CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-858

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

NDA NUMBER
21-455

NAME OF APPLICANT / NDA HOLDER
Hoffmann-La Roche Inc

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
BONIVA

ACTIVE INGREDIENT(S)	STRENGTH(S)
Ibandronate	2 mg and 3 mg

DOSAGE FORM
Solution for intravenous administration

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
4,927,814	5/22/1990	7/9/2007

d. Name of Patent Owner	Address *(of Patent Owner)*	
Boehringer Mannheim GmbH now, Roche Diagnostics GmbH	Sandhoferstrasse 116	
	City/State: Mannheim, Germany	
	ZIP Code: D-68305	FAX Number *(if available)*: +49 621 7596611
	Telephone Number: +49 621-7590	E-Mail Address *(if available)*:

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☒ Yes ☐ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☒ No

PSC Media Arts (301) 443-1090 EF

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1	Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
2.2	Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3	If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4	Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3**.		
2.5	Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6	Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7	If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1	Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
3.2	Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3	If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for* each *patent claim claiming a method of using the pending drug product for which approval is being sought. For* each *method of use claim referenced, provide the following information:

4.1	Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2	Patent Claim Number *(as listed in the patent)* 6	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No	
4.2a	If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* Treatment of osteoporosis in postmenopausal women.	

5. No Relevant Patents

	For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☐ Yes

4. Method of Use

Sponsors must submit the information in section 4 separately for* each *patent claim claiming a method of using the pending drug product for which approval is being sought. For* each *method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No

.2 Patent Claim Number *(as listed in the patent)*

8

Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No

4.2a If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.

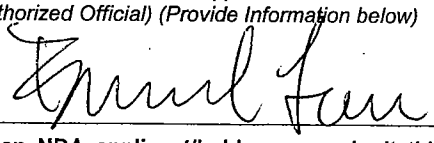
Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)*

Treatment of osteoporosis in postmenopausal women.

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
	October 29, 2004

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☒ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Bernard Lau	
Address Hoffmann-La Roche Inc. 340 Kingsland Street	City/State Nutley, New Jersey
ZIP Code 07110	Telephone Number (973) 235-4387
FAX Number *(if available)* (973) 235-2363	E-Mail Address *(if available)* Bernard.lau@roche.com

PSC Media Arts (301) 443-1090 EF

DEBARMENT CERTIFICATION

Hoffmann-La Roche Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

Dr. Judith L. Siegel
Vice President of Pharmaceutical Development Operations

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: February 28, 2006.

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

☑ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		

☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Cynthia Dinella, PharmD	Vice President, Drug Regulatory Affairs
FIRM/ORGANIZATION	
Hoffmann-La Roche Inc., 340 Kingsland Street, Nutley, New Jersey, 07110	
SIGNATURE	DATE
	11/18/2004

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

Created by: PSC Media Arts (301) 443-1090 EF

MEMORANDUM **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: January 3, 2006

FROM: Rita Ouellet-Hellstrom, Ph.D., M.P.H.
Epidemiologist
Division of Drug Risk Evaluation, HFD-430

THROUGH: Mark Avigan, M.D., C.M., Director
Division of Drug Risk Evaluation, HFD-430

TO: David Orloff, M.D., Director
Division of Metabolic and Endocrine Products, HFD-510

SUBJECT: *Renal Safety of Boniva Injection Compared to Oral Bisphosphonates*, preliminary evaluation of proposed postmarketing study

DRUGS: Boniva (ibandronate sodium) injection

NDAs: 021-858

REACTIONS: Renal toxicity

PID#: D050733

On December 21, 2005 the Division of Metabolic and Endocrine Products (DMEP) requested assistance from the Division of Drug Risk Evaluation (DDRE) to review the preliminary proposal of a possible postmarketing study[1] to monitor renal toxicity among postmenopausal osteoarthritic users of Boniva injection (IV) should approval be granted by the January 7, 2006 PADUFA due date.

I. POSTMARKETING SURVEILLANCE STUDY

Indication

Post-menopausal osteoporosis (PMO)

Safety Concern

- Animal studies suggest renal toxicity with intravenous (IV) bisphosphonate use is proportional to dose and rate of administration.
- Evidence from the zoledronate trials shows that the rate of renal toxicity is inversely proportional to the rate of IV administration.
- Over the two-year period of the single ibandronate IV clinical trial, mean creatinine levels increased minimally in all treatment groups and three subjects receiving intravenous ibandronate were reported to have either renal insufficiency or renal impairment.

[redacted] In the ibandronate IV clinical development program, however, IV bolus administration was used almost exclusively in the postmenopausal population and the sponsor is pursuing approval of the 15 – 30 second bolus administration. As a compromise, in addition to ongoing studies, the sponsor is proposing a postmarketing retrospective cohort study using medical and pharmaceutical claims data to monitor renal toxicity in the indicated population.

Proposed Postmarketing Study Surveillance Study

The sponsor proposes to monitor, establish, and compare rates of renal safety issues of ibandronate IV use compared to rate in oral ibandronate and to rates in other biphosphonates using data from claims databases including Medicaid and Medicare. Renal safety issues to be monitored include renal failure, renal insufficiency, proteinurea, abnormal renal function, adverse effect of drug, and rise (twice baseline) of blood urea nitrogen (BUN) or creatinine.

Study Design: Retrospective cohort study using medical and pharmaceutical claims databases.

Exposure: Drug therapy with IV ibandronate, oral ibandronate, and other bisphosphonates identified by NDC and HCPCS C-codes and J-codes.

[1] *Renal Safety of Boniva Injection Compared to Oral Bisphosphonates*

Endpoints: ICD-9 codes available in insurance claims:

Outcome	ICD-9 CM
Acute renal failure	584.xx
Chronic renal failure	585.xx
Renal failure associated w/ hypertension	403-404
Acute glomerulonephritis	580.xx
Nephritis and nephropathy	583.xx
Proteinurea	791.0
Abnormal renal function	794.4
Adverse effect of drug	995.2
Rise in BUN or creatinine	≥ twice baseline

Covariates: baseline age, sex, prior medical history or comorbidities that could affect renal functions and/or risk of renal complications (e.g. diabetes, ischemic heart disease, congestive heart failure, hypertension), and concomitant or prior therapy that could affect renal function (non-steroidal anti-inflammatory agents, antibiotics, anti-hypertensive agents, immunosuppressive or chemotherapeutic agents).

Objectives:

- Monitor medical and pharmaceutical claims databases for emerging renal safety issues or complications in patients receiving IV ibandronate for postmenopausal osteoarthritis (PMO).
- Establish rates of renal safety issues or complications in comparator groups.

Data Sources:

- [redacted]

Laboratory Data Availability:

Laboratory data are available for some but not all of the claims databases

- [redacted]

[2] www.ingenix.com/esg/products.php?cat2&pid=7
[3] www.ihcis.com/information_services/databases/
[4] www.medstat.com/1products/marketscan.asp
[5] www.pharmetrics.com
[6] www.surveillancedata.com/index.php?page_id=sur
[7] www.healthcore.com/index.php?id=8

3 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Administrative- 1

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

/s/

Rita Ouellet-Hellstrom
1/3/2006 03:37:17 PM
DRUG SAFETY OFFICE REVIEWER

Rosemary Johann-Liang
1/3/2006 03:44:08 PM
MEDICAL OFFICER

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA 21-858	Efficacy Supplement Type N/A	Supplement Number	
Drug: Boniva (ibandronate sodium) Injection		Applicant: Hoffman-La Roche	
RPM: Randy Hedin		HFD- 510	Phone # 301-796-1224

Application Type: (X) 505(b)(1) ( ) 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.) **If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.** ( ) Confirmed and/or corrected	Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):

❖ Application Classifications:	
• Review priority	(X) Standard ( ) Priority
• Chem class (NDAs only)	3
• Other (e.g., orphan, OTC)	N/A
❖ User Fee Goal Dates	January 7, 2006
❖ Special programs (indicate all that apply)	(X) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review ( ) CMA Pilot 1 ( ) CMA Pilot 2
❖ User Fee Information	
• User Fee	(X) Paid UF ID number 4858
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other (specify)
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) ( ) Other (specify)
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (X) No

• This application is on the AIP	( ) Yes (X) No
• Exception for review (Center Director's memo)	
• OC clearance for approval	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	(X) Verified
❖ Patent	
• Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	(X) Verified
• Patent certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ( ) Verified 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	
• [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next box below (Exclusivity)).*	(X) N/A (no paragraph IV certification) ( ) Verified
• [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. Answer the following questions for each paragraph IV certification: (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))). *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).* (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**No**," continue with question (3).* (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?	( ) Yes ( ) No ( ) Yes ( ) No ( ) Yes ( ) No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))). *If "**No,**" the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*	
(4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**No,**" continue with question (5).*	( ) Yes ( ) No
(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**Yes,**" a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.*	( ) Yes ( ) No

❖ Exclusivity (approvals only)	
• Exclusivity summary • Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)	January 6, 2006
• Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	( ) Yes, Application #_____ (**X**) No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	PM: February 4, 2003

General Information	
❖ Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	None
• Status of advertising (approvals only)	(X) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	( ) Yes (X) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(X) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling	January 5, 2006
• Original applicant-proposed labeling	December 6, 2004
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	PM January 6, 2006
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	PPI December 6, 2004
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	None
• Applicant proposed	December 6, 2004 January 5, 2006
• Reviews	December 16, 2005
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	
• Documentation of discussions and/or agreements relating to post-marketing commitments	January 5, 2006 Amendment
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	X
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	None
• Pre-NDA meeting (indicate date)	None
• Pre-Approval Safety Conference (indicate date; approvals only)	None
• Other	None
❖ Advisory Committee Meeting	
• Date of Meeting	None
• 48-hour alert	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	None

Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	Team Leader: January 5, 2006 Director: Concur, January 5, 2006
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	January 4, 2006
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	None
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	January 4, 2006
❖ Risk Management Plan review(s) *(indicate date/location if incorporated in another rev)*	None
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	Waiver
❖ Demographic Worksheet *(NME approvals only)*	None
❖ Statistical review(s) *(indicate date for each review)*	December 14, 2005
❖ Biopharmaceutical review(s) *(indicate date for each review)*	January 6, 2006
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	None
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	None Requested
• Bioequivalence studies	None Requested
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	December 16, 2005
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	December 16, 2005
• Review & FONSI *(indicate date of review)*	None
• Review & Environmental Impact Statement *(indicate date of each review)*	None
❖ Microbiology (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	September 8, 2005
❖ Facilities inspection (provide EER report)	Date completed: December 14, 2005 **(X)** Acceptable **( )** Withhold recommendation
❖ Methods validation	**(X)** Completed **( )** Requested **( )** Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	August 16, 2005
❖ Nonclinical inspection review summary	None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	None
❖ CAC/ECAC report	None

Appendix A to NDA/Efficacy Supplement Action Package Checklist

An application is likely to be a 505(b)(2) application if:

(1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
(2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
(4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

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/s/

Randy Hedin
1/6/2006 01:23:39 PM

Division of Metabolic and Endocrine Drug Products

PROJECT MANAGER LABELING REVIEW

Application Number: NDA 21-858

Name of Drug: Boniva (ibandronate sodium) Injection

Sponsor: Hoffmann-LaRoche Inc.

Material Reviewed

Submission Dates:

- December 6, 2004, submission containing draft labeling for the patient package insert (PPI)..

Background and Summary Description:

This new drug application (NDA) was submitted on December 6, 2004 and provides for an injection of ibandronate sodium every three months for the treatment of postmenopausal osteoporosis.

Review

Patient Package Insert

The draft PPI labeling submitted on December 6, 2004 was compared to the final printed labeling (FPL) text for the PPI (Identifier Number 27898799, Issued Date March 2005), submitted April 8, 2005. The following shows all the changes:

6 Page(s) Withheld

_____ Trade Secret / Confidential

✓ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Administrative- 2

The changes update the once- monthly tablet formulation to the every three month injection formulation and are acceptable.

Conclusions

An approval letter should be issued.

Reviewed by: Randy Hedin, R.Ph., Senior Regulatory Management Officer

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/s/

Randy Hedin
1/6/2006 10:20:50 AM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-858

Hoffmann-LaRoche
Attention: Margaret J. Jack
Director of Regulatory Affairs
340 Kingsland Street
Nutley, NJ 07110

Dear Ms. Jack:

Please refer to your December 6, 2004 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Boniva (ibandronate sodium) Injection.

On September 15, 2005, we received your September 14, 2005 major amendment to this application. The receipt date is within 3 months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is January 7, 2006.

If you have any questions, call me at (301) 827-6392.

Sincerely,

{See appended electronic signature page}

Randy Hedin
Senior Regulatory Management Officer
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Randy Hedin
10/3/2005 02:49:47 PM

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-858 Supplement # SE1 SE2 SE3 SE4 SE5 SE6 SE7 SE8

Trade Name: Boniva Injection
Generic Name: Ibandronate Sodium
Strengths: 3 mg/ml [redacted]

Applicant: Hoffmann-La Roche Inc.

Date of Application: December 6, 2004
Date of Receipt: December 7, 2004
Date clock started after UN: NA
Date of Filing Meeting: January 26, 2005
Filing Date: February 5, 2005
Action Goal Date (optional): October 7, 2005 User Fee Goal Date: October 7, 2005

Indication(s) requested: Treatment and prevention of postmenopausal osteoporosis.

Type of Original NDA: (b)(1) ____X_____ (b)(2) _____
OR
Type of Supplement: (b)(1) _____ (b)(2) _____

NOTE:

(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2), complete Appendix B.

(2) If the application is a supplement to an NDA, please indicate whether the NDA is a (b)(1) or a (b)(2) application:

____ NDA is a (b)(1) application OR ___ NDA is a (b)(2) application

Therapeutic Classification: S ____X_____ P _____
Resubmission after withdrawal? _____NA_____ Resubmission after refuse to file?___No_____
Chemical Classification: (1,2,3 etc.) ____3_____
Other (orphan, OTC, etc.) _____NA_____

User Fee Status: Paid ____X_____ Exempt (orphan, government) _____
Waived (e.g., small business, public health) _____

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx to OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the user fee staff.*

- Is there any 5-year or 3-year exclusivity on this active moiety in either a (b)(1) or a (b)(2) application?

YES X NO

If yes, explain: The original NDA (21-455) submitted by the same firm Hoffman-LaRoche should have gotten 5 years of exclusivity.

- Does another drug have orphan drug exclusivity for the same indication? YES NO X
- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES NO
- Is the application affected by the Application Integrity Policy (AIP)? YES NO X
  If yes, explain.
- If yes, has OC/DMPQ been notified of the submission? YES NO
- Does the submission contain an accurate comprehensive index? YES X NO
- Was form 356h included with an authorized signature? YES X NO
  If foreign applicant, both the applicant and the U.S. agent must sign.
- Submission complete as required under 21 CFR 314.50? YES X NO
  If no, explain:
- If an electronic NDA, does it follow the Guidance? N/A YES X NO
  If an electronic NDA, all certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format?

  Additional comments:
- If in Common Technical Document format, does it follow the guidance? N/A X YES NO
- Is it an electronic CTD? N/A YES NO X
  If an electronic CTD, all certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format?

  Additional comments:
- Patent information submitted on form FDA 3542a? YES X NO
- Exclusivity requested? YES, _____years NO X
  Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.
- Correctly worded Debarment Certification included with authorized signature? YES X NO
  If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

  NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e.,
  "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application."
  Applicant may not use wording such as "To the best of my knowledge . . . ."

- Financial Disclosure forms included with authorized signature? YES X NO
  (Forms 3454 and 3455 must be used and must be signed by the APPLICANT.)

- Field Copy Certification (that it is a true copy of the CMC technical section)? YES X NO

Refer to 21 CFR 314.101(d) for Filing Requirements

- PDUFA and Action Goal dates correct in COMIS? YES X NO
  If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections.

- List referenced IND numbers: HFD-510: IND 46,266, IND 50,378 HFD-150: IND 59,165, IND 59,166

- End-of-Phase 2 Meeting(s)? Date(s) July 9, 1998 NO
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) October 10, 2001 NO
  If yes, distribute minutes before filing meeting. September 16, 2004

Project Management

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?
  YES NO X

- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? YES NO X

- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A YES NO X

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted?
  N/A X YES NO

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS?
  N/A X YES NO
- Has DOTCDP been notified of the OTC switch application? YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?
  YES NO X

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES X NO
  If no, did applicant submit a complete environmental assessment? YES NO
  If EA submitted, consulted to Nancy Sager (HFD-357)? YES NO

• Establishment Evaluation Request (EER) submitted to DMPQ?		YES	X	NO
• If a parenteral product, consulted to Microbiology Team (HFD-805)?	NA	YES	X	NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: January 26, 2005

BACKGROUND:

Boniva 2.5 mg once-daily was approved on May 16, 2003 for the treatment and prevention of postmenopausal osteoporosis. The drug was not marketed by the firm. A supplement for Boniva 100 & 150 mg once-monthly for the treatment and prevention of postmenopausal osteoporosis was received by the Division on May 24, 2004. This new drug application is once-every-three-month therapy for the treatment of postmenopausal osteoporosis.

ATTENDEES:

ASSIGNED REVIEWERS:

Discipline	**Reviewer**
Medical:	Theresa Kehoe
Secondary Medical:	None
Statistical:	Cynthia Liu
Pharmacology:	Gemma Kuijpers
Statistical Pharmacology:	None
Chemistry:	Elsbeth Chikhale
Environmental Assessment (if needed):	Elsbeth Chikhale
Biopharmaceutical:	Johnny Lau
Microbiology, sterility:	Consult
Microbiology, clinical (for antimicrobial products only):	None
DSI:	None
Regulatory Project Management:	Randy Hedin
Other Consults:	

Per reviewers, are all parts in English or English translation? YES X NO
If no, explain:

CLINICAL FILE ___X___ REFUSE TO FILE _____

- Clinical site inspection needed: YES NO X
- Advisory Committee Meeting needed? YES, date if known _____ NO X
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?

N/A X YES NO

CLINICAL MICROBIOLOGY NA __X____ FILE _____ REFUSE TO FILE _____

STATISTICS		FILE ___X___	REFUSE TO FILE _____
BIOPHARMACEUTICS		FILE ___X___	REFUSE TO FILE _____
• Biopharm. inspection needed:			YES NO X
• Issues for 74 day letter.			YES NO X
PHARMACOLOGY	NA _____	FILE __X____	REFUSE TO FILE _____
• GLP inspection needed:			YES NO X
CHEMISTRY		FILE ___X___	REFUSE TO FILE _____
• Establishment(s) ready for inspection?			YES X NO
• Microbiology			YES X NO

ELECTRONIC SUBMISSION: Yes
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:

_____ The application is unsuitable for filing. Explain why:

___X____ The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.

____X___ No filing issues have been identified.

_____ Filing issues to be communicated by Day 74. List (optional):

- Goal to finish reviews with team leader sign-off: September 1, 2005
- Action Package should start circulating on September 8, 2005.
- Action Package should go to the Division Director on September 15, 2005.

ACTION ITEMS:

- None

_____
Regulatory Project Manager, HFD-510

Appendix A to NDA Regulatory Filing Review

An application is likely to be a 505(b)(2) application if:

(1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
(2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
(4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications

1. Does the application reference a listed drug (approved drug)? YES NO

   *If "**No**," skip to question 3.*

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):

3. The purpose of this and the questions below (questions 3 to 5) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval and that should be referenced as a listed drug in the pending application.

   (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?

   YES NO

   (***Pharmaceutical equivalents*** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and** **(3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

   *If "**No**," skip to question 4. Otherwise, answer part (b).*

   (b) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES NO
   (The approved pharmaceutical equivalent(s) should be cited as the listed drug(s).)

   *If "**Yes**," skip to question 6. Otherwise, answer part (c).*

   (c) Have you conferred with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007)?

   YES NO

   *If "**No**," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.*

4. (a) Is there a pharmaceutical alternative(s) already approved? YES NO

   (***Pharmaceutical alternatives*** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a

single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

*If "**No**," skip to question 5. Otherwise, answer part (b).*

(b) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES NO
(The approved pharmaceutical alternative(s) should be cited as the listed drug(s).)

***NOTE:** If there is more than one pharmaceutical alternative approved, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007) to determine if the appropriate pharmaceutical alternatives are referenced.*

*If "**Yes**," skip to question 6. Otherwise, answer part (c).*

(c) Have you conferred with the Director, Division of Regulatory Policy II, ORP? YES NO

*If "**No**," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.*

5. (a) Is there an approved drug product that does not meet the definition of "pharmaceutical equivalent" or "pharmaceutical alternative," as provided in questions 3(a) and 4(a), above, but that is otherwise very similar to the proposed product?

YES NO

*If "**No**," skip to question 6.*

*If "**Yes**," please describe how the approved drug product is similar to the proposed one and answer part (b) of this question. Please also contact the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007), to further discuss.*

(b) Is the approved drug product cited as the listed drug? YES NO

6. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

7. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). YES NO

8. Is the extent to which the active ingredient(s) is absorbed or otherwise made YES NO

available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 21 CFR 314.101(d)(9)).

9. Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application should be refused for filing under 21 CFR 314.101(d)(9). YES NO

10. Are there certifications for each of the patents listed for the listed drug(s)? YES NO

11. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

____ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

____ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

____ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

____ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)

*IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must **subsequently** submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)].*

____ 21 CFR 314.50(i)(1)(ii): No relevant patents.

____ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

____ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).

____ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.

12. Did the applicant:

- Identify which parts of the application rely on information (e.g. literature, prior approval of another sponsor's application) that the applicant does not own or to which the applicant does not have a right of reference?

  YES NO

- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

  YES NO

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

  N/A YES NO

- Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?

  N/A YES NO

13. If the (b)(2) applicant is requesting 3-year exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

- Certification that at least one of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

  YES NO

- A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

  YES NO

- EITHER

  The number of the applicant's IND under which the studies essential to approval were conducted.

  IND # _____ NO

  OR

  A certification that the NDA sponsor provided substantial support for the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

YES NO

14. Has the Associate Director for Regulatory Affairs, OND, been notified of the existence of the (b)(2) application?

YES NO

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/s/

Randy Hedin
2/4/05 03:51:21 PM
CSO

From: Hedin, Durand M
Sent: Tuesday, September 06, 2005 3:24 PM
To: 'Jack, Margaret {PDR~Nutley}'
Subject: NDA 21-858, Boniva (ibandronate sodium) Injection

Contacts: Margaret Jack {PDR~Nutley}

We have the following request for information for NDA 21-858, Boniva (ibandronate sodium) Injection:

> Provide details regarding how patients were allocated to treatment. In other words, how the adaptive minimization method was implemented.

Please provide a timeline as to when you will respond to this request. If you have any questions contact me.

Thanks,

Randy Hedin

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/s/

Randy Hedin
9/7/2005 08:45:26 AM
CSO

From: Hedin, Durand M
Sent: Friday, September 02, 2005 10:11 AM
To: 'Jack, Margaret {PDR~Nutley}'
Subject: NDA 21-858, Boniva (ibandronate sodium) Injection

Contacts: Margaret Jack {PDR~Nutley}

Hi Peggy,

Please submit the final study reports, and laboratory, disposition and demographic datasets for studies MF 4265 and MF 4328. Specifically, we are looking for the timing of the safety labs, and the renal and mineral laboratories.

If you have any questions, contact me.

Thanks,

Rand Hedin

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/s/

Randy Hedin
9/2/2005 10:30:10 AM
CSO

From: Hedin, Durand M
Sent: Wednesday, August 31, 2005 3:47 PM
To: 'Jack, Margaret'
Cc: 'Brace, Jeremy {PDR~Nutley}'
Subject: Ibandronate Injection, NDA 21-858 Response to August 25, 2005 E-mail

Hi Peggy:

We have the following answers to the questions in your August 25, 2005 E-mail. Our answers follow your questions:

"1. Please provide data and summary statistics of all subjects with protocol violations (major and minor) for study BM16550, by treatment group".

Roche's Point of Clarification:
There was some confusion on Roche's part regarding what was meant by major and minor protocol violations. In response to Question 1, Roche proposes to provide a data listing and summary tables of all protocol violations specified in the Data Reporting and Analysis Manual (or Analysis Plan). These include all violations that lead to patient exclusions from the analysis populations and all violations that lead to data exclusions from the BMD and serum CTX analyses. Please confirm that this is satisfactory.

This is acceptable.

2. Timelines for response to questions:
The estimated timelines for response to the seven questions included in the August 22 e-mail are as follows. We propose to provide answers to some of the questions early next week and will provide the remainder of the answers to the questions on or before September 7. Will this be acceptable?

This is acceptable.

3. Draft Label for NDA 21-858
In your voice message to Lisa Luther 2 weeks ago, you indicated that Roche may be receiving a draft label for NDA 21-858 the first week in September. Can you confirm that the timelines provided to Lisa Luther are feasible and if not, what are the current timelines for receipt of the draft label?

Draft labeling will be sent when the reviews are completed. This probably will not happen the first week in September.

4. Submission of 2yr data for BM16550
In Roche's response to previous clinical questions for NDA 21-858 (see Admentment 007, dated August 11, 2005) Roche requested that the Agency confirm the acceptability of submitting the 2yr safety and efficacy data for

BM16550 which includes the bone histomorphometry safety data, post-action date for the NDA 21-858. Can you confirm that this is the Agency's understanding as well.

The Division's response at the preNDA meeting is that while the approach seems reasonable, the need for second year histomorphometry data is a review issue.

If you have any questions, contact me.

Thanks,

Randy Hedin

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/s/

Randy Hedin
8/31/2005 04:10:18 PM
CSO

From: Hedin, Durand M
Sent: Monday, August 22, 2005 4:23 PM
To: 'Jack, Margaret {PDR~Nutley}'
Subject: NDA 21-858, Boniva (ibandronate sodium) Injection

Contacts: Margaret Jack {PDR~Nutley}

Hi Peggy,

We have the following comments concerning the clinical review of NDA 21-858, Boniva (ibandronate sodium) Injection. These comments pertain to Study BM16550.

1. Please provide data and summary statistics of all subjects with protocol violations (major and minor) for study BM16550, by treatment group
2. Please provide data and summary statistics outlining the number of previous osteoporotic fractures: the number of subjects per treatment group with 0, 1, 2, 3, 4, and ≥ 5 osteoporotic fractures
3. Please provide a more detailed analysis of vitamin D intake, duration and cumulative dose by treatment. Given that the protocol states

   All patients received plain vitamin D 400 IU/d and elemental calcium 500 mg/d, preferably as oral calcium carbonate, as a dietary supplement for the full duration of the study. In the event that a patient had been previously taking calcium supplements that provided more than 500 mg of calcium daily (but no more than 1500 mg daily), and wished to continue on this dose, she was permitted to do so using her own supplements. However, the study only dispensed sufficient calcium supplements to provide 500 mg of elemental calcium daily. Vitamin D supplementation was limited to 400 IU/day; therefore, patients were advised not to take additional supplements. Patients were instructed to take the calcium and the vitamin D in the evening.

   Based on a request by the Canadian Therapeutics Products Directorate, patients in the Canadian centers were provided with 1000 mg daily of calcium as supplemental therapy which is in accordance with the Ontario Guidelines for the Prevention and Treatment of Osteoporosis. In the event that a patient was previously taking calcium supplements that provided more than 1000 mg of calcium daily, the patient could continue on the increased dose provided it did not exceed 1500 mg.

   In these centers, the vitamin D dose remained at 400 IU daily. However, additional monitoring at months 3 and 12 was to be implemented to assess 25-hydroxy vitamin D levels.

   At the three month time point it was expected that patients who had a 25-hydroxy vitamin D at screening in the low normal range would show a trend towards increasing levels. Provided this was the case, patients were allowed to continue on vitamin D 400 IU daily.

   Patients who were not showing an upward trend towards a level of 40 nmol/L (16.7 ng/mL) of 25-hydroxy vitamin D were to be either withdrawn

or provided with 800 IU Vitamin D daily.
At one year, all patients were to have a serum 25-hydroxy vitamin D level of at least 40 nmol/L (16.7 ng/mL). Patients who had not achieved this threshold level for 25-hydroxy vitamin D were either to be withdrawn or provided with 800 IU vitamin D daily.

The decision to increase the dose of vitamin D or remove patient from study was to be made on a case by case basis, in conjunction with the treating physician and the sponsor.

Please specifically address:

a. Enumeration of all subjects with changes in vitamin D dosing during the study
b. Enumeration of the subjects from Canadian sites that were required to have the specified vitamin D analysis
c. The vitamin D levels at Month 3 and Month 12, with summary statistics
d. How many subjects were withdrawn from the study at Month 3? How many subjects required an increase in vitamin D dose to 800 IU daily?
e. How many subjects were withdrawn from the study at Month 12? How many subjects required an increase in vitamin D dose to 800 IU daily?

4. Please provide tr01_1bp: Listing of the treatments potentially affecting bone metabolism taken by patients prior to starting trial treatment is available upon request (Secondary Data Display Available Upon Request)
5. Please provide an accounting of all subjects in the ITT analysis population that were not included in the analyses of relative and absolute change in BMD at the lumbar and hip (total hip, femoral neck and trochanter) at Month 12. As well, please include the justification for removal. Please be specific regarding reasons if inadequate or biased BMD.
6. Please provide an accounting of all subjects in the ITT analysis population that were not included in the analyses of relative and absolute change in serum CTX. As well, please include the justification for removal.
7. Please provide an explanation for the total iv dose numbers provided in Table 58 (page 135) of BM16550 study report. Specifically, did subject(s) in the ibandronate 2.5 mg daily, placebo q3mo group actually receive i.v ibandronate in addition to the oral ibandronate? If so, please provide details as documentation could not be confirmed in dataset MEDT.

If you have questions please contact me at 301-827-6392.

Thanks,

Randy Hedin

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/s/

Randy Hedin
8/25/2005 04:46:31 PM
CSO

From: Hedin, Durand M
Sent: Friday, August 19, 2005 10:56 AM
To: 'Jack, Margaret {PDR~Nutley}'
Subject: NDA 21-858, Boniva (ibandronate sodium) Injection

Contacts: Margaret Jack {PDR~Nutley}

Hi Peggy,

We have the following request for information for NDA 21-858, Boniva (ibandronate sodium) Injection:

> Provide NONMEM control file and data file for pharmacokinetic-pharmacodynamic (both CTX and BMD) modeling (i.e., K-PD model and the conventional PK-PD model) in a plain text (i.e., .txt) format.

Please provide a timeline as to when you will respond to this request. If you have any questions contact me.

Thanks,

Randy Hedin

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/s/

Randy Hedin
8/19/2005 11:09:08 AM
CSO

From: Hedin, Durand M
Sent: Tuesday, July 12, 2005 3:17 PM
To: 'Jack, Margaret {PDR~Nutley}'
Subject: NDA 21-858

Contacts: Margaret Jack {PDR~Nutley}

Dear Ms. Jack,

We have the following comments concerning the chemistry review of NDA 21-858.

1. Provide more detailed information about the extraction study and the test results. Specifically:

   - Provide information about the storage temperature and length of storage for the drug product samples that were investigated for extractables/leachables (i.e. Figure 2 and Table 7 for batch 782426 and batch 782421).
   - For each possible extractable/leachable (Table 7 and 8), provide a quantitative value of the expected concentration in the drug product at expiration date, and provide a calculation on how this estimated concentration is obtained.
   - Provide any additional extraction/leachable study data using the drug product in its proposed pre-filled syringe (e.g. at intermediate temperature, different pH and/or media), if available.

2. Provide specifications in tabular form with the acceptance limits (instead of just "satisfactory"), specify which USP tests are performed and provide an example of typical supplier's test results (mentioned on pg. 108-109 of 3 mg/3 mL drug product section) obtained for each of the following:

   - Glass barrel (3 mL and 5 mL)
   - Stopper (for 3 mL and 5 mL barrel)
   - Tip cap (for 3 mL and 5 mL barrels)

3. Who is the supplier for the [redacted] and alcohol swap? What material is the [redacted] made of? Submit vendor's COAs for [redacted] and alcohol swap.

4. Clarify the title for Table 8, pg. 19, 2 mg/2 mL drug product section: Is this for 3 mg/3 mL or 2 mg/2 mL?

4. Clarify and justify the storage position (upright and/or inverted) of the syringe in the stability studies. Provide any additional stability data when available, preferably no later then the end of August.

If you have any questions, contact me at 301-827-6392.

Sincerely,

Randy Hedin, R.Ph.

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/s/

Randy Hedin
7/12/05 04:07:22 PM
CSO

MEMORANDUM OF TELECON

DATE: February 23, 2005
APPLICATION NUMBER: NDA 21-858

BETWEEN:

Name: Margaret Jack
Phone: 973-235-4463
Representing: Hoffman La-Roche

AND

Name: Randy Hedin
Division of Metabolism and Endocrine Drug Products, HFD-510

SUBJECT: Biopharm comment concerning NDA 21-858

I spoke with Ms. Jack concerning ibandronate injection, and requested that the firm submit the following:

1. 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

2. 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.

Ms Jack thanked me for the comments, and the conversation ended.

Randy Hedin, R.Ph.
Senior Regulatory Management Officer

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/s/

Randy Hedin
2/23/05 09:16:43 AM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-858

Hoffman-La Roche Inc.
Attention: Margaret Jack
Director of Regulatory Affairs
340 Kingsland Street
Nutley, NJ 07110-1199

Dear Ms. Jack:

Please refer to your December 6, 2004 new drug application (NDA), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Boniva (ibandronate sodium) Injection.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application was filed under section 505(b) of the Act on February 5, 2005 in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

If you have any questions, call Randy Hedin, R.Ph., Senior Regulatory Management Officer, at (301) 827-6392.

Sincerely,

{See appended electronic signature page}

Enid Galliers
Chief Project Management Staff
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

MEMORANDUM OF TELECON

DATE: February 4, 2005
APPLICATION NUMBER: NDA 21-858

BETWEEN:

Name: Margaret Jack
Phone: 973-235-4463
Representing: Hoffman La-Roche

AND

Name: Randy Hedin
Division of Metabolism and Endocrine Drug Products, HFD-510

SUBJECT: Statistical comment concerning NDA 21-858

I spoke with Ms. Jack concerning ibandronate injection, and requested the firm to submit subgroup analyses and descriptive statistics for the primary endpoint by age cut-point of 65 years of age instead of 70.

Ms Jack thanked me for the comment, and the conversation ended.

_____

Randy Hedin, R.Ph.
Senior Regulatory Management Officer

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/s/

Randy Hedin
2/4/05 03:45:58 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-858

Hoffman-La Roche, Inc.
Attn: Margaret J. Jack
Director of Regulatory Affairs
340 Kingland Street
Nutley, NJ 07110

Dear Ms. Jack:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Boniva™ (ibandronate sodium) 3mg/3ml [redacted] Injection
Review Priority Classification:	Standard (S)
Date of Application:	December 6, 2004
Date of Receipt:	December 7, 2004
Our Reference Number:	NDA 21-858

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 5, 2005, in accordance with 21 CFR 314.101(a). If we file the application, the user fee goal date will be October 7, 2005.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirements. We acknowledge receipt of your request for a waiver of pediatric studies for this application. Once the application has been filed, we will notify you whether we have waived the pediatric study requirement for this application.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

U.S. Postal Service/Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic & Endocrine Drug Products, HFD-510
Attention: Fishers Document Room, 8B45
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call me at (301) 827-6392.

Sincerely,

{See appended electronic signature page}

Randy Hedin, R.Ph.
Senior Regulatory Management Officer
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Julie Rhee
12/14/04 01:39:21 PM
Signed for Randy Hedin, R. Ph.

RTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

PRESCRIPTION DRUG USER FEE COVER SHEET

Form Approved: OMB No. 0910-0297
Expiration Date: December 31, 2006.

See Instructions on Reverse Side Before Completing This Form

eted form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the ide. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates und on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

NT'S NAME AND ADDRESS
garet J. Jack
n-La Roche Inc.
sland Street
New Jersey 07110

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER
N021858

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?
☒ YES ☐ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☒ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:
N021455 and N021455/S-001
(APPLICATION NO. CONTAINING THE DATA).

ONE NUMBER *(Include Area Code)*
) 235-4463

CT NAME
0955 Na•H20 Injection (USAN: ibandronate sodium, INN: ic acid) Tradename: Boniva™

6. USER FEE I.D. NUMBER
4858

APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE **EXCLUSIONS**? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92
(Self Explanatory)

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
(See item 7, reverse side before checking box.)

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY
(Self Explanatory)

WAIVER OF AN APPLICATION FEE BEEN GRANTED FORTHIS APPLICATION?
☐ YES ☒ NO
(See Item 8, reverse side if answered YES)

eporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing ns, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. mments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

ent of Health and Human Services
Drug Administration
FM-99
kville Pike
MD 20852-1448

and

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Drive, Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

RE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Margaret J Jack	Program Director, Drug Regulatory Affairs	10/8/2004

DA 3397 (12/03)

PSC Media Arts (301) 443-1090 EF

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA	**21-858**	**Brand Name**	**BONIVA™**
OCPB Division	**2**	**Generic Name**	**Ibandronate sodium**
Medical Division	**DMEDP, HFD-510**	**Drug Class**	**Bisphosphonate**
OCPB Reviewer	**S.W. Johnny Lau**	**Indication(s)**	**Treat postmenopausal osteoporosis**
OCPB Team Leader	**Hae-Young Ahn**	**Dosage Form**	**Injection solution**
Date of Submission	**6-DEC-2004**	**Dosing Regimen**	**3 mg/3mL/3 months**
Estimated Due Date of OCPB Review	**1-SEPT-2005**	**Route of Administration**	**Intravenous**
Division Due Date	**15-SEPT-2005**	**Sponsor**	**Hoffmann-La Roche Inc.**
PDUFA Due Date	**7-OCT-2005**	**Priority Classification**	**Standard**

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	X			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:	X	3		MF9853, MF4361, MF4411
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
QTc:				
	X	2		BM16650, JM16651
II. Biopharmaceutics				

Absolute bioavailability:				
Relative bioavailability -				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; multi dose:				
replicate design; single dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies	[redacted]	**5**		**Referenced NDA 21-455**

Filability and QBR comments		
	"X" if yes	**Comments**
Application filable ?	X	
Comments to be sent to firm?	x	• 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
QBR questions (key issues to be considered)		
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		