

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-455

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA	21-455 (original)
Submission Dates	July 15, 2002; January 17, 2003; March 6, 2003
Brand Name	BONVIVA®
Generic Name	ibandronate sodium
Reviewers	S.W. Johnny Lau and Wei Oiu
Team Leader	Hae-Young Ahn
OCPB Division	DPE II (HFD-870)
ORM division	Metabolic and Endocrine (HFD-510)
Sponsor	Hoffmann-La Roche Inc.
Relevant IND(s)	50.378
Submission Type: Code	original: S
Formulation: Strength(s)	oblong film-coated tablet: 2.5 mg
Indication	to prevent and treat postmenopausal osteoporosis

1 Executive Summary

The sponsor submitted NDA 21-455 to seek approval for 2.5 mg ibandronate daily to treat and prevent postmenopausal osteoporosis. Ibandronate sodium is a new 3rd generation bisphosphonate (nitrogen-containing) that inhibits osteoclast activity and reduces bone resorption as well as turnover. The commercial product will be available as a white, oblong, film-coated oral tablet that contains 2.813 mg ibandronate monosodium monohydrate (equivalent to 2.5 mg free acid). Patients should take one 2.5 mg ibandronate tablet once daily, 60 minutes before the 1st food or drink (other than water) in an upright position.

The sponsor submitted the results of 25 studies to elucidate the clinical pharmacology and biopharmaceutics of ibandronate sodium in Section 6 of NDA 21-455. Study distribution follows:

- 15 basic pharmacokinetic
- 7 special population
- 3 pharmacokinetic and pharmacodynamic

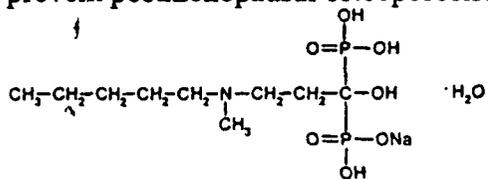
Briefly, the ibandronate clinical pharmacology and biopharmaceutics information follows:

The mean (SD) ibandronate oral absolute bioavailability was 0.58 (0.34)% for the 2.5 mg ibandronate oral tablet versus 0.5 mg ibandronate intravenous administration. Ibandronate protein binding in human serum was 85.7 - 99.5% over the therapeutic concentrations for osteoporosis. Ibandronate apparent terminal volume of distribution was at least 90 L. Ibandronate apparent terminal half-life ranged from 10 - 60 hours. In vitro incubation of ibandronate with human liver microsomes and liver pieces did not show signs of metabolism. Ibandronate did not inhibit cytochrome P450 isoenzymes and was excreted unchanged via the kidney. Ibandronate renal clearance was directly related to creatinine clearance. Dose-linearity for ibandronate kinetics had not been formally established. However, pooled pharmacokinetic data indicated nonlinearity. Ibandronate did accumulate upon chronic dosing. Ibandronate bioavailability and pharmacokinetics were similar in both men and women. Healthy postmenopausal women had 22.5% higher ibandronate exposure than that for healthy young men. No observable difference in exposure existed between young healthy male Asians and Caucasians. The mild to moderate renal impaired patients had 55% higher ibandronate exposure than

	Page
2 Table of Contents	
1 Executive Summary	1
1.1 Recommendations	2
2 Table of Contents	3
3 Summary of Clinical Pharmacology and Biopharmaceutics Findings	4
4 Question Based Review	
4.1 General Attributes	7
4.2 General Clinical Pharmacology	8
4.3 Intrinsic Factors	18
4.4 Extrinsic Factors	20
4.5 General Biopharmaceutics	24
4.6 Bioanalytical	25
5 Labeling Comments	28

3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

The sponsor developed ibandronate sodium, a bisphosphonate that inhibits bone resorption to treat and prevent postmenopausal osteoporosis.



Basic Pharmacokinetics of Ibandronate Sodium in Humans

The mean (SD) ibandronate oral absolute bioavailability was 0.58 (0.34)% for the 2.5 mg ibandronate oral tablet versus 0.5 mg ibandronate intravenous injection per AUC_{0-6h} .

Ibandronate apparent terminal volume of distribution is at least 90 L. Two separate studies yielded different ibandronate protein binding results in human serum. One study showed that 99.5% of ibandronate was bound at 2 ng/mL and 50% of ibandronate was bound at 50 μ g/mL. Another study showed that the mean (SD) ibandronate protein binding from 0.5 ng/mL to 10 ng/mL was 85.7 (1.9)%. Hence, the 2 studies' data were combined that ibandronate protein binding in human serum was 85.7 - 99.5% over the therapeutic concentrations for osteoporosis. Erythrocyte uptake of ibandronate was low. The ibandronate erythrocyte to plasma ratios were --- and not concentration-dependent from 5 - 5000 ng/mL. Ibandronate binding to human thrombocytes was 0 - 4% from 100 - 10000 ng ibandronate/mL of EDTAed human blood. Ibandronate bone uptake was estimated to be 40 - 50% of the circulating dose.

Ibandronate did not show sign of metabolism when incubated with human liver microsomes.

Ibandronate did not inhibit cytochrome P450 isozymes (CYP) 1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A4. However, ibandronate's potential to induce CYP isoenzymes remains unknown. A mass balance study showed that upon IV administration, the majority of radioactivity was excreted in the urine with only trace levels in the feces. After oral administration, the majority was excreted in the feces. Ibandronate is excreted unchanged via the kidney. The apparent terminal half-life ranged from 10 - 60 hours.

Dose-linearity for ibandronate kinetics (C_{max} and AUC) has not been formally established, despite many attempts. Results of 10 clinical pharmacology oral absorption studies were pooled. Log mean C_{max} or AUC_{∞} vs. log dose from 0.25 - 100 mg were plotted. The slope of the log mean C_{max} versus log dose plot was 1.02 and implied linearity. However, the slope of the log mean AUC_{∞} vs. log dose plot was 0.787 and far from 1. Hence, dose-linearity for ibandronate kinetics could not be substantiated.

Ibandronate accumulates upon chronic oral administration. The single dose and steady-state pharmacokinetics for 0.25, 0.5, 1, 2.5, or 5 mg ibandronate daily for 12 months in postmenopausal osteoporosis patients were studied. In general, ibandronate AUC_{0-6} and C_{max} both increased about 1.5- to 2-fold during the treatment period.

Per the results for 3 food and timing effect studies, ibandronate should be taken 1 hour before any food intake. Concomitant administration of food with ibandronate reduced the C_{max} and AUC_{∞} about 90%.

Ibandronate Pharmacokinetics in Special Populations

The effects of age, gender, and race on ibandronate kinetics were evaluated. The mean AUC_{∞} for healthy postmenopausal women (mean (SD); 47.7 (3.68) years of age and CL_{Cr} of 76.0 (20.6) mL/min) was 22.5% higher than that for healthy male subjects (mean (SD); 28.2 (5.31) years of age and CL_{Cr} of 161 (30.2) mL/min) upon single dose 2 mg ibandronate IV administration from cross study comparison. Gender and race effects appeared to not affect ibandronate kinetics.

Three groups of patients (Group 1: $CL_{Cr} < 30$ mL/min; Group 2: CL_{Cr} 40-70 mL/min; Group 3: $CL_{Cr} > 90$ mL/min) received single 0.5 mg IV injections of ibandronate. After a washout of 1-3 days, subjects in Groups 1 and 3 also received one 10 mg oral film coated tablet daily for 21 days. Ibandronate CL_r was directly related to CL_{Cr} . The mild to moderate renal impairment group (CL_{Cr} 40-70 mL/min) resulted in 55% increase in AUC_{∞} as compare to that for the normal renal function ($CL_{Cr} > 90$ mL/min) group. As CL_{Cr} fell below 30 mL/min, ibandronate exposure increased to > 2 fold as compare to that for $CL_{Cr} > 90$ mL/min.

No studies were conducted to assess the hepatic impairment effect on ibandronate pharmacokinetics. Ibandronate was not metabolized in human liver preparations.

Drug-Drug Interaction

Coadministration of ranitidine (IV 75 mg) with a 10 mg ibandronate sodium film-coated tablet resulted in 20 – 25% higher C_{max} , AUC_{0-t} , and AUC_{∞} . Similar observation exists with alendronate sodium's labeling.

Two mg IV ibandronate injection with and without 30 mg tamoxifen oral tablet resulted in superimposable mean serum ibandronate concentration-time curves and/comparable serum tamoxifen concentrations-time curves. Hence, no evidence existed for a pharmacokinetic interaction between ibandronate and tamoxifen.

Randomized multiple myeloma patients received IV melphalan (10 mg/m²) and oral prednisolone (60 mg/m²) either alone or concomitantly with a 6 mg ibandronate injection (washout >12 days). Mean serum ibandronate concentrations when administered alone were essentially the same as those observed when it was administered concomitantly with melphalan and prednisolone. Ibandronate did not affect either melphalan or prednisolone pharmacokinetics.

The absolute oral bioavailability study was also used to demonstrate the lack of hormone replacement therapy (HRT) effect on ibandronate kinetics. However, the identity and dose of the HRT could not be identified. Mean serum ibandronate concentrations and pharmacokinetic parameters after IV and oral administration were essentially the same in postmenopausal women taking HRT as in those not on HRT. Hence, HRT did not alter the ibandronate pharmacokinetics after either IV or oral administration. However, HRT and ibandronate might have pharmacodynamic interaction together, such as the increased effect on bone turnover suppression which were observed when alendronate were coadministered with estrogen ± progestin.

Ibandronate produced biochemical changes indicative of dose-dependent inhibition of bone resorption, including decreases of urinary biochemical markers of bone collagen degradation (such as deoxypyridinoline, and cross-linked C-telopeptide of type I collagen) in the daily oral dose range of 0.25 to 5.0 mg ibandronate in postmenopausal women.

Biochemical markers of bone turnover urinary C-terminal telopeptide of type I collagen (uCTX) and serum osteocalcin decreased and reached maximum reduction within approximately 3 and 6 months, respectively. A 30% to 50% reduction of uCTX was observed as early as 1 month after the start of treatment with oral ibandronate 2.5 mg daily.

Because a complete data analysis on PK/PD relationship was lacking, review on PK/PD relationship was not feasible.

Bioequivalence between the Clinically Tested and To-Be-Marketed Formulations

The to-be-marketed formulation is identical to the clinically tested formulation.

Proposed Dissolution Test and Specification

The sponsor did not propose an in vitro dissolution test and specification but proposed an in vitro disintegration method and specification instead. Disintegration test does not guarantee complete dissolution of the test products. Moreover, in vitro disintegration test cannot support any pre- and post-approval manufacturing process or site changes. Hence, an in vitro dissolution test is recommended for the 2.5 mg ibandronate oral tablet as follow:

Apparatus	USP Type 2 (paddle)
In vitro release medium	water
Volume of release medium	500 mL
Medium temperature	37 ± 0.5°C
Stirring speed	50 rpm
Sampling Time	15 minutes
Specifications	Q = — at 15 minutes

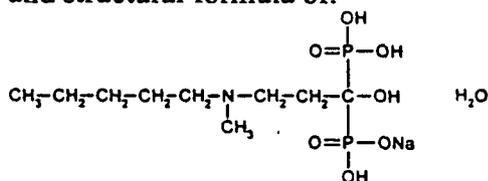
4 Question-Based Review

4.1 General Attributes

Ibandronate sodium is a new 3rd generation bisphosphonate (nitrogen-containing) that inhibits osteoclast activity and reduces bone resorption as well as turnover. The sponsor seeks approval for 2.5 mg ibandronate daily (taken 60 minutes with plain water before any food or medications) to treat and prevent postmenopausal osteoporosis via oral administration.

1. What are the highlights of the chemistry and physical-chemical properties of ibandronate sodium?

Ibandronate sodium has the empirical formula of $C_9H_{22}NO_7P_2Na \cdot H_2O$, molecular weight of 359.24, and structural formula of:



Ibandronate sodium is practically insoluble in water. Its aqueous solubility profile is as follow:

Its aqueous

2. What is the formulation of the to-be-marketed 2.5 mg ibandronate sodium oral tablet?

The sponsor intends to market the product as a white, oblong, film-coated oral tablet that contains 2.813 mg ibandronate monosodium monohydrate (equivalent to 2.5 mg free acid). The formulation of the to-be-marketed tablet follows:

COMPOSITION

Full statement of the quantitative composition of ibandronate film-coated tablets 2.5 mg.

Raw materials	Actual weights per tablet	Actual weights for pilot-scale batch ¹	Actual weights for production-scale batch ¹
Tablet kernel			
Ibandronate sodium ²	2.813 ³ mg		
Povidone ⁴			
Lactose Monohydrate			
Microcrystalline Cellulose			
Croscopovidone			
Purified Stearic Acid			
Colloidal Silicon Dioxide			
Purified Water ⁴			
Weight (final blend)			
Film-coat			
Polyethylene Glycol 6000			
Purified Water ⁴			
Total Weight	104.0	mg	

4.2 General Clinical Pharmacology

Ibandronate is the active pharmacologic moiety in the body as measured in human plasma, serum, and urine. No evidence exists that ibandronate is metabolized in animals or humans. Briefly, the sponsor used the following bioanalytical methods for clinical pharmacology studies (see Section F "Bioanalytical" for method validation):

Method	Analyte	Matrix	Study
	ibandronate	plasma, serum, urine	PK
	ibandronate	plasma, serum, urine	PK
	tamoxifen	plasma	interaction
	melphalan	plasma	interaction
	prednisolone	plasma	interaction
	¹⁴ C-ibandronate	blood, serum, urine, feces	mass balance

1. What are the basic pharmacokinetic characteristics of ibandronate sodium?

Absorption

Absolute oral ibandronate bioavailability was assessed in a randomized, open-label, single-dose, 3-way crossover (>2 weeks washout) study comparing a 0.5 mg ibandronate/30 second single intravenous injection with single oral administration of 2.5 and 20 mg ibandronate film coated tablets (Study MF 7159). Thirty-four healthy postmenopausal women completed (17 subjects on hormone replacement therapy (HRT) and 17 not). Blood and urine samples were collected for 48 h postdose to characterize ibandronate pharmacokinetics.

The mean (SD) ibandronate oral absolute bioavailability via AUC_{∞} was 0.63 (0.44)% after 20 mg ibandronate oral tablet versus 0.5 mg ibandronate intravenous administration. Absolute oral ibandronate bioavailability could not be adequately assessed for the 2.5 mg tablet via AUC_{∞} since 9 of 34 subjects had serum ibandronate concentrations below limit of quantification after 6 hours postdose. The mean (SD) ibandronate oral absolute bioavailability was 0.58 (0.34)% and 0.55 (0.42)% via AUC_{0-6h} for the 2.5 and 20 mg, respectively. Median ibandronate t_{max} for the 2.5 and 20 mg tablets were 1 and 0.875 h, respectively. Both 2.5 and 20 mg ibandronate doses showed < 1% of the dose being excreted in urine. These parameters were consistent with other marketed oral bisphosphonates. The 2.5 mg tablet was identical to the clinically tested formulation for osteoporosis. Whereas the 20 mg tablet was used in the oncology clinical study and its formulation is not proportionally similar to

Figure 1 Mean Serum Ibandronate Concentrations after I.v. Administration of 0.5 mg and Oral Administration of 2.5 mg and 20 mg to Healthy Postmenopausal Female Volunteers (Study MF 7159)

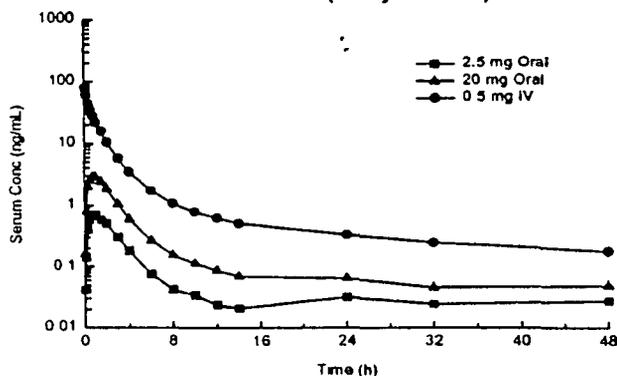


Table 16 Ibandronate Pharmacokinetic Parameters after Oral Administration of 2.5 mg and 20 mg to Healthy Postmenopausal Female Volunteers (Study MF 7159)

Parameter ¹	Dose and Route		
	0.5 mg I.v.	2.5 mg p.o.	20 mg p.o.
C_{max} (ng/mL)	78.1 ± 17.8	0.79 ± 0.41	6.22 ± 4.11
t_{max} (h)	0.083	1.00	0.88
AUC_0-t (h·ng/mL)	-	3.3 ± 1.6	20.0 ± 13.3
AUC_{∞} (h·ng/mL)	95.1 ± 16.6	-	23.0 ± 14.1
$t_{1/2}$ (h)	22.5 ± 2.52	-	32.3 ± 17.2
CL (mL/min)	90.0 ± 14.1	-	-
V_z (L)	175 ± 32.5	-	-
CL _r (mL/min)	60.8 ± 14.5	76.0 ± 1.54	58.8 ± 14.3
f_e (% Dose)	63.5 ± 10.4	0.62 ± 1.36	0.37 ± 0.44
F (%)	-	-	0.63 ± 0.44

n = 34

¹ Mean ± SD except for t_{max} for which the median is reported.

- The sponsor did not elaborate on this discrepancy in results between Studies 2027 and 2028. Hence, results of the 2 studies were combined that ibandronate protein binding in human serum was 85.7 - 99.5% over the therapeutic concentrations for osteoporosis.

Ibandronate partitioning in whole human blood was evaluated from 5 - 5000 ng/mL (Study 2029). Erythrocyte uptake of ibandronate was low. The ibandronate erythrocyte to plasma ratios were 0.18 - 0.24 and not concentration-dependent. Consistent with this observation, the ibandronate blood to plasma ratios were 0.59 - 0.64. Ibandronate binding to human thrombocytes was also evaluated in Study 2029 and was 0 - 4% from 100 - 10000 ng ibandronate/mL of EDTAed human blood.

Metabolism

In vitro incubation (Study L7) of ibandronate with human liver microsomes and liver pieces did not show signs of metabolism. This reviewer agrees with the sponsor that no data demonstrate systemic ibandronate metabolism. However, the sponsor studied only 1 liver sample from a tumor patient.

In vitro ibandronate's effect on drug metabolizing enzymes was studied in human liver samples from kidney transplantation donors (Study L26). Liver microsomes were incubated with cytochrome P450 (CYP) isozyme-specific substrates. The influence of ibandronate on these enzymes was determined at various concentrations in comparison to specific reference inhibitors. Ibandronate had no affinity for any of the following CYP-associated activities:

- 1A2 (ethoxyresorufin O-deethylase)
- 2A6 (coumarin 7-hydroxylase)
- 2C9 (tolbutamide methyl hydrolase)
- 2C19 (mephenytoin 4'-hydroxylase)
- 2D6 (dextromethorphan O-demethylase)
- 2E1 (chlorzoxazone 6-hydroxylase)
- 3A4 (testosterone 6 β -hydroxylase)

The highest ibandronate concentration studied was 1 mM, except for CYP2E1, which was 0.1 mM (corresponding to about 0.36 mg/mL and 0.036 mg/mL, respectively). This was 360,000 and 36,000 fold higher than C_{max} (1 ng/mL), which would be achieved after daily 2.5 mg ibandronate oral doses in postmenopausal osteoporotic patients. These results showed that ibandronate did not inhibit these 7 CYP isozymes. However, ibandronate's potential to induce CYP isoenzymes remains unknown.

An open, single-dose, parallel group study (MF 7165) on ibandronate mass-balance and metabolism was conducted in 6 male volunteers, 3 each for IV and oral administration. The oral dose was 20 mg in solution (10 mg with specific activity of 3000 kBq/mg). The IV dose was 0.5 mg (0.174 mg with specific activity of 3000 kBq/mg). Blood was collected until the radioactivity in plasma fell below 1 Bq/mL; urine and feces were collected until radioactivity fell below 50 dpm/mL of urine and 100 dpm/g of feces homogenate. Blood, plasma, urine, and feces were analyzed for total radioactivity, unchanged ibandronate, and metabolites.

Following IV or oral administration of ^{14}C -ibandronate, comparable mean plasma concentrations of total radioactivity and unchanged ibandronate (C_{max} and $\text{AUC}_{\text{0-12}}$) were observed during the quantifiable period for both, indicating little or no metabolism. Examination of plasma samples via ^{14}C showed no evidence of metabolites. Absolute oral ibandronate bioavailability was estimated to be 0.64%, consistent with that for Study MF 7159. After IV administration, the majority of radioactivity was excreted in the urine with only trace levels in the feces. After oral administration, the majority was excreted in the feces. However, CL_r was consistent for both routes of administration, indicating that the drug in the feces was most likely unabsorbed rather than excreted drug. The mean $t_{1/2}$ estimates upon IV administration were 3.6 hours and 56.3 hours via total radioactivity and unchanged ibandronate, respectively. This discrepancy may be explained via the bioanalytical methods used. The radiocarbon concentrations were below the LOQ 24 hours postdose. However, plasma ibandronate concentrations measured via ^{14}C were above LOQ 72 hours postdose.

Figure 7 Mean Plasma Total Radioactivity and Ibandronate Concentrations after i.v. Administration of ^{14}C -ibandronate to Healthy Male Volunteers (Study MF 7165)

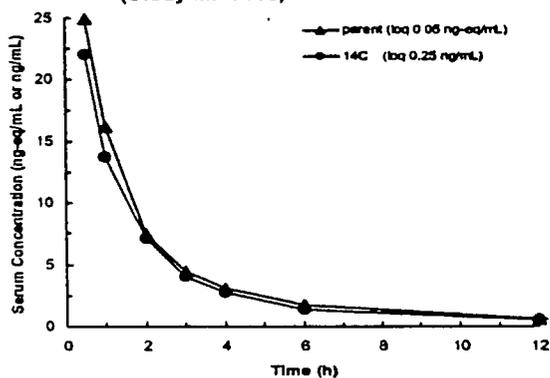


Figure 8 Mean Plasma Total Radioactivity and Ibandronate Concentrations after Oral Administration of ^{14}C -ibandronate to Healthy Male Volunteers (Study MF 7165)

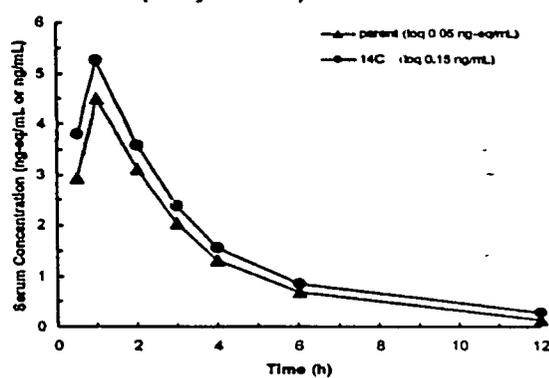


Figure 9 Mean Urinary and Fecal Excretion of Total Radioactivity after i.v. and Oral Administration of ^{14}C -ibandronate to Healthy Male Volunteers (Study MF 7165)

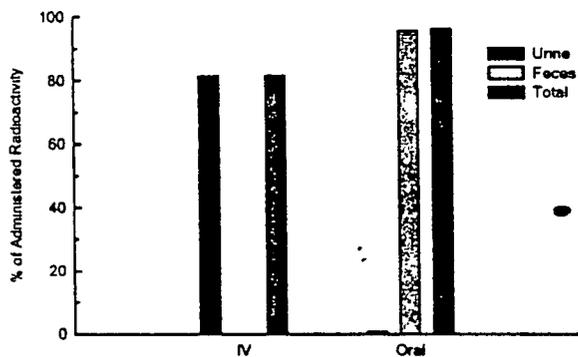


Table 25 Pharmacokinetic Parameters for Total Radioactivity and Ibandronate after i.v. and Oral Administration of ^{14}C -ibandronate to Healthy Male Volunteers (Study MF 7165)

Parameter ¹	Total Radioactivity	Unchanged Ibandronate
i.v. Administration (n = 3)		
Dose (mg)	0.43 ± 0.03	
C_{max} (ng-eq/g) or (ng/mL)	22.0 ± 3.27	24.9 ± 4.99
t_{max} (h)	0.5	0.5
$\text{AUC}_{\text{0-12}}$ (hr·ng-eq/g) or (hr·ng/mL)	46.5 ± 5.92	67.4 ± 24.4
k_{el} (hr)	3.88 ± 0.29	56.3 ± 24.5
CL (mL/min)	157 ± 26.7	107 ± 18.8
V_d (L)	48.6 ± 7.98	154 ± 27.7
CL_r (mL/min)	127 ± 21.7	
Excretion (% Dose)		
Urine	81.5 ± 6.46	
Feces	0.12 ± 0.010	
Total	81.6 ± 6.46	
Oral Administration (n = 3)		
Dose (mg)	17.1 ± 1.80	
C_{max} (ng-eq/g) or (ng/mL)	5.36 ± 1.21	4.51 ± 1.99
t_{max} (h)	1.00	1.00
$\text{AUC}_{\text{0-12}}$ (hr·ng-eq/g) or (hr·ng/mL)	19.7 ± 4.5	17.1 ± 2.18
k_{el} (hr)	3.40 ± 0.11	52.9 ± 1.51
CL_r (mL/min)	109 ± 14.2	
Excretion (% Dose)		
Urine	0.75 ± 0.13	
Feces	95.7 ± 1.12	
Total	96.4 ± 1.19	

¹ Mean ± SD except for t_{max} for which the median is reported.

Excretion

Ibandronate is excreted unchanged via the kidney.

2. Is the ibandronate absorption kinetics dose-linear?

No. The sponsor had not formally established dose-linearity for ibandronate kinetics (C_{max} and AUC). The sponsor pooled the results of 10 clinical pharmacology oral absorption studies and claimed that the ibandronate oral absorption was dose-linear from 0.25 - 100 mg via plotting log mean C_{max} or AUC $_{\infty}$ vs. log dose across formulations and studies. The slope of the log mean C_{max} versus log dose plot was 1.02 and implied linearity. However, the slope of the log mean AUC $_{\infty}$ vs. log dose plot was 0.787 and far from 1. Hence, dose-linearity for ibandronate kinetics could not be substantiated.

Figure 48 Relationship Between C_{max} and Dose in Healthy Male and Postmenopausal Female Volunteers

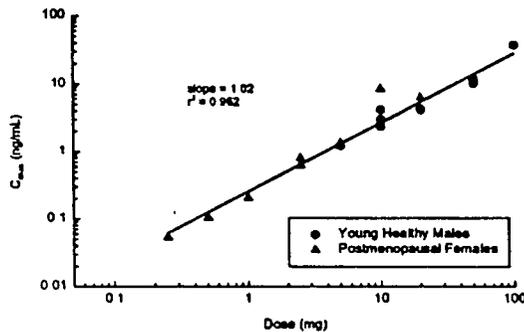
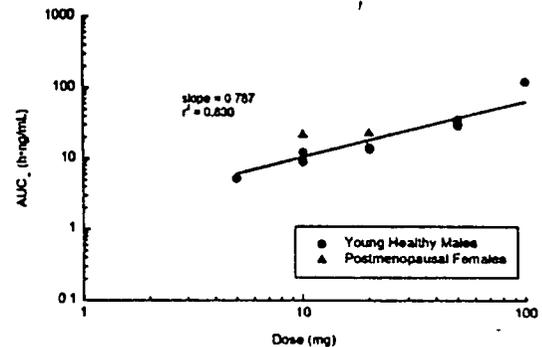


Figure 49 Relationship Between AUC $_{\infty}$ and Dose in Healthy Male and Postmenopausal Female Volunteers



The sponsor also tried to demonstrate the dose-linearity for ibandronate oral absorption via Study MF 7131. Nineteen healthy male volunteers received an oral 10, 20, or 50 mg ibandronate film coated tablet per a randomized 3-way crossover (2-week washout) design. Blood and urine samples were collected for 24 hours and 72 hours, respectively, to characterize the ibandronate pharmacokinetics. The mean C_{max} or AUC $_{\infty}$ vs dose plots appeared to be linear. When normalized to the 50 mg dose, the 90% confidence intervals for the C_{max} or AUC $_{\infty}$ ratios among doses were not all within the 0.80 - 1.25 bioequivalence window. Therefore, ibandronate dose-linearity had not been demonstrated.

See Study MF 4348 (Question 3 below) for the sponsor's further attempt to demonstrate dose-linearity for ibandronate kinetics.

Figure 12 Mean Serum Ibandronate Concentrations after Oral Administration of 10 mg, 20 mg, and 50 mg to Healthy Male Volunteers (Study MF 7131)

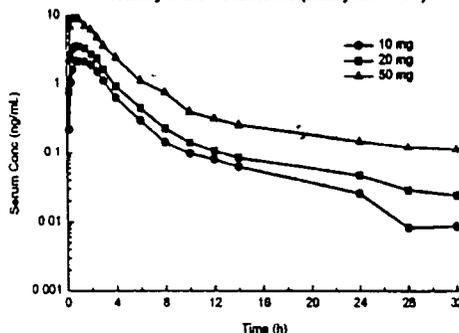


Table 27 Ibandronate Pharmacokinetic Parameters after Oral Administration of 10 mg, 20 mg, and 50 mg to Healthy Male Volunteers (Study MF 7131)

Parameter ¹	10 mg	20 mg	50 mg
C_{max} (ng/mL)	2.75 ± 0.99	4.21 ± 1.74	11.8 ± 5.76
t_{max} (h)	1.25	0.75	0.63
AUC $_{\infty}$ (hr*ng/mL)	9.29 ± 4.24	14.1 ± 6.39	35.4 ± 14.2
$t_{1/2}$ (h)	9.71 ± 5.86	9.86 ± 4.69	12.3 ± 2.40
CL _r (mL/min)	101 ± 23.4	91.5 ± 20.1	96.6 ± 23.3
f_e (% Dose)	0.54 ± 0.24	0.40 ± 0.22	0.40 ± 0.17

n = 17

¹ Mean ± SD except for t_{max} for which the median is reported

Figure 13 Mean Ibandronate C_{max} and AUC_{0-6} after Oral Administration of 10 mg, 20 mg, and 50 mg to Healthy Male Volunteers (Study MF 7131)

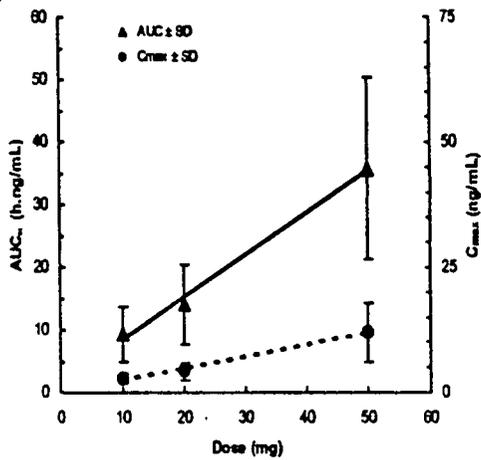


Table 28 Relative Bioavailability of Ibandronate after Oral Administration of 10 mg, 20 mg, and 50 mg Tablets to Healthy Male Volunteers (Study MF 7131)

Parameter	p-value ¹	Ratio (90% Confidence Interval) ²		
		10 mg vs 20 mg	10 mg vs 50 mg	20 mg vs 50 mg
C_{max}	0.0730	1.33 (1.08 - 1.64)	1.22 (0.99 - 1.50)	0.92 (0.75 - 1.13)
AUC_{0-6}	0.0609	1.31 (1.07 - 1.62)	1.29 (1.05 - 1.59)	0.99 (0.88 - 1.21)

¹ Based on ANOVA of natural log-transformed data. Values for the 10 mg and 20 mg doses were corrected to 50 mg prior to analysis.

² p-value for the treatment (dose) effect from the ANOVA.

3. How was the ibandronate pharmacokinetics altered following chronic oral dosing?

Ibandronate accumulated upon chronic oral administration. The single dose and steady-state ibandronate pharmacokinetics in 180 postmenopausal osteoporosis patients were examined in Study MF 4348. Thirty randomized patients received placebo, 0.25 mg, 0.5 mg, 1 mg, 2.5 mg, or 5 mg ibandronate film coated tablets daily for 12 months. Blood samples were collected for 6 hours after the first dose and after 12 months of therapy for serum ibandronate concentration measurement.

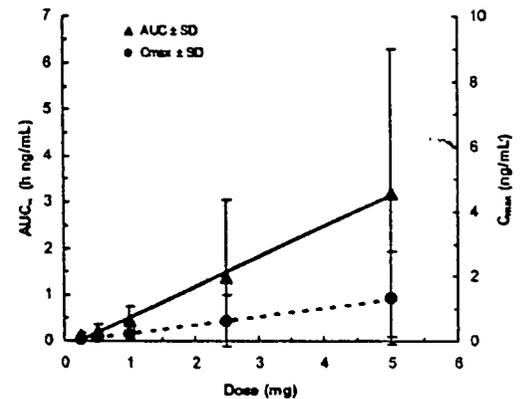
Mean serum ibandronate concentrations increased with dose after both the 1st dose and 12 months of treatment. The mean C_{max} or AUC_{0-6} vs. dose plots appeared to be linear with large variability. Clearance calculated up to 6 hours, however, seemed to decrease with dose. In general, C_{max} and AUC_{0-6} both increased about 1.5- to 2-fold during the treatment period. This degree of accumulation was consistent with a $t_{1/2}$ of about 16 h and a dosing interval of 24 h.

Table 31 Ibandronate Pharmacokinetic Parameters after Oral Administration of 0.25 mg to 5 mg Daily for 12 Months to Patients with Postmenopausal Osteoporosis (Study MF 4348)

Parameter ¹	Dose (mg/day)				
	0.25	0.5	1	2.5	5
First Dose					
n	29	28	29	28	30
C_{max} (ng/mL)	0.653 \pm 0.023	0.103 \pm 0.007	0.203 \pm 0.148	0.624 \pm 0.304	1.32 \pm 1.45
$t_{1/2}$ (h)	0.66	1.00	0.66	1.00	1.00
AUC_{0-6} (h·ng/mL)	0.126 \pm 0.061	0.218 \pm 0.152	0.462 \pm 0.201	1.39 \pm 1.65	3.20 \pm 3.10
After 12 Months					
n	21	22	25	24	19
C_{max} (ng/mL)	0.049 \pm 0.025	0.106 \pm 0.068	0.275 \pm 0.181	1.04 \pm 1.14	1.44 \pm 0.743
$t_{1/2}$ (h)	1.00	1.00	1.00	0.66	1.00
AUC_{0-6} (h·ng/mL)	0.134 \pm 0.083	0.208 \pm 0.153	0.756 \pm 0.379	2.51 \pm 2.47	4.15 \pm 2.11

¹ Mean \pm SD except for $t_{1/2}$ for which the median is reported.

Figure 18 Mean Ibandronate C_{max} and AUC_{0-6} after Oral Administration of 0.25 mg to 5 mg Daily for 12 Months to Patients with Postmenopausal Osteoporosis (Study MF 4348)



The single-dose and steady-state ibandronate pharmacokinetics upon daily 20 mg ibandronate capsule oral administration for 5 days were studied in 10 healthy male volunteers (Study MF 7113). Blood and urine samples were collected for 120 hours post 1st and 5th dose to characterize the ibandronate pharmacokinetics.

Pre-dose plasma ibandronate concentrations increased from Days 2 to 5. Day 5's mean C_{max} were 56% higher than that on Day 1. These observations were consistent with the t_{1/2}s. Mean ibandronate CL_r were consistent between Days 1 and 5.

Figure 14 Mean Plasma Ibandronate Concentrations after Oral Administration of 20 mg Daily for 5 Days to Healthy Male Volunteers (Study MF 7113)

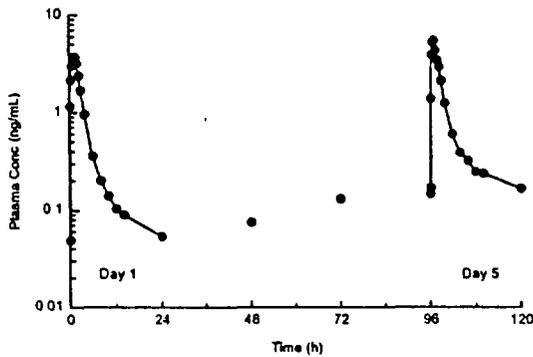


Table 29 Ibandronate Pharmacokinetic Parameters after Oral Administration of 20 mg Daily for 5 Days to Healthy Male Volunteers (Study MF 7113)

Parameter ¹	Day 1	Day 5
C _{max} (ng/mL)	4.10 ± 2.08	6.40 ± 3.50
t _{max} (h)	1.25	0.75
AUC _{0-∞} (h·ng/mL)	13.6 ± 7.38	-
AUC ₀₋₂₄ (h·ng/mL)	-	18.4 ± 10.5
t _{1/2} (h)	9.74 ± 5.66	17.4 ± 3.00
CL _r (mL/min)	80.6 ± 12.6	78.7 ± 7.57
f _e (% Dose)	0.30 ± 0.18	0.44 ± 0.26

n = 10

¹ Mean ± SD except for t_{max} for which the median is reported.

4. What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for ibandronate efficacy?

The bone mineral density (BMD) and bone turnover markers were evaluated as efficacy endpoints for the treatment and prevention of postmenopausal osteoporosis by ibandronate. Daily oral doses of ibandronate exhibited a dose dependent increase in BMD in the dose range of 0.25 to 5.0 mg (BMD increase may start to plateau at 2.5 mg) in patients with postmenopausal osteoporosis and in the range of 0.5 to 2.5 mg in healthy postmenopausal women. The suppression of bone resorption marker (urinary C-terminal telopeptide of type I collagen (uCTX)) and formation marker (osteocalcin) was also dose-dependent.

BMD:

The effect of ibandronate on lumbar spine BMD [L2-L4] was evaluated at different oral doses (0.25, 0.5, 1.0, 2.5, and 5 mg/day) of ibandronate during 12 months' treatment in patients with postmenopausal osteoporosis (MF 4348). After treatment with ibandronate, BMD of the lumbar spine (L2-L4) increased in a dose-dependent manner with a plateau at the 2.5 mg dose. The magnitudes of lumbar spine BMD gains with the 2.5 mg daily and 20 mg intermittent (20 mg INT) oral ibandronate dosing regimens (20 mg given every other day for 12 doses at the start of every 3 month cycle) were similar after 1 year and 2 year treatment (MF4433). Statistically significant BMD gains at the lumbar spine compared to placebo with 0.5 mg daily, 1.0 mg daily, 2.5 mg daily, 5.0 mg daily and 20 mg INT ibandronate were observed. The observed lumbar spine BMD increased rapidly during the first 6 months of therapy, and continued to increase at a lower rate thereafter.

Mean (SD) relative change (%) lumbar spine BMD[L2-L4] from baseline at Year 1(PP)

Dose regimen	MF4348 N=126 Post-dose fasting 60 min	
	N	Mean (SD)
Placebo	21	1.23 (2.47)
0.25 mg daily	24	1.56 (2.74)
0.5 mg daily	20	3.51 (3.90)
1.0 mg daily	22	3.31 (3.26)
2.5 mg daily	20	5.35 (2.66)
5.0 mg daily	16	5.61 (2.87)

The dose response of continuous oral ibandronate administration for the prevention of bone loss in postmenopausal women was evaluated at 0.5, 1.0, and 2.5 mg once daily (MF4499). Significant increases from baseline in the primary variable BMD of the lumbar spine (L1-L4) were observed at both the 1.0 mg and 2.5 mg doses after two years of daily treatment with oral ibandronate. Similarly, a dose-dependent effect on the prevention of bone loss was observed at 5, 10, and 20 mg weekly (MF4500). After 2 year treatment, lumbar spine [L1-L4] BMD significantly increased 0.95% and 3.01% from baseline at the 10 mg and 20 mg doses, respectively, as compared with placebo.

Spine BMD (L1-L4) mean relative change (%) after 1 and 2 year treatment (PP) (MF4499)

Treatment Group	Year 1		Year 2	
	N	Mean (SD)	N	Mean (SD)
Placebo	124	-0.38 (2.88)	125	-0.99 (3.49)
0.5 mg daily	129	-0.19 (2.80)	128	-0.76 (3.77)
1.0 mg daily	136	0.13 (3.08)	135	0.35 (3.65)
2.5 mg daily	124	2.08 (2.96)	124	2.15 (4.08)

It was observed that in both treatment and prevention trials for osteoporosis, doses beyond 1.0 mg daily exhibited significant difference in changes in BMD from placebo. However, the effect on BMD seems to be more efficacious in the patient groups who has osteoporosis than healthy population. It may be due to the difference in baseline. Median baseline in treatment trial (MF4348) was 0.85-0.91 g/cm² while the median baseline in prevention trial (MF 4499) was 0.97 g/cm². It was also noticed that post-dose fasting time was different. In treatment trials, the post-dose fasting time was at least 60 minutes, however, in prevention trial, the post-dose time was at least 30 minutes. It has already been shown that post-dose fasting time change from at least 60 minutes to 30 minutes decreased bioavailability by 30% and the efficacy was decreased as well.

Bone Resorption Marker: Urinary CTX

Oral ibandronate treatment at 1.0, 2.5, and 5.0 mg daily resulted in significant relative changes in uCTX excretion then that from placebo at Year 1 in postmenopausal women with osteoporosis (MF4348). Both the 2.5 mg once daily and 20 mg intermittent regimen resulted in a more than 60% suppression of uCTX at Year 1 (MF4433). Rapid suppression of bone resorption marker was obtained at 3 months and suppression retained throughout the treatment period.

Median (interquartile range) relative change (%) in uCTX/creatinine at month 12. (ITT) (MF4348)

Placebo	0.25 mg	0.5 mg	1.0 mg	2.5 mg	5.0 mg
-33.3	-39.4	-49.3	-62.9	-86.5	-90.9
			(-74.1, -40.6)*	(-90.8, -72.1)*	(-94.4, -78.1)*

*p<0.01 Wilcoxon-rank-sum-test vs. placebo. ITT = intent to treat

Oral ibandronate treatment at 1.0 mg and 2.5 mg once daily significantly decreased uCTX/creatinine excretion 19% and 41%, respectively, in postmenopausal women.

Median (range) uCTX/creatinine relative changes (%) from baseline after 24 months (ITT) (MF4499)

Treatment	Placebo	0.5 mg	1.0 mg	2.5 mg
Median (%)	-4.44	-0.53	-19.09*	-40.65*

* p<0.05 Wilcoxon-rank-sum-test vs. placebo. ITT = intent to treat

Weekly two-year treatment with oral ibandronate produced dose-dependent suppression of bone resorption as indicated by uCTX. The decrease in median uCTX/creatinine concentration differed significantly from placebo at month 24 for all treatment groups; 19%, 31%, and 46% for the 5 mg, 10 mg and 20 mg dose groups, respectively (MF4500).

Bone Formation Marker: Serum Osteocalcin

Ibandronate led to a dose-dependent decrease in the serum concentrations of osteocalcin during the course of treatment in the oral daily dose range from 0.25 to 2.5 mg. The 5.0 mg dose did not appear to result in a trend to further suppression. The differences from placebo with 1.0, 2.5, and 5.0 mg ibandronate were significant. Rapid suppression of bone formation marker attained at 6 months and suppression retained throughout the treatment period.

Median (interquartile range) relative change (%) in osteocalcin (N-mid epitope) at month 12 (ITT) (MF4348)

Placebo	0.25 mg	0.5 mg	1.0 mg	2.5 mg	5.0 mg
-5.6	-11.7	-16.5	-19.9	-37.5	-38.7
			(-31.5- -6.0)*	(-48.4- -20.6)**	(-49.1- -18.9)**

*p<0.05, **p<0.01 Wilcoxon-rank-sum-test vs. placebo. ITT = intent to treat

After 1 year treatment, osteocalcin was significantly reduced by 45.2% and 43.8% with the 2.5 mg once daily and 20 mg intermittent regimen, respectively. After 2 year treatment, osteocalcin was significantly reduced by 55.2% and 52.8% with the daily and intermittent regimen, respectively (Study MF4433).

Two year treatment of ibandronate in the dose range of 0.5 mg to 2.5 mg once daily resulted in significant, dose-dependent reductions in serum osteocalcin concentrations in postmenopausal women, as compared to placebo (MF4499). The weekly 10 mg and 20 mg groups showed significant dose-dependent reductions in osteocalcin concentrations by 30% and 47%, respectively, as compared to placebo at month 24 (MF4500).

Serum osteocalcin baseline and relative change (%) from baseline at 24 months (ITT) (MF4499)

	Placebo	0.5 mg	1.0 mg	2.5 mg
Baseline	32.54 (149)	30.295 (156)	29.585 (160)	31.59 (153)
Median (n) (%)	-10.26 (140)	-17.96 (143)	-22.08 (149)	-33.66 (139)
P-value	-	0.0374)	0.0002	0.0000

Kruskal-wallis-test:current treatment group versus placebo ITT = intent to treat

5. Is there a PK/PD relationship for efficacy parameters?

The time scales for the absorption and disposition of ibandronate, the effects on bone turnover markers and eventually on bone mineralization itself are very different. The fate of an ibandronate dose in relation to concentrations in serum and excreta can be described over a period of hours. Bone turnover markers such as uCTX can show a pronounced response within a few weeks after the start of treatment, whereas significant changes in bone mass as detected by densitometry are only reliable after a year of treatment. The sponsor explored preliminary PK/PD models for efficacy markers. According to the sponsor, changes in the marker uCTX have been linked to an intravenous 4-compartment PK model via an indirect PD response model. Later on a simpler "Dose Rate" model was developed. Since this "Dose Rate" model had some shortcomings that a faster onset of effect was predicted for oral treatments than that was observed. This "Dose Rate" model also predicted a faster and more complete recovery of the uCTX effect than that was seen following administration of ibandronate by either IV or oral route. The "Dose Rate" model was developed to include an element relating changes in vertebral BMD to uCTX.

6. What is the maximum tolerable dose of ibandronate?

A single oral dose of 100 mg is the maximum tolerable dose of ibandronate. In an initial investigation in healthy male volunteers (MF7100), tolerability of a single oral dose of 10, 50, and 100 mg ibandronate was evaluated. There were 8 subjects in each active treatment group and 6 subjects in placebo group. Ibandronate administered as a single oral dose of either 10 or 50 mg was well tolerated by the subjects in this study. However, all subjects in the 100 mg treatment group complained of symptoms such as myalgia (n=7) and chest pain (n=1) within 24 hours after drug administration which subsided without requiring medical intervention. Nearly all of them showed a slight increase in body temperature between 11 and 35 hour after administration. Nearly all of them showed a transient increase in lymphocytes 8-24 h after administration together with a transient increase in segmented neutrophils and a decrease in lymphocytes 12-24 h after administration. ECG, blood pressure and heart rate were not influenced by ibandronate. Thus, 100 mg as a single oral dose was assessed as the maximal tolerable dose.

7. What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety? Is there a PK/PD relationship for safety parameters?

The incidence of adverse events such as gastrointestinal irritation and pain like muscle ache was dose-dependent. Ibandronate 0.25 to 2.5 mg daily for 1 year was well-tolerated by postmenopausal women. No consistent difference in the safety profile was observed between placebo and 0.25-2.5 mg doses. With 5.0 mg, the withdrawal rate was 2-3 times higher than that in the other treatment groups and the overall incidence of related gastrointestinal adverse events, mainly those linked to the lower gastrointestinal tract, was higher with 5.0 mg.

In healthy male subjects, single oral doses up to 50 mg (MF7100) and multiple oral doses of 10 (MF7113) and 20 mg (MF7120) of ibandronate given daily for 5 and 20 days, respectively, were well tolerated. A low incidence of adverse events such as pain like muscle ache was recorded. While no apparent relationship between dose and adverse effect in this dose range was observed, a single oral dose of 100 mg ibandronate was not well tolerated. Study showed seven of eight subjects treated with this dose complained of myalgia and one experienced chest pain (non-cardiac), all of which occurred

within one day of drug administration and subsided within one to three days. This may be caused by the higher systemic exposure. More than two-fold higher exposure with 100 mg dose compared with 50 mg dose was observed.

For intravenous administration, it has been shown that as intravenous dose increased from 0.5, 1.0, and 2.0 mg, incidence of muscle ache like pain reported by the healthy male subjects increased (MF7144). Considering the bioavailability of an oral dose was 0.6%, these iv doses of 0.5, 1.0, and 2.0 mg would be approximately equivalent to 83 mg, 167, and 333 mg oral doses, respectively. Adverse effects such as gastrointestinal adverse events and muscle ache like pain can be concluded as dose-dependent. No PK/PD relationship for safety was explored.

8. Is QT interval prolonged by ibandronate?

No clinical significant QT prolongation was observed in Phase I tolerability studies. ECG measurements were taken at various time points in subjects receiving oral or intravenous ibandronate and placebo. There were no clinically significant vital sign or ECG abnormalities or QT prolongation at single oral dose up to 100 mg and intravenous dose up to 6 mg. These data support the findings of the negative in vitro and preclinical cardiotoxicity tests. As a result of negative findings in ECG record, vital signs and ECGs were not recorded in the Phase III clinical trials.

4.3 Intrinsic Factors

The sponsor studied age, gender, race, and renal insufficiency effects on ibandronate pharmacokinetics.

1. Do age, gender, and race effects exist for ibandronate pharmacokinetics?

Age (pediatrics and geriatrics)

Pediatrics

The sponsor did not study ibandronate pharmacokinetics in patients < 18 years of age.

Gender

The sponsor pooled 8 clinical pharmacology studies (cross study and population) that studied ibandronate pharmacokinetics after IV administration to assess total ibandronate clearance, renal clearance, and nonrenal clearance. Ibandronate total clearance for male subjects was higher than that for female subjects. This gender effect was also observed with ibandronate renal clearance. However, ibandronate nonrenal clearance appeared to be comparable across gender and subject population. Except male multiple myeloma patients in Study MF 7169, all male subjects were young, healthy volunteers with average age from 25.9 – 32.1 years. In contrast, all female subjects or patients were middle age or older from 47.7 – 52.9 years. Renal function decreased as a consequence of aging. Older subjects would have lower CL_{cr} than younger patients' CL_{cr}. Therefore, the apparent gender differences in ibandronate clearance were more likely a function of age and the associated decline in renal function, rather than attributable to gender difference.

Geriatrics

As described in the gender effect above, ibandronate CL_r was directly related to CL_{cr}. Renal function measured as CL_{cr} decreased with age and this was an established fact. Hence, ibandronate CL_r would decrease with increasing age of patients. The mean AUC_∞ for healthy postmenopausal women in Study MF 8902 (mean (SD); 47.7 (3.68) years of age and CL_{cr} of 76.0 (20.6) mL/min) was 22.5% higher than that for healthy male subjects in Study MF 7144 (mean (SD); 28.2 (5.31) years of age and CL_{cr} of

161 (30.2) mL/min) upon single dose 2 mg ibandronate IV administration from cross study comparison.

Table 35 Ibandronate Pharmacokinetic Parameters after i.v. Administration of 2, 4, and 6 mg to Healthy Postmenopausal Female Volunteers (Study MF 8902)

Parameter ¹	2 mg (n = 18)	4 mg (n = 19)	6 mg (n = 17)
C _{max} (ng/mL)	88.5 ± 28.7	159.1 ± 44.9	239.0 ± 26.8
t _{max} (h)	2.0	2.0	2.0
AUC _{0-∞} (hrng/mL)	316.4 ± 110.5	580.7 ± 169.2	908.3 ± 123.0
t _{1/2} (h)	9.65 ± 3.02	13.3 ± 4.41	14.1 ± 0.99
CL (mL/min)	113.3 ± 25.6	127.7 ± 52.3	112.1 ± 15.9
Vz (L)	90.4 ± 24.9	140.0 ± 60.2	137.3 ± 24.7
CLr (mL/min)	61.2 ± 23.4	50.1 ± 17.8	58.9 ± 20.0
f _e (% Dose)	57.4 ± 24.7	41.4 ± 12.5	49.6 ± 13.2

¹ Mean ± SD except for t_{max} for which the median is reported.

Table 33 Ibandronate Pharmacokinetic Parameters after i.v. Administration of 0.5, 1, and 2 mg to Healthy Male Volunteers (Study MF 7144)

Parameter ¹	0.5 mg (n = 16)	1 mg (n = 16)	2 mg (n = 16)
C _{max} (ng/mL)	87.7 ± 63.6	125.0 ± 13.6	246.0 ± 54.7
t _{max} (h)	0.033	0.033	0.033
AUC _{0-∞} (hrng/mL)	67.3 ± 6.69	130.9 ± 18.3	245.3 ± 29.8
t _{1/2} (h)	33.2 ± 7.26	30.5 ± 5.88	31.1 ± 6.83
CL (mL/min)	125.0 ± 11.7	129.6 ± 17.6	137.9 ± 17.8
Vz (L)	358.8 ± 80.9	334.9 ± 59.0	367.7 ± 74.3
CLr (mL/min)	87.5 ± 12.8	87.7 ± 15.7	88.6 ± 13.2
f _e (% Dose)	61.7 ± 4.52	60.6 ± 4.21	57.6 ± 7.21

¹ Mean ± SD except for t_{max} for which the median is reported.

Race

The sponsor did not directly study inter-ethnic comparative study. From cross study comparisons (Studies MF 9850 and MF 9852 for young healthy male Japanese and Study MF 7144 (see previous-table) for young healthy male Caucasians), no observable difference in exposure existed between the Japanese and Caucasians.

Table 34 Ibandronate Pharmacokinetic Parameters after i.v. Administration of 0.125, 0.25, and 0.5 mg to Healthy Male Japanese Volunteers (Study MF 9850)

Parameter ¹	0.125 mg (n = 8)	0.25 mg (n = 8)	0.5 mg (n = 8)
AUC _{0-∞} (hrng/mL)	17.1 ± 19.5	34.4 ± 5.06	77.2 ± 10.4
t _{max} (h)	15.7 ± 8.81	20.2 ± 4.39	21.3 ± 2.03
CL (mL/min)	123 ± 13.6	124 ± 21.3	109 ± 13.1
Vz (L)	159 ± 75.2	211 ± 32.5	201 ± 26.5
CLr (mL/min)	86.5 ± 12.3	83.6 ± 9.89	81.8 ± 14.3
f _e (% Dose)	68.8 ± 5.30	67.2 ± 11.6	72.9 ± 7.49

¹ Mean ± SD

Table 39 Ibandronate Pharmacokinetic Parameters after i.v. Administration of 0.50 mg to Healthy Male Japanese Volunteers (Study MF 9852)

Parameter ¹	0.5 mg i.v.
1st Administration	
AUC _{0-∞} (hrng/mL)	74.4 ± 8.81
t _{max} (h)	20.3 ± 1.22
CL (mL/min)	113 ± 13.4
Vz (L)	200 ± 30.4
CLr (mL/min)	77.9 ± 15.8
f _e (% Dose)	66.6 ± 5.99
2nd Administration	
t _{max} (h)	21.1 ± 1.56
f _e (% Dose)	65.0 ± 8.45

n = 8

¹ Mean ± SD

2. How does renal impairment affect ibandronate pharmacokinetics?

Ibandronate pharmacokinetics in patients with varying degrees of renal impairment was investigated in Study MF7148. Three groups of subjects (Group 1: CLcr < 30 mL/min; Group 2: CLcr 40-70 mL/min; Group 3: CLcr > 90 mL/min) all received single 0.5 mg ibandronate IV injections of ibandronate. After a washout of 1-3 days, subjects in Groups 1 and 3 also received one 10 mg ibandronate oral film-coated tablet daily for 21 days. Blood and urine samples for the measurement of ibandronate concentrations were collected for 72 hours after the IV dosing and for 24 and 48 hours after the first (Day 1) and final (Day 21) oral doses, respectively.

Ibandronate CLr was directly related to CLcr. Namely, decreases in CLr accompanied with decreases in CLcr. Total ibandronate CL also decreased with decrease in CLcr. The mild to moderate renal impairment group (CLcr 40 –70 mL/min) resulted in 22% increase in Cmax and 55% increase in AUC∞ as compared to that for the normal renal function (CLcr > 90 mL/min) group. As CLcr fell below 30 mL/min, ibandronate exposure increased to > 2 fold as compare to that for normal CLcr.

Figure 39 Total, Renal, and Nonrenal Ibandronate Clearances, In Subjects with Renal Impairment (Study MF 7148)^{1,nd}

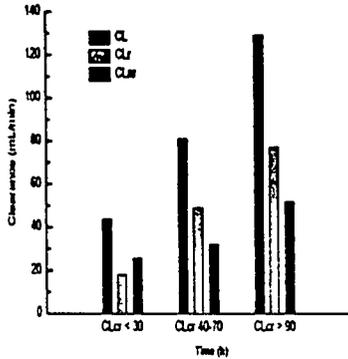


Table 42 Ibandronate Pharmacokinetic Parameters after Iv. Administration of 0.5 mg to Healthy Volunteers and Subjects with Renal Impairment (Study MF 7148)

Parameter ¹	CLcr < 30 mL/min (n = 12)	CLcr 40-70 mL/min (n = 8)	CLcr > 90 mL/min (n = 12)
C _{max} (ng/mL)	116 ± 127	61.9 ± 6.86	47.9 ± 14.4
t _{max} (h)	0.083	0.083	0.083
AUC _∞ (h·ng/mL)	201 ± 47.5	105 ± 14.5	67.6 ± 14.4
n (h)	42.2 ± 10.3	27.3 ± 3.79	36.8 ± 5.02
CL (mL/min)	43.6 ± 9.81	80.9 ± 11.3	129 ± 27.5
V _d (L)	158 ± 47.2	191 ± 32.1	110 ± 105
CLr (mL/min)	17.9 ± 7.67	48.9 ± 15.2	77.0 ± 24.2
f (% Dose)	34.1 ± 13.3	55.1 ± 13.7	53.9 ± 13.4

¹ Mean ± SD except for t_{max} for which the median is reported.

Table 43 Ibandronate Pharmacokinetic Parameters after Oral Administration of 10 mg/day for 21 Days to Healthy Volunteers and Subjects with Renal Impairment (Study MF 7148)

Parameter ¹	CLcr < 30 mL/min (n = 12)	CLcr > 90 mL/min (n = 12)
Day 1		
C _{max} (ng/mL)	2.58 ± 1.98	1.90 ± 1.07
t _{max} (h)	0.50	0.50
AUC _∞ (h·ng/mL)	9.91 ± 5.46	4.63 ± 2.40
t _{1/2} (h)	-	-
CLr (mL/min)	15.4 ± 7.27	76.8 ± 21.5
f (% Dose)	0.20 ± 0.18	0.27 ± 0.15
Day 21		
C _{max} (ng/mL)	3.01 ± 2.43	2.09 ± 1.41
t _{max} (h)	1.00	0.75
AUC _∞ (h·ng/mL)	19.4 ± 8.57	6.66 ± 4.63
t _{1/2} (h)	103.1 ± 28.8	54.7 ± 18.0
CLr (mL/min)	14.4 ± 5.7	62.8 ± 26.0
f (% Dose)	0.15 ± 0.086	0.10 ± 0.23

¹ Mean ± SD except for t_{max} for which the median is reported.
² AUC_∞ = area under the curve from 0 to 8 hours.

3. How does hepatic impairment affect ibandronate pharmacokinetics?

No studies were conducted to assess the hepatic impairment effect on ibandronate pharmacokinetics. Ibandronate was not metabolized in human liver preparations.

4.4 Extrinsic Factors

1. What do food and timing of food have any effect on the bioavailability of ibandronate?

The sponsor conducted 3 clinical pharmacology studies to assess the effect of food and timing of food intake on ibandronate pharmacokinetics.

Study MF 7122 concerned 20 healthy male volunteers received an oral 50 mg ibandronate sodium tablet at intervals of 1 week:

- 3 hours before (treatment A)
- 2 hours before (treatment B)
- 1 hours before (treatment C) consuming a standard meal
- immediately after (treatment D) or
- 2 hours after (treatment E) consuming a standard meal

Ibandronate sodium administration before 1 – 3 hours of meal consumption yielded similar pharmacokinetic parameters. Mean ibandronate C_{max} and AUC_∞ were reduced about 90% upon immediate administration after food consumption.

Figure 3 Mean Plasma Ibandronate Concentrations after Oral Administration of 50 mg at Specific Times Relative to a Meal to Healthy Male Volunteers (Study MF 7122)

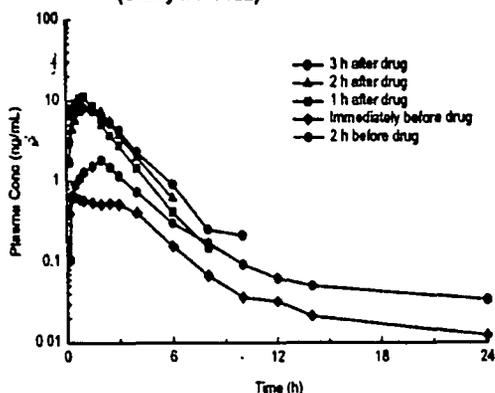


Table 18 Ibandronate Pharmacokinetic Parameters after Oral Administration of 50 mg at Specific Times Relative to a Meal to Healthy Male Volunteers (Study MF 7122)

Parameter ¹	Timing of Meal Relative to Ibandronate Dose				
	3 h After (n = 19)	2 h After (n = 20)	1 h After (n = 19)	Immediately Before (n = 18)	2 h Before (n = 19)
C_{max} (ng/mL)	11.1 ± 3.64	10.0 ± 4.00	13.3 ± 4.64	0.94 ± 1.08	2.15 ± 1.47
$t_{1/2}$ (h)	6.50	1.00	1.00	1.00	1.75
AUC _∞ (ng/mL)	30.7 ± 12.5	27.8 ± 11.3	25.9 ± 13.8	3.35 ± 4.35	7.20 ± 5.63
k_e (h)	2.11 ± 1.17	1.70 ± 1.41	1.36 ± 0.88	4.15 ± 4.82	7.20 ± 7.95
CL _r (mL/min)	70.3 ± 27.4	64.3 ± 43.9	47.5 ± 39.6	101 ± 38.4	47.9 ± 47.4
CL _r (mL/kg)	0.29 ± 0.11	0.31 ± 0.19	0.24 ± 0.14	0.03 ± 0.03	0.09 ± 0.06
AUC Ratio (%) (95% CI)	100	87 ¹ (67 - 107)	84 (57 - 110)	11 (4 - 32)	27 (12 - 42)

¹ Mean ± SD except for $t_{1/2}$ for which the median is reported.

Study MF 7154 compared the effect of food intake on the ibandronate pharmacokinetics when 18 healthy male subjects each received a 2.5 mg or 5 mg (2 x 2.5 mg) ibandronate oral dose as a film coated tablet 30 minutes before a standard meal or a 5 mg oral dose administered 2 hours before food intake according to a randomized crossover design. The intake of food 30 minutes after the dosing of ibandronate led to reductions in serum concentrations as compared to food intake 2 hours after dosing. Mean values for C_{max} were reduced about 20% and those for AUC_{∞} about 40%.

Food effect on ibandronate kinetics was also investigated (Study BP16304) in healthy postmenopausal female volunteers. The results for this study were consistent with that of the other 2 studies. Per the results for these 3 studies, ibandronate sodium should be taken 1 hour before any food intake.

2. What are the drug-drug interaction studies for ibandronate?

Ranitidine

Study MF 7187 concerned the effect of increased gastric pH on the absorption of orally administered ibandronate in 20 healthy volunteers (10 postmenopausal women and 10 men over 45 years of age). Each randomized volunteers received a 10 mg ibandronate oral film coated tablet concomitantly with IV normal saline or IV 75 mg ranitidine (25 mg injected 90 and 15 minutes before and 35 minutes after ibandronate administration). Treatments were separated by a 10-day washout (2-period crossover). Blood and urine samples for the measurement of ibandronate were collected for 24 hours after administration. Administration of ibandronate concomitantly with ranitidine, i.e. with an increased gastric pH, resulted in 20 - 25% higher plasma ibandronate concentrations with corresponding increases in C_{max} and AUC_{0-24} and AUC_{∞} . Similar observation existed in the labeling for alendronate "Intravenous ranitidine was shown to double the bioavailability of oral alendronate. The clinical significance of this increased bioavailability and whether similar increases will occur in patients given oral H_2 -antagonists is unknown."

Table 21 Ibandronate Pharmacokinetic Parameters after Oral Administration of 10 mg to Healthy Postmenopausal Women and to Men With and Without Concomitant Administration of Ranitidine (Study MF 7187)

Parameter ¹	Ibandronate	Ibandronate + Ranitidine	p-value ²
C _{max} (ng/mL)	5.63 ± 7.18	6.26 ± 4.66	0.1898
t _{max} (h)	0.88	0.75	0.2864
AUC ₀₋₂₄ (h·ng/mL)	14.3 ± 14.1	16.6 ± 11.5	0.1801
AUC _∞ (h·ng/mL)	15.4 ± 15.4	17.9 ± 12.4	0.1564
t _{1/2} (h)	7.72 ± 4.57	9.80 ± 4.43	0.0795
CL _r (mL/min)	77.7 ± 24.9	84.0 ± 23.8	0.3411
f _e (% Dose)	0.61 ± 0.44	0.79 ± 0.48	0.0329

n = 20

¹ Mean ± SD except for t_{max} for which the median is reported.

² p-value for the treatment effect from an analysis of variance (C_{max}, AUC_∞, t_{1/2}, CL_r, f_e) or Wilcoxon Rank Sum Test (t_{max}).

Tamoxifen

The sponsor conducted a randomized, 3-way crossover (2 and 3 weeks washout, respectively), partly 2-blind (periods 2 and 3) interaction study (MF 7167) between single doses of ibandronate and tamoxifen in 24 healthy postmenopausal women. Subjects received 3 treatments: 1) 2 mg ibandronate IV injection, 2) 30 mg tamoxifen oral tablet with placebo IV injection, 3) 30 mg tamoxifen oral tablet with 2 mg ibandronate IV injection. Blood and urine samples for ibandronate measurement were collected for 48 hours postdose and for tamoxifen (blood only) for 648 hours.

The 2 mg ibandronate injection with and without tamoxifen resulted in superimposable mean serum ibandronate concentration-time curves. With the exception of CL_r and f_e, all pharmacokinetic parameters were not significantly different between treatments. Ibandronate did not affect tamoxifen pharmacokinetics. Plasma tamoxifen concentration-time curves were similar and there were no significant differences in any of the tamoxifen pharmacokinetic parameters between treatments. No evidence existed for a pharmacokinetic interaction between ibandronate and tamoxifen.

Table 47 Ibandronate Pharmacokinetic Parameters after I.v. Administration of 2 mg to Healthy Postmenopausal Women With and Without Concomitant Oral Administration of 30 mg of Tamoxifen (Study MF 7167)

Parameter ¹	Ibandronate	Ibandronate + Tamoxifen	p-value ²
C _{max} (ng/mL)	290.3 ± 63.4	267.9 ± 62.7	0.117
t _{max} (h)	0.083	0.083	-
AUC ₀₋₂₄ (h·ng/mL)	380.9 ± 57.9	378.1 ± 59.2	0.779
t _{1/2} (h)	20.9 ± 3.44	21.5 ± 2.72	0.475
CL (mL/min)	89.4 ± 13.1	90.2 ± 14.1	0.742
V _d (L)	160.2 ± 27.3	167.8 ± 34.0	0.282
CL _r (mL/min)	52.3 ± 14.3	65.1 ± 16.4	0.007
f _e (% Dose)	55.1 ± 10.0	66.4 ± 12.6	0.004

n = 24

¹ Mean ± SD.

² p-value for the treatment effect from a two-way analysis of variance (subject and treatment).

Table 48 Tamoxifen Pharmacokinetic Parameters after Oral Administration of 30 mg to Healthy Postmenopausal Women With and Without Concomitant I.v. Administration of Ibandronate (Study MF 7167)

Parameter ¹	Tamoxifen	Tamoxifen + Ibandronate	p-value ²
C _{max} (ng/mL)	41.4 ± 15.6	43.9 ± 27.2	0.473
t _{max} (h)	3.00	3.00	-
AUC ₀₋₆₄₈ (h·ng/mL)	4787 ± 2051	4776 ± 2082	0.963
t _{1/2} (h)	271.0 ± 146.2	242.4 ± 62.4	0.351

n = 24

¹ Mean ± SD except for t_{max} for which the median is reported.

² p-value for the treatment effect from an analysis of variance.

Melphalan/Prednisolone

Interaction between single doses of ibandronate, melphalan, and prednisolone was examined in 24 patients with multiple myeloma (Study MF 7169). Randomized patients received IV melphalan (10 mg/m²) and oral prednisolone (60 mg/m²) either alone or concomitantly with a 6 mg ibandronate injection. After a washout (>12 days), patients received a single 6 mg ibandronate injection. After a

2nd 12-day washout, patients received the alternate to the first treatment (melphalan/prednisolone with or without ibandronate). Blood and urine samples for ibandronate measurement were collected for 24 hours, for 6 hours for melphalan (blood only), and for 12 hours for prednisolone (blood only) postdose. Mean serum ibandronate concentrations when administered alone were essentially the same as those observed when it was administered concomitantly with melphalan and prednisolone. Although statistically significant increases in CL, Vz, and t_{1/2} existed when ibandronate was administered with melphalan and prednisolone, the values for both treatments were within the ranges observed among doses and subject or patient populations in the other studies. Ibandronate did not affect either melphalan or prednisolone pharmacokinetics.

Table 49 Ibandronate Pharmacokinetic Parameters after Lv. Administration of 6 mg to Patients with Multiple Myeloma With and Without Concomitant Administration of Melphalan 10 mg/m² / Prednisolone (60 mg/m²) (Study MF 7169)

Parameter ¹	Ibandronate	Ibandronate + Melphalan + Prednisolone	p-value ²
C _{max} (ng/mL)	337.0 ± 55.3	339.0 ± 46.6	0.948
t _{max} (h)	1.00	1.00	-
AUC ₀₋₂₄ (hrng/mL)	366.2 ± 178.4	303.9 ± 113	0.021
t _{1/2} (h)	9.81 ± 1.51	11.7 ± 2.11	0.002
CL (mL/min)	119.6 ± 21.9	126.7 ± 17.3	0.431
Vz (L)	100.8 ± 22.5	126.3 ± 24.9	0.008
CLr (mL/min)	99.1 ± 21.1	67.3 ± 24.8	0.053
t _{1/2} (h) Dose ³	15.7 ± 14.4	48.3 ± 19.0	0.486

n = 24

¹ Mean ± SD except for t_{max} for which the median is reported.
² p-value for the treatment effect from an analysis of variance.

Table 50 Melphalan Pharmacokinetic Parameters after Lv. Administration 10 mg/m² to Patients with Multiple Myeloma With and Without Concomitant Lv. Administration of Ibandronate (Study MF 7169)

Parameter ¹	Melphalan	Melphalan + Ibandronate	p-value ²
C _{max} (ng/mL)	648.1 ± 210.0	644.5 ± 138.2	0.395
t _{max} (h)	0.063	0.066	-
AUC ₀₋₆ (hrng/mL)	522.6 ± 161.6	529.4 ± 92.5	0.821
t _{1/2} (h)	0.99 ± 0.10	0.90 ± 0.10	0.822
CL (mL/min)	687.3 ± 138.4	941.7 ± 119.6	0.263
Vz (L)	58.9 ± 29.7	50.7 ± 10.2	0.316

n = 24

¹ Mean ± SD.

² p-value for the treatment effect from an analysis of variance.

³ Numerical differences in t_{max} were a consequence of different sampling schemes and were therefore not statistically compared.

Table 51 Prednisolone Pharmacokinetic Parameters after Oral Administration of 60 mg/m² to Patients with Multiple Myeloma With and Without Concomitant Lv. Administration of Ibandronate (Study MF 7169)

Parameter ¹	Prednisolone	Prednisolone + Ibandronate	p-value ²
C _{max} (ng/mL)	1265 ± 257	1225 ± 302	0.617
t _{max} (h)	1.79	1.08	-
AUC ₀₋₁₂ (hrng/mL)	7129 ± 1724	6795 ± 954	0.159
t _{1/2} (h)	3.26 ± 0.52	3.19 ± 0.70	0.487

n = 24

¹ Mean ± SD except for t_{max} for which the median is reported.

² p-value for the treatment effect from an analysis of variance.

Hormone Replacement Therapy (HRT)

Interaction potential between ibandronate and HRT was assessed in a randomized, open-label, single-dose, 3-way crossover (>2 weeks washout) study comparing a 0.5 mg ibandronate/30 second single IV injection with single oral administration of 2.5 mg and 20 mg ibandronate film coated tablets (Study MF 7159). Thirty-four healthy postmenopausal women completed the study (17 subjects on HRT and 17 not). The identity and dose of the HRT were not provided in the study report. Blood and urine samples were collected for 48 hours postdose to characterize ibandronate pharmacokinetics.

Mean serum ibandronate concentrations and pharmacokinetic parameters after IV and oral administration were essentially the same in women taking HRT as in those not on HRT. Hence, HRT did not alter the ibandronate pharmacokinetics after either IV or oral administration. However, HRT and ibandronate might have pharmacodynamic interaction together, such as the increased effect on bone turnover suppression which were observed when alendronate were coadministered with estrogen ± progestin

Figure 47 Mean Serum Ibandronate Concentrations after I.v. Administration of 0.5 mg and Oral Administration of 2.5 mg and 20 mg to Healthy Postmenopausal Female Volunteers - With and Without Hormone Replacement Therapy (Study MF 7159)

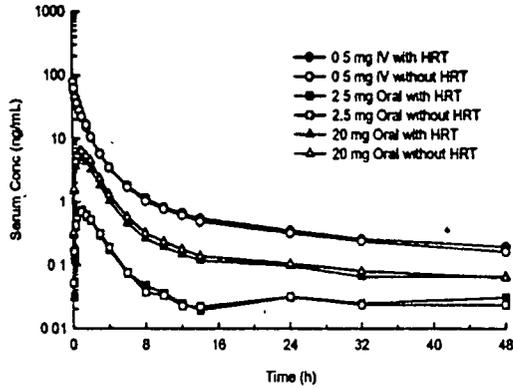


Table S2 Ibandronate Pharmacokinetic Parameters after I.v. Administration of 0.5 mg and Oral Administration of 2.5 mg and 20 mg to Healthy Postmenopausal Female Volunteers With and Without Hormone Replacement Therapy (Study MF 7159)

Parameter ¹	I.v. 0.5 mg		Oral 2.5 mg		Oral 20 mg	
	With HRT ² (n = 17)	Without HRT ² (n = 17)	With HRT ² (n = 17)	Without HRT ² (n = 17)	With HRT ² (n = 17)	Without HRT ² (n = 17)
C_{max} (ng/mL)	78.4 ± 17.8	77.8 ± 18.5	0.814 ± 0.206	0.776 ± 0.450	1.76 ± 1.66	6.68 ± 4.58
t_{max} (h)	0.083	0.083	1.08	1.00	0.75	1.08
AUC _{0-∞} (h·ng/mL)	95.6 ± 17.5	94.7 ± 16.2	1.57 ± 1.52	3.37 ± 1.68	21.0 ± 13.1	25.1 ± 19.1
$t_{1/2}$ (h)	33.2 ± 2.39	21.9 ± 2.55	·	·	72.5 ± 8.37	32.0 ± 19.4
CL (mL/min)	99.6 ± 14.3	90.2 ± 14.5	·	·	·	·
V_z (L)	179.3 ± 32.2	170.8 ± 33.3	·	·	·	·
CL _R (mL/min)	61.8 ± 17.6	60.6 ± 18.7	7.4 ± 1.02	30.6 ± 1.78	37.2 ± 13.4	46.4 ± 15.5
f (% Dose)	63.0 ± 12.4	64.0 ± 8.31	4.73 ± 1.73	8.52 ± 0.87	4.30 ± 0.29	8.44 ± 0.34

¹ Mean ± SD except for t_{max} for which the median is reported.
² HRT = hormone replacement therapy.
³ Parameter could not be calculated for this treatment.
⁴ Parameter not applicable to this treatment.

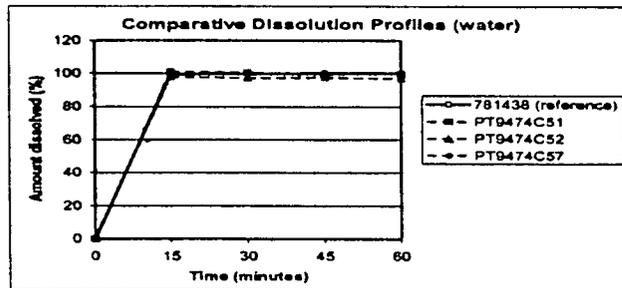
General Biopharmaceutics

1. Does difference exist between the to-be-marketed formulation and the pivotal clinical study formulation?

No difference existed between the to-be-marketed formulation and the pivotal clinical study formulation.

However, the manufacture of the product was transferred from the development site, Mannheim (Germany), to the commercial manufacturing site, Basel (Switzerland). The tablet was also changed from round (pivotal clinical study) to oblong (to-be-marketed) shape. This change had no influence either on the manufacturability of the tablets or their dissolution properties (reference batch 781438: round shape, all others: oblong). See the next question below for in vitro dissolution test and condition.

Figure 5 Comparative dissolution profiles



The manufacturing processes for the pivotal clinical study formulation and the to-be-marketed formulation were comparable. Therefore, the to-be-marketed formulation was deemed to be identical to the pivotal clinical study formulation.

2. What is the proposed in vitro dissolution test and specifications for the 2.5 mg ibandronate tablet?

The sponsor did not propose an in vitro dissolution test for the 2.5 mg ibandronate tablet. The sponsor proposed a USP in vitro disintegration test instead with the reasons that 1) > 80% of the ibandronate in the 2.5 mg tablet was dissolved in 15 minutes and 2) being consistent with ICH Topic Q6A. However, 4 marketed bisphosphonate oral tablets do have in vitro dissolution tests (alendronate and risedronate for osteoporosis treatment; etidronate and tiludronate for Paget's disease treatment). Moreover, USP 25 (page 2010) stated that "... disintegration does not imply complete solution of the unit or even of its active constituent." Disintegration test did not guarantee complete dissolution of test products. Moreover, in vitro disintegration test could not support any pre- and post-approval manufacturing process or site changes. Hence, an in vitro dissolution test was recommended for the 2.5 mg ibandronate oral tablet as follow:

Apparatus	USP Type 2 (paddle)
In vitro release medium	water
Volume of release medium	500 mL
Medium temperature	37 ± 0.5°C
Stirring speed	50 rpm
Sampling Time	15 minutes
Specifications	Q = 80% at 15 minutes

The sponsor used this in vitro dissolution test to substantiate the manufacturing site change from Mannheim to Basel (see the previous question).

4.5 Bioanalytical

1 Are the bioanalytical methods properly validated?

The sponsor developed a _____ method to measure ibandronate concentration, and _____ method each for measurement of tamoxifen, melphalan, and prednisolone. Validation for the assays below was acceptable.

Analysis of plasma and serum samples spiked to a concentration of 10 ng/mL yielded values of 11.29 ± 0.44 ng/mL and 10.66 ± 0.75 ng/mL, respectively, indicating that the method worked equally well in both matrices.

2 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

7 page(s) of
revised draft labeling
has been redacted
from this portion of
the review.

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

S.W. Johnny Lau
4/9/03 04:15:00 PM
BIOPHARMACEUTICS

Hae-Young Ahn
4/10/03 09:01:52 AM
BIOPHARMACEUTICS

IR ltr out
12/13/02

12/13/02

Memo to file

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

NDA:	21-455
Compound:	2.5 mg ibandronate sodium oral tablet
Sponsor:	Hoffmann-La Roche Inc.
Reviewer:	S.W. Johnny Lau, R.Ph., Ph.D.

The following request has been sent to the sponsor via a letter.

NDA 21-455 (2.5 mg ibandronate sodium film-coated tablet)

The sponsor should:

- develop an in vitro dissolution method and generate dissolution profiles for the 2.5 mg ibandronate sodium film-coated tablet with 3 different dissolution media range from pH 1 to pH 6.8. The test tablets should come from 3 different batches (2 batches for the pivotal clinical study and 1 batch for the to-be-marketed formulation) with 12 units per batch.
- provide individual in vitro dissolution results from the method as raw data plus descriptive statistics and plots
- include the in vitro dissolution method and acceptance criteria as part of the drug product's release and stability specifications

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

S.W. Johnny Lau
12/3/02 02:56:42 PM
BIOPHARMACEUTICS

Xiao-xiong Wei
12/3/02 04:11:39 PM
BIOPHARMACEUTICS