CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-455

CHEMISTRY REVIEW(S)

NDA 21-455
BONIVA (ibandronate sodium) Tablets 2.5 mg

CHEMISTRY DIVISION DIRECTOR REVIEW

Applicant: Roche Pharmaceuticals

Indication: Treatment and prevention of osteoporesis in postmenopausal women

Presentations: White oblong film-coated tablets, packaged in bottles of 30, 90, or 500 tablets

EER Status: acceptable, 2/25/2003
Consults: Tradename rejected by OPDRA but accepted by DMEDP; EA, acceptable 4/14/2003

Boniva Tablets is a product of ibandronate sodium, a nitrogen containing bisphosphate. Ibandronate sodium is a water-soluble monohydrate salt containing two polymorphic forms. Drug product performance is not expected to be influenced by the different polymorphs in the drug substance because two forms have a very similar solubility profile. Drug substance is manufactured by Roche Diagnostic GmbH in Mannheim, Germany. CMC information for ibandronate is included in DMF — for review. The drug substance is quite stable when stored at room temperature and based on the stability data, a 5 years of shelf-life was assigned.

Boniva is available as white oblong film-coated, immediate-release tablets containing 2.5 mg of ibandronate sodium, packaged in — bottles containing 30, 90, or 500 tablets. Dissolution profiles have shown that the tablets are very rapidly dissolving (— in 15 minutes); therefore, a disintegration test is used to replace normal dissolution test for release. This substitution is permitted according to conditions described in ICH Q6A. The batches used for clinical trials were round tablets, made in Mannheim, Germany, and the commercial batches are oblong tablets, made in Basel, Switzerland. These batches all have the exact same composition and are considered equivalent.

Chemistry review was completed on 4/14/03 and a number of deficiencies had been identified. These deficiencies, in subsequent communications with the applicant, have been adequately addressed (see Review #2). A few deficiencies identified during the review of DMF for drug substance have been determined as minor ones, which do not affect the quality and safety of the product. The DMF was judged as adequate to support this NDA. There is no pending chemistry issue.

The proposed expiry date is 36 months at 25°C (room temperature). Sufficient stability data have been provided to assign an expiry period of 3 years for the drug product, when stored at room temperature.

Overall Conclusion:
From a CMC perspective the application is recommended for approval.

Duu-Gong Wu, PhD
Deputy Director, DNDC II/ONDC

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/s/

Duu-gong Wu
5/13/03 07:11:48 PM
CHEMIST

NDA 21-455

BONIVA
(ibandronate sodium)
TABLETS

Hoffmann-La Roche Inc.

Elsbeth Chikhale, Ph.D.
Division of Metabolic and Endocrine Drug Products

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Chemistry Review Data Sheet

1. NDA 21-455

2. REVIEW #: 2

3. REVIEW DATE: 12-MAY-2003

4. REVIEWER: Elsbeth Chikhale, Ph.D.

5. PREVIOUS DOCUMENTS: Review #1, dated April 14, 2003

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	15-JUL-2002
Amendment to original[1]	17-JAN-2003
Amendment to original[2]	31-JAN-2003
Amendment to original[3]	30-APR-2003
Amendment to original[4]	Fax dated MAY 6, 7, and 9, 2003

1) The 1/17/03 amendment provides for a response to an information request letter from the Agency dated 12/13/2002.
2) The 1/31/2003 amendment provides for an updated trade name request.
3) The 4/30/2003 amendment provides for draft responses to the CMC and Biopharm comments dated 4/23/03 and 4/28/03 respectively
4) The faxed amendment provides for responses to the CMC and Biopharm comments dated 4/23/03 and 4/28/03 respectively

7. NAME & ADDRESS OF APPLICANT:

Name: Hoffmann-La Roche Inc.

Address: 340 Kingsland Street
Nutley, New Jersey 07110

Representative: Mark Hope (Regulatory Program Director)

Telephone: (973) 562-2926

8. DRUG PRODUCT NAME/CODE/TYPE:

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: 1 (new molecular entity)
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION:
This is a 505(b)(1) submission

10. PHARMACOL. CATEGORY:
Bone/calcium-phosphorous metabolism

11. DOSAGE FORM: tablet

12. STRENGTH/POTENCY: 2.5 mg/tablet

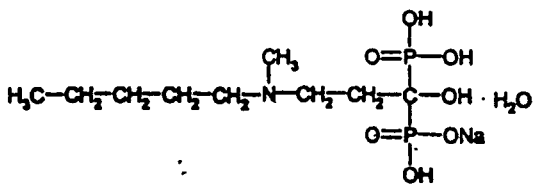
13. ROUTE OF ADMINISTRATION: oral

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
	II	Roche Diagnostics GmbH	Drug substance	1	Adequate	April 24, 2003	Reviewed by Elsbeth Chikhale, Ph.D.
	IV			4	N/A		
	I			2	N/A		
	I			2	N/A		
	III			1	Adequate	April 9, 2003	Reviewed by Elsbeth Chikhale, Ph.D.
	III			3	Adequate	January 4, 1999	Review by Don Klein, Ph.D., DMF strike force
	III			3	Adequate	September 27, 2000	Review by Don Klein, Ph.D., DMF strike force
	III			3	Adequate	September 26, 2000	Review by Don Klein, Ph.D., DMF strike force
	III			3	Adequate	August 25, 1999	Reviewed by D. Cummings
	III			3	Adequate	April 24, 2000	Reviewed by Milton Sloan, Ph.D.
	III			3	Adequate	April 30, 2001	Review by Don Klein, Ph.D., DMF strike force
	III			3	Adequate	October 7, 2002	Reviewed by Roa Puttagunta, 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)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	[redacted]	[redacted]
IND	[redacted]	Ibandronate sodium oral
IND	[redacted]	[redacted]
IND	[redacted]	Ibandronate sodium oral

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	2/25/03	Elsbeth Chikhale, Ph.D.
Pharm/Tox	N/A		
Clinical Pharmacology and Biopharmaceutics	Acceptable	4/10/03	Johnny Lau, Ph.D.
Methods Validation		pending	
ODS	Boniva is not acceptable* [redacted] is acceptable*	5/2/03	Alina Mahmud, R.Ph.
EA	Satisfactory (consult not needed)	CMC review #1 4/14/03	Elsbeth Chikhale, Ph.D.
Microbiology	N/A		

* The name Boniva was found acceptable by DMEDP and will be used for the drug product.

19. ORDER OF REVIEW: N/A

The Chemistry Review for NDA 21-455

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 21-455 is recommended for **approval** from the standpoint of chemistry, manufacture and controls.

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, described in this NDA, is an immediate release film coated tablet for oral administration. The product is intended to be used for the treatment and prevention of post-menopausal osteoporosis. The drug product strength is 2.5 mg/tablet and is packaged in high density polyethylene, —— bottles containing 30, 90, or 500 tablets. The batches used for clinical trials were round tablets, made in Mannheim, Germany, and the commercial batches are oblong tablets, made in Basel, Switzerland. These batches all have the exact same composition and are considered equivalent from a chemical as well as biopharmaceutical stand point. The proposed storage is at 25°C (room temperature), and the proposed expiry date is 36 months. The drug product is shown to be stable at 25°C (room temperature) for 36 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 insoluble in organic solvents such as methanol, ethanol, and dimethyl formamide. CMC information on the drug substance, ibandronate sodium, is provided by reference in DMF —— The drug substance is a monohydrate and it has 2 polymorphic forms. Drug product performance is not expected to be influenced by the different polymorphs in the drug substance because the drug product manufacturing process produces only tablets containing polymorph A drug substance. The drug substance is adequately stable when stored at room temperature (see DMF ——).

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

The drug product (2.5 mg tablet) has to be taken 60 minutes before the first food or drink (other than water) of the day or any other oral medication or supplementation, including calcium, antacids, or vitamins. The recommended dose for the drug product is 1 tablet (2.5 mg) daily, swallowed whole with a full glass of plain water. The drug product is intended to be used for a period up to 3 years.

C. Basis for Approvability or Not-Approval Recommendation

The drug product manufacturing process and in-process controls of the clinical batches and the to-be-marketed batches are practically the same. The formulation of the drug product used in the pivotal studies is exactly the same as proposed for the to-be-marketed product. The drug product specifications (release and stability) are the same, so that drug product quality is assured at release and during the 3 year shelf life. Sufficient stability data are provided to assign an expiry period of 3 years for the drug product, when stored at room temperature. No trends (upward or downward) were observed. All deficiencies listed in review #1, were adequately addressed by the sponsor. The cGMP status of all manufacturing and control facilities is acceptable.

III. Administrative

/S/

A. Reviewer's Signature

Elsbeth Chikhale, Ph.D.

B. Endorsement Block: in DFS

C. cc Block: in DFS

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

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/s/

Elsbeth Chikhale
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CHEMIST

Sheldon Markofsky
4/21/03 01:48:21 PM
CHEMIST