CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-455

ADMINISTRATIVE DOCUMENTS

DEBARMENT CERTIFICATION

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

BONVIVA® (ibandronate sodium)
Film-coated Tablets 2.5 mg

Roche

Item 13

NDA 21-455

Bonviva (ibandronate sodium)

Treatment and Prevention of Postmenopausal Osteoporosis

Patent Information / Market Exclusivity Request

Pursuant to the provisions of Section 505(c)(3)(D) and Section 505(j)(4)(D) of the Federal Food, Drug and Cosmetic Act ("Act") as amended, and to the provisions of 21 CFR 314(j)(4), we hereby claim a five (5) year market exclusivity period based upon the fact that new clinical investigations, which were conducted or sponsored by Hoffmann-La Roche Inc. and Boehringer Mannheim GmbH, Hoffmann-La Roche Inc.'s predecessor in interest, were essential to the approval of the above Application. During this market exclusivity period, FDA may not make the approval of an application of the type described in Sections 505(b)(2) or (j) of the Act for the condition of approval of Bonviva under the above NDA, effective before the expiration of five (5) years from the date of the approval of the above NDA.

In accordance with the further amendments of the Act, when the approval is made by the Food and Drug Administration, it is our understanding that this market exclusivity information will be included at the same time in the Approved Prescription Drug Product List ("Orange Book").

A Patent Information form is herewith attached.

PATENT INFORMATION FOR NDA NO. 21-455

1)	Active Ingredient(s)	Ibandronate sodium
2)	Strength(s)	2.5 mg
3)	Trade Name	Bonviva
4)	Dosage Form and Route of Administration	Film coated tablet for oral administration
5)	Applicant (Firm) Name	Hoffmann-La Roche Inc.
6)	NDA Supplement Number	N/A
7A)	First Approval Date of Original NDA	N/A not yet approved*
7B)	First Approval Date of Supplemental NDA	N/A
8)	Exclusivity: Date first ANDA could be approved	ANDA for change covered by pending NDA can not be approved for at least five (5) years from the date pending NDA is approved
9)	Patent Information	See Attachment

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.

ATTACHMENT 1 TO EXHIBITS A1-A3

This format repeats to allow up to three patents. If there are additional patents, please copy and attach.

First US Patent Number: 4,927,814

Expiration Date: 7/9/2007

Type of Patent-Indicate all that apply (check applicable boxes):

1.	Drug Substance (Active Ingredient)	[X]	Y	[ ]	N
2.	Drug Product (Composition/Formulation)	[X]	Y	[ ]	N
3.	Method of Use	[X]	Y	[ ]	N

If patent claims method(s) of use, please specify approved uses or uses for which approval is being sought that is covered by patent: postmenopausal osteoporosis.

Name of Patent Owner: Boehringer Mannheim GmbH

US Agent (if patent owner or applicant does not reside or have place of business in the US):

The following declaration statement is required if the above listed patent has Composition/Formulation or Method of Use claims.

The undersigned declares that the above stated United States Patent Number 4,927,814 covers the composition, formulation and/or method of use of Bonviva® ibandronate. This product is:

[ ] currently approved under the Federal Food, Drug, and Cosmetic Act.)

OR

[X] the subject of this application for which approval is being sought.)

BONVIVA® (ibandronate sodium)
Film-coated Tablets 2.5 mg

Roche

Item 13

Second US Patent Number: 6,143,326

Expiration Date: April 21, 2017

Type of Patent-Indicate all that apply:

1.	Drug Substance (Active Ingredient)	[ ]	Y	[ ]	N
2.	Drug Product (Composition/Formulation)	[ ]	Y	[ ]	N
3.	Method of Use	[X]	Y	[ ]	N

If patent claims method(s) of use, please specify approved uses or uses for which approval is being sought that is covered by patent: postmenopausal osteoporosis.

Name of Patent Owner: Roche Diagnostics GmbH

US Agent (if patent owner or applicant does not reside or have place of business in the US):

The following declaration statement is required if the above listed patent has Composition/Formulation or Method of Use claims.

The undersigned declares that the above stated United States Patent Number 6,143,326 covers the composition, formulation and/or method of use of Bonviva® (ibandronate). This product is:

[ ] currently approved under the Federal Food, Drug, and Cosmetic Act.)

OR

[X] the subject of this application for which approval is being sought.)

Third US Patent Number: 6,294,196 B1

Expiration Date: October 7, 2019

Type of Patent-Indicate all that apply:

1.	Drug Substance (Active Ingredient)	[ ]	Y	[ ]	N
2.	Drug Product (Composition/Formulation)	[X]	Y	[ ]	N
3.	Method of Use	[ ]	Y	[ ]	N

If patent claims method(s) of use, please specify approved uses or uses for which approval is being sought that is covered by patent:

_____.

Name of Patent Owner: Hoffmann-La Roche Inc.

US Agent (if patent owner or applicant does not reside or have place of business in the US):

The following declaration statement is required if the above listed patent has Composition/Formulation or Method of Use claims.

The undersigned declares that the above stated United States Patent Number 6,294,196 B1 covers the composition, formulation and/or method of use of Bonviva® (ibandronate). This product is:

[ ] currently approved under the Federal Food, Drug, and Cosmetic Act.)

OR

[X] the subject of this application for which approval is being sought.)

By: _____
Name: Patricia S. Rocha-Tramaloni
Date: Jan 22, 2010
Title: Senior Counsel
Telephone Number: (973) 235-2441

116668

A copy of the above information should be submitted with the NDA. For patents issued after the NDA is filed or approved, the applicant is required to submit that information within 30 days of the date of issuance of the patent.

To expedite publication in ***The Orange Book,**** a deskcopy should be submitted to:

Mailing address: (US Mail)

US Food and Drug Administration
Center for Drug Evaluation and Research
Division of Data Management and Services
Drug Information Services Team
HFD-93
5600 Fishers Lane
Rockville, MD 20857

OR

Location address: (for Federal Express deliveries)

US Food and Drug Administration
Center for Drug Evaluation and Research
Division of Data Management and Services
Drug Information Services Team
HFD-93 Room #235
Nicholson Lane Research Center
5516 Nicholson Lane
Building A
Kensington, MD 20895
Phone (301) 827-5470
OR faxed to: (301) 594-6463

EXCLUSIVITY SUMMARY for NDA # 21-455 SUPPL #
Trade Name Boniva Generic Name ibandronate sodium
Applicant Name Hoffman-La Roche Inc. HFD-510

Approval Date

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/_X_/ NO /___/

   b) Is it an effectiveness supplement? YES /___/ NO /___/

      If yes, what type(SE1, SE2, etc.)?

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES /_X_/ NO /___/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

   d) Did the applicant request exclusivity?

YES /_X_/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

Five

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_X_/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /___/ NO /_X_/

If yes, NDA # _____ Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /_X_/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

   YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study #

Investigation #2, Study #

Investigation #3, Study #

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /___/
Investigation #2	YES /___/	NO /___/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study #

Investigation #__, Study #

Investigation #__, Study #

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1	
IND # _____ YES /___/	NO /___/ Explain:
Investigation #2	
IND # _____ YES /___/	NO /___/ Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____
Investigation #2	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

_____

_____

Signature of Preparer Date
Title:

Signature of Office or Division Director Date

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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

/s/

Randy Hedin
5/19/03 10:01:31 AM

David Orloff
5/19/03 03:56:52 PM

Memorandum

Date: 15 May 2003

From: David E. Morse, Ph.D.
Assoc. Director (Pharm./Tox.), Office of Drug Evaluation II

To: Robert Meyer, M.D.
Director, Office of Drug Evaluation II

Cc: David G. Orloff, M.D., Dir., DMEP (HFD-510)
Karen Davis-Bruno, Ph.D., Sup. Pharm./Tox., DMEDP (HFD-510)
Gemma Kuijpers, Ph.D., Reviewing Pharmacologist, DMEDP (HFD-510)

Subject: NDA 21-455
BONIVA® Tablets (ibandronate sodium)
Review of Pharm./Tox. Information and Sections of Proposed Product Label

I. Materials Included in Review

1. Pharm./Tox. Review of NDA 21-455, dated 16 April 2003, G. Kuijpers, Ph.D.
2. Package Insert for BONIVA® Tablets, version of 13 May 2003
3. NDA 21-455 Action Package with Division Director Memo.
4. Related Product Labeling:
   - ACTONEL® (risedronate; NDA20835; osteoporosis)
   - AREDIA® (pamidronate; NDAs 20036/20927; Paget's disease)
   - DIDRONEL® (etidronate; NDAs 17831/19545; Paget's disease)
   - FOSAMAX® (alendronate; NDA 20560; osteoporosis)
   - FOSCAVIR® (foscarnet; NDA 20068; anti-viral [CMV])
   - SKELID® (tiludronate; NDA 20707; Paget's disease)
   - ZOMETA® (zoledronate; NDAs 21223/21386; Paget's disease)

II. Background

The sponsor (Hoffman LaRoche) is requesting approval of BONIVA® (ibandronate sodium) Tablets for use as chronic therapy for the treatment and prevention of post-menopausal osteoporosis.

Ibandronate, a nitrogen-containing bisphosphonate with high affinity for hydroxyapatite, inhibits osteoclast-mediated bone resorption. This inhibition indirectly suppresses bone formation and ultimately leads to an inhibition of bone turnover. In postmenopausal women bone loss is accelerated due to increased activation of basic multicellular units (BMU's) and a negative balance between bone formation and resorption occurs in the bone remodeling cycle. Ibandronate (and other bisphosphonates) inhibits or reverses bone loss by reducing the size of the remodeling space, increasing the degree of bone mineralization, and increasing focal bone balance in each newly formed bone unit. This results in an increase in bone volume and bone mass as reflected by an increase in bone mineral density (BMD).

III. Comments and Conclusions

1. A review of the action package for NDA 21-455, BONIVA® Tablets (ibandronate sodium), indicates that the product has been adequately evaluated in multiple acute, sub-chronic and chronic repeat-dose toxicity studies (up to 6 months oral administration in rats and 1 yr in dogs), reproductive toxicity studies (Segment I-III in rats and Segment II in rabbits), genotoxicity and carcinogenicity studies (3 studies in 2 species) for approval for the chronic treatment/prevention of postmenopausal osteoporosis. Additional, intravenous repeat-dose toxicology studies in rats and dogs, and reproductive toxicology studies in rodents, were conducted with ibandronate, but were not considered critical to the review of the oral product formulation.

2. A review of the reproductive toxicity data for ibandronate in rats and rabbits, suggests that the sponsor made use of a somewhat atypical measure of post-implantation embryofetal loss (i.e., post-implantation loss was defined by the number of live births/number of implantation sites X 100, vs. the more commonly used measurement of number of live fetuses [at caesarian]/implantation sites X 100). It should be noted that the measure used by the sponsor allows for potential interference in the true assessment of post-implantation loss if the dams (or does) were to cannibalize part or all of their litter prior to counting of the live births. Thus, it is not possible to determine the exact rate of in utero embryofetal loss in several of the reproductive toxicity studies conducted with ibandronate. However, based on a low but recurrent pattern of increased 'embryofetal loss' among drug treated animals in several studies conducted with ibandronate, and the consistency of this finding with several other members of this class of compounds, it may be concluded that this finding represents a drug related response.

   The administration of ibandronate in the rodent was associated with slight increases in the incidence of visceral tissue variations of the kidney (RPU; renal pelvis ureter syndrome). No dose related increases in the incidence of skeletal variations or malformations were noted in relationship to the administration of ibandronate in the rodent or rabbit. Oral dosing with ibandronate was associated with a non-dose-related reduction in fertility (pre-implantation loss) in rodents.

3. The potential for exposure in late gestation (in association with hypercalcemia of pregnancy), peri- and post-natal periods or from use in pediatric populations (although the product is not indicated for use in pediatric populations) may warrant more extensive testing for potential adverse effects on the developing skeleton of the fetus/neonate/prepubescent population. Approximately 50% of the absorbed dose of ibandronate is retained in the adult skeleton, while limited transplacental exposure data from other members of this drug class suggest that uptake by fetal skeleton is higher than in the adult. Moreover, once incorporated into the bone matrix, the bisphosphonates are retained in 'deep pools' with extended elimination half-time (measurable in months to years). Thus, the potential exists for an extended period of effect on bone remodeling in the immature organism following even a relatively short period of exposure during early skeletal development. There are no adequate clinical or non-clinical safety data to support long-term risk analyses for exposure/use of these products in pregnant or pediatric populations.

4.

5. The draft product label, as revised on 15 May 2003, adequately reflects the non-clinical safety/toxicology data for ibandronate sodium.

IV. Summary

A review of the action package for NDA 21-455, BONIVA® Tablets (ibandronate sodium), indicates that the product has been adequately evaluated in multiple acute through chronic repeat-dose toxicology studies (6-12 months in rats and dogs), full reproductive toxicity testing (Seg. I-III in rat and Seg. II in rabbit), genotoxicity and carcinogenicity testing, for approval for chronic use in the treatment or prevention of postmenopausal osteoporosis. There are no product specific issues requiring further toxicologic assessment at this time.

APPEARS THIS WAY
ON ORIGINAL

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

/s/

David Morse
5/16/03 04:52:38 PM
PHARMACOLOGIST

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center For Drug Evaluation and Research

DATE: April 29, 2003

FROM: David G. Orloff, M.D.
Director, Division of Metabolic and Endocrine Drug Products

TO: NDA 21-455
Boniva (ibandronate sodium)
Hoffman-La Roche, Inc.

SUBJECT: NDA review issues and recommended action

Background/summary

Ibandronate is a new molecular entity bisphosphonate, proposed for oral administration once daily for the prevention and treatment of post-menopausal osteoporosis. Ibandronate, like other bisphosphonates, works through inhibition of osteoclast-mediated resorption of bone, thus slowing bone turnover and altering the balance of bone formation and resorption favoring formation, with subsequent increase in bone mineral density. Animal and clinical studies support an effect of ibandronate to render mineralized bone that is of good quality (thus strength), and the clinical trials submitted to the NDA show an effect of ibandronate to increase BMD and to reduce incident vertebral fractures, both symptomatic and asymptomatic in post-menopausal women with osteoporosis. In animal studies, ibandronate inhibits bone resorption with approximately 10 times the potency of alendronate, an approved oral bisphosphonate.

Ibandronate sodium is approved for intravenous administration in several countries around the world for the treatment of hypercalcemia of malignancy and/or the treatment of osteoporosis.

The animal toxicology and clinical safety findings with this molecule are consistent with other members of the class and include esophageal and gastric irritation/inflammation and ulceration and effects on fetal development that lead to concerns not only about use during pregnancy but, because of the extremely long tissue (bone) half-life of the drug, also about the elapsed interval between discontinuation of therapy and pregnancy that is expected to be reasonably safe.

Clinical

The development program for ibandronate originally included studies of intravenous (iv) as well as oral administration for the treatment and prevention of osteoporosis. At a May 2000, type A meeting, the sponsor informed the division that the pivotal 3-year iv study had failed to meet its primary objective. The division stated its willingness to approve an oral dosage form and regimen assuming efficacy and safety were satisfactorily demonstrated in ongoing trials. Dr. Kehoe has reviewed the results of study 4380 comparing placebo to 0.5 mg and 1.0 mg iv

ibandronate administered every 3 months for 3 years. She points out that compared to the observed effects of oral ibandronate in the pivotal trial (4411, see below) in treatment of PMO, the iv dosing regimen studied in 4380 was suboptimal with regard to effects on BMD and markers of bone respiration and formation, thus plausibly explaining the lack of effect on fracture incidence.

The totality of the clinical safety and efficacy data related to oral ibandronate therapy are elaborated in detail in Dr. Kehoe's review. The following is a brief summary of the data from the pivotal trials for each indication.

Treatment of PMO

In "treatment" pivotal study 4411 in postmenopausal women with osteoporosis, ~3000 patients were randomized (1:1:1) to receive placebo, oral ibandronate 2.5 mg daily, oral ibandronate 20 mg intermittently and treated and followed for 3 years.

Results of this study showed an approximate 50% reduction in the incidence of new morphometric vertebral fractures in both ibandronate groups relative to placebo (~10% pbo, ~5% in both ibandronate groups). Ibandronate at both doses likewise reduced the incidence of worsening fractures (i.e., deterioration of existing compression fractures by morphometry) relative to placebo. The analysis prespecified and performed in this regard was on the combined endpoint of "new or worsening" vertebral fractures. Finally, ibandronate at both doses reduced the risk of symptomatic vertebral fractures relative to placebo (~5% vs. ~3% in both ibandronate groups).

Of note, and distinct from studies for other approved bisphosphonates, study 4411 failed to demonstrate a treatment effect on non-vertebral fractures. This is not interpreted by the division review team as a distinguishing therapeutic deficiency of this particular bisphosphonate. Rather, treatment effects on non-vertebral osteoporotic fractures (most of which are traumatic in ultimate origin) have historically been difficult to demonstrate due to the predominance of non-BMD-related risk factors for such fractures (i.e., risk factors for falling) that are not ameliorated by bisphosphonates.

Prevention of PMO

In "prevention" pivotal study 4499 in postmenopausal women without osteoporosis, ~650 patients were randomized (1:1:1:1) to receive placebo, oral ibandronate 0.5, 1.0, or 2.5 mg daily and treated and followed for 2 years.

Results of the study show highly significant increases in BMD relative to placebo in the 1.0 mg and 2.5 mg daily groups, with a marked dose-response supporting the proposal to market 2.5 mg only. The mean increase in BMD (placebo subtracted) at the lumbar spine in the 2.5 mg group was over 3% and consistent across strata by baseline BMD T-score. The effect on BMD was seen also at the proximal femur (~2% placebo subtracted).

Safety information

The numbers of patients exposed to ibandronate in this NDA are substantial, with more than 3500 patients receiving at least one dose in phase 2/3 clinical trials and with more than 1600

receiving the dose proposed for marketing, 2.5 mg daily. As above, pivotal trial 4411 of three years' duration provides the majority of this safety exposure. The patients were all women with virtually no non-Caucasians studied.

The safety and tolerability profile of ibandronate from the clinical trials program was consistent with the bisphosphonate class. There was a slight increase in the incidence of dyspepsia and diarrhea in ibandronate-treated patients vs. placebo-treated patients. There was likewise a small increased incidence of esophagitis in the large treatment trial (4411, 1.5% ibandronate, 1.0% pbo).

The medical reviewer and clinical team leader have recommended approval. They recommend that in future studies of IV and oral ibandronate, magnesium levels be followed to assess effect of drug on magnesium metabolism. There is no specific safety concern in this regard at this time, however.

Labeling

The division concurs with the proposed indications for ibandronate 2.5 mg daily for the prevention and treatment of PMO. Labeling negotiations are ongoing.

Biopharmaceutics
OCPB finds the biopharmaceutics package satisfactory. Like other bisphosphonates, ibandronate administered orally has very low bioavailability (<<1% compared to iv). It is highly protein bound and has a half-life in plasma of 10-60 hours (and an extremely long half-life in bone). The most significant impact on ibandronate kinetics is food, and the recommendation in labeling based on the trials to date is to delay eating for 60 minutes after morning administration of the drug.

The sponsor did not originally propose a dissolution test for purposes of quality control in manufacturing. OCPB recommended a method and specifications that were conveyed to the sponsor. A mutually satisfactory resolution has been reached.

Pharmacology/Toxicology
Pharm/Tox recommends approval with no toxicology findings novel to this member of the class.

Chemistry/ Microbiology
The ONDC review team recommends approval from the standpoint of CMC. Deficiencies identified in the original review were conveyed to the sponsor on 4-23-03 and are now resolved. There are no recommendations for phase 4 commitments, agreements, or risk management steps.

The deficiency list conveyed on 4-23-03 contained 12 items. These are filed in the package under "Corres/Memos/Faxes" and included the following principal deficiencies:
1. The DMF for the drug substance is inadequate.
2. Dissolution rather than disintegration should be tested as part of the release and stability specifications.
3. Insufficient site-specific stability data, with regard to data on dissolution and impurities were submitted.
4. The methods validation for the analytical methods to test for impurities is incomplete.

As above, these and the other deficiencies have been resolved.

The establishment inspections were all acceptable. An overall acceptable recommendation was rendered on 2-25-03.

A categorical exclusion from the environmental assessment was claimed by the sponsor and accepted by the Agency.

DSI/Data Integrity
Three clinical sites were audited, selected for inspection based on high enrollment. Forms 483 were issued to all three investigators for minor deficiencies. Final recommendation: data were deemed acceptable for review by DSI.

Financial disclosure
NDA # 21-455
Drug: Boniva (ibandronate)
Proposal: Prevention and Treatment of PMO
05/13/03

The financial disclosure information is in order. Dr. Kehoe has addressed the cases of two investigators in non-pivotal trials who reported SPOOS but did not provide details, despite due diligence by the sponsor. She concludes that there is no reason for concern about overall data integrity nor to question the results of the trials as presented.

ODS/nomenclature
The name "Boniva" was previously acceptable to the Division. DMETS has objected because of look-alike, sound-alike confusion with Bonine (OTC meclizine). The likelihood of medication errors involving these two products, one sold OTC and the other Rx-only, and with disparate dosage strengths, seems remote. Furthermore, the risk of a clinically significant event arising should there be an actual error involving these products is unlikely. "Boniva" is acceptable.

Recommendation
Approve.

APPEARS THIS WAY
ON ORIGINAL

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

/s/

David Orloff
5/13/03 03:00:20 PM
MEDICAL OFFICER

Robert Meyer
5/13/03 03:10:53 PM
MEDICAL OFFICER

MEMORANDUM

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

DATE: April 25, 2003

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

VIA: Randy Hedin, Regulatory Health Project Manager,
Division of Metabolic and Endocrine Drug Products
HFD-510

FROM: Jeanine Best, M.S.N., R.N., P.N.P.
Regulatory Health Project Manager
Division of Surveillance, Research, and Communication Support
HFD-410

THROUGH: Anne Trontell, M.D., M.P.H., Director
Division of Surveillance, Research, and Communication Support
HFD-410

SUBJECT: ODS/DSRCS Review of Patient Labeling for Boniva
(ibandronate sodium) Tablets, NDA 21-455

The patient labeling which follows represents the revised risk communication materials of the Patient Labeling for Boniva (ibandronate sodium) Tablets, NDA 21-455. It has been reviewed by our Office and by DDMAC. We have simplified the wording, made it consistent with the PI, removed promotional language and other unnecessary information (the purpose of patient information leaflets is to enhance appropriate use and provide important risk information about medications), and put it in the format that we are recommending for all patient information. Our proposed changes are known through research and experience to improve risk communication to a broad audience of varying educational backgrounds. We can provide marked-up and clean copies of the revised document in Word if requested by the review division.

Please let us know if you have any questions. Comments to the review Division are bolded, italicized, and underlined. We can provide marked-up and clean copies of the revised document in Word if requested by the review division.

5 page(s) of revised draft labeling has been redacted from this portion of the review.

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

/s/

Toni Piazza Hepp
4/25/03 11:06:57 AM
PHARMACIST
Reviewer: Jeanine Best; Signed by Toni Piazza-Hepp for Anne Trontell

MEMORANDUM OF TELECON

DATE: May 8, 2003

APPLICATION NUMBER: NDA 21-455, Boniva (ibandronate sodium) Tablets

BETWEEN:

Name: Mark Hope, Regulatory Program Director
Phone: 973-562-2926
Representing: Hoffman-La Roche Inc.

AND

Name: Randy Hedin, Senior Regulatory Management Officer
Division of Metabolic and Endocrine Drug Products, HFD-510

SUBJECT: The tradename "Boniva" is not acceptable.

I telephoned Mr. Hope and informed him that we reviewed the May 7, 2003 submission concerning re-evaluating the proprietary name "Boniva." I stated that the "Boniva" trade name is acceptable. Mr. Hope thanked me for the information.

{See appended electronic signature page}

Randy Hedin
Senior Regulatory Management Officer

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

/s/

Randy Hedin
5/8/03 01:18:29 PM
CSO

MEMORANDUM OF TELECON

DATE: May 5, 2003

APPLICATION NUMBER: NDA 21-455, [redacted] (ibandronate sodium) Tablets

BETWEEN:

Name: Mark Hope, Regulatory Program Director
Phone: 973-562-2926
Representing: Hoffman-La Roche Inc.

AND

Name: Randy Hedin, Senior Regulatory Management Officer
Division of Metabolic and Endocrine Drug Products, HFD-510

SUBJECT: The tradename "Boniva" is not acceptable.

I telephoned Mr. Hope and informed him that the tradename "Boniva" is not acceptable; however, the backup tradename [redacted] is. Mr. Hope asked why "Boniva" was rejected, and I explained that one of the main reasons the Division did not accept the name is its similarity to "Bonine." Mr. Hope stated he would inform his team of the Division's decision.

{See appended electronic signature page}

Randy Hedin
Senior Regulatory Management Officer

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

/s/

Randy Hedin
5/5/03 12:59:21 PM
CSO

MEMORANDUM OF TELECON

DATE: September 13, 2002

APPLICATION NUMBER: NDA 21-455, Ibandronate Sodium Tablets

BETWEEN:

Name: Mark Hope, Regulatory Program Director
Phone: 973-562-2926
Representing: Hoffmann-La Roche

AND

Name: Randy Hedin, Senior Regulatory Management Officer
Division of Metabolic and Endocrine Drug Products, HFD-510

SUBJECT: Trade-Name for Ibandronate Sodium

I telephoned Mr. Hope, and informed him that the Division and Office have discussed the trade-name "Bonviva" and have concluded that it is promotional, and not acceptable. I further stated that the firm should propose a new trade-name as soon as possible. Mr. Hope stated that the firm is disappointed; but, will propose a new name.

Randy Hedin
Senior Regulatory Management Officer

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

/s/

Randy Hedin
9/13/02 03:51:24 PM
CSO

From: Hedin, Durand M
Sent: Monday, April 28, 2003 12:54 PM
To: 'Hope, Mark {PDR-Nutley}'
Subject: Dissolution Test

Dear Mr. Hope,

Please refer to your new drug application (NDA 21-455) dated July 15, 2002.

We have completed the biopharm review of the application and have the following comment:

The proposed in vitro disintegration test and specification is not acceptable. The Division recommends in vitro dissolution test and specification for the 2.5 mg ibandronate oral tablet. We recommend the following:

Apparatus	USP Type 2 (paddle)
In vitro release medium	water
Medium temperature	37 ± 0.5°C
Stirring speed	50 rpm
Sampling Time	15 minutes
Specifications	Q = —— at 15 minutes

Please respond in writing if this is acceptable.

Sincerely,

Randy Hedin

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

/s/

Randy Hedin
4/28/03 01:01:32 PM
CSO

From: Hedin, Durand M
Sent: Wednesday, April 23, 2003 11:20 AM
To: 'Hope, Mark {PDR-Nutley}'
Subject: Chemistry Comments

Dear Mr. Hope,

Please refer to your new drug application (NDA 21-455) dated July 15, 2001.

We have completed the chemistry review of the original application and amendments dated January 17, and 31, 2003, and have the following comments:

1. The drug product specifications (both release and stability) should include limits for degradation products and related substances. The specification should be revised to include tests and the acceptance criteria [redacted] other impurities. In addition, all degradants/impurities should be identified by Rf value or retention time, if possible.

2. The disintegration test should be replaced by the dissolution test for release and stability specifications.

3. The proposed [redacted] method for determination of degradants/impurities is not a quantitative method. A commitment to develop and validate a quantitative method ([redacted] method) for determination of related substances ([redacted]) and degradants should be provided. If the [redacted] method is found to be unsuitable to separate the related substances [redacted] and/or degradation products, then validation data to support the use of [redacted] procedure should be provided (see ICH Q2A and Q2B).

4. The time points for the 'follow-up stability program" (Vol. 1, pp. 272) should be the same as the protocol for the "registration batches" (Vol. 1, pp. 271). In addition, the follow up stability protocol should indicate which tests are performed at each time point. Revised stability protocol should be provided.

5. In the package insert as well as on the bottle labels, the storage statement should be revised with the following (or similar) statement: "Store at 25°C (77°F); excursions permitted between 15° and 30°C (59° and 86°F) [see USP Controlled Room Temperature]".

6. In the patient information pamphlet, the film-coating ingredients should be added to the list of inactive ingredients.

7. Establish a process control for blend uniformity of the tabulating mixture obtained prior to compression, to assure adequate uniformity of the drug product.

8. Clarify how each lot of the drug substance, ibandronate is accepted by the drug product manufacturer (e.g. certificate of analysis and/or any acceptance tests).

9. Specify the maximum time allowed between the packaging of the drug product and the start of stability testing (T_0).

10. Provide a brief explanation regarding the chemistry behind the [redacted] method of the alternate [redacted] method for ibandronate assay.

11. Provide a reprocessing procedure if applicable, or if not applicable, provide a statement indicating that no reprocessing will be carried out.

12. Do you have a retest period for drug substance that is kept in storage?

Please telephone me when you get this E-mail.

Sincerely,

Randy Hedin

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

/s/

Randy Hedin
4/23/03 01:53:26 PM
CSO

From: Hedin, Durand M
Sent: Wednesday, January 22, 2003 4:24 PM
To: 'Hope, Mark (PDR-Nutley)'
Cc: Luther, Lisa (PDR-Nutley)
Subject: RE: NDA 21-455 Ibandronate Sodium in the Treatment and Prevention of Post-Menopausal Osteoporosis - Contact Details

Hi Mark,

The following information is provided to clarify our previous request. If you have any questions please contact me.

Submit a subgroup analysis stratified by baseline prevalent fractures for both MF 4411 (oral) and MF 4380 (iv). Some of the data for MF4411 is present and can be used as reference - MF 4411 table 17, page 87 shows the new incident vertebral fractures stratified by baseline fracture. MF 4411 Table 39, page 111 shows the stratified lumbar spine and total hip BMD data. This is the format we are looking for. We have been unable to locate similar stratified subgroup analyses for study MF4380.

In order of priority, please provide:

1) The rate of patients with new incident vertebral fractures stratified by baseline prevalent fractures for study MF4380 (similar to the way data is presented in Table 17 MF4411).
2) Change in lumbar spine and total hip BMD stratified by baseline prevalent fractures for study MF4380 (similar to the way data is presented in Table 39 MF4411).
3) the rate of patients with new clinical vertebral fractures stratified by baseline prevalent fractures for both studies MF4411 and MF4380 (similar to the way data is presented in Table 17 MF4411).
4) Other secondary variables stratified by baseline prevalent fractures for both studies MF4411 and MF4380.

Thanks,

Randy

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

/s/
Randy Hedin
1/23/03 04:29:46 PM
CSO

From: Hedin, Durand M
Sent: Wednesday, January 15, 2003 1:25 PM
To: 'Hope, Mark {PDR~Nutley}'
Subject: FW: NDA 21-455, Ibandronate Sodium Tablets, Information Request for Clinical Information

Hi Mark,

We are reviewing the clinical section of your submission and have the following request for additional information. We need your prompt written response to continue our evaluation of your NDA.

1. For studies MF4411 (oral) and MF4380 (iv) please provide the following outcome data stratified by baseline prevalent fractures, 0-1 fractures at baseline vs. 2 or greater fractures at baseline:

A. *Primary efficacy variables*:

- Rate of patients with new incident vertebral fractures

B. *Secondary efficacy variables*:

- Rate of patients with new clinical vertebral fractures
- Total number of new fractures
- Height
- Change in bone mineral density (BMD) of lumbar spine (L_2 - L_4)
- Change in BMD of proximal femur
- Change in BMD of distal forearm
- Pain and disability
- Urinary calcium excretion (calcium/creatinine)
- Urinary excretion of C-telopeptide (ratio of C-telopeptide/creatinine)
- Urinary excretion of N-telopeptide (ratio of NTX/creatinine)
- Serum osteocalcin concentration
- Serum concentration of bone-specific isotype of alkaline phosphatase (BSAP)
- Serum parathyroid hormone concentration

2. Please provide any preclinical data on bone quality in animals that were dosed in a manner similar to that used in study MF4380 (iv).

If you have any questions please contact me.

Thanks,

Randy Hedin

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

/s/

Randy Hedin
1/15/03 03:06:42 PM
CSO

From: Hedin, Durand M
Sent: Monday, January 13, 2003 1:05 PM
To: 'Hope, Mark {PDR~Nutley}'
Subject: NDA 21-455, Ibandronate Sodium Tablets, Rodent Carcinogenicity Studies

Hi Mark,

We are reviewing the pharmacology/toxicology section of your submission and have the following comments and information requests regarding your rodent carcinogenicity studies. We need your prompt written response to continue our evaluation of your NDA.

1. Historical control data for mice (studies J14, J15)

For the following neoplasms, please provide historical control incidences for Crl:NMRI/BR mice, from the laboratory in which the two mouse carcinogenicity studies with ibandronate (J14, J15) were performed (Boehringer Mannheim GmbH/Hoffmann LaRoche). Values for the last 10 years, approximately, are requested:

- Pituitary gland: adenoma, pars intermedia (males)
- Adrenal gland: subcapsular cell adenoma, type A and B (females) and subcapsular cell adenocarcinoma (females)
- Lung: pulmonary/bronchioalveolar adenoma and carcinoma (females)
- Liver: hepatocellular adenoma and carcinoma (males)
- Uterus: hemangiopericytoma (females)

2. Historical control data for rats (study J8)

For the following neoplasms, please provide historical control incidences for Wistar rats, from the laboratory in which the rat carcinogenicity study (J8) with ibandronate was performed Values for the last 10 years, approximately, are requested:

- Skin, histiocytoma (males)
- Thyroid, C-cell adenoma

3. Is cortical adenoma (adenocarcinoma) histologically distinct from subcapsular cell adenoma (adenocarcinoma) in NMRI mice?

If you have any questions please phone me.

Thanks,

Randy Hedin

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

/s/

Randy Hedin
1/13/03 01:32:56 PM
CSO

Meeting Date: May 9, 2003 Time: 11:05 - 11:15 AM Location: Conference Rm. 14B45

NDA 21-455 Boniva (ibandronate sodium) Tablets

Type of Meeting: Teleconference

Applicant: Hoffmann-La Roche Inc.

Meeting Chair: Dr. Johnny Lau

External participant lead: Mr. Mark Hope

Meeting Recorder: Mr. Randy Hedin

FDA Attendees and titles:

Division of New Drug Chemistry II
Elsbeth Chikhale, Ph.D., Reviewer
Division of Pharmaceutical Evaluation II:
Johnny Lau, Ph.D., Reviewer
Division of Metabolic and Endocrine Drugs
Randy Hedin, R.Ph., Senior Regulatory Management Officer

External participant Attendees and titles:

Rose-Marie Meier, Ph.D., Analytical Development
Joanne Barrett, Ph.D., Clinical Science
Fabian Schwarb, Ph.D., Technical Regulatory Affairs
Sarah Orris, Regulatory Affairs
Mark Hope, Regulatory Affairs

Meeting Objectives:

The NDA was submitted on July 15, 2002, and received on July 16, 2002, for the prevention and treatment of postmenopausal osteoporosis. The ten-month user fee goal date is May 16, 2003. The teleconference was held to discuss outstanding disintegration standard issues.

Discussion Points and Decisions (agreements) reached:

- The firm stated that the current in vitro disintegration test conforms to the European Pharmacopeia. The Division stated that this is not acceptable. The disintegration test should conform to the United States Pharmacopeia (USP) number 25 (701) DISINTEGRATION found on page 2010 of the USP. Specifically, 6 dosage units

should be used using water as the immersion fluid. At the end of the time limit (10 minutes), if 1 or 2 tablets fail to disintegrate completely repeat the test on 12 additional tablets: to pass, not less than 16 of the total of 18 tablets tested must disintegrate completely. The firm agreed to use the USP 25 in vitro disintegration test.

Unresolved or issues requiring further discussion:

- None

Action Items:

- The project manager will send the teleconference minutes to Hoffman-La Roche.

Signature, minutes preparer:

Concurrence Chair:

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

/s/

S.W. Johnny Lau
5/9/03 03:39:15 PM

5/5/03

Meeting Date: May 2, 2003 Time: 10:00 - 10:30 AM Location: Conference Rm. 13B45

NDA 21-455 Boniva (ibandronate sodium) Tablets

Type of Meeting: Teleconference

Applicant: Hoffmann-La Roche Inc.

Meeting Chair: Mamta Gautam-Basak, Ph.D.

External participant lead: Sarah Orris

Meeting Recorder: Mr. Randy Hedin

FDA Attendees and titles:

Division of New Drug Chemistry II
Sheldon Markofsky, Ph.D., Acting Team Leader
Mamta Gautam-Basak, Ph.D.,Team Leader
Elsbeth Chikhale, Ph.D., Reviewer
Division of Pharmaceutical Evaluation II:
Johnny Lau, Ph.D., Reviewer
Hae-Young Ahn, Ph.D., Team Leader

External participant Attendees and titles:

Rose-Marie Meier, Ph.D., Analytical Development
Hans Kaestle, Ph.D., Galenical Process Development
Fabian Schwarb, Ph.D., Technical Regulatory Affairs
Bernhard Pichler, Ph.D., Globa Technical Leader
Sarah Orris, US Technical Regulatory Affairs

Meeting Objectives:

The NDA was submitted on July 15, 2002, and received on July 16, 2002, for the prevention and treatment of postmenopausal osteoporosis. The ten-month user fee goal date is May 16, 2003, and the action package is due in ODE II on April 25, 2003. The teleconference was held to discuss outstanding Chemistry/Biopharm issues.

Discussion Points:

- Please refer to the attached draft response to chemistry and biopharm review comments E-mailed to the Division on April 29, 2003. The Division's answers to the questions in the order they were submitted, are as follows:

1. Based on your response it is acceptable that you propose to test for individual unspecified impurities with an acceptance criterion of maximum —— and total impurities/degradants with an acceptance criterion of maximum 1.0%. However, the proposed regulatory release specifications (NDA drug product section, pg. 64) are not acceptable. Specifically, the specifications should be revised to include testing of degradation products both at release and during shelf-life instead of for shelf-life only, as proposed. The firm agreed to submit revised drug product specification, as recommended.

2. In vitro disintegration method is acceptable for routine release testing (i.e., lot to lot consistency), however, any post-approval changes (formulation and/or manufacturing) should be supported by in vitro dissolution profile data. In addition, the disintegration specification time should be 10 minutes instead of 15 minutes, and should be done without disks. The firm agreed.

3. The Division stated that the firm's response to number 3 is acceptable.

4. Your proposal to revise the follow-up or post-approval stability program to include annual testing (only) is acceptable. Revised follow-up stability protocol should be provided to include testing at 0, 12, 24, and 36 months. However, any post approval change should be supported by stability data according to the original protocol. In addition, you should provide a commitment with the following or similar wording: "Any batch or lot stored under the labeled conditions that falls outside of the approved specifications for the drug product will be withdrawn from the market or the deviation will be discussed with the FDA if the sponsor believes that the deviation is a single occurrence that does not affect the safety and efficacy of the drug product. A justification for the continued distribution of the batch will be included in the discussion." Failing of batches/lots to meet the stability acceptance criteria should be reported to the Agency, as required under 21 CFR 314.81 (b)(1)(ii). The firm agreed.

5. The Division stated that the firm's response to number 5 is acceptable.

6. The Division stated that the firm's response to number 6 is acceptable.

7. The Division stated that the firm's response to number 7 is acceptable.

8. We recommended that (in addition to the certificate of analysis) the acceptance criteria for the drug substance should include a specific identity test performed on each lot of the drug substance. The firm agreed.

9. The Division stated that the firm's response to number 9 is acceptable.

10. The Division stated that the firm's response to number 10 is acceptable.

11. The Division stated that the firm's response to number 11 is acceptable.

12. The Division stated that the firm's response to number 12 is acceptable.

Decisions (agreements) reached:

- None

Unresolved or issues requiring further discussion:

- None

Action Items:

- The project manager will send the teleconference minutes to Hoffman-La Roche, and the firm will respond with a written correspondence acknowledging the agreements made at the teleconference.

Signature, minutes preparer:

Concurrence Chair:

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

/s/

Mamta Gautam-Basak
5/5/03 10:48:43 AM
Concur

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

Meeting Date: October 10, 2001 Time: 3:00 - 4:30 AM Location: Conf. Rm. "C"

IND —— BM 21.0955 (ibandronic acid) Oral & Injection

Type of Meeting: Pre-NDA

External participant: Roche Global Development

Meeting Chair: Dr. Eric Colman

External participant lead: Dr. Christine Conroy

Meeting Recorder: Mr. Randy Hedin

FDA Attendees and titles:

Division of Metabolic and Endocrine Drug Products:
David Orloff, M.D., Director,
Eric Colman, M.D., Clinical Team Leader
Karen Davis-Bruno, Ph.D., Pharmacology Team Leader
Gemma Kuijpers, Ph.D., Pharmacology Reviewer
Kati Johnson, R.Ph., Chief, Project Management Staff
Randy Hedin, R.Ph., Senior Regulatory Management Officer

Office of New Drug Chemistry:
Yvonne Yang, Ph.D., Reviewer
Duu-Gong Wu, Ph.D., Team Leader
Eric Duffy, Ph.D., Supervisor

Division of Pharmaceutical Evaluation II
Hae-Young Ahn, Ph.D., Team Leader

Division of Biometrics II
Japo Choudhury, Ph.D., Reviewer

Office of Drug Evaluation II
George Liao, Regulatory Health Information Specialist

External participant Attendees and titles:

Thorsten von Stein, M.D., Clinical Science Leader
Randall Stevens, M.D., Global Group Leader, Clinical Science
Tracy Mills, B.S., Biometrics
Sarah Orris, B.Sc., Technical Regulatory Program Manager
Mark Hope, B.Sc., (Hons), BIRA Dip, Regulatory Program Director

Christine Conroy, Pharm.D., Global Regulatory Leader
Philippe Van der Auwera, M.D., Ph.D., Project Team Leader

Meeting Objectives:

The meeting was requested by Roche Global Development to discuss phase 3 data in anticipation of submitting an NDA for oral ibandronate for the prevention and treatment of postmenopausal osteoporosis. The firm proposes a dose of 2.5 mg once daily, 20 mg once weekly, or 20 mg every other day for 12 doses at the start of each 3-month cycle. The focus of the meeting is to get the Agency's concurrence with the structure of the proposed NDA, get feedback on review issues, and to discuss further development of oral and intravenous ibandronate. Ibandronate Injection was originally submitted to the Division on September 30, 1994, for the treatment of hypercalcemia of malignancy, and postmenopausal osteoporosis. Oral ibandronate is being investigated under IND [redacted] and was submitted on April 15, 1996, for the same indications.

Discussion Points and Decisions (agreements) reached:

- The firm submitted the following questions in a background document dated August 15, 2001. The Division's answers (in *italics*) follow the questions.

  5.1 Initial Oral NDA

  a) Does the Division concur that the clinical data, as described herein, are sufficient to support submission of an initial NDA for oral ibandronate in the treatment and prevention of osteoporosis in postmenopausal women with recommendations for 2.5 mg daily, 20 mg weekly, and 20 mg intermittent treatment regimens?

  The data seem acceptable for filing; however, because the data proposed to support approval of the 20 mg weekly dose come from a one-year, non-inferiority study comparing BMD response to the 2.5 mg daily dose, approvability of the 20 mg weekly dose will involve among other things, assessment of the robustness of the fracture efficacy of the 2.5 mg dose.

  b) Based on the study results provided herein, does the Division believe Roche has taken a reasonable position with respect to draft wording for the Indications and Usage and Dosage and Administration sections of the package insert as presented in Section 3.1.4? When responding to this question, please note that Roche recognizes that FDA is not in a position to make firm commitments on labeling until after complete review of the NDA. Roche is nevertheless interested in comments on the proposed draft wording.

d) NDA Content and Format:

- Does the Division concur with Roche's proposals for Sections 8, 10, 11, and 12 as outlined in Section 3.2.4, and further detailed in the table entitled "Considerations for Sections 6, 8, 10, 11, 12 and Other" located in Appendix 7 (vol 1, page 215), with respect to report type (full, abbreviated, tabular summary) that Roche proposes to include for the various studies that provide differing levels of support to the application, and the studies for which electronic SAS data-sets, CRTs, CRFs, and narratives will be provided?

  Please follow the guidelines. A complete pharmacology/toxicology package will be needed. Upon submission of the NDA, please provide information that the high doses used in the carcinogenicity studies in mice (2 studies) and rats (1study) are adequate in terms of toxicity or pK endpoints. Also, please provide information that the data from the long-term monkey bone quality study using a monthly i.v. dosing regimen support bone safety of the intended daily, weekly and intermittent clinical dosing regimens.

- Which studies will the statistical reviewer require specific efficacy data-sets? Does the Statistical Reviewer have a required format for these data-sets?

  Please provide data-sets for Study MF 4411, and follow the Guidance for Industry, entitled, "Providing Regulatory Submissions in Electronic Format – NDAs" for the submission of the data-sets. The Division can only accept SAS transport files.

Please refer to Randy Levin, Associate Director for Information Management, if you have questions concerning an electronic submission.

- Does the Division concur with Roche's proposals for providing Investigator CVs and Financial Disclosure for studies in the program as outlined in the table in Appendix 7 (Vol. 1, page 215), entitled "Considerations for Sections 6, 8, 10, 11, 12, and Other"?

  The firm's proposal with regard to investigator CVs is acceptable. Please follow the guideline for financial disclosure entitled, "Guidance for Industry, Financial Disclosure by Clinical investigators".

- Does the Division anticipate any issues with the proposed structure of the ISE and ISS, as outlined in Sections 3.2.4.1 and 3.2.4.2? A broad overview of the studies to be included in each summary document are further elaborated in the table in Appendix 7 (Vol.1, page 215), entitled "Considerations for Sections 6, 8, 10, 11, 12, and Other"?

  The formats for the Integrated Summary of Efficacy (ISE), and Integrated Summary of Safety (ISS) appear acceptable.

- Does the Division concur with Roche's proposal for confirming plans for either an electronic NDA, or a combined paper and electronic NDA, in the near future?

  Submission of an electronic NDA is acceptable.

5.2 New Development

Roche would like to gain concurrence with FDA for the overall strategic approach to new development for monthly dosing with oral ibandronate and intermittent I.V. ibandronate on the basis of comparative BMD studies as outlined in Section 4. An important consideration to this approach is that study MF 4411 has demonstrated substantial reductions in vertebral fracture rates with both daily and intermittent (drug-free interval of 9-10 weeks) regimens. Vertebral fracture risk reduction was shown to be related to BMD gains. The objective of the new studies would be to demonstrate non-inferiority to oral ibandronate 2.5 mg daily, with lumbar spine BMD as the primary endpoint. Roche anticipates requesting review of the full study protocol for monthly dosing and intermittent I.V. dosing in accordance with the draft guidance, Special Protocol Assessment, but would like to gain preliminary feedback from FDA on Key aspects of the design and intent of these studies.

In particular, does FDA concur with Roche's proposal for these studies, including:

a) That a single adequately powered study as described, if positive, would be sufficient to extend the indication to include monthly dosing of oral ibandronate in the treatment and prevention of postmenopausal osteoporosis. In this case, the study would be submitted as a supplement to the initial oral ibandronate NDA.

b) That a single adequately designed and powered study as described, if positive, would be sufficient to extend the indication of ibandronate in the treatment and prevention of postmenopausal osteoporosis to intermittent I.V. dosing. In this case, a new NDA for I.V. ibandronate would be submitted, but it would rely on reference to the initial oral ibandronate NDA for established reduction in fracture rate with the control regimen (i.e., 2.5 mg daily).

For an individual dosing regimen two studies have been required to date, one study for treatment, and another for the prevention of postmenopausal osteoporosis.

c) That the design of these studies would include:

- A BMD non-inferiority approach using oral ibandronate 2.5 mg daily as an active control.

  This appears adequate, but the protocol and data analysis plan will need to be reviewed. The current study will have to be reviewed and an acceptable non-inferiority margin agreed upon.

- A patient population similar to that in Study MF 4411 with respect to baseline BMD (based on mean spine BMD T-score ≤ -2.0) and age range. As in study MF4411, patients from Europe and North America will be included; patients from Australia, South Africa, South America and Asia will be included as well for reasons of enrollment feasibility. There will be no requirement for prevalent vertebral fractures at study entry.

  The patient populations (treatment and prevention) should be as close demographically as possible to those studied in the initial studies.

- An overall study duration of two years, with the primary objective of showing BMD non-inferiority *at one year*. If positive, the analysis of the primary endpoint at one year would provide the basis for regulatory submission and approval. The studies would be continued for a second year, and Roche would commit to providing FDA additional safety and efficacy information from the second year post-approval.

  This is acceptable.

d) The choice of dosing regimens to be tested in the oral monthly study.

e) The choice of dosing regimens to be tested in the intermittent I.V. study.

This appears adequate, from the information provided.

f) In the new protocols, the maximum systemic exposure in the monthly oral ibandronate study is estimated to be 10.8 mg/year (150 mg/month), while the maximum systemic exposure in the I.V. study is 12 mg/year (2 mg/2 months or 3 mg/3 months). Given the higher systemic exposure in the I.V. study, this is the only protocol where histomorphometric evaluations will be done in a subset of patients (approximately 8-10%). Does the Division agree that this is sufficient to address bone safety for the higher total exposure of ibandronate in these trials, as compared to trials being submitted for the NDA?

This is acceptable.

5.3 Chemistry, Manufacturing, and Controls

As outlined in Section 3.2.1, Roche submitted proposals to IND ——for the transfer of manufacturing for oral ibandronate from Roche Mannheim, Germany to Roche Basel, Switzerland. With regard to these submissions, which are duplicate in Appendix 7 (vol. 1, page 185) of this briefing document for convenience, feedback from the Division on the following points is requested.

a) Does the Division agree that the proposed dissolution protocol is sufficient to establish the equivalence of the two sites?

The protocol appears adequate. The sponsor needs to submit dissolution profiles for 3 lots each from the two manufacturing sites using 3 different dissolution media. Although it is not related to the two manufacturing site issue, it is suggested that the sponsor submit dissolution data. The Division and sponsor need to agree on the dissolution media and specifications before the sponsor conducts stability studies.

b) Does the Division agree that the stability plan outlined in this proposal would be acceptable to propose a three-year expiry for each strength of ibandronate tablets in the NDA?

The proposed stability plan is acceptable.

Certificate of Analysis (COA) for three lots manufactured at the intended commercial site will be required at the end of the review cycle.

- *COA should include numerical test data.*
- *COA should include a certification that the validation process was completed successfully with any changes for regulatory process controls.*

All manufacturing establishments need to be ready for inspection when the NDA is submitted, and a certification should be included in the NDA.

Unresolved or issues requiring further discussion:

- None

Action Items:

- None

Signature, minutes preparer:_____

Concurrence Chair:_____

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

/s/

Randy Hedin
11/8/01 10:59:16 AM

Eric Colman
11/9/01 07:44:33 AM

ATTACHMENT

MEMO OF FILING MEETING

Date: August 20, 2002 Time: 10:00 - 10:30 AM Location: 14B-45

NDA 21-455 Bonviva (ibandronate sodium) Tablets

Type of Meeting: Filing Meeting

External participant: None

Meeting Chair: Mr. Randy Hedin

External participant lead: None

Meeting Recorder: Mr. Randy Hedin

FDA Attendees and titles:

Division of Metabolic and Endocrine Drug Products:

Theresa Kehoe, M.D., Clinical Reviewer
Randy Hedin, R.Ph., Senior Regulatory Management Officer

Office of New Drug Chemistry:
Elsbeth Chikhale, Ph.D., Reviewer
Sheldon Markofsky, Ph.D., Acting Team Leader

Division of Pharmaceutical Evaluation II
Johnny Lau, Ph.D., Reviewer

Division of Biometrics II
David Hoberman, Ph.D., Reviewer
Todd Sahlroot, Ph.D., Team Leader

External participant Attendees and titles:

None

Meeting Objectives:

To determine if NDA 21-455 will be filed, and discuss plans for the review of the NDA.

Discussion Points:

- Chemistry: The application is fileable.
- Pharmacology: The pharmacology reviewer was not present; however, she reviewed the application and stated that it is fileable.
- Biopharm: The application is fileable. A filing memorandum will be rendered in DFS within the next several weeks. Hoffman-La Roche proposed an in vitro disintegration test instead of the in vitro dissolution test. This will need to be resolved.
- Statistics: The application is fileable. However, the submitted electronic data sets are not adequate, and additional sets will be requested.
- Clinical: The application is fileable.
  - Financial disclosure data has been submitted.
  - Division of Scientific Investigations (DSI) audits will be requested.

Decisions (agreements) reached:

- The application will be filed.
- The review will be done as a standard review. The goal to finish the reviews with team leader signoff will be April 6, 2003
- The application will not be discussed at an Advisory Committee Meeting.
- Dr. Kehoe will consult with the Division of Scientific Investigations concerning the appropriate sites for audits.

Unresolved or issues requiring further discussion:

- None

Action Items:

- Schedule status meetings as appropriate.

Signature, Regulatory Project Manager, HFD-510

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

/s/

Randy Hedin
9/30/02 12:46:53 PM

NDA REGULATORY FILING REVIEW
(Includes Filing Meeting Minutes)

NDA Number, Requested Trade Name, Generic Name and Strengths (modify as needed for an efficacy supplement and include type):

Applicant: Hoffman-La Roche Inc.

Date of Application: July 15, 2002
Date of Receipt: July 16, 2002
Date of Filing Meeting: August 20, 2002
Filing Date: September 14, 2002

Indications requested: The treatment and prevention of post-menopausal osteoporosis

Type of Application: Full NDA __X__ Supplement _____
(b)(1) ____X____ (b)(2) _____
[If the Original NDA of the supplement was a (b)(2), all subsequent supplements are (b)(2)s; if the Original NDA was a (b)(1), the supplement can be either a (b)(1) or (b)(2)]

If you believe the application is a 505(b)(2) application, see the 505(b)(2) requirements at the end of this summary.

Therapeutic Classification: S___X___ P_____
Resubmission after a withdrawal or refuse to file __No___
Chemical Classification: (1,2,3 etc.)__1___
Other (orphan, OTC, etc.)____Rx___

Has orphan drug exclusivity been granted to another drug for the same indication? YES NO X

If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?

YES NO

If the application is affected by the application integrity policy (AIP), explain.

User Fee Status: Paid ____X_____ Waived (e.g., small business, public health) _____
Exempt (orphan, government) _____
Form 3397 (User Fee Cover Sheet) submitted: YES___X___ NO_____
User Fee ID#__4357_____
Clinical data? YES __X____ NO _____ Referenced to NDA# _____
Date clock started after UN _____NA_____

User Fee Goal date: ____May 16, 2002___

Action Goal Date (optional) _____

- Does the submission contain an accurate comprehensive index? YES X NO
- Form 356h included with authorized signature? YES X NO
  If foreign applicant, the U.S. Agent must countersign.

- Submission complete as required under 21 CFR 314.50? YES X NO
  If no, explain:

- If electronic NDA, does it follow the Guidance? YES X NO NA
  If an electronic NDA: all certifications must be in paper and require a signature.

- If Common Technical Document, does it follow the guidance? YES NO NA X

- Patent information included with authorized signature? YES X NO

- Exclusivity requested? YES; If yes, ___5____years NO

Note: An applicant can receive exclusivity without requesting it, therefore, requesting exclusivity is not a requirement.

- Correctly worded Debarment Certification included with authorized signature? YES X NO
  If foreign applicant, the U.S. Agent must countersign.

  Debarment Certification must have correct wording, e.g.: "I, the undersigned, hereby certify that _____ Co. did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with the studies listed in Appendix ____." Applicant may not use wording such as, " To the best of my knowledge, ..."

- Financial Disclosure included with authorized signature? YES X NO
  (Forms 3454 and/or 3455)
  If foreign applicant, the U.S. Agent must countersign.

- Has the applicant complied with the Pediatric Rule for all ages and indications? YES X NO
  If no, for what ages and/or indications was a waiver and/or deferral requested:

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

Refer to 21 CFR 314.101(d) for Filing Requirements

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

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

List referenced IND numbers:

End-of-Phase 2 Meeting? Date_7/9/98__ NO
If yes, distribute minutes before filing meeting.

Pre-NDA Meeting(s)? Date_10/10/01 NO
If yes, distribute minutes before filing meeting.

Project Management

Copy of the labeling (PI) sent to DDMAC? YES X NO

Trade name (include labeling and labels) consulted to ODS/Div. of Medication Errors and Technical Support?
YES X NO

MedGuide and/or PPI consulted to ODS/Div. of Surveillance, Research and Communication Support?
Will consult at first internal labeling meeting.

OTC label comprehension studies, PI & PPI consulted to ODS/ Div. of Surveillance, Research and Communication Support? YES NO NA X

Advisory Committee Meeting needed? YES, date if known _____ NO X

Clinical

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

Chemistry

- Did sponsor request categorical exclusion for environmental assessment? YES X NO
  If no, did sponsor submit a complete environmental assessment? YES NO
  If EA submitted, consulted to Nancy Sager (HFD-357)? YES NO
- Establishment Evaluation Request (EER) package submitted? YES X NO
- Parenteral Applications Consulted to Sterile Products (HFD-805)? YES NO NA X

If 505(b)(2), complete the following:

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

Name of listed drug(s) and NDA/ANDA #:

Is the application for a duplicate of a listed drug and eligible for approval under section 505(j)? (Normally, FDA will refuse-to-file such applications.)
YES NO

Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)?
If yes, the application must be refused for filing under 314 54(b)(1) YES NO

Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD?
YES NO

If yes, the application must be refused for filing under 314.54(b)(2)

Which of the following patent certifications does the application contain? Note that a patent certification must contain an authorized signature.

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

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

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

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

If filed, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must submit a signed certification that the patent holder was notified the NDA was filed [21 CFR 314.52(b)]. Subsequently, the applicant must submit documentation that the patent holder(s) received the notification ([21 CFR 314.52(e)].

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

____ 21 CFR 314.50(i)(1)(iii): Information that is submitted under section 505(b) or (c) of the act and 21 CFR 314.53 is for a method of use patent, and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent.

____ 21 CFR 314.54(a)(1)(iv): The applicant is seeking approval only for a new indication and not for the indication(s) approved for the listed drug(s) on which the applicant relies.

Did the applicant:

- Identify which parts of the application rely on information the applicant does not own or to which the applicant does not have a right of reference?

  YES NO

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

  YES NO

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

  YES NO

Has the Director, Div. of Regulatory Policy II, HFD-007, been notified of the existence of the (b)(2) application?

YES NO

ATTACHMENT

MEMO OF FILING MEETING

Date: August 20, 2002 Time: 10:00 - 10:30 AM Location: 14B-45

NDA 21-455 Bonviva (ibandronate sodium) Tablets

Type of Meeting: Filing Meeting

External participant: None

Meeting Chair: Mr. Randy Hedin

External participant lead: None

Meeting Recorder: Mr. Randy Hedin

FDA Attendees and titles:

Division of Metabolic and Endocrine Drug Products:

Theresa Kehoe, M.D., Clinical Reviewer
Randy Hedin, R.Ph., Senior Regulatory Management Officer

Office of New Drug Chemistry:
Elsbeth Chikhale, Ph.D., Reviewer
Sheldon Markofsky, Ph.D., Acting Team Leader

Division of Pharmaceutical Evaluation II
Johnny Lau, Ph.D., Reviewer

Division of Biometrics II
David Hoberman, Ph.D., Reviewer
Todd Sahlroot, Ph.D., Team Leader

External participant Attendees and titles:

None

Meeting Objectives:

To determine if NDA 21-455 will be filed, and discuss plans for the review of the NDA.

Discussion Points:

- Chemistry: The application is fileable.
- Pharmacology: The pharmacology reviewer was not present; however, she reviewed the application and stated that it is fileable.
- Biopharm: The application is fileable. A filing memorandum will be rendered in DFS within the next several weeks. Hoffman-La Roche proposed an in vitro disintegration test instead of the in vitro dissolution test. This will need to be resolved.
- Statistics: The application is fileable. However, the submitted electronic data sets are not adequate, and additional sets will be requested.
- Clinical: The application is fileable.
  - Financial disclosure data has been submitted.
  - Division of Scientific Investigations (DSI) audits will be requested.

Decisions (agreements) reached:

- The application will be filed.
- The review will be done as a standard review. The goal to finish the reviews with team leader signoff will be April 6, 2003
- The application will not be discussed at an Advisory Committee Meeting.
- Dr. Kehoe will consult with the Division of Scientific Investigations concerning the appropriate sites for audits.

Unresolved or issues requiring further discussion:

- None

Action Items:

- Schedule status meetings as appropriate.

Signature, Regulatory Project Manager, HFD-510

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

/s/

Randy Hedin
9/30/02 12:46:53 PM

5/2/03

CONSULTATION RESPONSE

DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)

DATE RECEIVED: February 14, 2003	**DUE DATE:** May 13, 2003	**ODS CONSULT #:** 03-0066, 03-0107

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

THROUGH: Randy Hedin
Project Manager
HFD-510

PRODUCT NAME:	**NDA SPONSOR:**
Boniva (Primary Name) (Ibandronate Sodium) 2.5 mg Tablets **NDA#:** 21-455	Hoffmann-La Roche Inc.

SAFETY EVALUATOR: Nora Roselle, PharmD

SUMMARY: In response to a request from the Division of Metabolic and Endocrine Drug Products (HFD-510), the Division of Medication Errors and Technical Support (DMETS) conducted a review of the proposed proprietary names "Boniva" and " ——— " to determine the potential for confusion with approved proprietary and established names as well as pending names.

RECOMMENDATION:

1. DMETS does not recommend the use of the proprietary name, "Boniva". However, DMETS has no objections to the use of the proprietary name, ——— We consider this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary and established names from this date forward.

2. DMETS recommends implementation of the label and labeling recommendations outlined in section III of this review.

3. DDMAC finds the names, Boniva and ——— acceptable from a promotional perspective.

Carol Holquist, RPh
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

Jerry Phillips, RPh
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; Parklawn Rm. 6-34
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: April 7, 2003

NDA#: 21-455

NAME OF DRUG: **Boniva** (Primary Name)
——— (Alternate Name)
(Ibandronate Sodium) 2.5 mg Tablets

NDA HOLDER: Hoffmann-La Roche Inc.

*****NOTE: This review contains proprietary and confidential information that should not be released to the public.*****

I. INTRODUCTION:

This consult is written in response to a request from the Division of Metabolic and Endocrine Drug Products, for review of the proposed proprietary names Boniva and ——— The proposed labels and labeling were reviewed for possible interventions to minimize medication errors. "Bonviva" was the original proprietary name submitted for this product. DMETS found the name acceptable in February 2000 (ODS Consult 99-056). However, in August 2002, the name was under re-review (ODS Consult 99-056-1) and was found unacceptable by DDMAC due to promotional concerns. The sponsor has modified the name to read "Boniva" and believes this significantly changes the phonetic properties and pronunciation, as well as any interpreted meaning.

PRODUCT INFORMATION

Boniva/ ——— is indicated for the treatment and prevention of osteoporosis in postmenopausal women. Boniva/ ——— will be available in a 2.5 mg strength and will be packaged in bottles of 30, 90, and 500 oral tablets. The recommended dose of Boniva/ ——— is one 2.5 mg tablet once daily. The drug should be taken 60 minutes before the first food or drink of the day or before any other oral medication or supplementation, including calcium, antacids, or vitamins. In addition, Boniva/ ——— should be swallowed whole with a full glass of plain water while the patient is standing or sitting in an upright position. Patients should be instructed not to lie down for 60 minutes after taking Boniva/ ———

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[1,2] as well as several FDA databases[3] for existing drug names that sound-alike or look-alike to Boniva and ~~~ to a degree where potential confusion between drug names could occur under the usual clinical practice settings. The Saegis[4] Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches.

A. EXPERT PANEL DISCUSSION

An Expert Panel Discussion was held by DMETS to gather professional opinions on the safety of the proprietary names Boniva and ~~~ Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. Several product names were identified in the Expert Panel Discussion (EPD) that were thought to have potential for confusion with Boniva and ~~~ These products are listed in Table 1 and Table 2 (see below and page 4) along with the dosage forms available and usual FDA-approved dosage.

2. DDMAC did not have concerns about the names Boniva and ~~~ with regard to promotional claims.

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Dosage form(s), Established name	Usual adult dose*	Other
Boniva	Ibandronate Sodium Tablet:2.5 mg	One 2.5 mg tablet daily	
Bonine	Meclizine Hydrochloride Chewable Tablet: 25 mg	1 to 2 tablets once daily	Look-alike, Sound-alike
Benicar	Olmesartan Medoxomil Tablet: 5 mg, 20 mg, 40 mg	20 mg once daily; may be increased to 40 mg daily	Look-alike
Renova	Tretinoin Cream: 0.02%, 0.05%	Apply to face once daily in the morning	Look-alike
Zometa	Zoledronic Acid for Injection Injection: 4 mg/vial	4 mg diluted in 100 mL of solution administered as IV infusion over 15 minutes every 3 to 4 weeks	Sound-alike
~~			

*Frequently used, not all-inclusive.
NOTE: This review contains proprietary and confidential information that should not be released to the public.

[1] MICROMEDEX Integrated Index, 2003, MICROMEDEX, Inc , 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems
[2] Facts and Comparisons, 2003, Facts and Comparisons, St Louis, MO
[3] The Division of Medication Errors and Technical Support [DMETS] database of proprietary name consultation requests, New Drug Approvals 98-03, and the electronic online version of the FDA Orange Book.
[4] Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at www.thomson-thomson.com

Table 2: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Dosage form(s), Established name	Usual adult dose*	Other
[redacted]	Ibandronate Sodium Tablet:2.5 mg	One 2.5 mg tablet daily	
Benadryl	Diphenhydramine Capsule (OTC): 25 mg, 50 mg Cream/Gel (OTC): 1%, 2% Oral Solution (OTC): 12.5 mg/5 mL Injection (Rx): 10 mg/mL, 50 mg/mL	Capsule: 25 mg - 50 mg every 6-8 hours Topical: Apply to affected areas of skin Injection: 10 mg - 50 mg as a single dose every 2-4 hours Oral Solution: 2 to 4 teaspoonfuls every 4-6 hours	Look-alike
Fentanyl (generic name)	Fentanyl Injection: 0.05 mg base/mL	Injection: General anesthetic- 0.05 mg/kg to 0.1 mg/kg	Look-alike
Relenza	Zanamivir Powder for Inhalation: 5 mg per blister	2 inhalations (10 mg total) twice daily for 5 days	Sound-alike
Avinza	Morphine Sulfate, Extended-release Capsule: 30 mg, 60 mg, 90 mg, 120 mg	1 to 2 tablets daily	Sound-alike
Albenza	Albendazole Tablet: 200 mg	≤60 kg weight: 15 mg/kg/day given in 2 divided doses twice daily with meals ≥60 kg weight: 400 mg twice daily with meals	Sound-alike

*Frequently used, not all-inclusive.
NOTE: This review contains proprietary and confidential information that should not be released to the public.

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Six separate studies were conducted within FDA for the proposed proprietary names to determine the degree of confusion of Boniva and [redacted] with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 105 health care professionals (pharmacists, physicians, and nurses) for each name. These exercises were conducted in an attempt to simulate the prescription ordering process. Inpatient orders and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for either Boniva or [redacted] (see page 5). These prescriptions were optically scanned and were delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

Boniva

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Outpatient RX: Boniva 1 po qd #30	Boniva Number thirty. One by mouth daily.
Inpatient RX: Boniva 1 po QD #30	

Bondenza

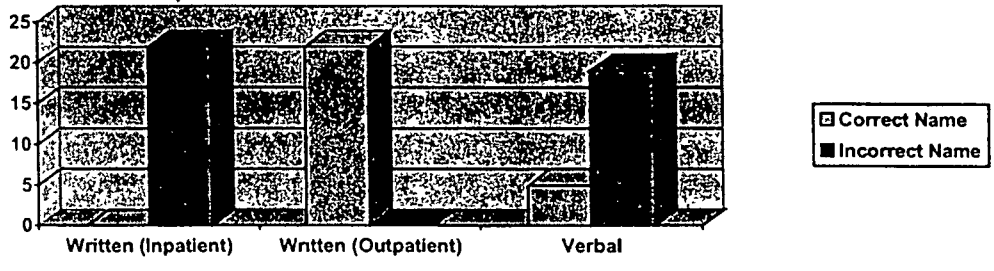
HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Outpatient RX: 2.5mg #30 Sig: 1 tab po qd 1 ref	2.5 mg Number thirty. One tablet PO QD. One refill.
Inpatient RX: 2.5mg 1 po qd	

2. Results:

   i. The results for **Boniva** are summarized in Table 3.

Table 3

Study	# of Participants	# of Responses (%)	Correctly Interpreted (%)	Incorrectly Interpreted (%)
Written Inpatient	31	22 (71%)	0 (0%)	22 (100%)
Written Outpatient	39	22 (56%)	22 (100%)	0 (0%)
Verbal	35	24 (69%)	5 (21%)	19 (79%)
Total	105	68 (65%)	27 (40%)	41 (60%)



Among the written inpatient prescription study participants for Boniva, 22 of 22 (100%) of the participants interpreted the name incorrectly. The incorrect responses were *Bonira (5), Banira (5), Banera (3), Benira (2), Beneva (1), Barina (1), Benina (1), Bonera (1), Banina (1),* and *Bonina (2).* None of the incorrect responses are names of currently marketed drug products; however, the incorrect interpretation *Bonina* is similar to the currently marketed name "Bonine".

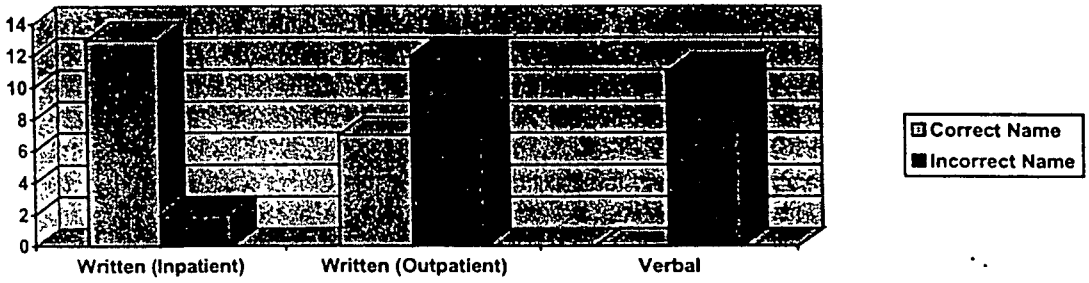
Among the written outpatient prescription study participants for Boniva, none of the participants interpreted the name incorrectly. However, one respondent commented that the name is "too similar to Bonine", a drug product currently marketed in the United States.

Among the verbal prescription study participants for Boniva, 19 of 24 (79%) of the participants interpreted the name incorrectly. The incorrect responses were *Beneva (14), Beniva (3), Boneva (1),* and *Beneven (1),* none of which are names of currently marketed drug products.

ii. The results for ~~~~ are summarized in Table 4.

Table 4

Study	# of Participants	# of Responses (%)	Correctly Interpreted (%)	Incorrectly Interpreted (%)
Written Inpatient	31	15 (48%)	13 (87%)	2 (13%)
Written Outpatient	39	19 (49%)	7 (37%)	12 (63%)
Verbal	35	11 (31%)	0 (0%)	11 (100%)
Total	105	45 (43%)	20 (44%)	25 (56%)



Among the written inpatient prescription study participants for ~~~~ , 2 of 15 (13%) of the participants interpreted the name incorrectly. The two incorrect responses were *Bundenza (1)* and *Bondemza (1).* None of the incorrect interpretations are names of drugs currently marketed in the United States.

Among the written outpatient prescription study participants for ~~~~ 12 of 19 (63%) of the participants interpreted the name incorrectly. The incorrect responses were *Bordenza (4), Bondenra (3), Bondensa (2), Bondeza (1), Bondenga (1),* and *Bandenra (1),* none of which are names of currently marketed drug products in the United States.

Among the verbal prescription study participants for ~~~~ , 11 of 11 (100%) of the participants interpreted the name incorrectly. The incorrect responses were *Bondanza (4), Borndanza (1), Bontanza (1), Vendanza (1), Bundenza (1), Brondenza (1),*

Bundanza (1), and *Bondana (1).* None of the incorrect interpretations are names of currently marketed drug products in the United States.

C. SAFETY EVALUATOR RISK ASSESSMENT:

1. Boniva

In reviewing the proposed proprietary name "Boniva", the primary concerns raised were related to five look-alike and/or sound-alike names. The products considered to have potential for name confusion with Boniva were Bonine, Benicar, Renova, Zometa, and ———***.

We conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that Boniva could be confused Bonine, Benicar, Renova, Zometa, or ——— However, negative findings are not always predicative as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to sample size. Among the written outpatient prescription study for Boniva, one respondent commented that the name is "too similar to Bonine", a drug product currently marketed in the United States.

Bonine was identified to have sound-alike and look-alike potential with the proposed proprietary name, Boniva. Bonine is an over-the-counter (OTC) drug product used in the prevention and treatment of motion sickness symptoms. Bonine contains the active ingredient meclizine and is available as a 25 mg chewable tablet. Boniva and Bonine have look-alike and slight sound-alike similarities in that each name contains the prefix "Boni-". When scripted, not only are the prefixes identical, the suffixes ("-va" vs. "ne") also look alike (see below) increasing the risk for confusion between the two names.

Bonine Boniva bonine Boniva

Both drugs share an overlapping dosage form (tablet), route of administration (oral), and dosing regimens (one tablet once daily). In addition, Boniva and Bonine share a numerically similar strength (2.5 mg vs. 25 mg). In this case, if the decimal point is overlooked or not clearly written one may easily misinterpret 2.5 mg as 25 mg, or vice versa, increasing the potential for error between the two drug names.

Post marketing experience has shown that errors can and do occur between prescription and over-the-counter drug products when product names are similar. Below are examples of errors that have been submitted to the Agency:

U042150/Date 10-29-96
A physician wrote an order for Colace 100 mg po BID. The order was misread and interpreted as Cozaar. The error occurred twice.

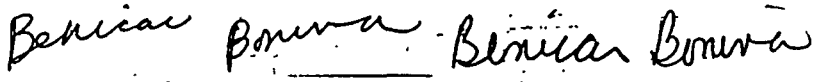
U050032/Date 3-25-97
An order was written for "Ascol one tablet po tid" and interpreted as Asacol. The order was actually for Os-Cal. The physician was called to verify the order but she never returned the call.

U050117/Date 4-14-97
Bisoprolol went out in the unit-dose drawer in place of Bisacodyl.

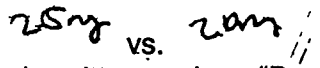
*** NOTE This review contains proprietary and confidential information that should not be released to the public.***

If a patient inadvertently receives Boniva instead of Bonine, one may have prolonged motion sickness symptoms. If a patient inadvertently receives Bonine instead of the Boniva, one may experience unintended drowsiness. Moreover, patients with emphysema, chronic bronchitis, glaucoma, or enlargement of the prostate may experience worsening of symptoms if inadvertently given Bonine, as this drug should not be used in these disease states. Thus, due to numerous product similarities, errors identified through post-marketing, as well as convincing look-alike characteristics, DMETS believes there is an increased risk for confusion and error between the two products.

Benicar has a look-alike similarity to Boniva. Benicar is used in the treatment of hypertension and is available in 5 mg, 20 mg, and 40 mg oral tablets. Each name contains similar looking prefixes ("Beni-" vs. "Boni") which differ only by one letter (see below). In addition, when scripted both names are similar in length (6 letters vs. 7 letters).

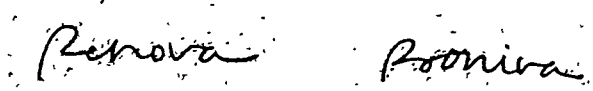


Besides look-alike similarities, Boniva and Benicar share an overlapping dosage form (tablet), route of administration (oral), and dosing regimen (one tablet once daily). In addition, both drugs may be located near each other in some pharmacies if alphabetized by brand name. One difference between the two drugs is that Benicar is available in three different strengths (5 mg, 20 mg, and 40 mg) while Boniva will only be available in a single strength (2.5 mg), a difference which may help minimize the potential for confusion with Boniva. However, when scripted (see below), the numbers 2.5 mg and 20 mg can look similar especially since both drugs have usual daily doses that begin with the number "2" (20 mg for Benicar vs. 2.5 mg for Boniva).



If a prescription is ambiguously written such as "Benicar 20 mg, use as directed, #30 or "Boniva 2.5 mg, use as directed, #30", one may inadvertently misinterpret the prescription due to the similarity in the name, and directions for use. Given the above-mentioned similarities, DMETS believes there is an increased risk for confusion and error between Boniva and Benicar.

Renova has a look-alike similarity to Boniva. Renova is used in the treatment of acne vulgaris, photodamaged skin, and some skin cancers. Renova is available as a 0.02% and 0.05% topical cream. The names have similar look-alike characteristics where each name is identical in length (6 letters) and contains an upstroke first letter (B v. R) followed by five similarly scripted letters ("-oniva" vs. "enova"). (see below)



Besides look-alike similarities, Boniva and Renova share overlapping daily dosing schedules (once daily). However, the two drugs do not share overlapping dosage forms (tablet vs. cream), routes of administration (oral vs. topical), strengths (2.5 mg vs. 0.02% and 0.05%), indications for use (acne vs. osteoporosis). In addition, Renova is available in two different strengths while Boniva is available in only a single strength. Therefore, a differentiating strength does not need to be identified for Boniva when prescribed. Due to the

differences between the two drugs, DMETS believes that there is decreased risk for confusion and error between Boniva and Renova.

Zometa has a sound-alike similarity to Boniva. Zometa is used in the treatment of multiple myeloma and bone metastases. Zometa is an intravenous injection of 4 mg per vial. When spoken, each name contains three syllables. In addition, Boniva and Zometa rhyme with one another if Boniva is pronounced "Bō-nē-vă" and Zometa is pronounced "Zō-mē-tă". Besides slight sound-alike similarities, Boniva and Zometa share an overlapping dosing regimen (once daily). However, the two drugs have different indications for use (osteoporosis vs. cancer), dosage forms (tablet vs. injection), routes of administration (oral vs. intravenous), and strengths (2.5 mg vs. 4 mg/vial). In addition, Zometa needs to be diluted in 100 mL of solution before it is administered by intravenous infusion. Zometa is given by IV infusion over 15 minutes every three to four weeks, while Boniva is given as one tablet by mouth once daily. Due to the above-mentioned differences, as well as lack of convincing sound-alike similarity, DMETS believes that there is a decreased risk for confusion and error between Boniva and Zometa.

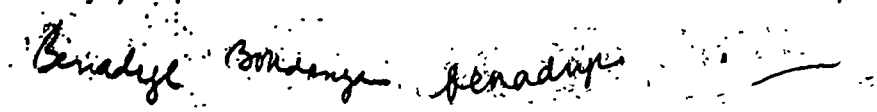
2.

In reviewing the proposed proprietary name the primary concerns raised were related to six look-alike and/or sound-alike names. The products considered to have potential for name confusion with were Benadryl, Fentanyl, Relenza, Avinza, Albenza, and Bondronat***.

We conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that could be confused with Relenza, Benadryl, Fentanyl, Avinza, Albenza, or Bondronat. However, negative findings are not always predicative as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to sample size.

*** NOTE: This review contains proprietary and confidential information that should not be released to the public ***

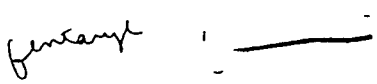
Benadryl has a slight look-alike similarity to [redacted] Benadryl is an antihistamine indicated for the relief of allergic symptoms. Benadryl is available in four dosage forms: capsule (25 mg and 50 mg), cream/gel (1% and 2%), oral solution (12.5 mg/5 mL), and injection (10 mg/mL and 50 mg/mL). The usual dose of Benadryl capsules is 25 mg to 50 mg three to four times a day. Each name begins with the prefix "Ben-" and has a similar downstroke letter ("z" vs. "y") towards the end of the name. However, the suffixes of each name ("-denza" vs. "dryl") help differentiate one name from the other when scripted (see below).



Besides some look-alike similarities, the two drugs can be given orally (tablet vs. capsule) and share a numerically similar strength (2.5 mg vs. 25 mg). However, [redacted] and Benadryl have different indications for use (osteoporosis vs. antihistamine) and dosing regimens (once daily vs. three to four times daily). Also, Benadryl is available in four different dosage forms each with varying strengths while [redacted] is proposed as an oral tablet with a single strength. In addition, Benadryl is often indicated for short courses of therapy to treat allergic symptoms. [redacted] on the other hand, is indicated for the treatment and prevention of osteoporosis and will most likely be prescribed as a maintenance medication for long courses of therapy. Based on the above-mentioned differences, as well as a lack of convincing look-alike similarity, DMETS believes there is minimal risk of error between the two drugs.

Relenza was identified to have sound-alike potential with the proposed proprietary name, [redacted] Relenza is used to treat acute illness due the influenza virus. Relenza is available as an oral powder for inhalation (5 mg per blister), and is dosed as 2 inhalations (10 mg total) twice daily for five days. The names Relenza and [redacted] sound similar because they share the rhyming suffixes "-lenza" and "-denza" and have three syllables when spoken. However, the prefixes of each name sound different ("Rel-" vs. "Bon-") which helps to differentiate one from the other. [redacted] and Relenza do not share overlapping dosage forms (tablet vs. powder for inhalation), routes of administration (oral vs. oral inhalation), indications for use (osteoporosis vs. influenza), strengths (2.5 mg vs. 5 mg), and dosing regimens (one tablet once daily vs. two inhalations twice daily). In addition, Relenza is an acute medication used for a total of five days, while [redacted] is used for a longer course of therapy. Due to the differences between the two products, DMETS believes there is a low risk of error between [redacted] and Relenza.

Fentanyl has look-alike similarities to [redacted] Fentanyl is indicated for the treatment of pain for a short duration during anesthesia and in the immediate postoperative period. Fentanyl is available as either an intravenous or intramuscular injection (0.05 mg/mL). Fentanyl is also available in transdermal (Duragesic) and transmucosal (Actiq) dosage forms. The usual dose of Fentanyl as a general anesthetic is 0.05 mg/kg to 0.1 mg/kg. When scripted the two names can look similar when written in lower case cursive as each name has common upstroke (d vs. t) and downstroke (f vs. b and z vs. y) letters (see below).



Besides look-alike similarities, the two drugs share little else in common. ——— and Fentanyl have a different indications for use (osteoporosis vs. pain), dosage forms (tablet vs. injectable), routes of administration (oral vs. IV or IM), dosage strengths (2.5 mg vs. 0.05 mg/mL), and dosing regimens (once daily vs. dosed during or after surgery). In addition, Fentanyl is a Schedule II controlled substance while ——— is a non-scheduled prescription medication. Based on the above-mentioned differences, DMETS believes there is minimal risk of error between the two drugs.

Avinza has a slight sound-alike similarity to ——— Avinza is indicated for the relief of moderate to severe pain. Avinza is an extended-release formulation of morphine sulfate and is available in 30 mg, 60 mg, 90 mg, and 120 mg oral capsules. ——— and Avinza have slight sound-alike characteristics in that the two names end with the letters "-nza" and contain three syllables when spoken. Yet, the prefixes of each name ("Avi-" vs. "Bonde-") help differentiate one name from the other. Besides slight sound-alike similarities, ——— and Avinza share an overlapping route of administration (oral), dosage form (tablet/capsule), and dosing regimen (one tablet daily vs. one to two tablets daily). However, ——— and Avinza have different indications for use (osteoporosis vs. pain) and strengths (2.5 mg vs. 30 mg, 60 mg, 90 mg, 120 mg). ——— is only available in a single strength that does not need to be identified when prescribed. Avinza, on the other hand, is available in four strengths and a differentiating strength would need to be indicated when prescribed helping to decrease the potential for confusion between Avinza and ———. In addition, Avinza is a Schedule II controlled substance while ——— is a non-scheduled prescription medication. DMETS believes that while there are similarities between the two drug products, the above-mentioned differences as well as lack of convincing sound-alike similarity, help differentiate the two names. DMETS believes there is a low risk for error between the ——— and Avinza.

*** NOTE: This review contains proprietary and confidential information that should not be released to the public.***

III. COMMENTS TO THE SPONSOR:

DMETS does not recommend the use of the proprietary name, Boniva. However, DMETS has no objections to the use of the proprietary name, ———

The products considered to have potential for name confusion with Boniva were Bonine and Benicar.

Bonine was identified to have sound-alike and look-alike potential with the proposed proprietary name, Boniva. Bonine is an over-the-counter (OTC) drug product used in the prevention and treatment of motion sickness symptoms. Bonine contains the active ingredient meclizine and is available as a 25 mg chewable tablet. Boniva and Bonine have look-alike and slight sound-alike similarities in that each name contains the prefix "Boni-". When scripted, not only are the prefixes identical, the suffixes ("-va" vs. "ne") also look alike (see below) increasing the risk for confusion between the two names.

Bonine Boniva bonine boniva

Both drugs share an overlapping dosage form (tablet), route of administration (oral), and dosing regimens (one tablet once daily). In addition, Boniva and Bonine share a numerically similar strength (2.5 mg vs. 25 mg). In this case, if the decimal point is overlooked or not clearly written one may easily misinterpret 2.5 mg as 25 mg, or vice versa, increasing the potential for error between the two drug names.

Post marketing experience has shown that errors can and do occur between prescription and over-the-counter drug products when product names are similar. If a patient inadvertently receives Boniva instead of Bonine, one may have prolonged motion sickness symptoms. If a patient inadvertently receives Bonine instead of the Boniva, one may experience unintended drowsiness. Moreover, patients with emphysema, chronic bronchitis, glaucoma, or enlargement of the prostate may experience worsening of symptoms if inadvertently given Bonine, as this drug should not be used in these disease states. Thus, due to numerous

product similarities, as well as convincing look-alike characteristics, DMETS believes there is an increased risk for confusion and error between the two products.

Benicar has a look-alike similarity to Boniva. Benicar is used in the treatment of hypertension and is available in 5 mg, 20 mg, and 40 mg oral tablets. Each name contains similar looking prefixes ("Beni-" vs. "Boni") which differ only by one letter (see below). In addition, when scripted both names are similar in length (6 letters vs. 7 letters).

Benicar Boniva Benicar Boniva

Besides look-alike similarities, Boniva and Benicar share an overlapping dosage form (tablet), route of administration (oral), and dosing regimen (one tablet once daily). In addition, both drugs may be located near each other in some pharmacies if alphabetized by brand name. One difference between the two drugs is that Benicar is available in three different strengths (5 mg, 20 mg, and 40 mg) while Boniva will only be available in a single strength (2.5 mg), a difference which may help minimize the potential for confusion with Boniva. However, when scripted (see below), the numbers 2.5 mg and 20 mg can look similar especially since both drugs have usual daily doses that begin with the number "2" (20 mg for Benicar vs. 2.5 mg for Boniva).

25mg vs. 20mg

If a prescription is ambiguously written such as "Benicar 20 mg, use as directed, #30 or "Boniva 2.5 mg, use as directed, #30", one may inadvertently misinterpret the prescription due to the similarity in the name, and directions for use. Given the above-mentioned similarities, DMETS believes there is an increased risk for confusion and error between Boniva and Benicar.

Additionally, DMETS reviewed the container label and insert labeling and has identified the following areas of possible improvement.

A. CONTAINER LABEL

1. We recommend decreasing the prominence of the net quantity statement by deleting the bold print or using a smaller font size.

2. We note the sponsor proposes to market this product in bottles containing 30 and 90 tablets. We consider these unit of use containers. Please ensure that the containers have a Child Resistant Container (CRC) cap in order to be compliant with the Poison Prevention Act.

3. Due to the large amount of patient information with regard to this product we recommend the addition of a Patient Package Insert (PPI).

B. INSERT LABELING

No comments at this time.

IV. RECOMMENDATIONS:

A. DMETS does not recommend the use of the proposed proprietary name, Boniva. However, DMETS has no objections to the use of the proposed proprietary name, ——— We consider this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary and established names from this date forward.

B. In addition, DMETS recommends the label and labeling revisions in section III of this review that might lead to safer use of the product. We would be willing to revisit these issues if the Division receives another draft of the labeling from the manufacturer.

C. DDMAC finds the proposed names, Boniva and ——— acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, Project Manager, at 301-827-3242.

Nora Roselle, PharmD
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

Alina Mahmud, RPh
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

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

/s/

Nora L. Roselle
5/1/03 03:04:00 PM
CSO

Alina Mahmud
5/2/03 07:08:08 AM
PHARMACIST

Carol Holquist
5/2/03 07:49:57 AM
PHARMACIST

Jerry Phillips
5/2/03 01:25:11 PM
DIRECTOR

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

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

Please mark the applicable checkbox.

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

Clinical Investigators		

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

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

NAME	TITLE
Cynthia Dinella, PharmD	Vice President, Drug Regulatory Affairs
FIRM/ORGANIZATION: Hoffmann-La Roche Inc. 340 Kingsland Street Nutley, New Jersey 07110	
SIGNATURE: for Cindy Dinella	DATE: July 1, 2002

Paperwork Reduction Act Statement

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

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

Created by Electronic Document Services/USDHHS. (301) 443-2454 EF