CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-858

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA	21-858
Submission Dates	December 6, 2004 (original); April 6, 2005 (N-000-SU); April 13, 2005 (N-000-BM), April 26, 2005 (N-000-BZ); September 2, 2005 (N-000-BB); September 7, 2005 (N-000-BB)
Brand Name	BONIVA™
Generic Name	Ibandronate sodium
Reviewer	S.W. Johnny Lau
Team Leader	Hae-Young Ahn
OCP Division	CP2
ORM Division	Metabolic and Endocrine Products
Sponsor	Hoffmann-La Roche Inc.
Relevant IND	46,266
Submission Type: Code	Original: S
Formulation: Strength(s)	Intravenous injection: 3 mg ([redacted] ibandronate
Indication	To treat postmenopausal osteoporosis in women

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1 Executive Summary

The sponsor submitted NDA 21-858 to seek approval for the intravenous (IV) 3 mg ibandronate injection administered over 15 – 30 seconds once every 3 months regimen to treat postmenopausal osteoporosis (PMO) in women. The sponsor has 2 approved oral ibandronate regimens (NDA 21455: 2.5 mg once daily on May 16, 2003 and NDA 21-455/S-001: 150 mg once monthly on March 24, 2005) that have the same proposed indication. Ibandronate is a nitrogen containing bisphosphonate that inhibits osteoclast activity and reduces bone resorption as well as turnover.

The sponsor conducted a pivotal clinical efficacy and safety study (BM16550) comparing lumbar spine bone mineral density (BMD) changes after a year's treatment with IV 2 mg ibandronate injection once every 2 months and IV 3 mg ibandronate injection once every 3 months to that with once daily oral dose of 2.5 mg ibandronate (see Dr. Theresa Kehoe's medical review). The sponsor submitted no new clinical pharmacology and biopharmaceutics (CPB) information but referred the ibandronate CPB

information to previous submissions. The sponsor conducted 2 QTc substudies from clinical studies (BM16550 and JM16651). The sponsor also conducted population pharmacokinetic/pharmacodynamic (PK/PD) analyses for a bone biomarker.

1.1 Recommendations

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 2 (OCP/CP2) reviewed NDA 21-858's clinical pharmacology information and finds it acceptable, if the sponsor agrees to the clinical pharmacology labeling comments on pages 8 - 13 of this review.

1.2 Phase IV Commitments

None.

1.3 Summary of Important Clinical Pharmacology Findings

PK

The PK is dose-proportional between 2 and 6 mg single IV ibandronate doses.

PD

The % change in lumbar spine BMD is IV ibandronate's primary efficacy measurement. The 2 IV ibandronate dosing regimens (2 mg/2 months and 3 mg/3 months) did not show inferior % change in lumbar spine BMD from baseline at Month 12 to that of the approved oral 2.5 mg daily regimen. Serum calcium and creatinine are IV ibandronate's primary safety measurements. The medical officer has concerns about Study BM16550's lack of serum calcium data and timing for the serum creatinine data to assess IV ibandronate's safety. Hence, the optimal IV ibandronate dose is hard to assess.

The sponsor's PK/PD model describes IV ibandronate PK and urinary excretion of C-telopeptide of the α chain of type I collagen, CTX (a bone resorption marker for efficacy), and applied it to characterize different ibandronate dosing regimens. This is the most comprehensively retrospectively validated model as compare to other bisphosphonate PK/PD model. However, this model awaits prospective validation and improvement of treatment regimens based on this model remains speculative.

QT Prolongation

Substudies BM16550 and JM16651 did not show apparent effect of IV ibandronate on QT prolongation for the 2 mg and 3 mg doses. However, the results should be cautiously interpreted since the substudies did not have positive control and the baseline ECGs were at least 4 months from active treatment's ECGs.

S.W. Johnny Lau, R.Ph., Ph.D.
OCP/CP2

FT signed by Hae-Young Ahn, Ph.D., Team Leader 12/ /05

An Optional Inter-Division Clinical Pharmacology Briefing for NDA 21-858 was conducted on December 12, 2005; participants included T. Kehoe, E. Chikhale, H. Malinowski, S. Huang, D. McNerney, H. Ahn, J. Vaidyanathan, and J. Lau.

2 Question-Based Review

2.1 General Attributes

2.1.1 What is the formulation of the to-be-marketed 3 mg [redacted] ibandronate IV injection?

The to-be-marketed product is a pre-filled syringe of [redacted] 3 mg/3 mL strength (Table 1 below).

Components/Composition	[redacted]		3 mg/3 mL strength	
	Nominal [redacted]	[redacted]	Nominal (mg/3 mL)	[redacted]
Ibandronate sodium[1]				
Sodium chloride, USP				
Glacial acetic acid, USP				
Sodium acetate, USP				
Water for injection, USP				
Total weight				
Total volume				

[1]Ibandronate monosodium monohydrate
[2]Equivalent to [redacted] 3.0 mg of the free acid, respectively
[3]The syringe contains a [redacted] to compensate for the non-injectable amount in the syringe and/or needle.

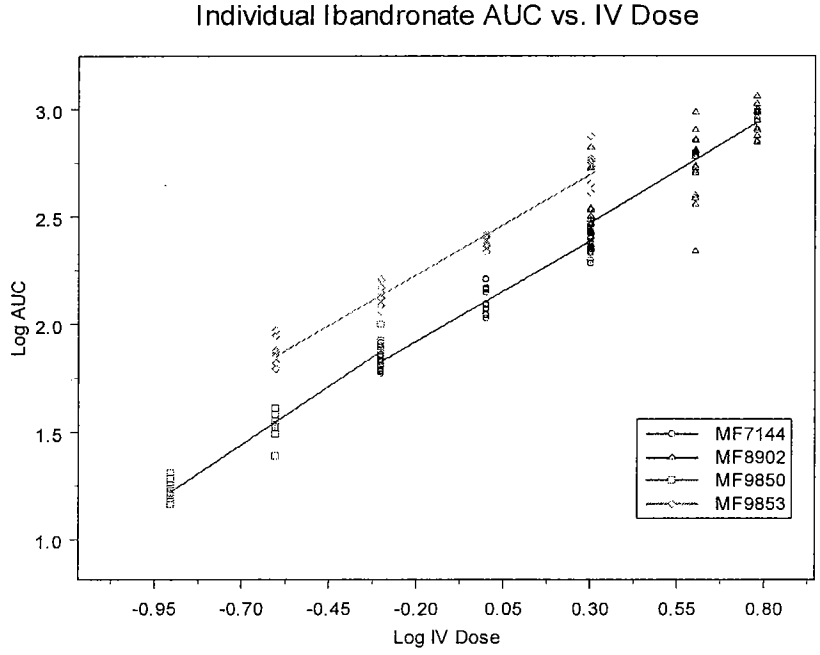
2.2 General Clinical Pharmacology

Ibandronate's clinical pharmacology information is available in the following articles:

- Barrett et al. Ibandronate: a clinical pharmacological and pharmacokinetic update. *J Clin Pharmacol* **44**:951-65 (2004)
- Ravn et al. Association between pharmacokinetics of oral ibandronate and clinical response in bone mass and bone turnover in women with postmenopausal osteoporosis. *Bone* **30**:320-4 (2002)
- Dooley and Balfour. Ibandronate. *Drugs* **57**:101-10 (1999)

2.2.1 Is IV ibandronate PK dose-proportional?

Yes, between IV 2 to 6 mg and close to dose-proportional between IV 0.5 and 2 mg ibandronate (Figure 1 below).



4 referenced IV studies with different ibandronate dose ranges are as follows (Table 2):

Study	Dose (mg)	Injection Duration	Slope (95% CI) of Log Cmax vs Log Dose	Slope (95% CI) of Log AUC_{inf} vs Log Dose	Subject Type
MF8902	2, 4, 6	2 hr	0.919 (0.777 – 1.061)	0.975 (0.813 – 1.137)	Healthy PM women
MF9853	0.25, 0.5, 1, 2	30 sec	0.867 (0.794 – 0.941)	0.936 (0.878 – 0.994)	Japanese osteopenic PM women
MF7144	0.5, 1, 2	30 sec	0.830 (0.651 – 1.009)	0.931 (0.870 – 0.993)	Healthy men
MF9850	0.125, 0.25, 0.5	30 sec	Not reported	1.086 (0.986 – 1.19)	Japanese healthy men

The power model assesses dose-proportionality as C_{max} or $AUC_{inf} = \alpha \bullet [Dose]^{\beta}$ (α depends on the subject and error; β is the dose-proportionality factor). After transformation, log C_{max} or log AUC_{inf} = log α + β•log IV Dose and $\beta = 1$ when dose-proportional (Gough et al. *DIJ* **29**:1039 (1995)).

> 2 mg: Per Study MF8902 (in healthy PM women), the slope, β, and its (95% CI) for log C_{max} vs. log IV Dose plot and log AUC_{inf} vs. log IV Dose plot are 0.919 (0.777 – 1.061) and 0.975 (0.813 – 1.137), respectively. The β values are close to 1 and their 95% CIs include 1. Hence, ibandronate PK is dose-proportional between 2 and 6 mg IV doses.

< 2 mg: Per Study MF9853 (in osteopenic PM women), the slope, β, and its (95% CI) for log C_{max} vs. log IV Dose plot and log AUC_{inf} vs. log IV Dose plot are 0.867 (0.794 – 0.941) and 0.936 (0.878 – 0.994), respectively. The β values are close to 1 but their 95% CIs do not include 1. Although the β values are close to 1 and the 95CIs include 1 for log C_{max} vs. log IV Dose plot (Study MF7144) and log AUC_{inf} vs. log IV Dose plot (Study MF9850), these analyses resulted from healthy young men. Per Cremers et al. Pharmacokinetics/pharmacodynamics of bisphosphonates use for optimisation of intermittent therapy for osteoporosis. *Clin Pharmacokinet* **44**:551-70 (2005), priority should be given to studies in osteoporotic patients when reviewing bisphosphonates' clinical PK. This is due to the bone architecture and turnover differences between osteoporotic patients and healthy volunteers. Hence, ibandronate PK is **close to** dose-proportional between 0.5 and 2 mg IV doses in osteopenic PM women. This conclusion is different from the sponsor's labeling claim of PK dose-proportionality between 0.5 and 6 mg IV doses. The sponsor also used Studies MF9852 and MF7159 to establish PK dose-proportionality. However, these 2 studies only have 1 IV dose group (0.5 mg).

2.2.2 Does chronic IV dosing cause ibandronate to accumulate?

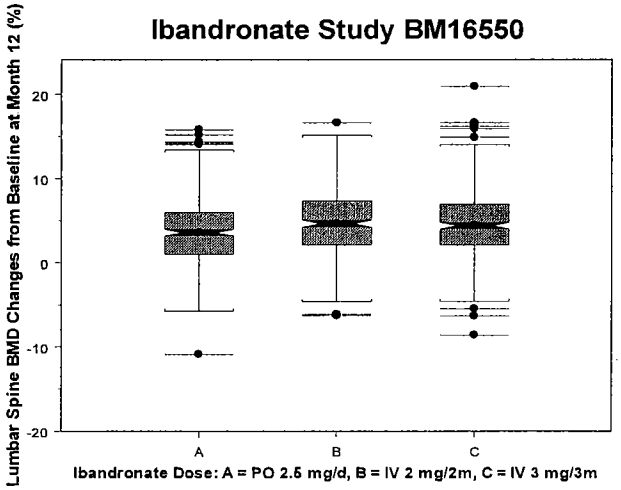
Blood or serum ibandronate concentrations should not accumulate upon IV administration with the 2 mg/2 months or 3 mg/3 months dosing regimen. Per Study MF8902, the terminal elimination half-life based on serum ibandronate concentrations ranges from 4.57 to 15.28 hours with a median of 9.53 hours for the 2 mg dose and ranges from 4.96 to 25.49 hours with a median of 13.73 hours for the 4 mg dose. The sponsor did not study the IV 3 mg ibandronate dose's PK but obtained agreement with the Division of Metabolic and Endocrine Products during the pre-NDA meeting to extrapolate IV 3 mg ibandronate's extent of exposure (AUC_{inf}) values from that of IV 2 mg's.

2.2.3 How were the IV 2 mg ibandronate/2 months and 3 mg ibandronate/3 months doses determined for Study BM16550?

The sponsor hypothesized that Study MF4380's failed ibandronate anti-fracture efficacy was due to suboptimal dosing (IV 0.5 mg/3 months and IV 1 mg/3 months dose groups). Study MF4470 explored the effect of IV 2 mg ibandronate/3 months on lumbar spine BMD. Study MF4470's BMD improvement matched the BMD improvement associated with anti-fracture efficacy in Study MF4411, which is the pivotal clinical study that supported the oral 2.5 mg ibandronate daily regimen's approval.

Although Study MF4470's IV 2 mg/3 months dose appeared to result in higher BMD gain than that for Study MF4380's IV 1 mg/3 months dose, concern arises that bone resorption may not remain adequately suppressed during the latter part of the 3-month dosing interval following the 2 mg dose. Hence, the sponsor increased the dose to IV 3 mg/3 months. Another strategy was to reduce the dosing interval from 3 months to 2 months (IV 2 mg/2 months).

2.2.4 What is the exposure-response relationship for IV ibandronate to treat PMO in women?
The pivotal study's primary efficacy measurement is % change of lumbar spine BMD from baseline at Month 12. Per Ms. Cynthia Liu's statistical review, the 2 IV dosing regimens (2 mg/2 months and 3 mg/3 months) did not show inferior % change of lumbar spine BMD from baseline at Month 12 than that of oral 2.5 mg daily regimen (Figure 2 below).



The sponsor also developed a PK-PD model to characterize IV ibandronate PK and urinary excretion of CTX upon different IV dosing regimens (Pillai et al. A semimechanistic and mechanistic population PK-PD model for biomarker response to ibandronate, a new bisphosphonate for the treatment of osteoporosis. *Br J Clin Pharmacol* **58**:618-31 (2004)). This model is further simplified to the kinetic (K)-PD model, in which the PK were "abstracted" and the effect of ibandronate on bone resorption was modeled via an indirect response model with only the measured PD data. The reduction in the synthesis rate (kS) of uCTX/Cr after ibandronate administration is modeled via a sigmoid E_{max} model. The simpler K-PD model provides a description of the uCTx/Cr time course that was virtually indistinguishable from that of the full PK-PD model with the advantage of faster computer run-times.

This K-PD model is validated with other clinical ibandronate studies. This is the most comprehensively retrospectively validated model as compare to other bisphosphonate PK/PD model. However, Pillai's model awaits prospective validation and improvement of treatment regimens based on this model remains speculative (Cremers et al. *Clin Pharmacokinet* **44**:551 (2005)).

Besides Pillai's 2004 article, Cremers at al. A pharmacokinetic and pharmacodynamic model for intravenous bisphosphonate (pamidronate) in osteoporosis. *Eur J Clin Pharmacol* **57**:883-90 (2002) is the only published detailed bisphosphonate PK/PD model. However, Cremers' model remains to be validated both computationally and clinically in prospective studies.

2.2.5 What is the exposure-safety information for IV ibandronate to treat PMO in women?
The medical officer has the following ibandronate renal safety concerns (see Dr. Kehoe's review), especially on the proposed IV bolus injection rate of 15 to 30 seconds:

- Animal studies with IV ibandronate clearly show renal toxicity is proportional to the dose and rate of administration.
- While there is no clear evidence that IV ibandronate in the doses and administration regimen studied adversely effects renal function in the population of PM women included in the pivotal noninferiority study, it is concerning that no subjects in the daily oral group, 4 subjects in the 2mg iv q2month group and 2 in the 3mg iv q3month group with baseline creatinine less than 1.4mg/dL did have elevations in creatinine of more than 0.5mg/dL. In addition, the shift tables for creatinine clearance showed a slightly higher percentage of subjects with mild renal impairment that received the 3mg dose shifted into moderate renal impairment (13% vs. 11% for the other 2 groups). There were an insufficient number of subjects with baseline creatinine values of greater than 1.4mg/dL to adequately assess the impact of ibandronate in this potentially higher - risk population - many of whom will be found in the target population for ibandronate .
- In the PMO population, there are no trials comparing the effects of IV bolus drug administration and IV infusion drug administration for the proposed doses.
- Table 3 below indicates that mean ibandronate C_{max} (exposure measure) may be about 10 fold higher upon 30-second IV bolus injection than the mean ibandronate C_{max} upon monthly oral administration. Even with a 2-hour IV infusion, mean ibandronate C_{max} may be 3 fold higher than the mean ibandronate C_{max} upon monthly oral administration.

Relative ibandronate exposure information (Table 3):

Status	approved	approved	proposed
Dose	2.5 mg	150 mg	3 mg
Administration Route	oral	oral	intravenous
Dosing Frequency	daily	monthly	every 3 months
Injection Rate	-	-	15 – 30 seconds
			30-second injection
*Mean (SD) C_{max} (ng/mL)	0.79 (0.41), Study MF7159, HPMW	57.3 (39.87), Study SB743830/002, HPMW	582 (108) OPMW, Study MF9853 378 (272) YHM, Study MF7141
			2-hour infusion
§Mean (SD) C_{max} (ng/mL)	-	-	133 (43), HPMW Study MF8902

*extrapolated mean ibandronate C_{max}s for Studies MF9853 and MF7141 assuming dose proportional PK; §intrapolated mean ibandronate C_{max} for Study MF8902 assuming dose proportional PK; HPMW = healthy postmenopausal women; OPMW = osteopenic postmenopausal women; YHM = young healthy men

Hence, the knowledge of renal toxicity with IV bisphosphonate administration and the benefit of longer infusion times for preserving renal function, coupled with lack of adequate data comparing different rates of ibandronate IV administration in the PM population, and the lack of data in PM women at greater risk of renal toxicity (i.e. baseline creatinine > 1.4mg/dL) suggest that an infusion time of at least 15 minutes, such as that used for zoledronic acid, would ensure greater safety than IV bolus administration.

Per IV ibandronate's renal toxicity potential and for its future risk management (should it be approved), the sponsor should monitor the renal function in a subset of PMO women receiving the regimen of IV 3 mg ibandronate over 15 – 30 seconds every 3 months .

2.2.6 What would be the recommended optimal IV ibandronate dosing regimen (3 mg/3 months vs. 2 mg/2 months) to treat PMO in women?

The annualized dose for both 2 mg ibandronate/2 months and 3 mg ibandronate/3 months is 12 mg ibandronate. Per Study BM16550, IV doses of 2 mg ibandronate/2 months and 3 mg ibandronate/3 months all increase lumbar spine BMD from baseline at Month 12 to the same extent as that for oral doses of 2.5 mg ibandronate daily. The medical officer has concerns about Study BM16550's lack of serum calcium data and timing for the serum creatinine data to assess IV ibandronate's safety. Hence, the optimal IV ibandronate dose is hard to assess per the risk-benefit ratio.

2.2.7 How does the sponsor address ibandronate's QT prolongation potential?

At 30 μM (about 19 times the extrapolated C_{max} from IV 3 mg human dose administered for 30 seconds per Study MF9853), ibandronate did not block the hERG K^+ channel. Dog repeat dose studies did not show ibandronate associated ECG changes. The sponsor did not conduct any ibandronate thorough QT/QTc study but conducted 2 ECG substudies from Studies BM16550 and JM16651. The sponsor did not collect any blood samples for PK analysis in these 2 QT substudies.

Study BM16550 has 4 treatment groups as follows:

A = IV 2 mg ibandronate/2 months and oral placebo daily
B = oral 2.5 mg ibandronate daily and IV placebo/2 months
C = IV 3 mg ibandronate/3 months and oral placebo daily
D = oral 2.5 mg ibandronate daily and IV placebo/3 months

The sponsor only collected treatments C (150 patients) and D (75 patients)'s ECGs for the substudy. Two baseline ECGs were obtained at Visit 1 (-60 and -30 min), patients received an IV or oral ibandronate dose, and 2 ECGs were obtained after that dose (5 min and 2 hr). Six months later at Visit 3, patients repeated the same procedure. The sponsor did not use Visit 1's -60 min ECGs. ECG changes (Visit 1's 5 min and 2 hr ECGs and Visit 3's -60 min, -30 min, 5 min, and 2 hr ECGs) from baseline were subtracted from Visit 1's -30 min ECGs.

The sponsor claims that no difference for the ECG data (heart rate, PR, QRS, QT, QTcB (Bazett's correction), and QTcF (Fridericia's correction)) exists between the ibandronate oral and IV regimens or between the 1st dose and the 6-month ibandronate dose. The sponsor also claims that they did not observe marked morphological ECG changes. However, Substudy BM16550's results should be cautiously interpreted since:

- This substudy does not have positive control to ascertain this study's sensitivity.
- This substudy does not have a placebo-placebo group's ECGs.
- Visit 1's -30 min ECGs are 6 months from Visit 3's ECGs and the baseline may have changed.
- This substudy did not average Visit 1's -60 and -30 min ECGs as the baseline to minimize variability.

Substudy JM16651's 4 treatment groups (number of ECG-measured Japanese PMO women) follows:

A = Placebo (24)
B = IV 0.5 mg ibandronate/month (23)
C = IV 1 mg ibandronate/month (26)
D = IV 2 mg ibandronate/2 months (24)

Two baseline ECGs were obtained at Visit 1 (-60 and -30 min), patients received an IV or placebo ibandronate dose, and 2 ECGs were obtained after that dose (5 min and 2 hr). Four months later at Visit 4, patients repeated the same procedure.

The sponsor did not use Visit 1's -60 min ECGs. ECG changes (Visit 1's 5 min and 2 hr ECGs and Visit 3's -60 min, -30 min, 5 min, and 2 hr ECGs) from baseline were subtracted from Visit 1's -30 min ECGs.

The sponsor claimed that the QT, QTcB, and QTcF intervals in the active treatment groups (0.5 mg, 1 mg, and 2 mg/month) at each point did not show much difference from those in the placebo group. However, Substudy JM16651's results should be cautiously interpreted since:

- This substudy does not have positive control to ascertain this study's sensitivity.
- Visit 1's -30 min ECGs are 4 months from Visit 3's ECGs and the baseline may have changed.
- This substudy did not average Visit 1's -60 and -30 min ECGs as the baseline to minimize variability.

In general, the bisphosphonate pharmacological class does not show QT prolongation. To date, 3 published human bisphosphonate-related QT prolongation cases exist and these 3 cases associate with hypocalcemia (Patel et al. Zoledronic acid-induced severe hypocalcemia in a prostate cancer patient with extensive osteoblastic bone metastases. *Tenn Med* **98**:83-5,89 (2005); Mishra et al. Prolonged, symptomatic hypocalcemia with pamidronate administration and subclinical hypoparathyroidism. *Endocrine* **14**:159-64 (2001); Varma et al. Electrocardiographic Q-Tc prolongation associated with infusion of intravenous pamidronate disodium. *Postgrad Med J* **69**:497-500 (1993)). Zoledronic acid and pamidronate were administered IV. Hence, the likelihood for IV ibandronate to cause QT prolongation may be secondary to ibandronate's hypocalcemic effect rather than its intrinsic effect to cause QT prolongation (also see Dr. Theresa Kehoe's medical review for IV ibandronate induced hypocalcemia).

2.3 General Biopharmaceutics

2.3.1 Does difference exist between the to-be-marketed injection formulation and the pivotal clinical study formulation?

No. The clinically-tested IV formulations and the to-be-marketed IV formulations are identical. Moreover, the clinically-tested 2.5 mg ibandronate oral tablet has the same formulation as the approved 2.5 mg ibandronate tablet; the clinically-tested pilot batch size is [redacted] tablets and the commercial batch size is [redacted] tablets.

2.4 Analytical

2.4.1 Are the ibandronate bioanalytical methods properly validated?

Not applicable since the sponsor did not conduct new clinical pharmacology study.

3 Detailed Labeling Recommendations

The following is clinical pharmacology comments to the proposed labeling dated April 6, 2005. The strikethrough text means deletion. The underlined text means addition. *The italic text means internal notes and not to be communicated with the sponsor.*

CLINICAL PHARMACOLOGY

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5 Page(s) Withheld

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/s/

Hae-Young Ahn
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Filing Memo

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

NDA:	**21-858**
Compound:	Ibandronate sodium (BONIVA™; 3mg/3 mL intravenous injection)
Sponsor:	Hoffmann-La Roche Inc.
Submission Date:	December 6, 2004
From:	S.W. Johnny Lau, R.Ph., Ph.D.

Background

The sponsor submitted NDA 21-858 to seek approval for the 3 mg ibandronate once every 3 months intravenous administration to treat postmenopausal osteoporosis (PMO) on December 6, 2004. Oral daily 2.5 mg ibandronate tablet was approved to treat and prevent PMO on May 16, 2003. The sponsor also has a submission being reviewed (NDA 21-455/S-001) for the oral administration of 100 or 150 mg ibandronate tablet once monthly to prevent and treat PMO.

Findings

The sponsor submitted the following to support NDA 21-858:

- a pivotal clinical efficacy and safety study (BM16550) comparing lumbar spine bone mineral density changes after 1 year's treatment with intravenous ibandronate administered 3 mg/3 months and 2 mg /2 months to the approved once daily oral dose of 2.5 mg ibandronate (non-inferiority study)
- The sponsor did not conduct new clinical pharmacology and biopharmaceutics studies for NDA 21-858. However, they referenced the clinical pharmacology and biopharmaceutics information from previous submissions for the oral ibandronate tablets (NDA 21-455).
- The formulation tested in Study BM16550 and the to-be-marketed formulation is the same except that the to-be-marketed formulation is packaged in individual pre-filled syringes.
- The sponsor developed a pharmacokinetic/pharmacodynamic model (via previously submitted studies) to predict the time course of urinary CTX excretion following oral and IV ibandronate administration.
- The sponsor did not conduct a single thorough QTc study for ibandronate but evaluated the effect of IV 3 mg ibandronate/3 months and oral placebo daily on QTc compared with baseline in Study BM16550. ECG recordings were made at baseline and 6 months. To maintain blinding, patients received IV placebo/3 months and oral 2.5 mg ibandronate daily served as the control in this ECG substudy.
- The sponsor substudied Study JM16651 to evaluate the effect of 0.5, 1, and 2 mg ibandronate IV and placebo on QTc when compared to baseline values.
- reports of ECG substudy for Studies BM16550 and JM16651
- annotated labeling (in the "Summary" folder of electronic submission) as separate labeling from the oral tablet labeling for review

Comments to the Sponsor

- provide all raw individual data for ECG measurements in SAS transport files for the ECG substudy of Study BM16550 and ECG substudy of Study JM16651
- provide the data that were used to develop and validate the mathematical pharmacokinetic-pharmacodynamic model to predict the time course on urinary CTX excretion in SAS transport files

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/s/

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