was therefore withdrawn.

The oral bioavailability of ibandronate is about 0.6%. There is a large inter-subject and intra-subject (CVs for AUC and Cmax were about 47-48%) variability. The low oral bioavailability of aminobisphosphonates is a class effect. A low oral bioavailability does not necessarily mean that the therapeutic needed systemically drug levels cannot be obtained by an oral application. It should be recalled that orally applied ibandronic acid has been successfully used, although with a smaller daily dose (2.5 mg/day), for the treatment of postmenopausal osteoporosis (MF4411). These results would support the suggestion that an appropriate systemic exposure can be achieved with oral ibandronate.

The evaluation of the efficacy of ibandronate in women with metastatic breast cancer was based on the primary composite endpoint Skeletal Morbidity Periode Rate (SMPR) comprising the 4 components vertebral fracture, non-vertebral fracture, radiotherapy to bone for treatment of fractures/impending fractures and surgery to bone for treatment of fractures. This composite endpoint has been considered acceptable in a previous CPMP scientific advice (CPMP/1878/00 dated 21 September 2000).

Effect size

A statistically significantly longer median time from randomisation to first new bone complication was observed for patients in the 6 mg (50.6 weeks) treatment group compared with placebo (33.1 weeks; p=0.018) in the i.v. study MF 4265. Analysis of the shifts in bone pain between baseline and last assessment indicated that a higher percentage of patients receiving 6 mg ibandronate (~37%) recorded an improvement in bone pain compared with either the 2 mg (~27%) or placebo (~23%) treatment groups. In addition, fewer patients in the 6 mg treatment group (~19%) recorded a worsening of their bone pain compared with the 2 mg (~40%) or placebo (~37%) groups. The difference between the 6 mg and placebo treatment groups was statistically significant ($p<0.001$) indicating that ibandronate (6 mg) treatment has a beneficial effect on bone pain. In MF 4434, the median time from randomisation to the first new bone event was numerically longer for subjects in both the 20 mg (76 weeks; p=0.106) and 50 mg treatment groups (54 weeks; p=0.297) than in the placebo group (48 weeks).

In study MF4265 the individual components, vertebral fracture and radiotherapy, and in the oral study MF4434, only the component radiotherapy were statistically significant. Reasons for the non-significant effect on vertebral fractures in the oral study (such as strict fracture definition criteria, absence of a requirement in the inclusion criteria of lytic bone lesions with at least 1 cm diameter) resulting probably in a lower fracture incidence of the placebo group are plausible and acceptable. Furthermore, it can be agreed that the sample size in the groups may be to small to reach a statistically significance in the individual components, and that the demonstration of a significant effect in the pre-defined composite primary endpoint in this severely ill patient population (for which the study was apparently powered) would sufficiently establish the efficacy of treatment.

The SMPR per patient year in the i.v. study MF4265 was reduced by 19.6% (p=0.004) vs. placebo and in the oral study MF4434 by 18.1% (p=0.037) vs. placebo. The percentage of patients with at least one bone event was only statically significantly reduced in MF4434, when the 20 mg and 50 mg groups were pooled (p=0.036). The time to fist new bone event or the time from the first event to second bone events in oral studies MF 4434 or MF4414 was numerically reduced, but did not reach statistically significance. The relative risk of an event based on time to multiple events in MF4414 and MF4434 was statistically significant.

Efficacy was demonstrated in study MF4434 at both the 20 and 50 mg doses, but not in study MF4414. The apparent lack of a statistically significant treatment effect on the primary efficacy endpoint suggested the presence of confounding factors within study 4414, which may have compromised the analysis. As mentioned previously, there was an imbalance in the baseline characteristics of the three treatment groups such as imbalance in prognostic factors, preferential drop-out in the placebo group and a high proportion of 'pre-scheduled' radiotherapy in particular in Russian centers. A univariate analysis on the time to first new bone event was conducted. Factors identified in the univariate model that were possibly predictive of an effect were carried forward into pre-specified multivariate analyses, the first of which employed the method of Cox. A Poisson regression model based on the number of periods with events or on the number of events was also employed.
This analysis resulted in a significant risk reduction of skeletal related events (SRE) in study MF4414 of 39 % (p = 0.004) versus placebo similarly to the 39% risk reduction in SRE vs. placebo (p = 0.004) in the oral study MF4434. These values compare to a 40% risk reduction in the i.v. study MF4265. The approach to demonstrate efficacy of the oral studies by using the Poisson regression analysis (in order to deal with the confounding factors in MF4414) as appropriate and acceptable.

The drop out rate of 58-60% % in studies MF4434 and MF4414 is high, but such a high drop out rate is to be expected in a study population with metastatic breast cancer over a period of 96 weeks (median survival time of about 2 years). Furthermore, the drop out rate is at least comparable to the drop out rate in the pamidronate study (66%-80%).

Lack of active comparator

The reason for the lack of a comparative study with an active comparator, i.v. ibandronate vs. other bisphosphonates was the lack of a suitable comparator at the time of conducting the i.v. study MF 4265 as the study started 1994, whilst the approval of i.v. pamidronate and and i.v. zoledronic acid for the treatment of women with metastatic breast cancer occurred later. No orally applied aminobisphosphonate is currently approved for the treatment of patients with metastatic breast cancer, which precludes a comparative study.

The MAH performed a post hoc-comparison between ibandronate (6 mg i.v. at intervals of 4 weeks) and pamidronate (90 mg i.v. at intervals of 4 weeks) regarding the effect on the Skeletal Morbidity Rate (SMR; number of events/year). The effect size was a 33% reduction in SMR with i.v. pamidronate (including hypercalcemia) or a 35% reduction (without hypercalcemia) vs. a 39% reduction with i.v. ibandronate. The limitations of such an approach are obvious because of several differences between studies, e.g. inclusion criteria, the definition of skeletal related events and individual components of the primary endpoint used for efficacy analysis (Ibandronate: SMPR including vertebral fracture, non-vertebral fracture, radiotherapy to bone for treatment of fractures/impending fractures, surgery to bone for treatment of fractures; Pamidronate: SMR including pathological fracture, spinal cord compression/collapse, radiation to bone for pain relief/to prevent spinal cord compression/to prevent pathological fractures, surgery to prevent spinal cord compression/to prevent pathological fractures, hypercalcaemia). Due to the fact that these evaluations are exploratory post-hoc analyses it is difficult to make a direct comparison and the conclusions drawn should be treated with caution. In general, despite of the limitations of the presented comparative analysis, the effect size on all bone events/patient year appears to be similar with i.v. ibandronate and i.v. pamidronate in women with metastatic breast cancer treated over an approximately similar time period. The above post-hoc analysis can not replace a direct comparative study, however, a comparative study between i.v. ibandronate and another bisphosphonate is not considered necessary.

Clinical safety

Adverse events, which were thought to be treatment related are somewhat different after oral (20 or 50 mg/day) or intravenous ibandronate (2 or 6 mg every 4 weeks). Treatment related AE (remotely, possibly, or probably related) after oral application were upper gastro-intestinal symptoms (abdominal pain, dyspepsia, nausea, esophagitis, hopocalcemia). For the oral Phase III studies MF 4414 and MF 4434 the following so-called treatment related AE were reported:

Abdominal pain:	placebo: n= 2 (0.7%), 20 mg p.o.: n= 1 (0.4%); 50 mg p.o.: n= 6 (2.7%)
Dyspepsia:	placebo: n= 13 (4.7%), 20 mg p.o.: n=16 (5.7%); 50 mg p.o.: n=20 (7.0%)
Naussea:	placebo: n= 4 (1.4%), 20 mg p.o.: n= 9 (3.2%); 50 mg p.o.: n=10 (3.5%)
Esophagitis:	placebo: n= 2 (0.7%), 20 mg p.o.: n= 4 (1.4%); 50 mg p.o.: n= 6 (2.1%)
Hypocalcemia:	placebo: n= 14 (5.1%), 20 mg p.o.: n=25 (5.9%); 50 mg p.o.: n=27 (9.4%)

Treatment related AE (remotely, possibly, or probably related) after i.v. application were acute phase reaction/flu-like syndrome, diarrhea, myalgia, asthenia, headache, a transient increase in bone pain, transient proteinuria, hypocalcaemia. It is noted that esophagitis was not observed after i.v. application of ibandronate.

In the phase II study MF 4328 fever within 72 h after ibandronate i.v. was observed in 8.8% (13/147 patients); four of these 13 patients experienced fever as a single symptom and 9 of the these 13 patients experienced also bone pain within this time frame (6 patients in the 6 mg ibandronate group and 3 patients in 4 mg ibandronate group). Thus fever plus bone pain experienced 24% (6/25 patients) and 25% (3/16 patients) in the 6 mg and 4 mg dose group, respectively. A transient exacerbation of bone pain within 72 h after administration of ibandronate i.v. experienced 8.4% (12/174) patients.

For the Phase III study MF 4265 the following so-called treatment related AE were reported:

Flu-like syndromes:	placebo: n= 2 (1.3%), 2 mg i.v.: n=8 (5.2%); 6 mg i.v.: n=8 (5.3%)
Diarrhea:	placebo: n= 1 (0.6%), 2 mg i.v.: n=7 (4.6%); 6 mg i.v.: n=8 (5.3%)
Myalgia:	placebo: n= 6 (3.8%), 2 mg i.v.: n=5 (3.3%); 6 mg i.v.: n=8 (5.3%)
Headache:	placebo: n= 4 (2.5%), 2 mg i.v.: n=4 (2.6%); 6 mg i.v.: n=9 (5.9%)
Hypocalcemia:	placebo: n= .. (3.1%), 2 mg i.v..: n=.. (5.9%); 6 mg i.v.: n=.. (7.9%)

Esophagitis, which was higher in the oral studies, was also reported as a serious adverse event in 3 patients given 20 mg ibandronate orally and in 1 patient given placebo.

The deaths observed in the oral studies [MF 4414, 4434] were higher in the 20 mg (17%) and 50 mg (19.9 %) ibandronate groups compared to placebo (15.2%). No deaths were considered as due to the study medication. There were fewer deaths in the i.v. study [MF 4265] in patients treated with 2 mg (7.2%) and 6 mg (5.3 %) ibandronate compared to placebo (9.6%).

Discontinuation due to adverse events

Withdrawals in the oral studies were mainly due to progression of the underlying disease. Notable reasons for withdrawals due to AE or serious AE in the oral studies were esophagitis (1 patients at 20 and 4 patients at 50 mg ibandronate, none in the placebo group), bone pain (5 and 7 patients at 20 and 50 mg ibandronate vs. 5 patients on placebo). The slight hypocalcaemia did not lead to any withdrawals. Withdrawals in the i.v. study were mainly due to progression of the under of the underlying disease and refusal of treatment .

Laboratory findings

Changes in laboratory parameters included hypocalcaemia (oral and intravenous studies) and anemia (14%, 16% and 21% for placebo, 20 and 50 mg ibandronate, respectively). Anemia was judged as drug related.

Discussion on Clinical safety

The majority of study patients experienced at least one adverse event during the course of the study. This was to be expected in a population with advanced metastatic malignant disease. Overall, there

were no obvious differences in the frequency or type of adverse event between the different dose groups, the safety profile of both treatment arms being, in general, similar to placebo. In addition the number of patients experiencing serious adverse events or adverse events leading to withdrawal was similar in all treatment groups. There was a slightly higher incidence of drug-related adverse events, driven mainly by hypocalcaemia, which is an adverse event frequently encountered with bisphosphonate therapy.

In the i.v. study 4265, a slightly higher percentage of patients in the active treatment groups compared with placebo recorded adverse events considered related to study treatment by the investigator. The most common treatment-related adverse events recorded during the study were asthenia, fever, flu syndrome, bone pain (more placebo patients), headache, nausea and diarrhoea being reported by up to 6.6% of patients in any one treatment group. The number of patients withdrawn as a result of an adverse event considered related to study treatment by the investigator was 2, 1 and 3 in the placebo, 2 mg ibandronate and 6 mg ibandronate treatment groups, respectively. Most of the related adverse events leading to withdrawal were in the digestive system (3 patients). Five patients in each of the 2 mg and 6 mg active treatment groups and 2 patients in the placebo group recorded vomiting which was considered related to treatment by the investigator. Diarrhoea was considered related to treatment in 1 placebo patient (0.6%), 7 patients (4.6%) receiving 2 mg ibandronate and 8 patients (5.3%) receiving 6 mg ibandronate.

In the oral studies, there was a higher incidence of adverse events considered related to treatment by the investigator in the active treatment groups. This increase was driven primarily by an increase in the number of related hypocalcaemic episodes and reports of dyspepsia and nausea among patients in the active treatment groups. None of these related events was classed as serious with the exception of 1 report of nausea recorded by a single subject in the 50 mg treatment group. Esophagitis was reported in a few cases.

The number of patients with renal adverse events was similar in the three treatment groups. There were more cases of renal failure in the two active treatment groups (20 mg; 6 patients, 50 mg; 5 patients) than in the placebo group (3 cases). However, there were more reports of increased creatinine in the placebo group (6 patients) than either the 20 mg (2 patients) or 50 mg (4 patients) treatment groups and so the overall number of events indicative of impaired renal function was similar in all three groups (8, 9 and 9 individuals, respectively, in the three arms who were reported to have either increased creatinine or kidney failure).

3. Overall conclusions, benefit/risk assessment and recommendation

Preclinical pharmacology and toxicology

Overall, the primary pharmacodynamic studies provided proof of concept for the proposed indication, but were too limited to guide the selection of human dose levels. From the pharmacokinetic point of view, the programme performed was satisfactory.
Overall, the toxicology programme is considered satisfactory in the context of the symptomatic treatment of metastatic bone disease due to breast cancer, that is, in severely ill cancer patients with a poor prognosis. Local tolerance studies have revealed that the tablets may cause irritation or burns to the oesophagus and gastric mucosa. This information has been included in the SPC.

Efficacy

Efficacy was demonstrated in terms of the primary efficacy endpoint an index of the combined skeletal morbidity, (pathological vertebral fractures, pathological non-vertebral fractures, bone complications requiring radiotherapy, bone complications requiring surgery).
Although in study MF4414, there was no statistically significant treatment effect a significant risk reduction of skeletal related events of 39 % vs placebo was shown. The lack of an active comparator has been justified.

Safety

It appears that ibandronate has an acceptable clinical safety profile. Clinical trial data and post-marketing surveillance have not shown any evidence of deterioration in renal function with long term Bondronat therapy. Nevertheless, according to clinical assessment of theindividual patient and cancer progression effects on organ function, it is recommended that renal function, serum calcium, phosphate and magnesium should be monitored in patients treated with Bondronat. A dose adjustment in patients with severe renal impairment (CL_{CR} <30 ml/min) has been included in the SPC.
The SPC was revised to include additional AEs and also regarding the incidence of AEs. The revision of SPC section 4.8 was done in line with the SPC guideline.

Benefit/risk assessment

On the basis of the above, the benefit/ risk for the extension of the indication to include prevention of skeletal events (pathological fractures, bone complications requiring radiotherapy or surgery) in patients with breast cancer and bone metastases is favourable.
Therefore, the 50 mg film-coated tablet is recommended for approval together with concentrate for solution for infusion 6mg/ ml (II/25) since these are justified by this new indication.

Recommendation

”Based on the CPMP review of data on quality, safety and efficacy, the CPMP considered by consensus that the benefit/risk profile of Bondronat in the prevention of skeletal events (pathological fractures, bone complications requiring radiotherapy or surgery) in patients with breast cancer and bone metastases, was favourable.