



PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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OFFICE OF PETITIONS

In re United States Patent No. 4,927,814

Inventors: Gall et al.

Issue Date: May 22, 1990

For: **DIPHOSPHONATE DERIVATIVES, PHARMACEUTICAL COMPOSITIONS
AND METHODS OF USE**

**APPLICATION FOR EXTENSION OF PATENT
TERM UNDER 35 U.S.C. §156**

Nutley, New Jersey 07110
July 11, 2003

Mail Stop Patent Ext.
Commissioner for Patents P.O. Box 1450
Arlington, VA 22313-1450

Dear Sir:

Pursuant to 35 U.S.C. § 156, Hoffmann-La Roche Inc. ("ROCHE"), a corporation organized under the laws of the State of New Jersey, having been authorized to act as an agent for Roche Diagnostics GmbH (formerly named Boehringer Mannheim GmbH, which is the owner of U.S. Patent No. 4,927,814 as evidenced by assignment recorded at reel 4786, frame 617) for purpose of filing and prosecuting this Application For Extension of Patent Term, and transacting all business in the U.S. Patent and Trademark Office connected therewith, submits this Application for extension of its term.

Applicant seeks extension of the term of U.S. Patent No. 4,927,814 for three (3) years and three hundred thirty four (334) days, from July 9, 2007 to and including June 9, 2011 and certification that it is entitled to the rights derived from this patent as set forth in 35 U.S.C. § 156(b).

2004E-0444

APP 1

The information contained in this document and its Exhibits is provided in accordance with 35 U.S.C. § 156(d) and 37 C.F.R. § 1.740 and is listed in the manner set forth in § 1.740.

(1) A Complete Identification Of The Approved Product As
By Appropriate Chemical And Generic Name, Physical
Structure Or Characteristics

The approved product, having the trademark Boniva™ Tablets, contains ibandronate as its active ingredient. The product is approved for the treatment and prevention of postmenopausal osteoporosis. Ibandronate is a nitrogen containing bisphosphonate that inhibits osteoclast-mediated bone resorption.

The Boniva™ Tablet is available as a white, oblong, 2.5-mg. film coated tablet for oral administration. One tablet contains 2.813 mg ibandronate monosodium monohydrate, equivalent to 2.5 mg. free acid. The Boniva™ Tablet also contains the following inactive ingredients: lactose monohydrate, povidone, microcrystalline cellulose, crospovidone, purified stearic acid, colloidal silicone dioxide, and purified water. The tablet film coating contains hypromellose, titanium dioxide, talc, polyethylene glycol 6000, and purified water. A copy of the approved product label is annexed as Exhibit A.

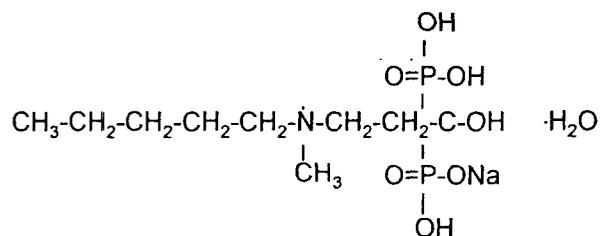
"Ibandronate sodium" is the non-proprietary name approved by the USAN council for the Boniva™ Tablets.

Ibandronate sodium, also known as RO 2005450, has the chemical name:
3-(N-methyl-N-pentyl)amino-1-hydroxypropane-1,1-diphosphonic acid,
monosodium salt, monohydrate, with the molecule formula $C_9H_{22}NO_7P_2Na \cdot H_2O$ and a

molecular weight of 359.24 or 1-hydroxy-3-(N-methyl-N-pentylamino)-propane-1,1-diphosphonic acid and the physiological active salt thereof

Claim 4 reads on the approved product.

Ibandronate sodium is a white- to off-white powder. It is freely soluble in water and practically insoluble in organic solvents. Ibandronate sodium has the following structural formula:



The action of ibandronate on bone tissue is based on its affinity for hydroxyapatite, which is part of the mineral matrix of bone. Ibandronate inhibits osteoclast activity and reduces bone resorption and turnover. In post-menopausal women, it reduces the elevated rate of bone turnover, leading to, on average, a net gain in bone mass. Therefore, it is approved for the treatment and prevention of osteoporosis in postmenopausal women.

The term "approved product" is defined in 35 U.S.C. § 156(a) as the "product" referred to in paragraphs (4) and (5) of subsection (a). In turn, the word "product" is defined in 35 U.S.C. § 156(f)(1)(A) to comprise a "drug product" which is described in 35 U.S.C. § 156(f)(2) to include "the active ingredient of a new drug ... including any salt or ester of the active ingredient, as a single entity or in combination with another active ingredient." The approved product subject to this Application, thus includes ibandronic acid, and any salts and esters thereof as a single entity or in combination with another active ingredient.

- (2) A Complete Identification Of The Federal Statute Including The Applicable Provision Of Law Under Which The Regulatory Review Occurred

The regulatory review occurred under Section 505 of the Federal Food, Drug and Cosmetic Act ("FD&C Act"), 21 U.S.C. § 301 *et seq.*

- (3) An Identification Of The Date On Which The Product Received Permission For Commercial Marketing Or Use Under The Provision Of Law Under Which The Applicable Regulatory Review Period Occurred

Boniva™ Tablets were approved by the Food and Drug Administration ("FDA") for commercial marketing or use under Section 505 of the FD&C Act on May 16, 2003. A copy of the FDA approval letter is annexed hereto as Exhibit B.

- (4) In The Case Of A Drug Product, An Identification Of Each Active Ingredient In The Product And As To Each Active Ingredient, A Statement That It Has Not Been Previously Approved For Commercial Marketing Or Use Under The Federal Food, Drug, And Cosmetic Act, The Public Health Service Act, Or The Virus-Serum-Toxin Act, Or A Statement Of When The Active Ingredient Was Approved For Commercial Marketing Or Use (Either Alone Or In Combination With Other Active Ingredients), The Use For Which It Was Approved, And The Provision Of Law Under Which It Was Approved

The sole active ingredient in the approved product is ibandronate, which active ingredient has not been previously approved for commercial marketing or use under the FD&C Act, The Public Health Services Act or the Virus-Serum-Toxin Act.

- (5) A Statement That The Application Is Being Submitted Within The Sixty Day Period Permitted For Submission Pursuant to 37 C.F.R. § 1.720(f) And An Identification Of The Date Of The Last Day On Which The Application Could Be Submitted

This application is being submitted within the permitted sixty (60) day period, the last day of which is July 15, 2003.

- (6) A Complete Identification Of The Patent For Which An Extension Is Being Sought By The Name Of the Inventor, The Patent Number, The Date Of Issue, And The Date of Expiration

The complete identification of the patent for which an extension is being sought is:

Inventor(s): Rudi Gall
 Elmar Bosies

Patent No: 4,927,814

Issue Date: May 22, 1990

Expiration Date: July 9, 2007 (without extension)

- (7) A Copy Of The Patent For Which An Extension Is Being Sought, Including The Entire Specification (Including Claims) And Drawings

A copy of U.S. Patent No. 4,927,814 is annexed as Exhibit C.

U.S. Patent No. 4,927,814
Issue Date: May 22, 1990

- (8) A Copy Of Any Disclaimer, Certificate Of Correction, Receipt Of Maintenance Fee Payment, Or Reexamination Certificate Issued In the Patent

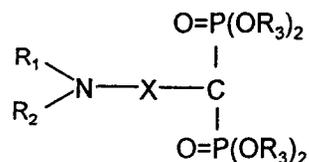
No disclaimer or reexamination certificate has been issued for U.S. Patent No. 4,927,814. A copy of a certificate of correction is annexed at the end of the patent in Exhibit C. A copy of the maintenance fee payment receipt for the 4, 8 and 12th year payments from the record of the U.S. Patent and Trademark Office through its web-site for U.S. Patent No. 4,927,814 is annexed as Exhibit D.

- (9) A Statement That The Patent Claims The Approved Product Or A Method Of Using Or Manufacturing The Approved Product, And A Showing Which Lists Each Applicable Patent Claim And Demonstrates The Manner In Which At Least One Such Patent Claim Reads On (i) The Approved Product, If The Listed Claims Include Any Claim To The Approved Product; (ii) The Method Of Using The Approved Product If The Listed Claim Include Any Claim To The Method Of Using The Approved Product; And (iii) The Method Of Manufacturing The Approved Product, If The Listed Claim Include Any Claim To The Method Of Manufacturing The Approved Product

U.S. Patent No. 4,927,814 claims the approved product, a method of treatment or prophylaxis using the approved product, and a pharmaceutical composition containing the approved product in claims 1, 2, 4 and 6-12.

Claim 1, as corrected by the certificate of correction, reads as follows:

1. A diphosphonate compound of the formula:



wherein

R₁ is methyl or n-propyl which is optionally substituted by phenyl or cyclohexyl,

R₂ is isobutyl, pentyl, nonyl or benzyl wherein said aliphatic hydrogen is optionally substituted by phenyl or oxygen, and wherein said oxygen is an ester or an ether,

R₃ is hydrogen,

X is ethylene, and

Y is hydroxyl; and the pharmacologically acceptable salt thereof.

When R₁ is methyl, R₂ is pentyl, R₃ is H, X is ethyl and Y is hydroxy, claim 1 reads on the approved product.

Claim 2 reads as follows:

2. A disphonate compound of claim 1, wherein R₁ is methyl.

When R₂ is pentyl, R₃ is H, X is ethyl and Y is hydroxy, claim 2 reads on the approved product.

Claim 4 reads as follows:

4. The diphosphonate compound of claim 1 designated 1-hydroxy-3-(N-methyl--N-pentylamino)-propane-1,1-diphosphonic acid and the physiological active salt thereof.

Claim 4 reads on the approved product.

Claim 6 reads as follows:

6. A method for the treatment or prophylaxis of calcium metabolism disturbance or disease comprising administering a pharmaceutically effective amount of the compound of claim 1.

The approved product is covered by claim 1. (see above)

Since the FDA approved indication (treatment and prevention of osteoporosis in postmenopausal women) falls within the treatment of calcium metabolism disturbance or disease, claim 6 reads on the use of the approved product.

Claim 7 reads as follow:

7. The method of claim 6 wherein 0.01-10 mg P/kg of the pharmaceutically acceptable diphosphonate compound are administered per day.

Administrating the Boniva' Tablets (having an active ingredient of 2.813 mg of ibandronate sodium monohydrate, equivalent to 2.5 mg free acid - see package insert) is within the scope of claim 7.

Claim 8 reads as follows:

8. A method for the treatment or prophylaxis of calcium metabolism disturbance or disease comprising administering a pharmaceutically effective amount of at least one of the compounds designated 1-hydroxy-3-(N-methyl-N-nonylamino)-propane-1,1-diphosphonic acid, 1-hydroxy-3-(N-methyl-N-pentylamino)-propane-1,1-diphosphonic acid and 1-hydroxy-3-(N-isobutyl-N-methylalino)-propane-1,1-diphosphonic acid.

Since the FDA approved indication (treatment and prevention of osteoporosis in postmenopausal women) falls under the treatment of calcium metabolism disturbance or disease, claim 8 reads on the use of the approved product.

Claim 9 reads as follows:

9. The method of claim 8 wherein 0.01-10 mg P/kg of the pharmaceutically acceptable diphosphonate are administered per day.

Administrating the Boniva™ Tablets (having an active ingredient of 2.813 mg of ibandronate sodium monohydrate, equivalent to 2.5 mg free acid - see package insert) is within the scope of claim 9.

Claim 10 reads as follows:

10. A pharmaceutical composition for the treatment of prophylaxis or calcium metabolism disturbance or disease containing an effective amount of at least one compound of claim 1 in a pharmaceutically acceptable carrier.

The approved product is covered by claim 1. (see above)

Since the FDA approved indication (treatment and prevention of osteoporosis in postmenopausal women) falls within the treatment of calcium metabolism disturbance or disease, claim 10 reads on the composition for the approved product.

Claim 11 reads as follows:

11. A pharmaceutical composition for the treatment or prophylaxis of calcium metabolism disturbance or disease containing an effective amount of at least one compound of claim 2 in a pharmaceutically acceptable carrier.

The approved product is covered by claim 2. (see above)

Since the FDA approved indication (treatment and prevention of osteoporosis in postmenopausal women) falls within the treatment of calcium metabolism disturbance or disease, claim 11 reads on the composition for the approved product.

Claim 12 reads as follows:

12. A pharmaceutical composition for the treatment of prophylaxis of calcium metabolism disturbance or disease containing an effective amount in a pharmaceutically

acceptable carrier of at least one compound designated 1-hydroxy-3-(N-methyl-N-nonylamino)-propane-1,1-diphosphonic acid, 1-hydroxy-3-(N-methyl-N-pentylamino)-propane-1,1-diphosphonic acid and 1-hydroxy-3-(N-isobutyl-N-methylalino)-propane-1,1diphosphonic acid.

1-hydroxy-3-(N-methyl-N-pentylamino)-propane-1,1-diphosphonic acid and the physiological active salt thereof reads on the approved product.

Since the FDA approved indication (treatment and prevention of osteoporosis in postmenopausal women) falls under the treatment of calcium metabolism disturbance or disease, claim 12 reads on the composition for the approved product.

In summary, as demonstrated above, claims 1, 2, 4, and 6-12 read on the approved product.

(10) A Statement, Beginning on a New Page, of The Relevant Dates And Information Pursuant To 35 U.S.C. § 156(g) In Order To Enable The Secretary Of Health and Human Services or the Secretary of Agriculture, As Appropriate, To Determine the Applicable Regulatory Review Period as Follows (i): For A Patent Claiming A Human Drug Product, Antibiotic, or Human Biological Product, The Effective Date Of The Investigational New Drug (IND) Application And The IND Number; The Date On Which A New Drug Application (NDA) or a Product License Application (PLA) Was Initially Submitted And The NDA or PLA Number And The Date On which The NDA Was Approved or the Product License Issued

- | | | |
|----|--|--|
| a) | Effective date of the investigational new drug application (IND) and IND number: | May 15, 1996
(Exhibit E)
IND No. 50,378 |
| b) | Date on which a New Drug Application (NDA) was initially submitted and NDA number: | July 15, 2002
(Exhibit F)
NDA No. 21-455 |
| c) | Date on which NDA was approved: | May 16, 2003
(Exhibit B) |

(11) A Brief Description Beginning On A New Page Of The Significant Activities Undertaken By The Marketing Applicant During The Applicable Regulatory Review Period With Respect To The Approved Product And The Significant Dates Applicable To Such Activities

A chronology of significant activities undertaken by applicant during the regulatory review period with respect to the approved product is annexed as Exhibit G. This Exhibit specifically is directed to the communications between applicant and the FDA. The Exhibit provides the nature of each correspondence with the FDA, including a brief summary of its subject matter, and the date of the correspondence. For convenience, the chronology is divided into two sections: "Testing Phase - IND" and "Application Phase - NDA."

If necessary, applicant reserves the right to supplement its chronology in Exhibit G with materials from which it was derived and other evidence related to applicant's conduct in obtaining the approval of Boniva™ Tablets. See, e.g., 21 C.F.R. § 60.32.

- (12) A Statement Beginning On A New Page That In The Opinion Of The Applicant The Patent Is Eligible For The Extension And A Statement As To The Length Of The Extension Claimed, Including How The Length Of Extension Was Determined

Eligibility

Under the law and in the opinion of Applicant, U.S. Patent No. 4,927,814 is eligible for an extension under 35 U.S.C. § 156.

In particular, 35 U.S.C. § 156(a) in its relevant parts, provides that the term of a patent shall be extended if the following requirements are satisfied: (1) the patent claims a product, a method of using a product or a method of manufacturing a product; (2) the term of the patent has not expired before an application for extension is submitted; (3) the term of the patent has never been extended; (4) an application for extension is submitted by the owner of record of the patent or its agent and in accordance with 35 U.S.C. § 156(d); (5) the product has been subject to a regulatory review period as defined in 35 U.S.C. § 156(a) before its commercial marketing or use; and (6) the permission for the commercial marketing or use of the product after the regulatory review period is the first permitted commercial marketing or use of the product under the provision of law under which such regulatory review period occurred.

These requirements are met as follows:

1. U.S. Patent No. 4,927,814 claims a product and a method of use.
2. The term of U.S. Patent No. 4,927,814 presently will expire on July 9, 2007 and thus, the patent has not expired before submission of this Application.
3. The term of U.S. Patent No. 4,927,814 has never been extended under 35 U.S.C. § 156.

4. This Application is submitted by ROCHE, an agent authorized to act on behalf of the patent owner of record of U.S. Patent No. 4,927,814. This Application is submitted in accordance with 35 U.S.C. § 156(d) and 37 C.F.R. § 1.740 within the sixty (60) day period beginning on May 16, 2003 and ending on July 15, 2003. The product received permission for marketing or use under FD&C Act. This Application contains the information required under 35 U.S.C. § 156(d) and 37 C.F.R. § 1.740.
5. The product was subject to a regulatory review period under Sections 505 of the FD&C Act before its commercial marketing or use, as evidenced by the chronology (Exhibit G) and the Letter of Approval from the FDA, dated May 16, 2003 (Exhibit B).
6. The permission for the commercial marketing or use of approved product, after the regulatory review period is the first permitted commercial marketing or use of a product having ibandronate in any form as its active ingredient, under the provisions of the FD&C Act under which such regulatory review period occurred. This is confirmed by the absence of any approved drug application for the active ingredient (ibandronate) of the approved product (Boniva™ Tablets) in any form prior to May 16, 2003.

Accordingly, U.S. Patent No. 4,927,814 satisfies the requirements for an extension under 35 U.S.C. § 156.

Length

In the opinion of Applicants, the term of U.S. patent No. 4,927,814 should be extended for a period of three (3) years and three hundred thirty four (334) days, from June 9, 2007 to and including June 9, 2011.

This extension was determined on the following basis:

Testing Phase (37 C.F.R. § 1.775(c) (1))

For the approved product, that portion of the regulatory review period as defined in 35 U.S.C. § 156 (g) (1) (B) (i) ("Testing Phase") commenced on May 15, 1995 and ended on July 15, 2002, which is 2,252 days.

Application Phase (37 C.F.R. § 1.775(c) (2))

For the approved product, that portion of the regulatory review period as defined under 35 U.S.C. § 156 (g) (1) (B) (ii) ("Application Phase") commenced on July 15, 2002 and ended on May 16, 2003, which is 305 days.

Regulatory Review Period (37 C.F.R. § 1.775(c))

As defined in 35 U.S.C. § 156 (g) (1) (B), the regulatory review period is the sum of the Testing Phase and the Application Phase, which is a total of 2,557 days.

Reduction for Review Prior to the Issue of The Patent (37 C.F.R. § 1.775 (d) (1) (i))

The applicable regulatory review period is reduced by that period of review occurring before and on the date the patent issued.

U.S. Patent No. 4,927,814 (Exhibit C) issued May 22, 1990 and the effective date of the IND was May 15, 1996. Accordingly, no reduction is applicable for review prior to the issue of the patent.

Due Diligence Reduction to Regulatory Review Period (37 C.F.R. § 1.775 (d) (1) (ii))

Under 35 U.S.C. § 156(c) (1), the Testing Phase and Application Phase of the regulatory review period are reduced by the period during which the applicant for the patent extension, in the regulatory review period, did not act with due diligence. In the opinion of the Applicant and illustrated by the chronology in Exhibit G, Applicant acted

with due diligence during both periods of time. Thus, there is no reduction in the regulatory review period because of lack of due diligence.

One-Half Testing Phase Reduction (37 C.F.R. § 1.775 (d) (1) (iii))

Under 35 U.S.C. § 156(c) (2), the 2,557 day regulatory review period is reduced by one-half of the 2,252 day Testing Phase. One-half of the Testing Phase is 1,126 days. Thus, the 2,557 day regulatory review period is reduced by 1,126 days, leaving a final revised regulatory review period of 1,431 days.

Fourteen Year Cap (37 C.F.R. § 1.775 (d) (2) - (4))

Under 35 U.S.C. § 156(c) (3), should the period of time remaining in the term of the patent after the date of approval when added to the period of extension exceeds fourteen (14) years, the period of extension is reduced so that the total of both such periods does not exceed fourteen (14) years. In applying section 156(c) (3), the final revised regulatory review period as calculated above (1,431 days) is added onto the end of the original term of the patent, July 9, 2007, resulting in a date of June 9, 2011. Alternatively, fourteen (14) years is added to the NDA approval date (May 16, 2003) resulting in a date of May 14, 2017. The earlier of the above two dates, June 9, 2011 is thus selected.

Two and Five Year Extension Limits (37 C.F.R. § 1.775 (d) (5) & (6))

A patent issued after September 24, 1984 is limited to a maximum extension of five years.

U.S. Patent No. 4,927,814 (Exhibit C) issued on May 22, 1990. Accordingly, the patent is eligible for an extension of up to five years.

U.S. Patent No. 4,927,814
Issue Date: May 22, 1990

As set forth above, the term of U.S. Patent No. 4,927,814 is eligible for an extension of three (3) years and three hundred thirty four (334) days from July 9, 2007 to June 9, 2011.

(13) **A Statement That Applicant Acknowledges A Duty To Disclose To The Commissioner Of Patents And Trademarks And The Secretary Of Health And Human Services Any Information Which Is Material To The Determination Of Entitlement To The Extension Sought**

Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks ("the Commissioner") and the Secretary of Health and Human Services ("the Secretary") any information which is material to any determinations of entitlement to the extension sought in the Application.

Applicant brings to the Commissioner's and the Secretary's attention the following U.S. patents assigned to Boehringer Mannheim GmbH, Roche Diagnostic Inc. or Hoffmann - La Roche Inc.:

U.S. Patent No. 5,366,965 covering methods for treating or preventing osteoporosis, including regimens for intermittent dosing of bone resorption inhibiting polyphosphonate compound or a pharmaceutically acceptable salt or ester of any such compound;

U.S. Patent No. 5,662,918 covering pharmaceutical preparations that are stable on storage, which contain at least one diphosphonic acid and/or at least one physiologically acceptable salt of such an acid as the active substance;

U.S. Patent No. 6,143,326 covering well tolerated pharmaceutical compositions for oral application, containing ibandronate or a physiologically tolerable salt thereof as active substance;

U.S. Patent No. 4,927,814
Issue Date: May 22, 1990

U.S. Patent No. 6,476,008 covering the use of diphosponic acids or physiologically compatible salts or esters thereof for preventive treatment or after-effects of extension of urine bladder or replacement thereof;

U.S. Patent No. 4,942,157 covering diphosphonate derivatives as well as the pharmaceutically acceptable salts thereof, and processes for the preparation of these diphosphonate acid derivatives and pharmaceutical compositions containing thereof the prophylaxis treatment of diseases or disturbances of calcium metabolism;

U.S. Patent No. 6,294,196 covering a solid pharmaceutical form of administration containing a diphosphonic acid or a physiologically compatible salt thereof as the active substance; and

U.S. Patent No. 6,419,955 covering a process for the preparation of bisphosphate-containing pharmaceutical compositions for oral administration wherein the active substance is wet-granulated in a fluidized-bed granulator and the wet granulate is dried in the fluidized bed granulator.

These U.S. patents have been listed because they relate to ibandronate, and some could have been subject of this Application, but have not been so chosen.

Applicant also brings to the Commissioner's and Secretary's attention that Phase I and Phase II trials were conducted in Europe by Boehringer Mannheim GmbH, located in Mannheim, Germany. Boehringer Mannheim GmbH became Roche Diagnostics GmbH. The information submitted in the NDA in support of the safety and efficacy of the BonivaTM Tablets for the treatment and prevention of post-menopausal osteoporosis was derived from studies conducted under INDs 50,378 and 46,266 and from foreign preclinical and clinical studies conducted under the sponsorship of F. Hoffmann-La Roche and Company, Ltd., Basel, Switzerland, an affiliate of ROCHE. This information is summarized in Exhibits E and F.

14) The Prescribed Fee for Receiving and Acting Upon
the Application for Extension

Applicant encloses (in duplicate) a transmittal letter requesting the amount of \$1120.00 under 37 C.F.R. § 1.200)(1) be charged to Account No. 08-2525.

(15) The Name, Address and Telephone Number Of The
Person to Whom Inquiries and Correspondence
Relating To The Application For Patent Term
Extension Are To Be Directed

Please address all correspondence to:

George W. Johnston
Hoffmann-La Roche Inc.
Patent Law Department
340 Kingsland Street
Nutley, New Jersey 07110

Please direct all telephone calls to:

Bernard Lau
(973) 235-4387

Other Matters:

(a) Additional Copies of Application

Applicant hereby submits two additional copies of this Application in compliance with 37 C.F.F. § 1.740. Additionally, Applicant submits an additional two copies, for a total of five copies under MPEP 2753.

(b) An Oath or Declaration

Applicant attaches a First Declaration and Power of Attorney for Application for Extension of Patent Term Under 35 U.S.C. §156, signed by authorized personnel of

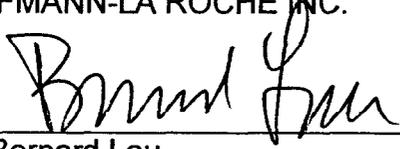
U.S. Patent No. 4,927,814
Issue Date: May 22, 1990

Roche Diagnostics GmbH (formerly named Boehringer Mannheim GmbH), which is the assignee and owner of record of U.S. Patent No. 4,927,814 to appoint Hoffmann-La Roche as an agent for Roche Diagnostics under 35 U.S.C. §156 with the authority to sign, submit and prosecute this Application and transact all business in the U.S. Patent and Trademark Office and with the U.S. Secretary of Health and Human Services connected therewith, and a Second Declaration and Power of Attorney for Application for Extension of Patent Term Under 35 U.S.C. §156, signed by an officer of ROCHE, who is authorized to practice before the U.S. Patent and Trademark Office and who has general authority to act on ROCHE's behalf in patent matters.

Request for Extension

Having included in this Application all of the requisite information under 35 U.S.C. § 156 and 37 C.F.R. § 1.740, Applicant requests (i) an extension of U.S. Patent No. 4,927,814 for three (3) years three hundred thirty four (334) days from July 9, 2007 to and including June 9, 2011, by reason of its claims encompassing the approved product and its salts and esters as a single entity or in combination with another active ingredient and (ii) certification that it is entitled to the rights derived from this patent as set forth in 35 U.S.C. § 156(b).

Respectfully submitted,
HOFFMANN-LA ROCHE INC.

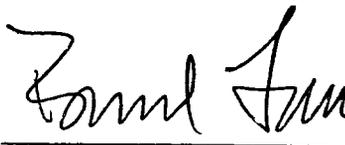
By: 

Bernard Lau
Senior Counsel
Registration No. 38,218
Date: July 11, 2003

U.S. Patent No. 4,927,814
Issue Date: May 22, 1990

Certification

The undersigned certifies that this Application for Extension of Patent Term Under 35 U.S.C. § 156 including its exhibits is being submitted as duplicate originals.

By: 
Bernard Lau
Registration No. 38,218
Date: July 11, 2003

brl:132047



PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re United States Patent No. 4,927,814

Inventors: Gall et al.

Issue Date: May 22, 1990

For: DIPHOSPHONATE DERIVATIVES, PHARMACEUTICAL COMPOSITIONS
AND METHODS OF USE

**FIRST DECLARATION AND POWER OF ATTORNEY FOR
APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. §156**

Nutley, New Jersey 07110
July 10, 2003

Mail Stop Patent Ext.
Commissioner for Patents
P.O. Box 1450
Arlington, VA 22313-1450

Dear Sir:

We, Hubert Witte and Herbert Fouquet, both Senoir Patent Counsels of the patent department of F. Hoffmann-La Roche Ltd., which is an affiliated company of Roche Diagnostics GmbH ("ROCHE DIAGNOSTICS")(formerly named Boehringer Mannheim GmbH), and the owner of the above-identified patent, designate Hoffmann-La Roche Inc. as an agent to submit the attached Application for Extension of Patent Term Under 35 U.S.C. § 156, of the same date as this Declaration, declare that:

- (1) Boehringer Mannheim GmbH is the assignee and owner of U.S. Patent No. 4,927,814;
- (2) Boehringer Mannheim GmbH has changed its corporate name to ROCHE DIAGNOSTICS;

U.S. Patent No. 4,927,814
Issue Date: May 22, 1990

(3) we have general authority from ROCHE DIAGNOSTICS to act on its behalf in patent matters; and

(4) we hereby appoint Hoffmann-La Roche Inc. as an agent for ROCHE DIAGNOSTICS under 35 U.S.C. § 156 with the authority to sign, submit and prosecute this Application and transact all business in the U.S. Patent and Trademark Office and with the U.S. Secretary of Health and Human Services connected therewith.

Send correspondence to: George W. Johnston
Hoffmann-La Roche Inc.
Patent Law Department
340 Kingsland Street
Nutley, New Jersey 07110

Direct telephone calls to: Bernard Lau
(973) 235-4387

We declare further that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this patent extension application or any extension of U.S. Patent No. 4,927,814.

Respectfully submitted,
ROCHE DIAGNOSTIC GMBH


By: _____

Dr. Hubert Witte
authorized signatory

Dr. Herbert Fouquet
holder of procuration

Date: July 3, 2003



PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re United States Patent No. 4,927,814

Inventors: Gall et al.

Issue Date: May 22, 1990

For: DIPHOSPHONATE DERIVATIVES, PHARMACEUTICAL COMPOSITIONS
AND METHODS OF USE

**SECOND DECLARATION AND POWER OF ATTORNEY FOR
APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. §156**

Nutley, New Jersey 07110
July 11, 2003

Mail Stop Patent Ext.
Commissioner for Patents
P.O. Box 1450
Arlington, VA 22313-1450

Sir:

I, George W. Johnston, a Vice President of Hoffmann-La Roche Inc. ("ROCHE"), which submits the attached Application for Extension of Patent Term Under 35 U.S.C. § 156, of the same date as this Declaration, declare that:

- (1) Roche Diagnostics GmbH (formerly named Boehringer Mannheim GmbH) is the owner of U.S. Patent No. 4,927,814;
- (2) Roche Diagnostics GmbH has appointed ROCHE and in particular the undersigned as an agent under 35 U.S.C. § 156 with the authority to sign, submit and prosecute this Application and transact all business in the U.S. Patent and Trademark Office and with the U.S. Secretary of Health and Human Services connected therewith.

(3) I am a patent attorney authorized to practice before the Patent and Trademark Office and have authority from ROCHE to act on its behalf in patent matters and authority from Roche Diagnostics GmbH to act on its behalf in this matter;

(4) I have reviewed and understand the contents of the Application being submitted for extension of the term of U.S. Patent No. 4,927,814 pursuant to 35 U.S.C. § 156 and 37 C.F.R. § 1.710 et seq;

(5) I believe this patent is subject to extension under 35 U.S.C. § 156 and 37 C.F.R. § 1.710;

(6) I believe an extension of the length claimed is justified under 35 U.S.C. § 156 and the applicable regulations; and

(7) I believe the patent for which the extension is being sought meets the conditions for extension of the term of a patent as set forth in 35 U.S.C. § 156, and more particularly, in 37 C.F.R. § 1.720.

I hereby appoint the following attorneys as agents under 35 U.S.C. § 156 with the authority to sign, submit and prosecute this Application and transact all business in the Patent and Trademark Office and with the Secretary of Health and Human Services connected therewith: George W. Johnston (Reg. No. 28090), Dennis P. Tramaloni (Reg. No. 28542), Patricia S. Rocha-Tramaloni (Reg. No. 31054) and Bernard Lau (Reg. No. 38218).

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PATENT APPLICATION

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**EXHIBITS FOR APPLICATION FOR
EXTENSION OF PATENT TERM UNDER 35 U.S.C. §156**

Exhibit A - Approved Package Insert

Exhibit B - FDA Approval Letter

Exhibit C - U.S. Patent No. 4,927,814

Exhibit D - Maintenance Fee Statements

Exhibit E - IND Application and Receipt

Exhibit F - NDA Application and Receipt

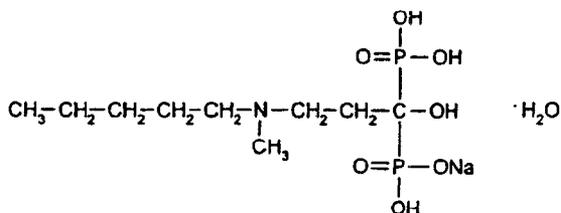
Exhibit G - Chronology Listing of Regulatory Interactions for INDs and NDAs



BONIVA™
(ibandronate sodium)
TABLETS

DESCRIPTION

BONIVA (ibandronate sodium) is a nitrogen-containing bisphosphonate that inhibits osteoclast-mediated bone resorption. The chemical name for ibandronate sodium is 3-(*N*-methyl-*N*-pentyl)amino-1-hydroxypropane-1,1-diphosphonic acid, monosodium salt, monohydrate with the molecular formula $C_9H_{22}NO_7P_2Na \cdot H_2O$ and a molecular weight of 359.24. Ibandronate sodium is a white- to off-white powder. It is freely soluble in water and practically insoluble in organic solvents. Ibandronate sodium has the following structural formula:



BONIVA is available as a white, oblong, 2.5-mg film-coated tablet for oral administration. One tablet contains 2.813 mg ibandronate monosodium monohydrate, equivalent to 2.5 mg free acid. BONIVA also contains the following inactive ingredients: lactose monohydrate, povidone, microcrystalline cellulose, crospovidone, purified stearic acid, colloidal silicon dioxide, and purified water. The tablet film coating contains hypromellose, titanium dioxide, talc, polyethylene glycol 6000, and purified water.

CLINICAL PHARMACOLOGY

Mechanism of Action

The action of ibandronate on bone tissue is based on its affinity for hydroxyapatite, which is part of the mineral matrix of bone. Ibandronate inhibits osteoclast activity and reduces bone resorption and turnover. In postmenopausal women, it reduces the elevated rate of bone turnover, leading to, on average, a net gain in bone mass.

Pharmacokinetics

Absorption

The absorption of ibandronate occurs in the upper gastrointestinal tract. After a 2.5 mg oral dose, the time to maximum observed plasma ibandronate concentrations ranged from 0.5 to 2 hours (median 1 hour) in fasted healthy postmenopausal women. The mean oral bioavailability of 2.5 mg ibandronate was about 0.6% compared to intravenous dosing. The extent of absorption is impaired by food or beverages (other than plain water). The oral bioavailability of ibandronate is reduced by about 90% when BONIVA is administered with a standard breakfast in comparison with bioavailability observed in fasted subjects. There is no meaningful reduction in bioavailability when ibandronate is taken at least 60 minutes before a meal.

However, both bioavailability and the effect on bone mineral density (BMD) are reduced when food or beverages are taken less than 60 minutes following an ibandronate dose.

Distribution

After absorption, ibandronate either rapidly binds to bone or is excreted into urine. In humans, the apparent terminal volume of distribution is at least 90 L, and the amount of dose removed from the circulation via the bone is estimated to be 40% to 50% of the circulating dose. In vitro protein binding in human serum was 99.5% to 90.9% over an ibandronate concentration range of 2 to 10 ng/mL in one study and approximately 85.7% over a concentration range of 0.5 to 10 ng/mL in another study.

Metabolism

There is no evidence that ibandronate is metabolized in humans.

Elimination

The portion of ibandronate that is not removed from the circulation via bone absorption is eliminated unchanged by the kidney (approximately 50% to 60% of the absorbed dose). Unabsorbed ibandronate is eliminated unchanged in the feces.

The range of observed apparent half-lives is broad and dependent on the dose studied and on assay sensitivity, but the apparent terminal half-life is generally in the range of 10 to 60 hours. However, early plasma levels fall quickly, reaching 10% of peak values within 3 and 8 hours after intravenous or oral administration, respectively.

Total clearance of ibandronate is low, with average values in the range 84 to 160 mL/min. Renal clearance (about 60 mL/min in healthy postmenopausal females) accounts for 50% to 60% of total clearance and is related to creatinine clearance. The difference between the apparent total and renal clearances likely reflects bone uptake of the drug.

Special Populations

Pediatrics

The pharmacokinetics of ibandronate has not been studied in patients <18 years of age.

Gender

The bioavailability and pharmacokinetics of ibandronate are similar in both men and women.

Geriatric

Since ibandronate is not known to be metabolized, the only difference in ibandronate elimination for geriatric patients versus younger patients is expected to relate to progressive age-related changes in renal function (see Special Populations: **Renal Impairment**).

Race

Pharmacokinetic differences due to race have not been studied.

Renal Impairment

Renal clearance of ibandronate in patients with various degrees of renal impairment is linearly related to creatinine clearance (CL_{cr}).

Following a single dose of 0.5 mg ibandronate by intravenous administration, patients with CL_{cr} 40 to 70 mL/min had 55% higher exposure (AUC_∞) than the exposure observed in subjects with CL_{cr} >90 mL/min. Patients with CL_{cr} <30 mL/min had more than a two-fold increase in exposure compared to the exposure for healthy subjects (see DOSAGE AND ADMINISTRATION: **Patients with Renal Impairment**).

Hepatic Impairment

No studies have been performed to assess the pharmacokinetics of ibandronate in patients with hepatic impairment since ibandronate is not metabolized in the human liver.

Drug Interactions

Ibandronate does not undergo hepatic metabolism and does not inhibit the hepatic cytochrome P450 system.

Ibandronate is eliminated by renal excretion. Based on a rat study, the ibandronate secretory pathway does not appear to include known acidic or basic transport systems involved in the excretion of other drugs.

Products containing calcium and other multivalent cations (such as aluminum, magnesium, iron), including milk, food, and antacids are likely to interfere with absorption of ibandronate, which is consistent with findings in animal studies.

H2 Blockers and Proton Pump Inhibitors (PPIs)

A pharmacokinetic interaction study in healthy volunteers demonstrated that 75 mg ranitidine (25 mg injected intravenously 90 and 15 minutes before and 30 minutes after ibandronate administration) increased the oral bioavailability of 10 mg ibandronate by about 20%. This degree of increase is not considered to be clinically relevant.

Tamoxifen

A pharmacokinetic interaction study in healthy postmenopausal women demonstrated that there was no interaction between oral 30 mg tamoxifen and intravenous 2 mg ibandronate.

Pharmacodynamics

Osteoporosis is characterized by decreased bone mass and increased fracture risk, most commonly at the spine, hip, and wrist. The diagnosis can be confirmed by a finding of low bone mass, evidence of fracture on x-ray, a history of osteoporotic fracture, or height loss or kyphosis indicative of vertebral fracture. While osteoporosis occurs in both men and women, it is most common among women following menopause. In healthy humans, bone formation and resorption are closely linked; old bone is resorbed and replaced by newly formed bone. In postmenopausal osteoporosis, bone resorption exceeds bone formation, leading to bone loss and increased risk of fracture. After menopause, the risk of fractures of the spine and hip increases; approximately 40% of 50-year-old women will experience an osteoporosis-related fracture during their remaining lifetimes.

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

Treatment with 2.5 mg daily BONIVA resulted in decreases in biochemical markers of bone turnover, including urinary C-terminal telopeptide of type I collagen (uCTX) and serum osteocalcin, to levels similar to those in premenopausal women. Changes in markers of bone formation were observed later than changes in resorption markers, as expected, due to the coupled nature of bone resorption and formation. Treatment with 2.5 mg daily BONIVA decreased levels of uCTX within 1 month of starting treatment and decreased levels of osteocalcin within 3 months. Bone turnover markers reached a nadir of approximately 64% below baseline values by 6 months of treatment and remained stable with continued treatment for up to 3 years.

Following treatment discontinuation, there is a return to pretreatment baseline rates of elevated bone resorption associated with postmenopausal osteoporosis.

Clinical Studies

Treatment of Postmenopausal Osteoporosis

Effect on Vertebral Fracture

The effectiveness and safety of BONIVA were demonstrated in a randomized, double-blind, placebo-controlled, multinational study (Treatment Study) of 2946 women aged 55 to 80 years, who were on average 21 years post-menopause, who had lumbar spine BMD 2 to 5 SD below the premenopausal mean (T-score) in at least one vertebra [L1-L4], and who had one to four prevalent vertebral fractures. BONIVA was evaluated at oral doses of 2.5 mg daily and 20 mg intermittently. The main outcome measure was the occurrence of new radiographically diagnosed, vertebral fractures after 3 years of treatment. The diagnosis of an incident vertebral fracture was based on both qualitative diagnosis by the radiologist and quantitative morphometric criterion. The morphometric criterion required the dual occurrence of 2 events: a relative height ratio or relative height reduction in a vertebral body of at least 20%, together with at least a 4 mm absolute decrease in height. All women received 400 IU vitamin D and 500 mg calcium supplementation per day.

BONIVA 2.5 mg daily significantly reduced the incidence of new vertebral and of new and worsening vertebral fractures. Over the course of the 3-year study, the risk for vertebral fracture was 9.6% in the placebo-treated women and 4.7% in the women treated with BONIVA 2.5 mg ($p < 0.001$) (see Table 1).

Table 1 Effect of BONIVA on the Incidence of Vertebral Fracture in the Three-Year Osteoporosis Treatment Study*

	Proportion of Patients with Fracture (%)			
	Placebo n=975	BONIVA 2.5 mg daily n=977	Absolute Risk Reduction (%) 95% CI	Relative Risk Reduction (%) 95% CI
New Vertebral Fracture 0-3 Year	9.6	4.7	4.9 (2.3, 7.4)	52** (29, 68)
New and Worsening Vertebral Fracture 0-3 Year	10.4	5.1	5.3 (2.6, 7.9)	52 (30, 67)
Clinical (Symptomatic) Vertebral Fracture 0-3 Year	5.3	2.8	2.5 (0.6, 4.5)	49 (14, 69)

*The endpoint value is the value at the study's last time point, 3 years, for all patients who had a fracture identified at that time; otherwise, the last post-baseline value prior to the study's last time point is used.

**p=0.0003 vs. placebo

Effect on Nonvertebral Fractures

There was a similar number of nonvertebral osteoporotic fractures reported in women treated with BONIVA [9.1%, (CI: 7.1%, 11.1%)] and placebo [8.2%, (CI: 6.3%, 10.2%)]. The two treatment groups were also similar with regard to the number of fractures reported at the individual non-vertebral sites: pelvis, femur, wrist, forearm, rib, and hip.

Effect on Bone Mineral Density (BMD)

BONIVA significantly increased BMD at the lumbar spine and hip relative to treatment with placebo. In the 3-year osteoporosis treatment study, BONIVA 2.5 mg produced increases in lumbar spine BMD that were progressive over 3 years of treatment and were statistically significant relative to placebo at 6 months and at all later timepoints. Lumbar spine BMD increased by 6.4% after 3 years of treatment with 2.5 mg daily BONIVA compared with 1.4 % in the placebo group. Table 2 displays the significant increases in BMD seen at the lumbar spine, total hip, femoral neck, and trochanter compared to placebo. Thus, overall BONIVA reverses the loss of BMD, a central factor in the progression of osteoporosis.

Table 2 Mean Percent Change in BMD from Baseline to Endpoint in Patients Treated with BONIVA 2.5mg or Placebo in the 3-Year Osteoporosis Treatment Study*

	Placebo	BONIVA 2.5 mg
Lumbar spine	1.4 (n = 693)	6.4 (n = 712)
Total Hip	-0.7 (n = 638)	3.1 (n = 654)
Femoral Neck	-0.7 (n = 683)	2.6 (n = 699)
Trochanter	0.2 (n = 683)	5.3 (n = 699)

*The endpoint value is the value at the study's last time point, 3 years, for all patients who had BMD measured at that time; otherwise the last post-baseline value prior to the study's last time point is used.

Bone Histology

The effects of BONIVA 2.5 mg daily on bone histology were evaluated in iliac crest biopsies from 16 women after 22 months of treatment and 20 women after 34 months of treatment.

The histological analysis of bone biopsies showed bone of normal quality and no indication of osteomalacia or a mineralization defect.

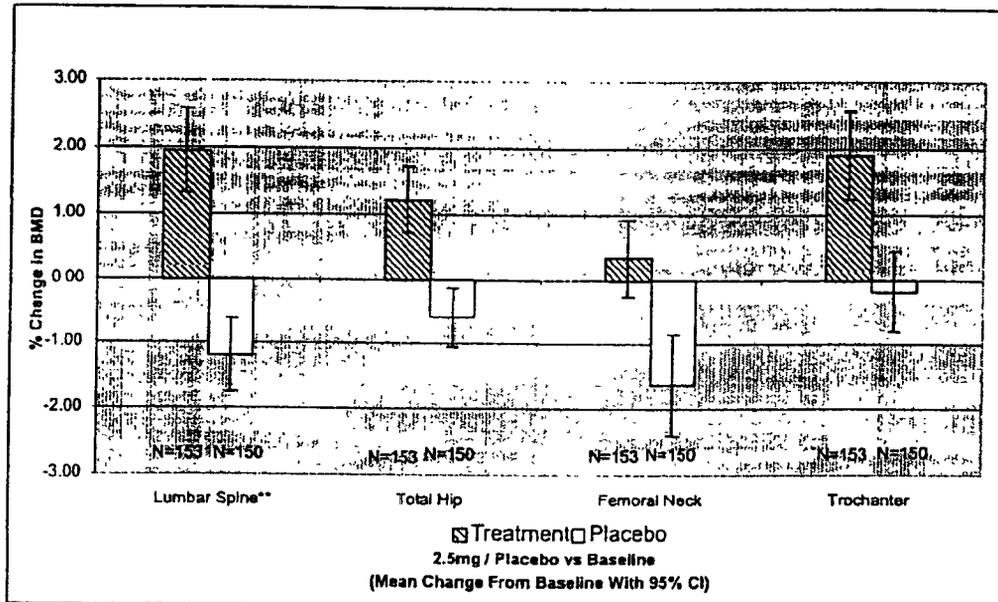
Prevention of Postmenopausal Osteoporosis

BONIVA 2.5 mg prevented bone loss in a majority of women in a randomized, double-blind, placebo-controlled 2-year study (Prevention Study) of 653 postmenopausal women without osteoporosis at baseline. Women were aged 41 to 82 years, were on average 8.5 years post-menopause, and had lumbar spine BMD T-scores >-2.5 . Women were stratified according to time since menopause (1 to 3 years, >3 years) and baseline lumbar spine BMD (T score: >-1 , -1 to -2.5). The study compared daily BONIVA at three dose levels (0.5 mg, 1.0 mg, 2.5 mg) with placebo. All women received 500 mg of supplemental calcium per day.

The primary efficacy measure was the change in BMD of lumbar spine after 2 years of treatment. BONIVA 2.5 mg daily resulted in a mean increase in lumbar spine BMD of 3.1% compared with placebo following 2 years of treatment (see Figure 1). Increases in BMD were seen at 6 months and at all later timepoints. Irrespective of the time since menopause or the degree of pre-existing bone loss, treatment with BONIVA resulted in a higher BMD response at the lumbar spine compared with placebo across all four baseline strata [time since menopause (1-3 years, >3 years) and baseline lumbar spine BMD (T score: >-1 , -1 to -2.5)].

Compared with placebo, treatment with BONIVA 2.5 mg daily increased BMD of the total hip by 1.8%, the femoral neck by 2.0%, and the trochanter by 2.1% (see Figure 1).

Figure 1 Mean Percentage Change in BMD from Baseline to Endpoint in Patients Treated with BONIVA 2.5 mg or Placebo in the Two-Year Osteoporosis Prevention Study*



*The endpoint value is

the value at the study's last time point, 2 years, for all patients who had BMD measured at that time; otherwise the last post-baseline value prior to the study's last time point is used

**lumbar spine BMD $p < 0.001$ vs. placebo

Animal Pharmacology

Animal studies have shown that ibandronate is an inhibitor of osteoclast-mediated bone resorption. In the Schenk assay in growing rats, ibandronate inhibited bone resorption and increased bone volume, based on histologic examination of the tibial metaphyses. There was no evidence of impaired mineralization at the highest dose of 5 mg/kg/day (subcutaneously), which is 1000 times the lowest antiresorptive dose of 0.005 mg/kg/day in this model, and 5000 times the optimal antiresorptive dose of 0.001 mg/kg/day in the aged ovariectomized rat. This indicates that BONIVA administered at therapeutic doses is unlikely to induce osteomalacia.

Long-term daily or intermittent administration of ibandronate to ovariectomized rats or monkeys was associated with suppression of bone turnover and increases in bone mass. Vertebral BMD, trabecular density, and biomechanical strength were increased dose-dependently in rats and monkeys, at doses up to 15 times the human oral 2.5 mg/day dose, based on body surface area (mg/m^2) or AUC comparison. Ibandronate maintained the positive correlation between bone mass and strength at the ulna and femoral neck. New bone formed in the presence of ibandronate had normal histologic structure and did not show mineralization defects.

INDICATIONS AND USAGE

BONIVA is indicated for the treatment and prevention of osteoporosis in postmenopausal women.

Treatment of Osteoporosis

In postmenopausal women with osteoporosis, BONIVA increases BMD and reduces the incidence of vertebral fractures (see CLINICAL STUDIES). Osteoporosis may be confirmed by the presence or history of osteoporotic fracture or by a finding of low bone mass (BMD more than 2 standard deviations below the premenopausal mean [i.e., T score]).

Prevention of Osteoporosis

BONIVA may be considered in postmenopausal women who are at risk of developing osteoporosis and for whom the desired clinical outcome is to maintain bone mass and to reduce the risk of fracture.

Factors such as family history of osteoporosis, early menopause, previous fracture, high bone turnover, reduced BMD (at least 1.0 SD below the premenopausal mean), thin body frame, Caucasian or Asian race, and smoking, are associated with an increased risk of developing osteoporosis and fractures. The presence of these risk factors may be important when considering the use of BONIVA for preventing osteoporosis.

CONTRAINDICATIONS

- Known hypersensitivity to BONIVA or to any of its excipients
- Uncorrected hypocalcemia (see PRECAUTIONS: General)
- Inability to stand or sit upright for at least 60 minutes (see DOSAGE and ADMINISTRATION)

WARNINGS

BONIVA, like other bisphosphonates administered orally may cause upper gastrointestinal disorders such as dysphagia, esophagitis, and esophageal or gastric ulcer (see PRECAUTIONS).

PRECAUTIONS

General

Mineral Metabolism

Hypocalcemia and other disturbances of bone and mineral metabolism should be effectively treated before starting BONIVA therapy. Adequate intake of calcium and vitamin D is important in all patients.

Upper Gastrointestinal Effects

Bisphosphonates administered orally have been associated with dysphagia, esophagitis, and esophageal or gastric ulcers. This association has been reported for bisphosphonates in postmarketing experience but has not been found in most preapproval clinical trials, including those conducted with BONIVA. Therefore, patients should be advised to pay particular attention to and be able to comply with the dosing instructions to minimize the risk of these effects (see DOSAGE AND ADMINISTRATION).

Severe Renal Impairment

BONIVA is not recommended for use in patients with severe renal impairment (creatinine clearance < 30 mL/min).

Information for Patients

Patients should be instructed to read the Patient Information Leaflet carefully before taking BONIVA, to re-read it each time the prescription is renewed and to pay particular attention to the dosing instructions in order to maximize absorption and clinical benefit.

- BONIVA should be taken at least 60 minutes before the first food or drink (other than water) of the day and before any oral medications containing multivalent cations (including antacids, supplements or vitamins).
- To facilitate delivery to the stomach, and thus reduce the potential for esophageal irritation, BONIVA tablets should be swallowed whole with a full glass of plain water (6 to 8 oz) while the patient is standing or sitting in an upright position. Patients should not lie down for 60 minutes after taking BONIVA.
- Plain water is the only drink that should be taken with BONIVA. Please note that some mineral waters may have a higher concentration of calcium and therefore should not be used.
- Patients should not chew or suck the tablet because of a potential for oropharyngeal ulceration.

Patients should receive supplemental calcium and vitamin D if dietary intake is inadequate. Intake of supplemental calcium and vitamin D should be delayed for at least 60 minutes following oral administration of BONIVA in order to maximize absorption of BONIVA.

Physicians should be alert to signs or symptoms signaling a possible esophageal reaction during therapy, and patients should be instructed to discontinue BONIVA and seek medical attention if they develop symptoms of esophageal irritation such as new or worsening dysphagia, pain on swallowing, retrosternal pain, or heartburn.

Drug Interactions

See CLINICAL PHARMACOLOGY: Pharmacokinetics: Drug Interactions

Calcium Supplements/Antacids

Products containing calcium and other multivalent cations (such as aluminum, magnesium, iron) are likely to interfere with absorption of BONIVA. BONIVA should be taken at least 60 minutes before any oral medications containing multivalent cations (including antacids, supplements or vitamins) (see PRECAUTIONS: Information for Patients).

H2 Blockers and Proton Pump Inhibitors (PPIs)

Of over 3500 patients enrolled in the BONIVA osteoporosis Treatment and Prevention Studies, 15% used anti-peptic agents (primarily H2 blockers and PPIs). Among these patients, the incidence of upper gastrointestinal adverse experiences in the patients treated with BONIVA was similar to that in placebo-treated patients.

Aspirin/Nonsteroidal Antiinflammatory Drugs (NSAIDs)

In the large, placebo-controlled osteoporosis Treatment Study, aspirin and nonsteroidal antiinflammatory drugs were taken by 62% of the 2946 patients. Among aspirin or NSAID users, the incidence of upper gastrointestinal adverse events in patients treated with ibandronate 2.5 mg daily (28.9%) was similar to that

in placebo-treated patients (30.7%). However, since aspirin, NSAIDs, and bisphosphonates are all associated with gastrointestinal irritation, caution should be exercised in the concomitant use of aspirin or NSAIDs with BONIVA.

Drug/Laboratory Test Interactions

Bisphosphonates are known to interfere with the use of bone-imaging agents. Specific studies with ibandronate have not been performed.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

In a 104-week carcinogenicity study, doses of 3, 7, or 15 mg/kg/day were administered by oral gavage to Wistar rats (systemic exposures in males and females up to 12 and 7 times, respectively, human exposure at the recommended oral dose of 2.5 mg/day, based on AUC comparison). There were no significant drug-related tumor findings in male or female rats. In a 78-week carcinogenicity study, doses of 5, 20, or 40 mg/kg/day were administered by oral gavage to NMRI mice (exposures in males and females up to 475 and 70 times, respectively, human exposure at the recommended dose of 2.5 mg/day, based on AUC comparison). There were no significant drug-related tumor findings in male or female mice. In a 90-week carcinogenicity study, doses of 5, 20, or 80 mg/kg/day were administered in the drinking water to NMRI mice. A dose-related increased incidence of adrenal subcapsular adenoma/carcinoma was observed in female mice, which was statistically significant at 80 mg/kg/day (220 to 400 times human exposure at the recommended oral dose of 2.5 mg/day, based on AUC comparison). The relevance of these findings to humans is unknown.

Mutagenesis

There was no evidence for a mutagenic or clastogenic potential of ibandronate in the following assays: *in vitro* bacterial mutagenesis assay in *Salmonella typhimurium* and *Escherichia coli* (Ames test), mammalian cell mutagenesis assay in Chinese hamster V79 cells, and chromosomal aberration test in human peripheral lymphocytes, each with and without metabolic activation. Ibandronate was not genotoxic in the *in vivo* mouse micronucleus tests for chromosomal damage.

Impairment of Fertility

In female rats treated from 14 days prior to mating through gestation, decreases in fertility, corpora lutea, and implantation sites were observed at an oral dose of 16 mg/kg/day (45 times human exposure at the recommended oral dose of 2.5 mg/day, based on AUC comparison).

Pregnancy

Pregnancy Category C

In female rats given oral doses of 1, 4, or 16 mg/kg/day beginning 14 days before mating and continuing through lactation, maternal deaths were observed at the time of delivery in all dose groups (≥ 3 times human exposure at the recommended oral dose of 2.5 mg/day, based on AUC comparison). Perinatal pup loss in dams given 16 mg/kg/day (45 times human exposure at the recommended oral dose of 2.5 mg/day, based on AUC comparison) was likely related to maternal dystocia. In pregnant rats given oral doses of 6, 20, or 60 mg/kg/day during gestation, calcium supplementation (32 mg/kg/day by subcutaneous injection from gestation day 18 to parturition) did not completely prevent dystocia and periparturient mortality in any of

the treated groups (≥ 16 times human exposure at the recommended oral dose of 2.5 mg/day, based on AUC comparison). A low incidence of postimplantation loss was observed in rats treated from 14 days before mating throughout lactation or during gestation only, at doses causing maternal dystocia and periparturient mortality. In pregnant rats dosed orally with 1, 5, or 20 mg/kg/day from gestation day 17 through lactation day 21 (following closure of the hard palate through weaning), maternal toxicity, including dystocia and mortality, and perinatal and postnatal pup mortality were observed at doses ≥ 5 mg/kg/day (equivalent to human exposure at the recommended oral dose of 2.5 mg/day, based on AUC comparison). Periparturient mortality has also been observed with other bisphosphonates and appears to be a class effect related to inhibition of skeletal calcium mobilization resulting in hypocalcemia and dystocia.

Exposure of pregnant rats during the period of organogenesis resulted in an increased fetal incidence of RPU (renal pelvis ureter) syndrome at oral doses ≥ 10 mg/kg/day (≥ 30 times human exposure at the recommended oral dose of 2.5 mg/day, based on AUC comparison). Impaired pup neuromuscular development (cliff avoidance test) was observed at 16 mg/kg/day when dams were dosed from 14 days before mating through lactation (45 times human exposure at the recommended oral dose of 2.5 mg/day, based on AUC comparison).

In pregnant rabbits given oral doses of 1, 4, or 20 mg/kg/day during gestation, dose-related maternal mortality was observed in all treatment groups (≥ 8 times the recommended human oral dose of 2.5 mg/day, based on body surface area comparison, mg/m^2). The deaths occurred prior to parturition and were associated with lung edema and hemorrhage. No significant fetal anomalies were observed.

There are no adequate and well-controlled studies in pregnant women. BONIVA should be used during pregnancy only if the potential benefit justifies the potential risk to the mother and fetus.

Nursing Mothers

In lactating rats treated with intravenous doses of 0.08 mg/kg, ibandronate was present in breast milk at concentrations of 8.1 to 0.4 ng/mL from 2 to 24 hours after dose administration. Concentrations in milk averaged 1.5 times plasma concentrations. It is not known whether BONIVA is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when BONIVA is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Of the patients receiving BONIVA in postmenopausal osteoporosis studies, 52% were over 65 years of age, and 10% were over 75 years of age. No overall differences in effectiveness or safety were observed between these patients and younger patients but greater sensitivity in some older individuals cannot be ruled out.

ADVERSE REACTIONS

Oral BONIVA has been studied in over 3900 patients in postmenopausal osteoporosis trials of up to 3 years duration. The overall adverse event profile of BONIVA 2.5 mg once daily in these studies was similar to that of placebo.

Treatment and Prevention of Postmenopausal Osteoporosis

Most adverse events were mild or moderate and did not lead to discontinuation. The incidence of serious adverse events was 20% in the placebo group and 23% in the BONIVA 2.5 mg daily group. The percentage of patients who withdrew from treatment due to adverse events was approximately 17% in both the BONIVA 2.5 mg group and the placebo group. Overall, and according to body system, there was no difference between BONIVA and placebo, with adverse events of the digestive system being the most common reason for withdrawal.

Table 3 lists adverse events from the Treatment and Prevention Studies reported in $\geq 2\%$ of patients and in more patients treated with BONIVA than patients treated with placebo. Adverse events are shown without attribution of causality.

Table 3 Adverse Events Occurring at a Frequency $\geq 2\%$ and in More Patients Treated with BONIVA than in Patients Treated with Placebo in the Osteoporosis Treatment and Prevention Studies

Body System	Placebo % (n=1134)	BONIVA 2.5mg % (n=1140)
Body as a Whole		
Back Pain	12.2	13.5
Pain in Extremity	6.4	7.8
Infection	3.4	4.3
Asthenia	2.3	3.5
Allergic Reaction	1.9	2.5
Digestive System		
Dyspepsia	9.8	11.9
Diarrhea	5.0	6.8
Tooth Disorder	2.3	3.5
Vomiting	2.1	2.7
Gastritis	1.9	2.2
Metabolic and Nutritional Disorders		
Hypercholesterolemia	4.2	4.8
Musculoskeletal System		
Myalgia	5.1	5.7
Joint Disorder	3.3	3.6
Arthritis	2.7	3.2
Nervous System		
Headache	5.8	6.5
Dizziness	2.6	3.7
Vertigo	2.5	3.0
Nerve Root Lesion	1.9	2.2
Respiratory System		
Upper Respiratory Infection	33.2	33.7
Bronchitis	6.8	10.0
Pneumonia	4.3	5.9
Pharyngitis	1.5	2.5
Urogenital System		
Urinary Tract Infection	4.2	5.5

Ocular Adverse Events

Although not reported in the pre-approval trials of oral ibandronate, reports in the medical literature indicate that bisphosphonates may be associated with ocular inflammation such as uveitis and scleritis. In some cases, these events did not resolve until the bisphosphonate was discontinued.

Laboratory Test Findings

There were no clinically significant changes from baseline values or shifts in any laboratory variable for each of the treatment groups. As expected with bisphosphonate treatment, a decrease in total alkaline phosphatase levels was seen in the active treatment groups compared to placebo. There was no difference compared with placebo for laboratory abnormalities indicative of hepatic or renal dysfunction, hypocalcemia, or hypophosphatemia.

OVERDOSAGE

No specific information is available on the treatment of overdose with BONIVA. However, based on knowledge of this class of compounds, oral overdose may result in hypocalcemia, hypophosphatemia, and upper gastrointestinal adverse events, such as upset stomach, dyspepsia, esophagitis, gastritis, or ulcer. Milk or antacids should be given to bind BONIVA. Due to the risk of esophageal irritation, vomiting should not be induced, and the patient should remain fully upright. Dialysis would not be beneficial.

DOSAGE AND ADMINISTRATION

The recommended dose of BONIVA for treatment and prevention of postmenopausal osteoporosis is one 2.5 mg film-coated tablet once daily (see INDICATIONS AND USAGE).

- To maximize absorption and clinical benefit, BONIVA should be taken at least 60 minutes before the first food or drink (other than water) of the day or any oral medication or supplementation, including calcium, antacids, or vitamins (see PRECAUTIONS: Information for Patients and Drug Interactions).
- To facilitate delivery to the stomach and thus reduce the potential for esophageal irritation, BONIVA tablets should be swallowed whole with a full glass of plain water (6 to 8 oz) while the patient is standing or sitting in an upright position. Patients should not lie down for 60 minutes after taking BONIVA (see PRECAUTIONS: General and Information for Patients).
- Plain water is the only drink that should be taken with BONIVA. Please note that some mineral waters may have a higher concentration of calcium and therefore should not be used.
- Patients should not chew or suck the tablet because of a potential for oropharyngeal ulceration.

Patients should receive supplemental calcium or vitamin D if dietary intake is inadequate. (see PRECAUTIONS: Information for Patients).

Patients with Hepatic Impairment

No dose adjustment is necessary (see CLINICAL PHARMACOLOGY: Special Populations).

Patients with Renal Impairment

No dose adjustment is necessary for patients with mild or moderate renal impairment where creatinine clearance is equal to or greater than 30 mL/min.

BONIVA is not recommended for use in patients with severe renal impairment (creatinine clearance of <30 mL/min) (see CLINICAL PHARMACOLOGY: Special Populations).

Geriatric Patients

No dosage adjustment is necessary in the elderly (see PRECAUTIONS: Geriatric Use).

HOW SUPPLIED

BONIVA 2.5 mg tablets: supplied as white, oblong, film-coated tablets, engraved with "RO" on one side and "L3" on the other side and packaged in bottles of 30 tablets (NDC 0004-0185-23), bottles of 90 tablets (NDC 0004-0185-52), and bottles of 500 tablets (NDC 0004-0185-14).

Storage

Store at 25°C (77°F); excursions permitted between 15° and 30°C (59° and 86°F) [see USP Controlled Room Temperature].

R_x only

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Draft-0503

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Printed in USA

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Patient Information

BONIVA™ [bon-EE-va] (ibandronate sodium) TABLETS

Read this patient information carefully before you start taking BONIVA. Read this patient information each time you get a refill for BONIVA. There may be new information. This information does not take the place of talking with your health care provider about your condition or your treatment. Talk about BONIVA with your health care provider before you start taking it, and at your regular check-ups.

What is the most important information I should know about BONIVA?

BONIVA may cause serious problems in the stomach and the esophagus (the tube that connects your mouth and stomach) such as trouble swallowing, heartburn, and ulcers (see "What are the possible side effects of BONIVA?").

You must take BONIVA exactly as prescribed for BONIVA to work for you and to lower the chance of serious side effects (see "How should I take BONIVA?").

What is BONIVA?

BONIVA is a prescription medicine used to treat or prevent osteoporosis in women after menopause (see the end of this leaflet for "What is osteoporosis?").

BONIVA may reverse bone loss by stopping more loss of bone and increasing bone mass in most women who take it, even though they won't be able to see or feel a difference. BONIVA may help lower the chances of breaking bones (fractures).

For BONIVA to treat or prevent osteoporosis, you have to take it as prescribed. BONIVA will not work if you stop taking it.

Who should not take BONIVA?

Do not take BONIVA if you:

- have low blood calcium (hypocalcemia)
- cannot sit or stand up for at least 1 hour (60 minutes)
- have kidneys that work very poorly
- are allergic to ibandronate sodium or any of the other ingredients of BONIVA (see the end of this leaflet for a list of all the ingredients in BONIVA)

Tell your health care provider before using BONIVA:

- if you are pregnant or planning to become pregnant. It is not known if BONIVA can harm your unborn baby.
- if you are breast-feeding. It is not known if BONIVA passes into your milk and if it can harm your baby.
- have swallowing problems or other problems with your esophagus (the tube that connects your mouth and stomach)
- if you have kidney problems
- **about all the medicines you take** including prescription and non-prescription medicines, vitamins and supplements. Some medicines, especially certain vitamins, supplements, and antacids can stop BONIVA from getting to your bones. This can happen if you take other medicines too close to the time that you take BONIVA (see “How should I take BONIVA?”).

How should I take BONIVA?

- Take BONIVA exactly as instructed by your health care provider.
- Take BONIVA first thing in the morning at least 1 hour (60 minutes) before you eat, drink anything other than plain water, or take any other medicine.
- Take BONIVA with 6 to 8 ounces (about 1 full cup) of plain water. Do not take it with any other drink besides plain water. Do not take it with other drinks, such as mineral water, sparkling water, coffee, tea, dairy drinks (such as milk), or juice.
- Swallow BONIVA whole. Do not chew the tablet or keep it in your mouth to melt or dissolve.
- After taking BONIVA you must wait at least 1 hour (60 minutes) before:
 - Lying down. You may sit, stand, or do normal activities like read the newspaper or take a walk.
 - Eating or drinking anything except for plain water.
 - Taking other medicines including vitamins, calcium, or antacids. Take your vitamins, calcium, and antacids at a different time of the day from the time when you take BONIVA.
- If you forget to take your BONIVA in the morning, **do not** take it later in the day. Just return to your normal schedule and take 1 tablet the next morning. **Do not** take two tablets on the same day.
- If you take too much BONIVA, drink a full glass of milk and call your local poison control center or emergency room right away. Do not make yourself vomit. Do not lie down.
- Keep taking BONIVA for as long as your health care provider tells you. BONIVA will not work if you stop taking it.
- Your health care provider may tell you to exercise and take calcium and vitamin supplements to help your osteoporosis.
- Your health care provider may do a test to measure the thickness (density) of your bones or do other tests to check your progress.

What should I avoid while taking BONIVA?

- Do not take other medicines, or eat or drink anything but plain water before you take BONIVA and for at least 1 hour (60 minutes) after you take it.
- Do not lie down for at least 1 hour (60 minutes) after you take BONIVA.

What are the possible side effects of BONIVA?

Stop taking BONIVA and call your health care provider right away if you have:

- pain or trouble with swallowing
- chest pain
- very bad heartburn or heartburn that does not get better

BONIVA may cause:

- pain or trouble swallowing (dysphagia)
- heartburn (esophagitis)
- ulcers in your stomach or esophagus (the tube that connects your mouth and stomach)

Common side effects with BONIVA are:

- diarrhea
- pain in extremities (arms or legs)
- dyspepsia (upset stomach)

These are not all the possible side effects of BONIVA. For more information ask your health care provider or pharmacist.

What is osteoporosis?

Osteoporosis is a disease that causes bones to become thinner. Thin bones can break easily. Most people think of their bones as being solid like a rock. Actually, bone is living tissue, just like other parts of the body, such as your heart, brain, or skin. Bone just happens to be a harder type of tissue. Bone is always changing. Your body keeps your bones strong and healthy by replacing old bone with new bone.

Osteoporosis causes the body to remove more bone than it replaces. This means that bones get weaker. Weak bones are more likely to break. Osteoporosis is a bone disease that is quite common in women after menopause. At first, osteoporosis has no symptoms, but people with osteoporosis may develop loss of height and are more likely to break (fracture) their bones, especially the back (spine), wrist, and hip bones.

Osteoporosis can be prevented, and with proper therapy it can be treated.

Who is at risk for osteoporosis?

Talk to your health care provider about your chances for getting osteoporosis.

Many things put people at risk for osteoporosis. The following people have a higher chance of getting osteoporosis:

Women who:

- are going through or who are past menopause (“the change”)
- are white (Caucasian) or Oriental (Asian)

People who:

- are thin
- have a family member with osteoporosis
- do not get enough calcium or vitamin D
- do not exercise
- smoke
- drink alcohol often
- take bone thinning medicines (like prednisone) for a long time

General information about BONIVA

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use BONIVA for a condition for which it was not prescribed. Do not give BONIVA to other people, even if they have the same symptoms you have. It may harm them.

Store BONIVA at 77 °F (25°C) or at room temperature between 59° and 86°F (15° and 30°C).

Keep BONIVA and all medicines out of the reach of children.

This leaflet summarizes the most important information about BONIVA. If you would like more

information, talk with your health care provider. You can ask your health care provider or pharmacist for information about BONIVA that is written for health professionals.

For more information about BONIVA, call 1-800-xxx-xxxx or visit www.xxxxxx.com.

What are the ingredients of BONIVA?

BONIVA (active ingredient): ibandronate sodium

BONIVA (inactive ingredients): lactose monohydrate, povidone, microcrystalline cellulose, crospovidone, purified stearic acid, colloidal silicon dioxide, and purified water. The tablet film coating contains hypromellose, titanium dioxide, talc, polyethylene glycol 6000 and purified water.

R_x only

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Draft-0503

Issued: May 2003

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

/s/

Robert Meyer
5/16/03 03:07:03 PM



RECEIVED

MAY 27 2003

Food and Drug Administration
Rockville MD 20857

NDA 21-455

Hoffmann-La Roche Inc.
Attention: Mark Hope
Regulatory Program Director
340 Kingsland Street
Nutley, NJ 07110

HLR# 2003-1667

Dear Mr. Hope:

Please refer to your new drug application (NDA) dated July 15, 2002, received July 16, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Boniva (ibandronate sodium) Tablets.

We acknowledge receipt of your submissions dated September 4, 5, and 20, November 15 and 18, and December 11 and 20, 2002, and January 9, 17, 20, and 31, February 12, 21(2), 25, 26, and 28(2), March 6, 14, 19, 21, 24, and 28, April 9, 29, and 30, and May 5, 7, 9, and 16, 2003.

This new drug application provides for the use of Boniva (ibandronate sodium) Tablets for the treatment and prevention of postmenopausal osteoporosis.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed-upon labeling text. Accordingly, the application is approved effective on the date of this letter.

Sufficient stability data has been submitted to support a 36-month expiration date.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert, patient package insert, and container labels submitted May 16, 2003). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 21-455." Approval of this submission by FDA is not required before the labeling is used.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to the Division of Metabolic and Endocrine Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products. You should refer to the Guidance for Industry on Qualifying for Pediatric Exclusivity (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request." FDA generally does not consider studies submitted to an NDA before issuance of a Written Request as responsive to the Written Request. Applicants should obtain a Written Request before submitting pediatric studies to an NDA.

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/Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Attention: Fishers Document Room
5600 Fishers Lane
Rockville, Maryland 20857

NDA 21-455
Page 3

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

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

Sincerely,

{See appended electronic signature page}

Robert Meyer, M.D.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

[54] **DIPHOSPHONATE DERIVATIVES,
PHARMACEUTICAL COMPOSITIONS AND
METHODS OF USE**

[75] Inventors: Rudi Gall, Hirschberg; Elmar Bosies,
Weinheim, both of Fed. Rep. of
Germany

[73] Assignee: Boehringer Mannheim GmbH,
Mannheim, Fed. Rep. of Germany

[21] Appl. No.: 71,471

[22] Filed: Jul. 9, 1987

[30] Foreign Application Priority Data

Jul. 11, 1986 [DE] Fed. Rep. of Germany 3623397

[51] Int. Cl.⁵ C07F 9/38; A61K 31/66

[52] U.S. Cl. 514/108; 558/158;
562/13

[58] Field of Search 558/158; 260/502.5 C;
514/108; 562/13

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Primary Examiner—Anton H. Sutto
Attorney, Agent, or Firm—Felfe & Lynch

[57] ABSTRACT

The present invention provides diphosphonates of the general formula:



wherein R₁ is a straight-chain or branched, saturated or unsaturated aliphatic hydrocarbon radical of 1-9 carbon atoms which is optionally substituted by phenyl or cyclohexyl, R₂ is cyclohexyl or cyclohexylmethyl, benzyl or a straight-chained or branched, saturated or unsaturated aliphatic hydrocarbon of 4 to 18 carbon atoms which is optionally substituted by phenyl or oxygen wherein the oxygen can be esterified or etherified, R₃ is hydrogen or a straight-chain or branched alkyl of 1-4 carbon atoms, X is a straight-chain or branched alkylene chain of 1-6 carbon atoms and Y is hydrogen, hydroxyl or an amino group optionally substituted by alkyl radicals of 1-6 carbon atoms; as well as the pharmacologically acceptable salts thereof.

The present invention also provides processes for the preparation of these diphosphonic acid derivatives and pharmaceutical compositions containing them for the prophylaxis treatment of diseases or disturbances of calcium metabolism such as osteoporosis, Pagets disease, Bechterew's disease, bone metastases, urolithiasis, heterotropic ossifications, rheumatoid arthritis, osteoarthritis and degenerative arthrosis.

12 Claims, No Drawings

**DIPHOSPHONATE DERIVATIVES,
PHARMACEUTICAL COMPOSITIONS AND
METHODS OF USE**

The present invention is concerned with new diphosphonic acid derivatives, processes for the preparation thereof and pharmaceutical compositions containing them.

Federal Republic of Germany Patent Specification No. 18,13,659 describes diphosphonic acid derivatives, of which 1-hydroxyethane-1,1-diphosphonic acid has achieved importance as an agent for the treatment of Paget's disease. Belgian Patent Specification No. 896,453, Federal Republic of Germany Patent Specification No. 25,34,391 and European Patent Specification No. 0,096,931 described aminoalkane-1,1-diphosphonic acids as good calcium complex formers which can also be used for the treatment of increased bone resorption. However, in the case of therapeutically effective dosages, such compounds frequently display side effects.

Consequently, there is a need to provide new aminoalkane-diphosphonates which manifest a therapeutic effectiveness at the lowest possible dosage level.

We have now found that analogous derivatives of these compounds in which the nitrogen atom is completely alkylated, the alkyl radical thereby containing at least 4 carbon atoms, fulfil this requirement and can be used as good calcium complex formers for the broader treatment of calcium metabolism disturbances. In particular, they can be well used where the bone formation and breakdown is disturbed, i.e. they can be used for the treatment of diseases of the skeletal system, for example osteoporosis, Paget's disease, Bechterew's diseases and the like.

However, on the basis of these properties, they can also be used for the therapy of bone metastases, urolithiasis and for the prevention of heterotopic ossifications. Due to their influence on calcium metabolism, they also form a basis for the treatment of rheumatoid arthritis, osteoarthritic and degenerative arthrosis.

Thus, according to the present invention, there are provided diphosphonates of the general formula:



wherein R_1 is a straight-chained or branched, saturated or unsaturated aliphatic hydrocarbon radical containing up to 9 carbon atoms which is optionally substituted by phenyl or cyclohexyl radicals, R_2 is a cyclohexyl or cyclohexylmethyl radical, a benzyl radical or a straight-chained or branched, saturated or unsaturated alkyl radical containing 4 to 18 carbon atoms which is optionally substituted by phenyl radicals or oxygen, which can be esterified or etherified, R_3 is a hydrogen atom or a straight-chained or branched alkyl radical containing up to 4 carbon atoms, X is a straight-chained or branched alkylene chain containing up to 6 carbon atoms and Y is a hydrogen atom, a hydroxyl group or an amino group optionally substituted by alkyl radicals containing up to 6 carbon atoms, as well as the pharmacologically compatible salts thereof.

The substituent R_1 is preferably a methyl, n-propyl, isopropyl, 3-methylbutyl, pentyl or nonyl radical.

R_2 is preferably a butyl, isobutyl, 3-methylbutyl, pentyl, heptyl, nonyl, decyl, undecyl, dodecyl, tetradecyl, hexadecyl, octadecyl, cyclohexyl, cyclohexylmethyl or benzyl radical.

The ethers and esters which can be formed with the oxygen in the case of the substituent R_2 mean alkyl- or alkyl-CO radicals containing up to 18 and preferably 9 to 18 carbon atoms, the nonyloxy, tetradecyloxy, hexadecylcarbonyloxy and octadecylcarbonyloxy radicals being preferred.

The substituent R_3 is preferably a hydrogen atom or a methyl, ethyl or isobutyl radical.

The asymmetrical carbon atoms occurring in R_1 , R_2 and X can have the R-, S- or R,S-configuration.

The group X is preferably an ethylene, propylene, butylene, 1-methylpropylene, 2-methylpropylene, 1-methyl-butylene or 2-methylbutylene radical.

The group Y is preferably a hydrogen atom, a hydroxyl group or an amino group which can be substituted by methyl, ethyl or isopropyl.

Preferred compounds of general formula (I) according to the present invention are those in which R_1 is a methyl radical and R_2 is a C_4 - C_6 radical, especially the compounds 1-hydroxy-3-(N-methyl-N-pentyl-amino)-propane-1,1-diphosphonic acid and 1-hydroxy-3-(N-isobutyl-N-methylamino)-propane-1,1-diphosphonic acid.

The compounds of general formula (I) according to the present invention can be prepared by known processes:

I. For the case in which Y in general formula (I) represents a hydrogen atom, the compounds are preferably prepared as follows:

(a) a compound of the general formula:



wherein R_1 , R_2 and X have the above-given meanings and B is a reactive residue, for example a halogen atom or a sulphonate group, is reacted with a compound of the general formula:

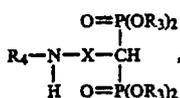


wherein R' is an alkyl radical containing up to 4 carbon atoms, preferably a methyl, ethyl or isobutyl radical, to give a diphosphonate of the general formula:



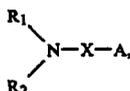
wherein R_1 , R_2 , X and R' have the above-given meanings, and the resultant tetraester is optionally saponified to the corresponding diester or free acid of general formula (I); or

(b) a compound of the general formula:



wherein R_3 and X have the above-given meanings and R_4 is a hydrogen atom or has the same meaning as R_2 , is mono- or dialkylated and the resultant tetraester is optionally saponified to the corresponding diester or free acid of general formula (I); or

II. for the case in which Y in general formula (I) is an amino group optionally substituted by alkyl radicals, a carboxylic acid derivative of the general formula:



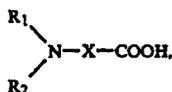
wherein R_1 , R_2 and X have the above-given meanings and A is a nitrile or imino ether group or a carboxamide group optionally substituted on the nitrogen atom by a lower alkyl radical, is reacted with a phosphorus compound of the general formula:

$$\text{PT}_3$$

wherein T is a halogen atom, a hydroxyl group or an OR' group, R' having the above-given meaning, and optionally subsequently saponified to give a compound of general formula (I); or

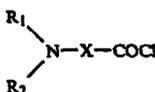
III. for the case in which Y in general formula (I) is a hydroxyl group,

(a) a carboxylic acid of the general formula:



wherein R_1 , R_2 and X have the above-given meanings, is reacted with a mixture of phosphorous acid or phosphoric acid and a phosphorus halide and subsequently saponified to a free diphosphonic acid of general formula (I); or

(b) a carboxylic acid chloride of the general formula:



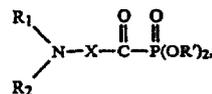
wherein R_1 , R_2 and X have the above-given meanings, is reacted with a trialkyl phosphite of the general formula:

$$\text{P}(\text{OR}')_3$$

wherein R' has the above-given meaning, to give an acyl phosphonate of the general formula:

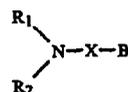
(V)

5



(XI)

10



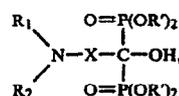
(II)

wherein R_1 , R_2 , X and B have the above-given meanings, subsequently reacted with a dialkyl phosphite of the general formula:



(XII)

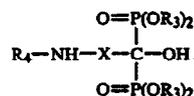
wherein R' has the above-given meaning, to give a diphosphonate of the general formula:



(XIII)

wherein R_1 , R_2 , X and R' have the above-given meanings, and the resultant tetraester is optionally saponified to the corresponding diester or free acid of general formula (I); or

(c) a compound of the general formula:



(XIV)

wherein R_3 and X have the above-given meanings and R_4 is a hydrogen atom or has the same meaning as R_2 , is mono- or dialkylated and the resultant tetraester is optionally saponified to the corresponding diester or free acid of general formula (I); and, if desired, the compounds thus prepared are converted into their pharmacologically compatible salts.

In the case of process I (a), the methylene-diphosphonic acid ester of general formula (III) is used in the form of its sodium or potassium salt. For this purpose, it is reacted with sodium, potassium or the appropriate hydride in an inert solvent, for example benzene, toluene or dimethylformamide, at a temperature of from 0° to 40° C. and preferably of 25° C. The alkali metal salt is, without isolation, reacted with an appropriate halide or sulphate, the temperature used hereby being from 20° to 110° C.

In the case of the reductive alkylation according to process I (b), a mixture of primary or secondary amine of general formula (V) and of a carbonyl compound or of an acetal thereof is treated in the presence of a hydrogenation catalyst, for example palladium on charcoal or nickel, with hydrogen at atmospheric or increased pressure or with the use of formic acid as reducing agent. Subsequently, alkylation of a secondary amine of general formula (V) can be carried out especially advantageously according to the phase transfer process with dialkyl sulphates.

In the case of process II, the nitriles of general formula (VI) are reacted with phosphorous acid at a temperature of from 110° to 180° C. The reaction can be carried out without or in the presence of aprotic solvents, for example diglycol dimethyl ether or diglycol diethyl ether. However, the nitriles can also be reacted with a phosphorus trihalide, for example phosphorus tribromide or phosphorus trichloride, in an inert solvent, for example dioxan or tetrahydrofuran, optionally with the addition of water, at a temperature of from 20° to 80° C. Imino ethers of general formula (VI) are preferably reacted with dialkyl phosphites in the presence of equimolar amounts of sodium in inert solvents, for example diethyl ether, dioxan or also benzene, the reactions usually taking place at the reflux temperature of the solvent used. Acid amides of general formula (VI) can be reacted in inert solvents, for example halogenated hydrocarbons or ethers, such as diethyl ether, with a mixture of a phosphorus pentahalide/phosphorous acid or also of oxalyl chloride/trialkyl phosphite.

The carboxylic acids of general formula (VIII) used in process III (a) are reacted with 1 to 2 and preferably 1.5 mole phosphorous acid or phosphoric acid and 1 to 2 and preferably 1.5 mole phosphorus trihalide at a temperature of from 80° to 130° C. and preferably of from 100° to 110° C. The reaction can also be carried out in the presence of diluents, for example halogenated hydrocarbons, especially chlorobenzene or tetrachloroethane, or also dioxan. The subsequent hydrolysis takes place by boiling with water but preferably with semi-concentrated hydrochloric or hydrobromic acid.

In the case of process III (b), the acid chloride of general formula (IX) is reacted with the trialkyl phosphite of general formula (X) at a temperature of from 0° to 60° C. and preferably of from 20° to 40° C. The reaction can be carried out without a solvent or also in the presence of inert solvents, for example diethyl ether, tetrahydrofuran, dioxan or also halogenated hydrocarbons, for example methylene chloride. The acyl phosphonate of general formula (XI) formed as intermediate can be isolated or further reacted directly. The subsequent reaction is carried out in the presence of a weak base, preferably of a secondary amine, for example dibutylamine, at a temperature of from 0° to 60° C. and preferably of from 10° to 30° C.

As phosphorus trihalides in the above-mentioned processes, there can be used, for example, phosphorus trichloride or phosphorus tribromide.

In the case of process III (c), there applies analogously the remarks made with regard to process I (b).

The tetraalkyl esters possibly obtained in processes I and III can be saponified to the corresponding diesters or to the free tetra acids. The saponification to diesters usually takes place by treating the tetraalkyl esters with an alkali metal halide, preferably sodium iodide, in an appropriate solvent, for example acetone, at ambient temperature. There is hereby obtained the symmetrical diester/diacid salt which, if desired, can be converted into the diester/diacid by means of an acidic ion exchanger. The saponification to the free diphosphonic acids usually takes place by boiling with hydrochloric or hydrobromic acid. However, a cleavage with a trimethylsilyl halide, preferably the bromide or iodide, can also be carried out. On the other hand, the free diphosphonic acids can be converted again into the tetraalkyl esters by boiling with orthoformic acid alkyl esters. The free diphosphonic acids of general formula (I) can be isolated as the free acids or in the form of their

mono- or dialkali metal salts. The alkali metal salts can usually be readily purified by reprecipitation from water/methanol or from water/acetone.

As pharmacologically acceptable salts, there are preferably used the alkali metal or ammonium salts which can be prepared in the usual way, for example by titration of the compounds with inorganic or organic bases, for example sodium or potassium hydrogen carbonates, aqueous solutions of sodium or potassium hydroxide or aqueous solutions of ammonia or of amines, for example trimethyl or triethylamine.

The new compounds of general formula (I) according to the present invention and the salts thereof can be administered enterally or parenterally in liquid or solid form. For this purpose, there can be used all conventional forms of administration, for example tablets, capsules, dragees, syrups, solutions, suspensions and the like. As injection medium, it is preferred to use water which contains the additives usual in the case of injection solutions, for example stabilising agents, solubilising agents and buffers. Additives of this kind include, for example, tartrate and citrate buffers, ethanol, complex formers (such as ethylenediaminetetraacetic acid and the non-toxic salts thereof) and high molecular weight polymers (such as liquid polyethylene oxide) for viscosity regulation. Liquid carrier materials for injection solutions must be sterile and are preferably placed in ampoules. Solid carrier materials include, for example, starch, lactose, mannitol, methyl cellulose, talc, highly dispersed silicic acids, high molecular weight fatty acids (such as stearic acid), gelatine, agar agar, calcium phosphate, magnesium stearate, animal and vegetable fats and solid high molecular weight polymers (such as polyethylene glycol). Compositions suitable for oral administration can, if desired, also contain flavouring and sweetening agents.

The dosage can depend upon various factors, such as the mode of administration, species, age and/or individual condition. The dosages to be administered daily are about 1 to 1000 mg. in the case of humans and preferably 10 to 200 mg. and can be given once or several times per day.

Preferred compounds according to the present invention are, apart from the compounds mentioned hereinafter in the specific Examples and apart from the compounds which can be derived by combination of all of the meanings given in the claims, the following diphosphonates, as well as the methyl and ethyl esters thereof:

- 1-amino-3-(N-methyl-N-nonylamino)-propane-1,1-diphosphonic acid
- 1-dimethylamino-3-(N-methyl-N-nonylamino)-propane-1,1-diphosphonic acid
- 3-(N-methyl-N-nonylamino)-propane-1,1-diphosphonic acid
- 3-(N-methyl-N-octadecylamino)-propane-1-hydroxy-1,1-diphosphonic acid
- 3-(N-methyl-N-tetradecylamino)-propane-1-hydroxy-1,1-diphosphonic acid
- 3-(N-decyl-N-methylamino)-propane-1-hydroxy-1,1-diphosphonic acid
- 3-(N-heptyl-N-methylamino)-propane-1-hydroxy-1,1-diphosphonic acid
- 1-hydroxy-4-methyl-4-(N-nonyl-N-methylamino)-butane-1,1-diphosphonic acid
- 4-(N-dodecyl-N-methylamino)-butane-1-hydroxy-1,1-diphosphonic acid
- 3-(N-dodecyl-N-isopropylamino)-propane-1-hydroxy-1,1-diphosphonic acid

1-hydroxy-5-methyl-5-(N-nonyl-N-methylamino)-pentane-1,1-diphosphonic acid

1-[hydroxy-3-(N-cyclohexylmethyl)-N-propylamino]-propane-1,1-diphosphonic acid

2-(N-methyl-N-isobutylamino)-ethane-1,1-diphosphonic acid

2-(N-methyl-N-pentylamino)-ethane-1,1-diphosphonic acid.

The following Examples illustrate some of the process variants which can be used for the synthesis of the compounds according to the present invention. The structures of these compounds were verified by H— and P—NMR spectroscopy and the purity by means of P—NMR spectroscopy, thin layer electrophoresis (cellulose, oxalate buffer of pH 4.0) and by means of C, H, N, P and Na analyses. For the characterisation of the individual compounds, there are given the M_{rel} values (relative mobilities) referred to pyrophosphate ($M_{rel}=1.0$).

EXAMPLE 1

1-Hydroxy-3-(N,N-dipentylamino)-propane-1,1-diphosphonic acid

13.3 g. 3-N,N-Dipentylaminopropionic acid are kept for 20 hours at 100° C. with 7.1 g. phosphorous acid and 14.8 ml. phosphorus trichloride in 67 ml. chlorobenzene. The solvent is then decanted off and the residue is stirred under reflux with 180 ml. 6N hydrochloric acid for 8 hours. Insoluble material is filtered off and the filtrate is concentrated and applied to a column of Amberlite IR 120 (H⁺ form). The elution with water is monitored electrophoretically. The desired fractions are combined, evaporated and stirred up with acetone and the crystals obtained are isolated. There are thus obtained 12.9 g. of crude product. After recrystallising twice from water, there are obtained 4.7 g. (22% of theory) of analytically pure product in the form of the hemihydrate; m.p. 114° C. with sintering, 189°–191° C. (decomp.); $M_{rel}=0.24$.

The starting material is obtained as follows: Dipentylamine is reacted with methyl acrylate in toluene in the mole ratio of 1:3. There is obtained a yield of 28% of theory of the oily dipentylaminopropionic acid ester which is saponified with 1N aqueous sodium hydroxide solution to give a yield of 56% of theory of the desired acid; m.p. 47°–49° C.

EXAMPLE 2

1-Hydroxy-3-(N-methyl-N-nonylamino)-propane-1,1-diphosphonic acid

In a manner analogous to that described in Example 1, from 3-N-methyl-N-nonylamino propionic acid there is obtained the corresponding diphosphonate in a yield of 10% of theory; m.p. 159° C. with sintering, 178°–184° C.; $M_{rel}=0.22$.

The starting material is obtained as follows: Nonylamine is reacted with benzaldehyde to give the oily Schiff base in a yield of 96% of theory. Hydrogenation with palladium-charcoal catalyst gives N-benzyl-N-nonylamine as an oil in a yield of 94% of theory. From this, with formaldehyde and formic acid, there is obtained the oily N-benzyl-N-methyl-N-nonylamine in a yield of 98% of theory. Hydrogenolytic splitting off of the benzyl radical with palladium-charcoal catalyst gives a quantitative yield of the secondary amine in the form of an oil which is reacted with methyl acrylate and saponified in the manner described in Example 1. The

yield of the oily ester is 81% of theory and that of the pasty acid is 95% of theory.

EXAMPLE 3

3-(N-Cyclohexyl-N-methylamino)-1-hydroxy-propane-1,1-diphosphonic acid.

15 g. 3-N-Cyclohexyl-N-methylaminopropionic acid (prepared from N-cyclohexyl-N-methylamine (commercially available) and methyl acrylate in toluene; yield of ester 76% of theory, m.p. 131°–134° C., yield of acid 92% of theory, m.p. 101°–105° C.) are heated to 80° C. with 13.3 g. phosphorous acid. The melt is mixed with 14.1 ml. phosphorus trichloride and kept at the same temperature for 16 hours. 240 ml. water are then added thereto and the reaction mixture is stirred for 1 day at 100° C. It is then filtered, the filtrate is concentrated in a vacuum and the oil obtained is poured into 1 litre of acetone, crystallisation thereby commencing. The crystals are dissolved in water and purified by ion exchanger chromatography in the manner described in Example 1. Yield 4.5 g. (16.9% of theory) as monohydrate; m.p. 142° C. with sintering, 182° C. (decomp.); $M_{rel}=0.3$.

EXAMPLE 4

1 g. 3-N-Cyclohexylaminopropane-1-hydroxy-1,1-diphosphonic acid is suspended in 30 ml. methylene chloride, 2.5 ml. of a concentrated aqueous solution of sodium hydroxide are added thereto and, with cooling, mixed with 1 g. tetrabutylammonium hydrogen sulphate and 0.3 ml. dimethyl sulphate. The reaction mixture is then vigorously stirred for several hours at ambient temperature. After working up in the usual manner, the identity of the product obtained with that prepared according to Example 3 is demonstrated by mass spectroscopy after silylation.

The diphosphonic acid used as starting material is obtained as follows: Cyclohexylamine is reacted with acrylic acid in pyridine to give a yield of 70% of theory of 3-N-cyclohexylaminopropionic acid; m.p. 170°–171° C. The reaction with phosphorous acid and phosphorus trichloride gives a yield of 31% of theory of the diphosphonic acid; m.p. 164° C. (decomp.).

EXAMPLE 5

3-(N-Cyclohexylmethyl-N-methylamino)-propane-1-hydroxy-1,1-diphosphonic acid

3-(N-Cyclohexylmethyl-N-methylamino)-propionic acid (prepared from N-benzyl-N-methylamine by hydrogenation with platinum catalyst, yield 70% of theory; b.p. 60° C./16 mm.Hg; reaction with methyl acrylate in toluene, yield 37% of theory of methyl 3-(N-cyclohexylmethyl-N-methylamino)-propionate; saponification with 1N aqueous sodium hydroxide solution to give the acid in a yield of 63% of theory; m.p. 98°–102° C.) is reacted analogously to Example 3 with phosphorous acid/phosphorus trichloride to give the diphosphonic acid in a yield of 34% of theory; m.p. 180°–194° C. (decomp.); $M_{rel}=0.31$.

EXAMPLE 6

1-Hydroxy-3-(N-nonyl-N-propylamino)-propane-1,1-diphosphonic acid

In a manner analogous to that described in Example 3, from 3-N-nonyl-N-propylaminopropionic acid there

is obtained the corresponding diphosphonic acid in a yield of 50% of theory; m.p. 100°-105° C.; M_{rel} =0.23.

The starting material is obtained as follows: 2 mole nonylamine are reacted with 1 mole propionyl chloride to give a quantitative yield of the acid amide which is reduced with lithium aluminium hydride to give the secondary amine in a yield of 71% of theory; b.p. 113°-117° C./16 mm.Hg. 1 mole N-nonyl-N-propylamine is reacted with 3 mole methyl acrylate in toluene to give an oil in a yield of 81% of theory which is saponified with 1N aqueous sodium hydroxide solution to give the desired acid in a yield of 14% of theory; m.p. 45°-47° C.

EXAMPLE 7

500 mg. of the diphosphonic acid prepared according to Example 1 are suspended in 5 ml. water, dissolved with 2.68 ml. 1N aqueous sodium hydroxide solution, concentrated somewhat and brought to crystallisation by pouring into acetone. There are thus obtained 440 mg. (78% of theory) of the disodium salt of 1-hydroxy-3-(N,N-dipentylamino)-propane-1,1-diphosphonic acid in the form of the monohydrate. The melting point is above 300° C.

EXAMPLE 8

1-Hydroxy-3-(N-nonyl-N-pentylamino)-propane-1,1-diphosphonic acid

2 mole nonylamine are reacted with 1 mole valeroyl chloride in diethyl ether, the suspension is filtered off with suction, the filtrate is evaporated and N-nonyl-valeric acid amide is thus obtained quantitatively; m.p. 29°-31° C. Reduction with 1.65 mole lithium aluminium hydride in diethyl ether gives a colourless oil in a yield of 78% of theory; b.p. 142°-146° C./16 mm.Hg. The addition of this N-nonyl-N-pentylamine to methyl acrylate (oil; yield 96% of theory) and subsequent saponification with 1N aqueous sodium hydroxide solution gives a yield of 64% of theory of pasty 3-(N-nonyl-N-pentylamino)-propionic acid which is reacted analogously to Example 3 to give the diphosphonic acid; yield 87% of theory; m.p. 168°-176° C.; M_{rel} =0.14.

EXAMPLE 9

In a manner analogous to that described in Example 2, there are prepared:

A. Intermediate products:	yield	m.p.
N-benzylidene-pentylamine	94%	oil
N-benzyl-N-pentylamine	74%	paste
N-benzyl-N-methyl-N-pentylamine	95%	oil
N-methyl-N-pentylamine	49%	oil
methyl 3-(N-methyl-N-pentylamino)-acrylate	93%	oil
3-(N-methyl-N-pentylamino)-propionic acid	34%	deliquescent crystals
<u>End product:</u>		
1-hydroxy-3-(N-methyl-N-pentylamino)-propane-1,1-diphosphonic acid	M_{rel} = 0.44	84° C. decomp.

B. Intermediate products:	yield	m.p.
N-benzylideneisobutylamine	96%	oil
N-benzyl-N-isobutylamine	71%	oil
N-benzyl-N-isobutyl-N-methylamine	93%	oil
N-isobutyl-N-methylamine	96%	oil
methyl 3-(N-isobutyl-N-methylamino)-acrylate	90%	oil

-continued-

B. Intermediate products:	yield	m.p.
3-(N-isobutyl-N-methylamino)-propionic acid	57%	oil
<u>End product:</u>		
1-hydroxy-3-(N-isobutyl-N-methylamino)-propane-1,1-diphosphonic acid	M_{rel} = 0.40	m.p. 140° C. decomp.
	yield 39%	

C. Intermediate products:	yield	m.p.
N-benzylidenehexadecylamine	85%	oil
N-benzyl-N-hexadecylamine	76%	wax
N-benzyl-N-hexadecyl-N-methylamine	93%	oil
N-hexadecyl-N-methylamine	98%	wax
methyl 3-(N-hexadecyl-N-methylamino)-acrylate	100%	wax
3-(N-hexadecyl-N-methylamino)-propionic acid	37%	58-60° C.
<u>End product:</u>		
3-(N-hexadecyl-N-methylamino)-propane-1-hydroxy-1,1-diphosphonic acid	M_{rel} = 0.1	198-254° C. decomp.
	yield 72%	

The oily intermediate products are further reacted without distillation. The purification of the end products is carried out by ion exchange chromatography.

EXAMPLE 10

3-N,N-Dinonylaminopropane-1-hydroxy-1,1-diphosphonic acid

In a manner analogous to that described in Example 3, from 3-N,N-dinonylaminopropionic acid there is obtained the corresponding diphosphonic acid as the hemihydrate in a yield of 49% of theory; m.p. 83° C. sinters, 161°-171° C. melts with gas evolution; M_{rel} =0.16.

The reaction sequence for the preparation of the starting material is analogous to that described in Example 6:

pelargonic acid N-nonylamide;	yield 100% of theory; m.p. 52-55° C.
N,N-dinonylamide;	yield 79% of theory; m.p. 37-39° C.
methyl 3-N,N-dinonylaminopropionate;	yield 71% of theory; oil
3-N,N-dinonylaminopropionic acid;	yield 18% of theory; deliquescent crystals.

EXAMPLE 11

1-Hydroxy-4-(N,N-di-3-methylbutylamino)-butane-1,1-diphosphonic acid

4 g. 4-Amino-1-hydroxybutane-1,1-diphosphonic acid are dissolved in 64 ml. 1N aqueous sodium hydroxide solution, mixed with 3.8 ml. isovaleraldehyde and, after the addition of 2.5 g. of 10% palladium-charcoal, hydrogenated at a pressure of 5 bar. The course of the reaction is monitored electrophoretically until the starting material has disappeared. The reaction mixture is filtered, acidified with Amberlite R 120 (H+ form) and evaporated until crystallisation commences, 1.3 g. of crystals thus being obtained in a yield of 20% of theory; m.p. 225°-227° C. (decomp.); M_{rel} =0.39. 1-Hydroxy-4-(N-3-methylbutylamino)-butane-1,1-diphosphonic acid remaining in the mother liquor, which is formed as an

intermediate, can be used again for the reductive alkylation.

EXAMPLE 12

3-(N-Benzyl-N-methylamino)-propane-1-hydroxy-1,1-diphosphonic acid

Analogously to Example 3, from 3-N-benzyl-N-methylaminopropionic acid there is obtained the desired diphosphonic acid as monohydrate in a yield of 36% of theory; decomposition point 117° C.; $M_{rel}=0.37$.

The starting material is obtained as follows: N-Benzyl-N-methylamine is reacted with methyl acrylate analogously to Example 1 and the ester obtained in a yield of 76% of theory is, without distillation, saponified with 1N aqueous sodium hydroxide solution. The oily acid is thus obtained in a yield of 67% of theory and is used without further purification.

EXAMPLE 13

3-(N-Dodecyl-N-methylamino)-propane-1-hydroxy-1,1-diphosphonic acid

Analogously to Example 3, from 3-N-dodecyl-N-methylaminopropionic acid there is obtained the desired compound in a yield of 28% of theory; decomposition point 200°-216° C.; $M_{rel}=0.1$.

The starting material is obtained as follows: The oily Schiff base obtained from dodecylamine and benzaldehyde (yield 81% of theory) is hydrogenated with palladium catalyst to give the oily N-benzyl compound in a yield of 74% of theory. The reductive alkylation with formalin-formic acid gives the tertiary amine, which is also oily, in a yield of 82% of theory. The catalytic removal of the benzyl radical by hydrogenolysis is quantitative. The oily secondary amine is reacted directly with methyl acrylate to give a pasty product in a yield of 50% of theory which is saponified without purification. The desired acid is obtained as a viscous mass in a yield of 39% of theory and is used directly.

EXAMPLE 14

3-(N-Benzyl-N-propylamino)-propane-1-hydroxy-1,1-diphosphonic acid

Analogously to Example 3, from 3-(N-benzyl-N-propylamino)-propionic acid there is obtained the desired compound in a yield of 35% of theory; m.p. 112°-115° C. (decomp.); $M_{rel}=0.33$.

The starting material is obtained as follows: The oily Schiff base from propylamine and benzaldehyde (yield 86% of theory) is hydrogenated in the presence of palladium catalyst and gives N-benzyl-N-propylamine in a yield of 81% of theory. The oily secondary amine is now reacted with methyl acrylate to give the oily ester in a yield of 69% of theory from which, by alkaline saponification, there is obtained the acid, which is also an oil, in a yield of 88% of theory.

EXAMPLE 15

In a manner analogous to that described in Example 2, there are prepared:

A. Intermediate products:	yield	m.p.
N-benzylidene-2-butylamine	89%	oil
N-benzyl-2-butylamine	92%	oil
N-benzyl-N-2-butyl-N-methylamine	85%	oil
N-2-butyl-N-methylamine, HCl	98%	40-46° C.

-continued

A. Intermediate products:	yield	m.p.
methyl 3-(N-2-butyl-N-methylamino)-propionate	88%	oil
3-(N-2-butyl-N-methylamino)-propionic acid	95%	oil
<u>End product:</u>		
3-(N-2-butyl-N-methylamino)-propane-1-hydroxy-1,1-diphosphonic acid	39%	95-105° C.

B. Intermediate products:	yield	m.p.
methyl 3-N-butylaminopropionate; b.p. 95-100° C./20 mm.Hg	75%	oil
methyl 3-(N-butyl-N-methylamino)-propionate	—	oil
3-(N-butyl-N-methylamino)-propionic acid	78%	oil
(yield referred to first intermediate product)		
<u>End product:</u>		
3-(N-butyl-N-methylamino)-propane-1-hydroxy-1,1-diphosphonic acid	65%	116-121° C.
$M_{rel} = 0.39$		

C. Intermediate product:	yield	m.p.
4-(N-methyl-N-nonylamino)-butyric acid	47%	oil
<u>End product:</u>		
1-hydroxy-4-(N-methyl-N-nonylamino)-butane-1,1-diphosphonic acid dipotassium salt dihydrate	11%	300° C.
$M_{rel} = 0.25$		

D. Intermediate products:	yield	m.p.
3-N-undecylaminopropionic acid	62%	76-80° C.
3-N-methyl-N-undecylaminopropionic acid	59%	wax
<u>End product:</u>		
1-hydroxy-3-N-methyl-N-undecylamino)-propane-1,1-diphosphonic acid dipotassium salt dihydrate	23%	238° C. foaming up

The oily intermediate products are further reacted directly without distillation. The structure is verified spectroscopically. The end products are purified by ion exchanger chromatography.

EXAMPLE 16

Test Report

Male Wistar rats from our own breeding weighing about 160 g were thyroparathyroidectomized on day 1. On day 5, the success of the operation was controlled by measuring calcemia after a night fasting. From that day on, all the animals were group-fed, that means all of them ate the same quantity of food. Furthermore, the animals received then daily for 3 days 2 subcutaneous injections, one containing 25 µg of a synthetic retinoid, the other one the bisphosphonate to be tested. Additionally, all animals were given 2 µg of thyroxine the first and last day of treatment. 24 h after the last injection of the retinoid and the biphosphonates and after one night fasting, blood was taken by retroorbital puncture under ether anesthesia. Plasma calcium was then analyzed by means of atomic absorption.

The bisphosphonates were given first at a dose of 0.1 mg P/kg in a volume of 2 ml/kg, the less active also at 1 and 10 mg P/kg.

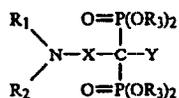
TABLE I

Examples	dosage [mg P/kg]		
	0.01	0.1	1
2	1.75	5.74	
6		2.26	5.90
8		0.49	1.74
9A	4.59	7.34	
9B	3.36	6.06	
12	0.69	4.34	
15A	1.43	3.12	

It will be understood that the specification and examples are illustrative but not limitative of the present invention and that other embodiments within the spirit and scope of the invention will suggest themselves to those skilled in the art.

What is claimed:

1. A diphosphonate compound of the formula:



2. A diphosphonate compound of claim 1, wherein R_1 is methyl.

3. The diphosphonate compound of claim 1 designated 1-hydroxy-3-(N-methyl-N-nonylamino)-propane-1,1-diphosphonic acid and the physiologically active salt thereof.

4. The diphosphonate compound of claim 1 designated 1-hydroxy-3-(N-methyl-N-pentylamino)-propane-1,1-diphosphonic acid and the physiologically active salt thereof.

5. The diphosphonate compound of claim 1 designated 1-hydroxy-3-(N-isobutyl-N-methylamino)-pro-

pane-1,1-diphosphonic acid and the physiologically active salt.

6. A method for the treatment or prophylaxis of calcium metabolism disturbance or disease comprising administering a pharmaceutically effective amount of the compound of claim 1.

7. The method of claim 6 wherein 0.01-10 mg P/kg of the pharmaceutically acceptable diphosphonate compound are administered per day.

8. A method for the treatment or prophylaxis of calcium metabolism disturbance or disease comprising administering a pharmaceutically effective amount of at least one of the compounds designated 1-hydroxy-3-(N-methyl-N-nonylamino)-propane-1,1-diphosphonic acid, 1-hydroxy-3-(N-methyl-N-pentylamino)-propane-1,1-diphosphonic acid and 1-hydroxy-3-(N-isobutyl-N-methylamino)-propane-1,1-diphosphonic acid.

9. The method of claim 8 wherein 0.01-10 mg P/kg of the pharmaceutically acceptable diphosphonate are administered per day.

10. A pharmaceutical composition for the treatment or prophylaxis of calcium metabolism disturbance or disease containing an effective amount of at least one compound of claim 1 in a pharmaceutically acceptable carrier.

11. A pharmaceutical composition for the treatment or prophylaxis of calcium metabolism disturbance or disease containing an effective amount of at least one compound of claim 2 in a pharmaceutically acceptable carrier.

12. A pharmaceutical composition for the treatment or prophylaxis of calcium metabolism disturbance or disease containing an effective amount in a pharmaceutically acceptable carrier of at least one compound designated 1-hydroxy-3-(N-methyl-N-nonylamino)-propane-1,1-diphosphonic acid, 1-hydroxy-3-(N-methyl-N-pentylamino)-propane-1,1-diphosphonic acid, and 1-hydroxy-3-(N-isobutyl-N-methylamino)-propane-1,1-diphosphonic acid.

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UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 4,927,814
DATED : May 22, 1990
INVENTOR(S) : Rudi Gall et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 13, line 29, after formula insert: wherein
R₁ is methyl or n-propyl which is optionally substituted by
phenyl or cyclohexyl,

R₂ is isobutyl, pentyl, nonyl or benzyl wherein said
aliphatic hydrocarbon is optionally substituted by phenyl
or oxygen, and wherein said oxygen is an ester or an ether,

R₃ is hydrogen,

X is ethylene, and

Y is hydroxyl; and the pharmacologically acceptable
salt thereof.

Signed and Sealed this
Twelfth Day of January, 1993

Attest:

DOUGLAS B. COMER

Attesting Officer

Acting Commissioner of Patents and Trademarks



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4927814

The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 11, "STAT" below.

If a maintenance fee payment is defective, the reason is indicated by code in column 11, "STAT" below. **TIMELY CORRECTION IS REQUIRED IN ORDER TO AVOID EXPIRATION OF THE PATENT. NOTE 37 CFR 1.377. THE PAYMENT(S) WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION. IF PAYMENT OR CORRECTION IS SUBMITTED DURING THE GRACE PERIOD, A SURCHARGE IS ALSO REQUIRED. NOTE 37 CFR 1.20(k) and (l).**

If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. **THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.**

ITEM NBR	PATENT NUMBER	FEE CDE	FEE AMT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT
1	4,927,814	183	930	0	07/071,471	05/22/90	07/09/87	04	NO	PAID
5487										

ITEM NBR ATTY DKT NUMBER

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Page**Maintenance Fee Statement****4927814**

The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 11, "STAT" below.

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If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

ITEM NBR	PATENT NUMBER	FEE CDE	FEE AMT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT
1 5487	4,927,814	184	2050	0	07/071,471	05/22/90	07/09/87	08	NO	PAID

ITEM NBR	ATTY DKT NUMBER

1

BOER714 - PFF/

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Maintenance Fee Statement

4927814

The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 11, "STAT" below.

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If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. **THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.**

ITEM NBR	PATENT NUMBER	FEE CDE	FEE AMT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT
1	4,927,814	185	2990	0	07/071,471	05/22/90	07/09/87	12	NO	PAID
5487										

ITEM NBR ATTY DKT NUMBER

1

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626-1



BOEHRINGER MANNHEIM
Pharmaceuticals Corporation
701 Orchard Ridge Drive
Salthersburg, MD 20878
USA
Telephone: +1 (301) 216-3900
Fax: Main +1 (301) 990-3815
Fax: Sales +1 (301) 990-3825

Dr. Solomon Sobel, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Metabolic and Endocrine Drug Products, HFD-510
Attention: Document Control Room #14-B-19
5600 Fishers Lane
Rockville, MD 20857-1706

April 15, 1996

Re: **BM 21.0955 Na-H₂O oral**
Initial Investigational New Drug Application
Serial Number: 000

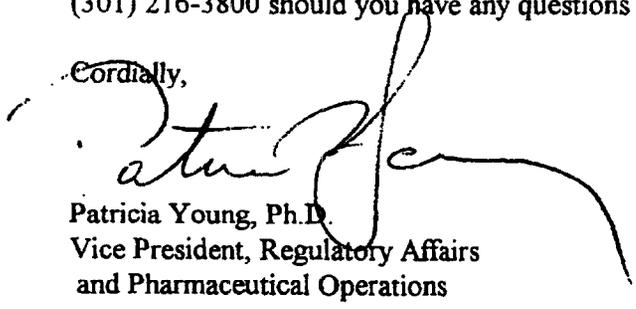
Dear Dr. Sobel:

Enclosed are three (3) copies of our Investigational New Drug Application for BM 21.0955, a new bisphosphonate formulation, which is being submitted as an oral dosage form for the indication of metastatic bone disease. Phase I and Phase II trials have been conducted in Europe by Boehringer Mannheim, located in Mannheim, Germany and, based upon the results of this program, we are proposing the initiation of a Phase III clinical trial in the United States. This trial will be conducted in patients with breast cancer. A copy of the protocol is included in Item 6 of this IND.

As you are aware, we currently have on file at the FDA an IND for an injectable form of BM 21.0955 Na-H₂O (IND 46,266 submitted on September 30, 1994). The Phase III program using this formulation is currently in progress.

Please contact Mr. Michael G. Harlow, Associate Manager Regulatory Affairs at (301) 216-3800 should you have any questions regarding this information.

Cordially,


Patricia Young, Ph.D.
Vice President, Regulatory Affairs
and Pharmaceutical Operations

**CONFIDENTIAL/TRADE SECRET INFORMATION
SUBJECT TO 18-USEC-1905 AND TO WHICH ALL
CLAIMS OF PRIVILEGE AND CONFIDENTIALITY
ARE ASSERTED IN BOTH STATUTORY AND
COMMON LAW.**

MGH/kmr

Attachment

o:\bisiam\indamd\T000.mgh

00 000001



July 15, 2002



Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
12229 Wilkins Avenue
Rockville, MD 20852

Dear Sirs and Madams:

**RE: NDA 21-455
BONVIVA® (ibandronate sodium) film-coated tablets in the treatment and prevention of
post-menopausal osteoporosis
Original New Drug Application**

In accordance with 21CFR Part 314.50, Hoffmann-La Roche Inc. hereby submits an original New Drug Application (NDA 21-455) for BONVIVA (ibandronate sodium) film-coated tablets, a new bisphosphonate for use in the treatment and prevention of post-menopausal osteoporosis. BONVIVA has been the subject of INDs 50,378 and 46,266, sponsored originally by Boehringer Mannheim. Following the acquisition of Boehringer Mannheim by Hoffmann-La Roche Inc., the sponsor of the INDs was transferred to Roche Global Development in Palo Alto and subsequently to Hoffmann-La Roche Inc., Nutley, New Jersey.

The information submitted in this NDA in support of the safety and efficacy of BONVIVA in the treatment and prevention of post-menopausal osteoporosis has been derived from studies conducted under INDs 50,378 and 46,266 and from foreign preclinical and clinical studies conducted under the sponsorship of Hoffmann-La Roche and Company, Ltd., Basel, Switzerland.

This NDA documents the safety and effectiveness of BONVIVA for the treatment and prevention of post-menopausal osteoporosis. The information includes data derived from over 3900 patients treated with oral BONVIVA in the Treatment and Prevention of PMO for a duration of up to 3 years, including data from the pivotal studies MF 4411 in the treatment of PMO and MF 4499 in the prevention of PMO.

FDA/Sponsor Interactions

This NDA incorporates a number of agreements reached as a result of discussions and interactions with the Division during the development program of BONVIVA. These interactions have been primarily driven by various key milestones during the development program. A summary of key agreements pertinent to the current NDA is provided below, along with an outline of the key interactions that have taken place during the development period:

- agreement on the data analysis plan for the key pivotal I.V. study, MF 4380, including the reporting of the primary vertebral fracture endpoint and using vertebral height and vertebral height ratios to determine morphometric vertebral fractures
- agreement on data analysis plan for MF 4411
- agreement that the oral ibandronate program (oral treatment study MF 4411, oral prevention studies MF 4499 and MF 4500, plus supportive information) would be sufficient to support an NDA for ibandronate in the treatment and prevention of PMO, assuming the data was sufficiently positive. In particular a robust effect in the oral trial MF 4411 would be required and the correlation between BMD and fracture should be substantiated

Hoffmann-La Roche Inc.

340 Kingsland Street
Nutley, New Jersey 07110-1199



- fracture endpoint data in phase 3 studies to be presented as the proportion of patients with new fractures
- fracture data in the phase 3 treatment studies to be presented according to the following anatomic locations: morphometric vertebral, clinical (symptomatic) vertebral, hip, wrist, total osteoporotic non-vertebral fractures, total clinical fractures, total fractures and ribs
- fracture and BMD data would be analyzed by geographic location (EU vs. NA) in the phase III trials
- general agreement on the content and format of the NDA, including the ISE and ISS, clinical study reports, SAS datasets and CRFs
- agreement that only narratives for deaths, *drug-related* SAEs and *drug-related* AEs leading to premature withdrawal to be included in the NDA

Date	Interaction
Oct - Nov 1995	General correspondence and meeting to discuss preclinical bone quality studies
Jan - Apr 1996	Correspondence concerning dose selection in carcinogenicity studies
June 5, 1996	End of phase II meeting to discuss phase III clinical development program
July 9, 1998	End of phase II meeting to discuss phase III clinical development program
August 3, 1999	Pre-NDA CMC meeting
September 8, 1999	Pre-NDA meeting to discuss plans for the simultaneous submission of NDAs for IV and oral ibandronate for the treatment of PMO
May 18, 2000	Type A meeting following outcome of MF 4380 in order to discuss future development of IV and oral ibandronate
October 2000	Data Analysis Plan for MF 4411 submitted to FDA for review and comment
October 10, 2001	Pre-NDA meeting to discuss oral ibandronate phase 3 data and plans for submission of an NDA for oral ibandronate in the prevention and treatment of PMO
March - May 2002	Format and Content Questions submitted to IND 50,378

Further information on these interactions and agreements is provided in the Application Summary in Item 3 of the NDA.

NDA copies and content

This application is being submitted as a full Electronic Submission in accordance with 21 CFR 314.20 and is organized in accordance with the recommendations included in "Guidance for Industry: Providing Regulatory Submission in Electronic Format - NDAs, January 1999."

The approximate size of the submission is 11.0 GB (including 3.78 GB for the CRT patient profiles and datasets, and 5.39 GB for the Case Report Forms), provided on one DLT tape. The submission has been scanned with Norton AntiVirus, Version 7.03 and is virus free.

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 July 15, 2002
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In addition, paper desk copies are also provided as follows, as per agreement with the Review Division:

NDA Item (Volumes)	Reviewer(s) Desk Copies	Total Copies
Item 1 (TOC)	Pharmacology/Toxicology Reviewer Biometrics Team Leader Medical Reviewer CMC Reviewer	4
Item 2 (Labeling)	Pharmacology/Toxicology Reviewer Biometrics Team Leader Medical Reviewer CMC Reviewer	4
Item 3 (Summary)	Pharmacology/Toxicology Reviewer Biometrics Team Leader Medical Reviewer CMC Reviewer	4
Item 5 (Nonclinical pharmacology and toxicology)	Pharmacology/Toxicology Reviewer	1

Item 8 Clinical

As per previous agreements with the Division, clinical study reports are provided in full for all oral studies in the treatment and prevention of post-menopausal osteoporosis (MF 4348, MF 4433, MF 4411, MF 4491, M75003, MF 4499, MF 4500) as well as for the supportive IV studies, MF 4380 and MF 4470. Abbreviated reports are provided for the remaining studies, including other supportive IV studies in the treatment and prevention of PMO and other miscellaneous studies for other osteoporosis indications.

SAS datasets for Clinical Studies

Electronics datasets (as SAS transport files) along with define files and annotated CRFs are provided in Item 11 of the NDA for all oral studies in the treatment and prevention of osteoporosis (MF 4348, MF 4433, MF 4411, MF 4491, M75003, MF 4499, MF 4500) and for the supportive IV studies MF 4380 and MF 4470, as previously agreed with the Division (March 8, 2002; IND 50,378; S-129).

SAS datasets for PK Studies

Electronic PK datasets (as SAS transport files) along with define files and annotated CRFs are provided in Item 11 of the NDA for phase I studies, as previously agreed with the Division (May 3, 2002; IND 50,378; S-133). The PK datasets provided include demographic data, individual plasma/urine concentration data and derived key PK parameters. For two studies (MF 9850 and MF 9852, carried out in Japan) SAS datasets and define files have also been included, but it should be noted that fully complete annotated CRFs are not available. Descriptive statistics are provided as part of the final study reports for all studies.

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July 15, 2002
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Patient Profile Conversion Tables

Due to the use of different dictionaries (MEDDRA and HARTS) being used for some clinical studies, conversion tables have been provided, where appropriate, for patient profiles and are located in Item 11 of the NDA.

CRFs

Electronic CRFs for Deaths and Dropouts due to adverse events are provided in Item 12 of the NDA for all oral studies in the treatment and prevention of post-menopausal osteoporosis, for all supportive I.V. studies in the treatment and prevention of post-menopausal osteoporosis and other miscellaneous supportive studies.

References

Each report or publication referenced in this NDA has been assigned a unique four-digit Master Reference Number (MRN), which is used each time the report is referred to. With a few exceptions, each reference is provided once in the submission, even if it is referenced in more than one section of the NDA. Each reference is hyperlinked to the corresponding source file, the reference appearing in the margin of the report or summary, to the right of the text as: *MRN: filename.* (e.g. **7018: mf4361.pdf**). The filename, as indicated in blue, is hyperlinked to the source file. The reference also appears with the full citation, master reference number, and hyperlinked filename in the reference list at the end of each summary body.

Item 2 Labeling

A Professional Package Insert (USPI), Patient Package Insert and carton labels are provided for BONVIVA film-coated tablets 2.5mg. All labeling documents for both the professional and patient labeling are provided in Item 2. All documents provided in Item 2 have the appropriate file names, bookmarks and hypertext linking as recommended in the Guidance to Industry.

An annotated USPI is also provided, as part of Item 3: Application Summary. Annotation includes a hyperlink to the appropriate report, along with, where appropriate, a reference to the relevant section number of the report.

Drug Master File Cross References

The list of Drug Master File references in this NDA are attached to Form FDA 356h. Letters of authorization to the Drug Master Files are located in Item 4 of the NDA.

Field Office Copy

In accord with 21 CFR 314.50 (1)(3), we certify that an identical copy of the technical section of this dated submission is available to the home district office upon request. A copy of the submission cover letter, application form, and application summary are being provided to the district office at the address below:

Ms. Regina Brown
Pre-Approval Program Manager
Food and Drug Administration
120 North Central Drive
New Brunswick, New Jersey 08902

A copy of the Field Copy Certification is located in Item 17 of the NDA.

Hoffmann-La Roche Inc.

340 Kingsland Street
Nutley, New Jersey 07110-1199

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**Patent Information**

Patent information on the drug substance, drug product and method of use (US Patents 4,927,814 and 6,143,326 and 6,294,196 B1) is provided following this letter. Additional patent information is included in Item 13 of the NDA.

Tradename

The Tradename "BONVIVA" has been submitted to the Division for review by OPDRA (December 20, 2001; IND 50,378; S-126). To date, no response has been received by the Sponsor from FDA.

Pediatric studies

Pediatric studies for BONVIVA in the treatment and prevention of PMO have not been carried out and are not planned. A waiver has been granted by the FDA following a request by the Sponsor (January 2, 2002; IND 50,378; S-127 and March 15, 2002; IND 50,378; S-131).

User Fee

The User Fee Payment for this NDA was previously wired to the FDA, with a value date of June 26, 2002. The User Fee I.D. number is 4357. Following this letter is the original, signed User Fee Cover Sheet (Form FDA 3397). This form is also provided in Item 18 of the NDA.

Financial Disclosure

Investigator financial disclosure information follows this letter and is also provided in Item 19 of the NDA. An original, signed Form FDA 3454 for the listed investigators who do not have financial information to disclose is attached. An original, signed Form FDA 3454 is also attached for the listed investigators for whom we have acted with due diligence to obtain financial disclosure information, but whom have not provided the required information. Original, signed Form FDA 3455s for each investigator who has financial information to disclose are attached.

Roche Contact

In order to facilitate the review, we encourage the Division to contact us to clarify any issues or address any questions. Please contact Ms. Sarah Orris at (973) 562-3688 with any chemistry, manufacturing and controls questions and Mr. Mark Hope (973) 562-2926 with any clinical, preclinical or other general questions.

Confidential Information

Since the New Drug Application has not yet been approved, this submission is considered as constituting trade secrets or commercial or financial information which is privileged or confidential within the meaning of the Freedom of Information Act (5 USC 552). It is requested that this submission not be published until the New Drug Application has been approved.



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July 15, 2002
Page 6 of 6

Please do not hesitate to contact the undersigned should you have any questions or require any further information.

Yours sincerely,

HOFFMANN-LA ROCHE INC.

A handwritten signature in black ink, appearing to read "M. Hope".

Mark Hope
Regulatory Program Director
Phone: 973-562-2926
Fax: 973-562-3700

MH/aa
HLR No. 2002-1439

Attachments:

1 DLT tape

Paper desk copies - Items 1, 2, 3, and 5 (as described above)

cc: Ms. Regina Brown – (356h form, cover letter, and application summary)

BONIVA® TABLETS

TESTING PHASE - IND 50,378

<u>COMMUNICATION</u>	<u>DATE OF COMMUNICATION</u>
Pre-IND Submission - Request for meeting with FDA	12/22/1994
File Note - Telephone call setting date for Pre-IND meeting	1/11/1995
File Note - Telephone call confirming date and time for Pre-IND/NDA Meeting	1/20/1995
File Note - Telephone call inquiring status of FDA's interim analysis review	5/31/1995
IND original for the treatment of Metastatic Bone Disease	4/15/1996
FDA letter acknowledging receipt of original IND	4/19/1994
Fax providing revised attendance list for meeting	4/26/1996
Fax of cover letter requesting an FDA meeting	4/26/1996
Fax of submission regarding Clinical Plan Meeting	5/10/1996
Fax regarding plan to initiate a phase III study	5/23/1996
File Note - Telephone call providing comments regarding phase III study	5/31/1996
File Note - Schedule clinical plan meeting	7/1/1996
Protocol Amendment: New Investigators, Protocol	7/8/1996
IND Other - General Correspondence: Items for review and comments	7/30/1996
Protocol Amendment: New Investigators, Protocol	8/1/1996
File Note - Inquiring FDA comments regarding prior submission	8/20/1996
Information Amendment: CMC - inform FDA that the amendment to IND 46,266, serial no. 048 made on 7/9/96 applies to IND 50,378	8/21/1996
Protocol Amendment: New Investigator; Information Amendment - Clinical	9/13/1996
Protocol Amendment: New Protocol; Information Amendment: Clinical, and CMC - provided support for protocol	9/25/1996
FDA Letter - Informing completion of preliminary review of Original IND Submission and informed us we may proceed	9/27/1996
Protocol Amendment: New Investigators, Protocol	10/16/1996
Fax of the proposed submission to respond to the "Request for Information"	10/22/1996
Response to FDA Request for Additional Information	10/30/1996
Information Amendment: Pharmacology/Toxicology	11/4/1996

File Note - Telephone call to FDA regarding submission	11/14/1996
Protocol amendment - New Investigators Protocol; Information Amendment - Clinical	12/19/1996
General Correspondence with FDA	2/28/1997
Protocol Amendment: New Investigators Protocol	3/12/1997
Request for United States Adopted Name (USAN) for Ibandronic Acid	3/24/1997
NDA Electronic Submission Fax regarding intent to file NDA	3/25/1997
IND Safety Report; ADE	4/4/1997
Protocol Amendment: New Investigator Protocol	4/30/1997
IND Safety Report; ADE	5/8/1997
File Note - Telephone call regarding status of submission	5/19/1997
FDA Letter - Fax providing comments	5/23/1997
Fax to FDA inquiring acceptability of a term	5/30/1997
Protocol Amendment: New Investigator	6/18/1997
IND Annual Report	7/2/1997
E-Mail to FDA regarding Protocol Amendment	8/12/1997
Protocol Amendment: Change in Protocol	8/14/1997
Submission informing FDA of termination of a clinical site	9/24/1997
IND Safety Report: ADE	12/15/1997
IND Safety Report: ADE	1/30/1998
Updated Investigator Information Protocol	4/15/1998
Protocol Amendment; Change in Protocol, Information Amendment: CMC	4/29/1998
Change of Sponsor	5/12/1998
IND Annual Report	5/13/1998
Change of Sponsor, Letter of Acceptance	5/14/1998
Submission to request a meeting for update	6/10/1998
Pre-Meeting Information Package	6/17/1998
Updated List of Attendees for Meeting regarding updated clinical development program	7/2/1998
Information Amendment: CMC	7/6/1998
Protocol Amendment: New Protocol/Change in Protocol	7/31/1998
Protocol Amendment: New Protocol	8/10/1998
Protocol Amendment: New Investigator, Information Amendment: Clinical	8/31/1998
File Note - Telephone call regarding adverse report	9/28/1998
IND Amendment - Protocol Amendment	9/30/1998
IND Safety Report: ADE	10/6/1998
File Note - Telephone call regarding the stage of development	10/9/1998
IND Safety Report; ADE	10/21/1998

Draft Minutes of Meeting regarding clinical development program	10/21/1998
IND Amendment - Protocol Amendment; New Investigators, Information Amendment: Chemistry/Microbiology, Clinical	10/29/1998
Protocol Amendment: Change in Protocol and New Investigator	11/30/1998
IND Safety Report; ADE	12/17/1998
IND Amendment - Protocol Amendment; Change in Protocol, Information Amendment: Clinical	12/18/1998
IND Amendment - Information Amendment - Clinical and additional subinvestigator information	1/29/1999
IND Amendment - Information Amendment; Clinical and subinvestigator information	2/26/1999
General Correspondence requesting a response from FDA	3/2/1999
File Note - voice mail to FDA regarding forthcoming submission and requesting comments	3/11/1999
General Correspondence - following up telephone call with FDA	3/23/1999
FDA Letter from FDA containing a summary and FDA's recommendation	3/25/1999
FDA Letter from FDA requesting information	4/21/1999
IND Amendment - Information Amendment: Clinical and subinvestigator information	4/28/1999
IND Amendment - Protocol Amendment: Change in Protocol	5/6/1999
Fax letter to FDA responding to request for information	5/14/1999
Response to FDA's request for information	5/14/1999
Information Amendment: Clinical and subinvestigator information	5/28/1999
IND Annual Report	6/15/1999
File Note - Telephone message/conversations concerning a proposed amendment	6/17/1999
File Note - Telephone message/conversations concerning a proposed amendment	6/17/1999
Submit cited reference to FDA in response to FDA's request	6/18/1999
Fax letter to FDA regarding cited reference in response to FDA's request	6/18/1999
Request meeting of FDA regarding proposals of CMC for postmenopausal osteoporosis	6/21/1999
Information Amendment: Clinical and subinvestigator information	6/30/1999

Fax letter to FDA regarding Postmenopausal Osteoporosis Pre-NDA Meeting Request	7/16/1999
Request for Pre-NDA meeting with FDA regarding simultaneous submission	7/16/1999
Protocol Amendment: New Protocol; Change in Protocol; Clinical	7/22/1999
File Note - Pre-NDA CMC meeting to discuss CMC plans	8/3/1999
General Correspondence - providing a copy of the Pre-NDA	8/23/1999
Protocol Amendment: New Investigator; Information Amendment: Clinical	8/31/1999
Submitting attendance list for Pre-NDA meeting	9/3/1999
Fax letter to FDA submitting attendance list for Pre-NDA meeting	9/3/1999
File Note - Pre-NDA clinical/pre-clinical meeting for simultaneous submission	9/8/1999
Correspondence requesting Review of Proposed Tradename	9/13/1999
Fax to FDA containing Request for Review of Proposed Tradename	9/13/1999
FDA letter regarding completed review of submission and providing comments	9/15/1999
FDA Fax letter informing completion of review of submission and providing comments	9/15/1999
Information Amendment: Clinical and subinvestigator information	9/30/1999
FDA Fax letter containing minutes from meetings	9/30/1999
File Note - Telephone call discussing transfer of indications	10/15/1999
File Note - FDA telephone call to follow-up on outstanding issues	10/19/1999
FDA e-mail letter responding to questions	10/21/1999
Protocol Amendment: New Investigators; Information Amendment: Chemistry/Microbiology	10/22/1999
Right of cross-reference conferred to HLR, Nutley	10/25/1999
Protocol Amendment: New Investigators, and other related investigator information	11/11/1999
Meeting minutes in response to outstanding issues from Pre-NDA CMC Meeting	12/6/1999
Protocol Amendment: New Investigators, and other related investigator information; Information Amendment - Clinical	12/10/1999
Telephone call with FDA concerning review of the tradename	12/15/1999
Voicemail message to FDA describing the use of ibandronate in a particular study, not conducted under US NDA	1/3/2000
Telephone message from FDA regarding proposed markings	1/5/2000

IND Safety Report: Follow-up to a Written Report	1/5/2000
File Note - Voicemail message to FDA regarding reported cases	1/7/2000
Protocol Amendment - New Investigators; Information Amendment - Clinical	1/28/2000
Information Amendments - Updated Investigator Information	2/28/2000
Information Amendments - Updated Investigator Information	3/29/2000
General Correspondence regarding Type A meeting request	3/31/2000
Response to FDA's request for CMC information	4/7/2000
Fax letter sent to FDA responding to request for CMC information	4/7/2000
File Note - Telephone call with FDA regarding submission	4/7/2000
Protocol Amendment: New Investigator, and updated investigator information	4/14/2000
File Note - Telephone call with FDA to follow-up on meeting request	4/19/2000
File Note - Telephone call with FDA regarding a date for meeting	4/25/2000
General Correspondence: Briefing Document for meeting	5/3/2000
IND Safety Report: Initial Written Report, ADE: periorbital edema	5/8/2000
File Note - Providing Final Minutes from Meeting regarding clinical development program	5/18/2000
IND Safety Report: Initial Written Report	5/19/2000
IND Safety Report: Second Follow-up to a Written Report	5/23/2000
IND Safety Report: Follow-up to a Written Report	5/25/2000
Information Amendment - Updated investigator information	5/26/2000
General Correspondence: Change in name of Sponsor's Legal Entity, Change in Clinical and Safety Monitor, Proposed IND Expedited Safety Reporting Procedure	6/8/2000
FDA Letter providing minutes from the meeting	6/8/2000
IND Annual Report	6/15/2000
IND Safety Report: Initial Written Report	6/27/2000
IND Safety Report: Follow-up to a Written Report	7/6/2000
IND Safety Report: Follow-up to a Written Report	7/7/2000
IND Safety Report: Follow-up to a Written Report	7/7/2000
File Note: Telephone call to FDA to verify the submission and review procedures	7/11/2000
IND Safety Report: Follow-up to an Initial Written Report	7/17/2000
E-mail sent to FDA providing anticipated submission procedure	7/19/2000

File Note: Providing a copy of the official minutes from FDA for meeting	7/24/2000
File Note: Telephone call with FDA to explore trademark issues	7/25/2000
Information Amendment - updated Investigator information, Protocol	7/31/2000
IND Safety Report: Third and Fourth Follow-up to a Written Report	8/25/2000
Replacement Submission: IND Safety Reports: Third and Fourth Follow-up to Written Report	8/28/2000
Information Amendment - Updated Investigator Information, Protocol	8/31/2000
IND Safety Report: Initial Written Report	9/8/2000
IND Safety Report: Fifth Follow-up to a Written Report	9/12/2000
Protocol Amendment: Change in Protocol and updated investigator information	9/29/2000
Protocol Amendment: Protocol Change	10/6/2000
IND Safety Report: Follow-up to a Written Report	10/6/2000
IND Safety Report: Follow-up to a Written Report	10/20/2000
Protocol Amendment - New Investigator; Information Amendment - Pharmacology/Toxicology	10/31/2000
FDA Fax Letter containing FDA comments regarding amendment	11/22/2000
File Note - Several telephone calls to and from FDA regarding the status of FDA's review of protocol	11/27/2000
Information Amendment - Updated Investigator Information	11/30/2000
Response to FDA Request for Information and Protocol Amendment Study	12/4/2000
Protocol Amendment - Updated Investigator Information	12/21/2000
IND Safety Report: Initial Written Report	12/29/2000
File Note - Telephone call with FDA regarding expedited safety report	1/22/2001
Protocol Amendment: New Investigator and updated investigator information	1/31/2001
Response to FDA Request for Information: Comments on Protocol Amendment	2/2/2001
IND Safety Report: First Follow-up to a Written Report	2/2/2001
Chemistry, Manufacturing and Controls (CMC) Proposal	2/9/2001
IND Safety Report: Initial Written Report	2/9/2001
Protocol Amendment - Updated Investigator Information	2/15/2001
Protocol Amendment - Updated Investigator Information	3/1/2001

File Note - Telephone call with FDA to follow-up on the status of FDA comments	3/8/2001
Submission of CMC Proposal	3/8/2001
IND Safety Report: Sixth Follow-up to a Written Report	3/12/2001
IND Safety Report: First Follow-up to a Written Report	3/19/2001
Protocol Amendment - Updated Investigator Information	3/30/2001
File Note - Telephone call with FDA regarding FDA's status to CMC proposals	4/10/2001
Protocol Amendment - Updated Investigator Information; and Information Amendment - Pharmacology/Toxicology	4/30/2001
IND Safety Report: Initial Written Report	6/6/2001
IND Safety Report: Second Follow-up to a Written Report	6/20/2001
IND Annual Report	6/29/2001
General Correspondence: Meeting Request (Pre-NDA and New Development)	7/3/2001
Information Amendment: Pharmacology/Toxicology	7/24/2001
General Correspondence: Response to Questions about Meeting Request	7/31/2001
File Note: Telephone call from FDA concerning submission	8/2/2001
General Correspondence: Submitting Briefing Document for Pre-NDA and New Development Meeting	8/15/2001
General Correspondence: Designation of Regulatory Agent; Change in Clinical and Safety Monitor	10/18/2001
Meeting Minutes - FDA Pre-NDA Meeting to discuss results	10/30/2001
Protocol Amendment: New Protocol	10/30/2001
E-Mail - Provided a copy of submission regarding Protocol Amendment	11/12/2001
E-Mail - Information Request Response	11/12/2001
Information Amendment - Clinical	11/16/2001
Information Amendment - Clinical	11/21/2001
FDA Letter requesting another electronic copy of document	12/3/2001
E-Mail submitting electronic copy of document	12/5/2001
Fax - Confirmation of telephone conversation with FDA	12/10/2001
File Note - Telephone calls to NDA	12/19/2001
Request FDA Review of Proposed Tradename	12/20/2001
FDA Letter - Providing comments in response to submission	12/26/2001
FDA Letter - Providing comments regarding submission	12/26/2001
FDA Letter - Providing comments regarding submission	1/2/2002
General Correspondence - Request for Waiver/Deferral for Pediatric Studies	1/2/2002
Protocol Amendment: New Protocol	2/21/2002

File Note: Telephone call from FDA regarding protocol submission	3/4/2002
File Note - Telephone call to FDA regarding the status of the Tradename application	3/4/2002
File Note - Telephone call from FDA inquiring a deferral date regarding pediatric studies	3/8/2002
Information Amendment: Clinical	3/8/2002
General Correspondence: Request for FDA Feedback on the Format, Content and Administrative Handling of the NDA	3/8/2002
File Note - Telephone call to FDA to follow-up on FDA's special protocol review	3/13/2002
General Correspondence: Clarification and Modification of Pediatric Waiver/Deferral Submission	3/15/2002
Information Amendment: CMC	3/15/2002
FDA Letter - E-Mail from FDA regarding Protocol	3/21/2002
File Note - Telephone call with FDA regarding Financial Disclosure guidelines	3/26/2002
File Note - Telephone call with FDA clarifying request for Protocol	3/27/2002
FDA Letter inquiring whether new protocol meets certain criteria	4/10/2002
FDA Letter informing reviewed submissions requesting deferral and waiver for pediatric studies	4/26/2002
File Note - Summary of calls to follow-up on status of submission	4/29/2002
E-Mail - Question on NDA Format and Content	4/29/2002
General Correspondence regarding Questions/Clarifications for NDA Electronic Submission	5/3/2002
File Note - Telephone call with FDA regarding protocol amendment	5/6/2002
E-Mail - Question on NDA Format and Content - Request for status of FDA response to questions	5/17/2002
FDA Letter - E-Mail response to E-mails regarding question on NDA Format and Content	5/21/2002
Protocol Amendment: New Investigators	5/29/2002
Information Amendment: Preclinical Pharmacology/ Toxicology Amended Reports	5/30/2002
General Correspondence - E-mail to FDA requesting confirmation on understanding of previous discussions with FDA	5/30/2002
FDA Letter - E-mail from FDA responding to e-mail	5/31/2002

General Correspondence: Requested FDA feedback and confirmation of understanding of previous discussions	6/3/2002
Protocol Amendment: Change in Protocol	6/20/2002
File Note - Voicemail message with FDA and sent e-mail asking acceptability of submitting an administrative Annual Report; received e-mail response	6/26/2002
Protocol Amendment: New Investigators	7/11/2002
Administrative IND Annual Report	7/16/2002
Protocol Amendment: New Investigators	8/9/2002
Protocol Amendment: New Investigators	9/13/2002
Protocol Amendment: Additional Investigator Information	10/7/2002
General Correspondence: Meeting Request	10/8/2002
FDA Letter informing it has reviewed submission of questions and meeting request	10/25/2002
IND Safety Report: Initial Written Report	10/25/2002
General Correspondence regarding Briefing Package	11/4/2002
Information Amendment: CMC	11/25/2002
Information Amendment: CMC	12/16/2002
File Note: FDA inquiring on status of submission requesting FDA feedback on proposed development plan	12/19/2002
Protocol Amendment: New Investigators	1/9/2003
Information Amendment: Chemistry, Manufacturing and Controls	1/10/2003
File Note - Telephone call with FDA inquiring status of submission review	1/13/2003
Protocol Amendment: New Protocols	1/17/2003
Information Amendment - CMC	2/7/2003
IND Safety Report: First and Second Follow-up	2/27/2003
Protocol Amendment: Change in Protocol	2/28/2003
Protocol Amendment: New Investigators and Additional Investigator Information	3/14/2003
General Correspondence: PK Data and Request for Feedback on Revised Development Plan	4/7/2003
IND Safety Report: Initial Written Report	4/9/2003
Protocol Amendment: Study	4/11/2003
Protocol Amendment: Additional Investigator Information	4/17/2003
IND Safety Report: First Follow-up Report	4/23/2003
Information Amendment: Chemistry, Manufacturing and Controls (CMC)	4/25/2003

BONIVA® TABLETS

APPLICATION PHASE - NDA 21-455

COMMUNICATION	DATE OF COMMUNICATION
NDA Original - Boniva for treatment and prevention of post-menopausal osteoporosis	7/15/2002
Provided a field copy of documents	7/15/2002
FDA request for Reviewer Desk Copy of the Administrative documents and labeling, etc.	7/17/2002
File Note - Telephone call with FDA confirming safe receipt of the electronic submission of NDA	7/17/2002
Response to FDA Request for Information: Desk Copy for FDA	7/22/2002
File Note - Telephone call from FDA requesting original signatures for documents	7/22/2002
File Note - Telephone calls to and from FDA regarding navigation help to FDA in locating information from electronic file	7/26/2002
File Note - Telephone call to FDA to confirm receipt and acceptance of submission of original signatures	7/26/2002
File Note - Arranged teleconference in response to FDA's request to clarify dataset that were submitted in the NDA	7/29/2002
File Note - Provided clarification	7/29/2002
File Note - FDA telephone call requesting check on User Fee number	7/30/2002
Fax to FDA in response to FDA Request for information	8/2/2002
FDA Fax letter to FDA providing comments/questions regarding datasets	8/2/2002
File Note - Telephone calls to FDA regarding receipt of the proc contents and printouts	8/5/2002
E-mail - ISE Subpopulation/Demographic Information - Per telephone conversation with FDA	8/5/2002
FDA letter acknowledged receipt of Original NDA	8/5/2002
File Note - Telephone calls with FDA regarding question on NDA	8/6/2002
File Note - Telephone call with FDA in follow-up to teleconference	8/7/2002
Fax to FDA regarding teleconference	8/8/2002
File Note - Telephone calls from FDA to discuss datasets	8/12/2002
FDA Request for Reviewer Desk Copy of CMC data	8/14/2002

File Note - Telephone call to FDA to inquire whether FDA identified any major issues with the NDA following internal meeting	8/26/2002
File Note - Telephone call from FDA to inform that FDA had their internal meeting	8/26/2002
File Note - Telephone call from FDA informing receipt of fax and FDA's acceptance of dataset proposal	8/26/2002
Fax to FDA in response to FDA Request for Information	8/26/2002
NDA Amendment to provide additional datasets	9/4/2002
Proposal for 4-Month Safety Update	9/5/2002
E-Mail to FDA regarding proposal for 4-Month Safety Update	9/5/2002
E-Mail from FDA informing agreement to proposal for the 4-Month Safety Update	9/9/2002
File Note - FDA telephone call informing tradename not accepted, and requested information	9/18/2002
NDA Amendment - Electronic Amendment	9/20/2002
File Note - Telephone call to FDA to inquire about the status of review	10/4/2002
FDA Fax Letter - FDA Statistical Reviewer provided a list of preliminary requests for additional information	10/18/2002
File Note - Telephone call from FDA to inform of new statistical reviewer	10/22/2002
Voicemail from FDA requesting information for clinical study sites	10/22/2002
File Note - FDA called to outline request for Audit Information	10/25/2002
Response to FDA Request for information on Investigational Sites for Studies	11/14/2002
Response to FDA Request for information on Investigational Sites for Studies	11/14/2002
Response to FDA Request for information on Investigational Sites for Studies	11/14/2002
Response to FDA Request for information on Investigational Sites for Studies	11/14/2002
Response to FDA Request for information on Investigational Sites for Studies	11/14/2002
Letter to FDA regarding response to FDA Request for Information; CMC Information	11/15/2002
Provided FDA with 4-Month Safety Update	11/15/2002
E-mail from FDA requesting information	11/18/2002
FDA request information	11/18/2002
File Note - FDA telephone call informing receipt of responses to information request	11/20/2002
E-mail sent to FDA regarding dataset program to aid in identification of treatment group	12/11/2002

Responses to FDA regarding information request; follow-up response	12/11/2002
FDA Letter provided comments and requests regarding the Human Pharmacokinetics & Bioavailability, and CMC	12/13/2002
E-mail to FDA responding to FDA e-mail concerning the Decode+ clarification	12/17/2002
File Note - Telephone call to FDA requesting the status of the submission requesting feedback from FDA on the proposed development plan	12/19/2002
Responses to FDA regarding FDA's Information Request	12/20/2002
E-mail response to FDA regarding FDA's Information Request	12/23/2002
E-mail to FDA clarifying report	1/7/2003
Response to FDA regarding FDA's Information Request	1/9/2003
E-mail Letter from FDA informing certain responses were not satisfactory	1/13/2003
File Note - Telephone call to FDA inquiring status of review	1/13/2003
FDA Letter informing status of review for pharmacology/toxicology section of submission	1/13/2003
FDA E-mail Letter requesting additional information regarding clinical information	1/15/2003
E-mail to FDA providing response to Clinical Information	1/16/2003
Response to FDA's Information Request regarding review of the Human Pharmacokinetics and Bioavailability and Chemistry, Manufacturing, and Controls	1/17/2003
Responses to Information Request from FDA	1/20/2003
FDA E-mail Letter from FDA requesting information/clarification	1/22/2003
Responses to FDA's Information Request	1/22/2003
FDA E-mail Letter requesting document	1/27/2003
Submission of Alternative Tradename to FDA	1/31/2003
FDA E-mail Letter from FDA requesting additional information	2/10/2003
E-mail to FDA to request clarification on FDA's Information Request	2/10/2003
FDA E-mail Letter from FDA clarifying information request regarding Study	2/11/2003
Response to FDA regarding its information request for clinical information	2/12/2003
File Note - FDA telephone call; discussed NDA and status of NDA and Trademark submission	2/14/2003
E-mail to FDA regarding Biopharm review; question on Data; responded to information request	2/21/2003
Response to preclinical questions	2/21/2003
Response to clinical questions	2/21/2003
File Note - Telephone call with FDA regarding NDA review	2/24/2003

Provided response to FDA's E-mail request for information	2/25/2003
Response to Clinical Questions from FDA	2/26/2003
E-mail response to FDA statistical reviewer questions	2/27/2003
E-mail response to FDA regarding supporting references	2/28/2003
Response to information request regarding backup tradename	2/28/2003
Information Request from FDA regarding supporting references for Animal Pharmacology Section of USPI	2/28/2003
E-mail from FDA informing completion of a review submitted with the NDA	2/28/2003
E-mail to FDA submitting a powerpoint file containing a poster presentation in support of answer to a question	3/3/2003
E-mail sent to FDA informing submission of information	3/5/2003
E-mail from FDA requesting information in the NDA	3/5/2003
FDA requesting information regarding Human Pharmacology Summary	3/6/2003
File Note - Teleconference with FDA regarding clarification	3/10/2003
E-mail to FDA responding to voicemail request for information	3/12/2003
E-mail from FDA requesting information	3/13/2003
E-mail to FDA responding to information request	3/14/2003
Response to information request	3/14/2003
Response to information request; clinical questions	3/19/2003
Response to FDA's request for information	3/21/2003
E-mail responding to FDA's request for information	3/24/2003
Response to FDA's request for information	3/24/2003
Response to FDA's request for information	3/28/2003
File Note - Telephone call with FDA; bottle labels	4/1/2003
Response to information request; monkey studies	4/9/2003
E-mail from FDA regarding the draft label	4/10/2003
E-mail response to information request; patent PI	4/14/2003
File Note - Provided a summary of telephone conversations with FDA	4/17/2003
E-mail response to FDA regarding FDA proposed changes	4/22/2003
E-mail response to FDA	4/23/2003
E-mail from FDA regarding chemistry comments	4/23/2003
E-mail response to FDA providing clean version of current USPI	4/23/2003
E-mail response to FDA; teleconference request	4/24/2003
E-mail from FDA; animal	4/29/2003
E-mail from FDA; pharmacodynamics	4/29/2003
E-mail response to FDA; animal pharmacology	4/29/2003

E-mail response to FDA; draft response to chemistry and biopharm comments	4/29/2003
Response to FDA comments	4/29/2003
E-mail from FDA; revised draft label	4/30/2003
E-mail to FDA; pharmacodynamics	4/30/2003
NDA Amendment; efficacy programs	4/30/2003
E-mail from FDA requesting information	5/1/2003
Response to FD request; USPI	5/2/2003
File Note - FDA inform completion of trademark review	5/5/2003
FDA letter providing meeting minutes	5/5/2003
NDA Amendments - follow-up information	5/5/2003
File Note - teleconference summary	5/5/2003
Fax to FDA regarding CMC	5/6/2003
NDA Amendment; USPI	5/6/2003
Fax to FDA responding to information request; chemistry and biopharm	5/6/2003
E-mail to FDA responding to information request; USPI	5/6/2003
Request for FDA to re-evaluate tradename	5/7/2003
Fax to FDA responding to comments; CMC	5/7/2003
E-mail to FDA updating patient package insert	5/7/2003
Fax to FDA; comments on tradename	5/8/2003
E-mail to FDA responding to information request	5/8/2003
E-mail to FDA regarding tradename	5/8/2003
Fax to FDA updating; directions for routine tests	5/9/2003
E-mail response to FDA information request; CMC/Biopharm issues	5/9/2003
Response to FDA comments; USPI	5/9/2003
FDA Letter providing summary of the teleconference	5/9/2003
File Note - provided summary of the teleconference	5/9/2003
E-mail responding to information request; USPI	5/12/2003
E-mail to FDA responding to request for information; PPI	5/13/2003
Produced cleaned version of PPI and USPI	5/13/2003
E-mail clean version of PPI and USPI to FDA	5/15/2003
E-mail to FDA; labels	5/15/2003
E-mail to FDA responding to request to provide USPI and PPI	5/16/2003
E-mail to FDA responding to request to provide USPI	5/16/2003
E-mail to FDA providing final versions of USPI and PPI	5/16/2003
FDA letter providing approval of NDA	5/16/2003