CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-858

CHEMISTRY REVIEW(S)

BONIVA™ (ibandronate sodium) injection
NDA 21-858

Summary of the Basis for the Recommended Action from Chemistry, Manufacturing, and Controls

Applicant: Hoffmann-La Roche Inc
340 Kingsland Street
Nutley, NJ 07110

Indication: Treatment of post-menopausal osteoporosis.

Presentation: Sterile parenteral solution of [redacted] 3 mg/3 mL for i.v. injection, packaged in single use disposable pre-filled syringe.

EER Status: Acceptable 14-DEC-2005

Consults: Microbiology – Acceptable 29-AUG-2005
EA – Categorical exclusion granted under 21 CFR §25.31(b)
Methods Validation – Revalidation by Agency not requested

Original Submission: 06-DEC-2004

Post-Approval Agreements:

The applicant agrees to place one batch of the approved strength, annually, in the post-approval stability program.

Drug Substance:

Ibandronate sodium is a nitrogen-containing bisphosphonate, which inhibits osteoclast activity and reduces bone resorption, without effecting bone formation. It is a fine white to off-white crystalline powder, freely soluble in water, but practically insoluable in organic solvents such as methanol, ethanol, and dimethyl formamide. The drug substance is adequately stable when stored at room temperature (see DMF 15429). CMC information on the drug substance, ibandronate sodium, is provided by reference to DMF 15429. A letter of authorization to allow the Agency to review this DMF was provided. The DMF was found adequate to support this NDA (see review #3 by Elsbeth Chikhale dated 5/25/05).

Conclusion: Drug substance is acceptable.

Drug Product:

The drug product, Boniva™ (ibandronate sodium) injection, described in this NDA is a pre-filled syringe for i.v. injection, which is a new dosage form of the already approved (NDA 21-455) tablets. The proposed product is indicated for the treatment of post-menopausal osteoporosis. The drug

product strengths are 2 mg/2 mL and/or 3 mg/3 mL. Since the final

The proposed storage is at 25°C, and the proposed expiry date is 2 years. Submitted stability data support an expiry dating of 24 months. Specifications for the drug product include: description of container and content, identification by TLC, assay by HPLC, purity/impurity by TLC, particulate matter by light obscuration, extractable volume, and microbial testing. All test methods have been appropriately validated for their intended purpose.

Conclusion: Drug product is satisfactory.

Additional Items:

All associated Drug Master Files (DMFs) are acceptable or the pertinent information has been adequately provided in the application or by reference to other DMFs.

The sponsor has adequately responded to all CMC labeling comments. The package insert and container cartons are acceptable from chemistry standpoint.

Overall Conclusion:

From a CMC perspective, the application is recommended for approval.

Blair A. Fraser, Ph.D.
Branch Chief, Branch II
DPA I/ONDQA

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/s/

Blair Fraser
12/28/2005 01:40:48 PM
CHEMIST

NDA 21-858

BONIVA™
(ibandronate sodium)
INJECTION

Hoffmann-La Roche Inc.

Elsbeth Chikhale, Ph.D.
Division of Metabolism and Endocrinology Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-858

2. REVIEW #: 1

3. REVIEW DATE: 16-DEC-2005

4. REVIEWER: Elsbeth Chikhale, Ph.D.

5. PREVIOUS DOCUMENTS: NA

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	06-DEC-2004
Amendment to original[1]	17-JUN-2005
Amendment to original[2]	22-JUL-2005
Amendment to original[3]	31-AUG-2005
Amendment to original[4]	5-DEC-2005
Amendment to original[5]	13-DEC-2005

1) The 6/17/05 amendment provides for updated stability data
2) The 7/22/05 amendment provides for a response to an information request letter from the Agency dated 7/12/05.
3) The 8/31/05 amendment provides for additional response to the information request letter from the Agency dated 7/31/05 and additional stability data.
4) The 12/5/05 amendment provides for a sample of the container closure system and for a statement about the [redacted]
5) The 12/13/05 amendment provides for a response to the Agency's labeling comments.

7. NAME & ADDRESS OF APPLICANT:

Name: Hoffmann-La Roche Inc.

Address: 340 Kingsland Street
Nutley, New Jersey 07110

Representative: Margaret J. Jack (Regulatory Program Director)

Telephone: (973) 235-4463

8. DRUG PRODUCT NAME/CODE/TYPE:

Chemistry Review Data Sheet

a) Proprietary Name: Boniva
b) Non-Proprietary Name (USAN): Ibandronate sodium
c) Code Name/#: BM 21.0955 $Na \cdot H_2O$
d) Chem. Type/Submission Priority:

- Chem. Type: 3 (new dosage form)
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY:

Bone/calcium-phosphorous metabolism

11. DOSAGE FORM: Injection (pre-filled syringe)

12. STRENGTH/POTENCY: [redacted] 3 mg/3 mL

13. ROUTE OF ADMINISTRATION: i.v.

14. Rx/OTC DISPENSED: _x_Rx ___OTC

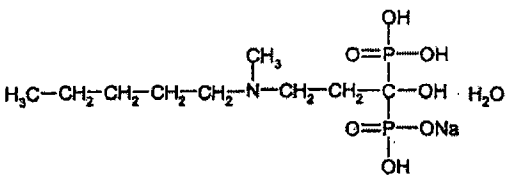
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product ___ Form Completed

__x__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

3-(N-methyl-N-pentyl)amino-1-hydroxypropane-1,1-diphosphonic acid, monosodium salt, monohydrate



$C_9H_{22}NO_7P_2Na \cdot H_2O$
Molecular Weight: 359.24 (for monohydrate)

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
15429	II	Roche Diagnostics GmbH	Drug substance	1	Adequate	May 25, 2005	Reviewed by Elsbeth Chikhale, Ph.D.
[redacted]	III	[redacted]	[redacted]	1	Adequate	July 12, 2005	Reviewed by Elsbeth Chikhale, Ph.D.
	III			1	Inadequate*	November 25, 2005	Reviewed by Elsbeth Chikhale, Ph.D.
	III			1	Adequate	September 9, 2005	Reviewed by Don Klein, Ph.D., DMF strike force
	III			1	Adequate	November 25, 2005	Review by Elsbeth Chikhale, Ph.D.
	III			1	Adequate	August 29, 2005	Reviewed by Elsbeth Chikhale, Ph.D.
	III			1	Adequate	November 14, 2005	Reviewed by Elsbeth Chikhale, Ph.D.

[1] Action codes for DMF Table:
1 – DMF Reviewed
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

*Note: DMF [redacted] is inadequate to support NDA 21-858 because the relevant information is not in the DMF. However, the missing information is cross-referenced in DMF [redacted] (Vol. 32.3 and 32.5).

Chemistry Review Data Sheet

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	46,266	Ibandronate sodium injection
IND	50,378	Ibandronate sodium oral
IND	59,165	Ibandronate sodium injection
IND	59,166	Ibandronate sodium oral
NDA	21-455	Ibandronate sodium tablet

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	112/14/05	Elsbeth Chikhale, Ph.D.
Pharm/Tox	N/A		
Clinical Pharmacology and Biopharmaceutics	Pending	Pending	Johnny Lau, Ph.D.
Methods Validation	Acceptable	12/16/05	Elsbeth Chikhale, Ph.D.
ODS	N/A		
EA	Satisfactory (consult not needed)	12/16/05	Elsbeth Chikhale, Ph.D.
Microbiology	Approval	8/29/05	John Metcalfe, Ph.D.

19. ORDER OF REVIEW: N/A

The Chemistry Review for NDA 21-858

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 21-858 is recommended for **approval** from the standpoint of chemistry, manufacture and controls. The submitted stability data support an **expiration date** of **24 months.**

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

1) **Drug Product**

The drug product, Boniva™ (ibandronate sodium) injection, described in this NDA is a pre-filled syringe for i.v. injection, which is a new dosage form of the already approved (NDA 21-455) tablets. The proposed product is indicated for the treatment of post-menopausal osteoporosis. The drug product strengths are [redacted] 3 mg/3 mL. Since the final selection of strength (based on review of efficacy and safety data) will not occur until later into the review cycle, this CMC review will cover both strengths. The drug product used for the first clinical trials was a pH 6 solution containing 1 mg/1mL. Subsequent clinical trials used a pH 4 solution containing 1 mg/1 mL. The proposed drug product has a pH 4, which provides better drug product stability. The main challenges in the CMC review of this NDA are the evaluation of extractables/leachables studies, which is part of the evaluation of the container closure system, and the determination of the expiry date. The proposed storage is at 25°C (room temperature), and the proposed expiry date is 2 years. Submitted stability data support an expiry dating of 24 months.

2) **Drug Substance**

Ibandronate sodium is a nitrogen-containing bisphosphonate, which inhibits osteoclast activity and reduces bone resorption, without effecting bone formation. It is a fine white to off-white crystalline powder, freely soluble in water, but practically insoluable in organic solvents such as [redacted] The drug substance is adequately stable when stored at room temperature (see DMF 15429). The drug substance is best described as a monohydrate and it has [redacted] forms. Drug product performance is not expected to be influenced by the [redacted] in the drug substance because the drug product is a solution in which the drug substance is dissolved, thus not existing in a [redacted] CMC information on the drug substance, ibandronate sodium, is provided by reference to DMF 15429. A letter of authorization to allow the Agency to review this DMF was provided. The DMF was found adequate to support this NDA (see review #3 by Elsbeth Chikhale dated 5/25/05).

B. Description of How the Drug Product is Intended to be Used

The drug product is a disposable pre-filled syringe intended for one-time use. The drug product should be taken [redacted] once every 3 months (3 mg/3 mL). Patients

should receive supplemental calcium and/or vitamin D. Submitted stability data support a 24 months expiry.

C. Basis for Approvability or Not-Approval Recommendation

This NDA is recommended for approval, pending a satisfactory EES recommendation, because:

- The applicant has demonstrated that the manufacturing of the drug product is adequately controlled and assures a consistent high quality drug product.
- Extraction/leachables studies have demonstrated that even upon extended storage at room temperature and accelerated conditions, the levels of extractables/leachables are so low (ppb range) that there is no safety concern.
- The choice of container closure system was found acceptable.
- The product is expected to be sterile and safe from a product quality microbiology perspective.
- Adequate stability data were provided to support the proposed expiration dating period for Boniva injection (24 months).

III. Administrative

A. Reviewer's Signature

Elsbeth Chikhale, Ph.D.

B. Endorsement Block: in DFS

C. cc Block: in DFS

34 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Chemistry-2

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/s/

Elsbeth Chikhale
12/16/2005 03:41:47 PM
CHEMIST

Blair Fraser
12/16/2005 05:28:26 PM
CHEMIST