

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-386
21-223/S-003

ADMINISTRATIVE DOCUMENTS
CORRESPONDENCE

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

| | | |
|---|-------------------------------|--|
| DA 21-386 | Efficacy Supplement Type SE-6 | Supplement Number |
| Drug: Zometa (zoledronic acid for injection) | | Applicant: Novartis Pharmaceuticals Corporation |
| RPM: Debra Vause | HFD-150 | Phone #301-594-5724 |
| Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) | | Reference Listed Drug (NDA #, Drug name): 21-223 / Zometa |
| ❖ Application Classifications: | | |
| • Review priority | | <input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority |
| • Chem class (NDAs only) | | bisphosphonate |
| • Other (e.g., orphan, OTC) | | |
| ❖ User Fee Goal Dates | | February 21, 2002 |
| ❖ Special programs (indicate all that apply) | | <input checked="" type="checkbox"/> None Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review |
| ❖ User Fee Information | | |
| • User Fee | | <input checked="" type="checkbox"/> Paid |
| • User Fee waiver | | <input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other |
| • User Fee exception | | <input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) <input type="checkbox"/> Other |
| ❖ Application Integrity Policy (AIP) | | |
| • Applicant is on the AIP | | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No |
| • This application is on the AIP | | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No |
| • Exception for review (Center Director's memo) | | |
| • OC clearance for approval | | |
| ❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent. | | <input checked="" type="checkbox"/> Verified |
| ❖ Patent | | |
| • Information: Verify that patent information was submitted | | <input checked="" type="checkbox"/> Verified |
| • Patent certification [505(b)(2) applications]: Verify type of certifications submitted | | 21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> I <input type="checkbox"/> II <input type="checkbox"/> III <input type="checkbox"/> IV 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii) |
| • For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice). | | <input type="checkbox"/> Verified |
| Exclusivity Summary (approvals only) | | Yes-Div. Dir.- R. Pazdur to sign |
| Administrative Reviews (Project Manager, ADRA) (indicate date of each review) | | |

| Actions | |
|---|---|
| • Proposed action | (X) AP () TA () AE () NA |
| • Previous actions (specify type and date for each action taken) | NA |
| • Status of advertising (approvals only) | X Materials requested in AP letter () Reviewed for Subpart H |
| ❖ Public communications | |
| • Press Office notified of action (approval only) Kathleen Kolar 7-3414 | (X) Yes () Not applicable |
| • Indicate what types (if any) of information dissemination are anticipated | (X) None () Press Release () Talk Paper () Dear Health Care Professional Letter |
| ❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable)) | |
| • Division's proposed labeling (only if generated after latest applicant submission of labeling) | 2/21/02 |
| • Most recent applicant-proposed labeling | 8/21/01 |
| • Original applicant-proposed labeling | 8/20/01 |
| • Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings (indicate dates of reviews and meetings) | February 4,6,13,15, 2002 |
| • Other relevant labeling (e.g., most recent 3 in class, class labeling) | |
| ❖ Labels (immediate container & carton labels) | |
| • Division proposed (only if generated after latest applicant submission) | |
| • Applicant proposed | |
| • Reviews | |
| ❖ Post-marketing commitments | |
| • Agency request for post-marketing commitments | Yes |
| • Documentation of discussions and/or agreements relating to post-marketing commitments | See EOP2 Mtg Min, Pre-NDA Min and Approval Letter |
| ❖ Outgoing correspondence (i.e., letters, E-mails, faxes) | Yes |
| ❖ Memoranda and Telecons | Yes |
| ❖ Minutes of Meetings | |
| • EOP2 meeting (indicate date) | 4/13/99 |
| • Pre-NDA meeting (indicate date) | 2/13/01 |
| • Pre-Approval Safety Conference (indicate date; approvals only) | |
| • Other | |
| ❖ Advisory Committee Meeting | |
| • Date of Meeting | 1/31/02 |
| • 48-hour alert | 1/31/02 |
| ❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable) | DESI - 12/18/01 |

| CLINICAL REVIEW | |
|--|--|
| Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review) | 2/22/02 Division Director 2/21/02 Medical Team Leader |
| ❖ Clinical review(s) (indicate date for each review) | 2/22/02 |
| ❖ Microbiology (efficacy) review(s) (indicate date for each review) | NA |
| ❖ Safety Update review(s) (indicate date or location if incorporated in another review) | 2/22/02 |
| ❖ Pediatric Page (separate page for each indication addressing status of all age groups) | NA |
| ❖ Statistical review(s) (indicate date for each review) | 2/13/02 |
| ❖ Biopharmaceutical review(s) (indicate date for each review) | 2/15/02 |
| ❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review) | NA |
| ❖ Clinical Inspection Review Summary (DSI) | |
| • Clinical studies | Completed for 3 waiting 1 due 2/18/02 |
| • Bioequivalence studies | NA |
| CMC REVIEW | |
| ❖ CMC review(s) (indicate date for each review) | 11/29/01 |
| ❖ Environmental Assessment | |
| • Categorical Exclusion (indicate review date) | 11/29/01 |
| • Review & FONSI (indicate date of review) | NA |
| • Review & Environmental Impact Statement (indicate date of each review) | NA |
| ❖ Micro (validation of sterilization & product sterility) review(s) (indicate date for each review) | NA |
| Facilities inspection (provide EER report) | Date completed: 9/24/01 (X) Acceptable () Withhold recommendation |
| ❖ Methods validation | () Completed () Requested NA () Not yet requested |
| Nonclinical Pharm/Tox Information | |
| ❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review) | 1/31/02 |
| ❖ Nonclinical inspection review summary | NA |
| ❖ Statistical review(s) of carcinogenicity studies (indicate date for each review) | NA |
| ❖ CAC/ECAC report | NA |

USER FEE VALIDATION SHEET

NDA # 21-386 Supp. Type & # N000 UFID # 4183
 (e.g., N000, SLR001, SE1001, etc.)

1. YES NO User Fee Cover Sheet Validated? MIS_Elements Screen Change(s):

2. YES NO APPLICATION CONTAINS CLINICAL DATA?
 (Circle YES if NDA contains study or literature reports of what are explicitly or implicitly represented by the application to be adequate and well-controlled trials. Clinical data do not include data used to modify the labeling to add a restriction that would improve the safe use of the drug (e.g., to add an adverse reaction, contraindication or warning to the labeling).

REF IF NO CLINICAL DATA IN SUBMISSION, INDICATE IF CLINICAL DATA ARE CROSS REFERENCED IN ANOTHER SUBMISSION. *(CMC & Pharm (Tox) N 21-223)*

3. YES NO SMALL BUSINESS EXEMPTION

4. YES NO WAIVER GRANTED

5. YES NO NDA BEING SPLIT FOR ADMINISTRATIVE CONVENIENCE (other than bundling).
 If YES, list all NDA #s, review division(s) and those for which an application fee applies.

| | | | |
|---------|------------|-----|--------|
| NDA # | Division | Fee | No Fee |
| N _____ | HFD- _____ | Fee | No Fee |
| N _____ | HFD- _____ | Fee | No Fee |

6. YES NO BUNDLING POLICY APPLIED CORRECTLY? No Data Entry Required
 (Circle YES if application is properly designated as one application or is properly submitted as a supplement instead of an original application. Circle NO if application should be split into more than one application or be submitted as an original instead of a supplement. If NO, list resulting NDA #s and review division(s).

| | | | |
|-----------------|-----------------|---------|------------|
| NDA # | Division | NDA # | Division |
| N <u>21-223</u> | HFD- <u>540</u> | N _____ | HFD- _____ |

7. P S PRIORITY or STANDARD APPLICATION?

 / / 8/28/01 / / 7-28-01
 PM Signature / Date CPMS Concurrence Signature / Date

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: 04-30-01

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

| | |
|---|--|
| <p>1. APPLICANT'S NAME AND ADDRESS</p> <p>Novartis Pharmaceuticals Corporation 59 Rt. 10 East Hanover, New Jersey 07936</p> | <p>3. PRODUCT NAME</p> <p>Zometa (zoledronic acid for injection)</p> |
| <p>2. TELEPHONE NUMBER (Include Area Code)</p> <p>(973) 781-6869 - Robert Kowalski, PharmD.</p> | <p>4. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.</p> <p>IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:</p> <p><input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.</p> <p><input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO <u>21-223</u> (APPLICATION NO. CONTAINING THE DATA).</p> |
| <p>5. USER FEE I.D. NUMBER</p> <p>4183</p> | <p>6. LICENSE NUMBER / NDA NUMBER</p> <p>NDA 21-386</p> |

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

| | |
|--|--|
| <input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 <i>(Self Explanatory)</i> | <input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE <i>(See item 7, reverse side before checking box.)</i> |
| <input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act <i>(See item 7, reverse side before checking box.)</i> | <input type="checkbox"/> THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act <i>(See item 7, reverse side before checking box.)</i> |
| <input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY <i>(Self Explanatory)</i> | |

FOR BIOLOGICAL PRODUCTS ONLY

| | |
|---|--|
| <input type="checkbox"/> WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION | <input type="checkbox"/> A CRUDE ALLERGENIC EXTRACT PRODUCT |
| <input type="checkbox"/> AN APPLICATION FOR A BIOLOGICAL PRODUCT FOR FURTHER MANUFACTURING USE ONLY | <input type="checkbox"/> AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT LICENSED UNDER SECTION 351 OF THE PHS ACT |
| <input type="checkbox"/> BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92 | |

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? YES NO
(See reverse side if answered YES)

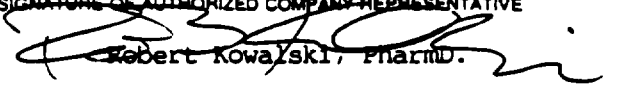
A completed form must be signed and accompany each new drug or biologic product application and each new supplement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment.

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

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0297)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

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.

Please DO NOT RETURN this form to this address.

| | | |
|---|---|----------------------------|
| <p>SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE</p> <p> Robert Kowalski, PharmD.</p> | <p>TITLE</p> <p>Director, Global Head Planning & Administration - DRA</p> | <p>DATE</p> <p>7/20/01</p> |
|---|---|----------------------------|

Number of Pages
Redacted 23



Draft Labeling
(not releasable)



Paula E. Rinaldi
Director
Regulatory Affairs

Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080

Tel 973-781-7712
Fax 973-781-6325

February 20, 2002

Richard Pazdur, MD Director
Division of Oncology Drug Products,
HFD-150
Food and Drug Administration
Ctr for Drug Evaluation and Research
Attn: Division Document Room 3067
5600 Fishers Lane
Rockville, Maryland 20857

NDA 21-386

ZOMETA[®] (zoledronic acid for injection)

• **Phase IV Commitment**

Dear Dr. Pazdur,

Reference is made to our NDA 21-386 submitted on August 21, 2001. Reference is also made our February 15, 2002 letter indicating that we agreed to two Phase IV Commitments. We are now sending a new Phase IV Commitment agreement letter which contains all of the same information as the February 15, 2002 letter, with the addition of a study start date for each study.

We agree to the following Phase IV Commitments with the time frame provided:

1. Conduct a Phase IV pharmacokinetic, safety and efficacy study in patients with renal dysfunction and serum creatinine ≥ 3 mg /dl. The dose of Zometa to be administered should be adjusted to match the AUC 0-24 h in patients with normal renal function, and safety, efficacy and biomarker suppression should be assessed. A suitable patient population may be patients with multiple myeloma.

Draft Protocol Submission Date: April 15, 2002
Study Start Date: July 15, 2002
Target Final Submission to FDA: July 30, 2004

2. Conduct a drug-drug interaction study to evaluate the effect of thalidomide on the pharmacokinetics and safety of Zometa in patients with multiple myeloma.

Draft Protocol Submission Date: April 15, 2002
Study Start Date: July 15, 2002
Target Final Submission to FDA: July 30, 2004

New Drug Application 21-386 Zometa® (zoledronic acid for injection)
Phase IV Commitment

Page 2
February 20, 2002

If you have any questions concerning this submission, please contact me at (973) 781-7712.

Sincerely,



Paula E. Rinaldi
Director
Drug Regulatory Affairs

per:

cc: Debra Vause/HFD-150

APPEARS THIS WAY
ON ORIGINAL



Paula E. Rinaldi
Director
Regulatory Affairs

Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080

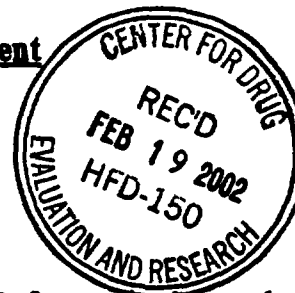
Tel 973-781-7712
Fax 973-781-6325

February 15, 2002

NDA 21-386

ZOMETA® (zoledronic acid for injection)

- Phase IV Commitment



Richard Pazdur, MD Director
Division of Oncology Drug Products,
HFD-150
Food and Drug Administration
Ctr for Drug Evaluation and Research
Attn: Division Document Room 3067
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Pazdur,

Reference is made to our NDA 21-386 submitted on August 21, 2001. Reference is also made to the February 15, 2002 email from Debbie Vause, Project Manager, seeking agreement to two Phase IV Commitments.

We agree to the following Phase IV Commitments with the time frame provided:

1. Conduct a Phase IV pharmacokinetic, safety and efficacy study in patients with renal dysfunction and serum creatinine ≥ 3 mg/dl. The dose of Zometa to be administered should be adjusted to match the AUC 0-24 h in patients with normal renal function, and safety, efficacy and biomarker suppression should be assessed. A suitable patient population may be patients with multiple myeloma.

Draft Protocol Submission Date: April 15, 2002
Target Final Submission to FDA: July 30, 2004

2. Conduct a drug-drug interaction study to evaluate the effect of thalidomide on the pharmacokinetics and safety of Zometa in patients with multiple myeloma.

Draft Protocol Submission Date: April 15, 2002
Target Final Submission to FDA: July 30, 2004

If you have any questions concerning this submission, please contact me at (973) 781-7712.

Sincerely,

Paula E. Rinaldi
Director
Drug Regulatory Affairs

per:
cc: Debra Vause/HFD-150

Patent Submission

Time Sensitive Patent Information

pursuant to 21 C.F.R. 314.53

for

NDA # 21-386

The following is provided in accordance with the Drug Price Competition and Patent Term Restoration Act of 1984:

- Trade Name: Zometa™
- Active Ingredient(s): Zoledronate/Zoledronic Acid
- Strength(s): 4 mg
- Dosage Form: Lyophilized powder for injection
- Approval Date: Pending

A. This section should be completed for each individual patent

U.S. Patent Number: 4,939,130

Expiration Date: November 13, 2007

Type of Patent—Indicate all that apply:

- | | | |
|---|------------|----------|
| 1. Drug substance (Active Ingredient) | <u>✓ Y</u> | <u>N</u> |
| 2. Drug Product (Composition/Formulation) | <u>Y</u> | <u>N</u> |
| 3. Method of Use | <u>Y</u> | <u>N</u> |

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

Name of Patent Owner: Novartis Corporation

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

U.S. Patent Number: 4,777,163

Expiration Date: July 24, 2007

Type of Patent—Indicate all that apply:

- | | | |
|---|------------|----------|
| 1. Drug substance (Active Ingredient) | <u>✓ Y</u> | <u>N</u> |
| 2. Drug Product (Composition/Formulation) | <u>Y</u> | <u>N</u> |
| 3. Method of Use | <u>Y</u> | <u>N</u> |

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

Name of Patent Owner: Boehringer Mannheim GmbH

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

B. The following declaration statement is required if any of the above listed patents have Composition/Formulation or Method of Use claims.

The undersigned declares that the above stated United States Patent Number covers the composition, formulation and/or method of use of (name of drug product). This product is:

- currently approved under section 505 of the Federal Food, Drug, and Cosmetic Act)

or

- the subject of this application for which approval is being sought.)


B. The following declaration statement is required if any of the above listed patents have Composition/Formulation or Method of Use claims.

The undersigned declares that the above stated United States Patent Number covers the composition, formulation and/or method of use of (name of drug product). This product is:

- currently approved under section 505 of the Federal Food, Drug, and Cosmetic Act)

or

- the subject of this application for which approval is being sought.)

Signed: 

Title: Patent Attorney

Date: June 26, 2001

Telephone Number: (908) 522-6932

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

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

Mailing address: (US Mail)

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

OR

Location address: (for FedEx deliveries)

U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Division of Data Management and Services
Information Services Team
Building A
HFD-93 Room #235
Nicholson Lane Research Center
5516 Nicholson Lane
Kensington, MD 20895

OR faxed to: (301)-594-6463

* - Please note that patents for unapproved compositions, formulations, or uses will NOT be published in the *The Orange Book*.

g:\...Caro\PATENT SUB (Zometa)

**APPEARS THIS WAY
ON ORIGINAL**

EXCLUSIVITY SUMMARY for NDA # 21-386 SUPPL # _____
Trade Name Zometa Generic Name Zoledronic Acid for injection
Applicant Name Novartis Pharmaceuticals Corporation HFD-150
Approval Date- February 21, 2002

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/___/ NO / X /

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

If yes, what type(SE1, SE2, etc.)? SE6 _____

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 / ___ / NO / X /

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

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 / X / NO / /

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

NDA # 21-223

zoledronic acid.

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 / X /

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: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

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 / X / 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 / /

Literature was submitted to support mechanism of action, etc., but not directly to support the NDA.

- (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: Not applicable

(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 /_X_/

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 # 010

Investigation #2, Study # 011

Investigation #3, Study # 039

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 /_X_/

Investigation #2 YES /___/ NO /_X_/

Investigation #3 YES /___/ NO /_X_/

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 /_X_/

Investigation #2 YES /___/ NO /_X_/

Investigation #3 YES /___/ NO /_X_/

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 #21-386 , Study # _____ 010

Investigation #21-386 , Study # _____ 011

Investigation #21-386 , Study # _____ 039

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 # <u> </u> ES / <u> X </u> / | NO / <u> </u> / Explain: <u> </u> |
| Study # 010 | <u> </u> |
| | <u> </u> |
| Investigation #2 | : |
| IND # <u> </u> YES / <u> </u> / | NO / <u> </u> / Explain: <u> </u> |
| Study # 011 | <u> </u> |
| | <u> </u> |
| Investigation #3 | : |
| IND # <u> </u> YES / <u> </u> / | NO / <u> </u> / Explain: <u> </u> |
| Study # 039 | <u> </u> |
| | <u> </u> |

(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? NA

| | |
|---|--|
| Investigation #1 | : |
| YES / <u> </u> / Explain <u> </u> | NO / <u> </u> / Explain <u> </u> |
| <u> </u> | <u> </u> |
| <u> </u> | <u> </u> |
| 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 /_X_/

If yes, explain: _____

Signature of Preparer

Date

Title: Project Manager

Signature of Office or Division Director

Date

CC:
Archival NDA 21-386
HFD- 150/Division File
HFD-dv /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

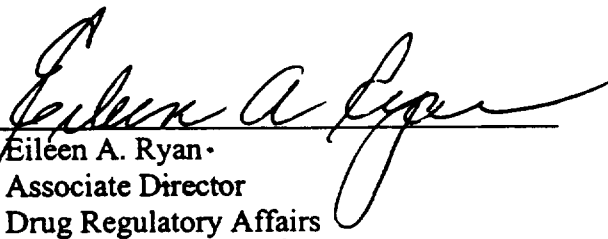
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Drug Regulatory Affairs

Zometa® (zoledronic acid for injection)

NDA-21-386
Type 6 Supplement
Debarment Certification

NOVARTIS PHARMACEUTICALS CORPORATION 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.


Eileen A. Ryan
Associate Director
Drug Regulatory Affairs

Date 7/11/01

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TELECON MEETING MINUTES

MEETING DATE: July 26, 2001 **TIME:** 3:30pm-4pm **LOCATION:** Conference Room A
IND/NDA _____ Meeting Request Submission Date: July 26, 2001 (N165)
Briefing Document Submission Date: July 26, 2001
Additional Submission: July 24, 2001 (N164)

DRUG: zoledronate for injection

SPONSOR/APPLICANT: Novartis Pharmaceuticals Corporation

TYPE of MEETING:

1. Follow-up to an pre-NDA meeting 2-13-01
2. **Proposed Indication:** For : _____

FDA PARTICIPANTS:

Richard Pazdur, Director, Division of Oncology Drug Products (DODP)
Susan Honig, M.D., Medical Reviewer
Ann Staten, RD, Project Manager

INDUSTRY PARTICIPANTS:

John Seaman, Pharm. D., Clin. Team Leader
Eileen Ryan, Drug Reg. Affairs
Bee Chen, Ph.D., Biostat.
David Parkinson, M.D., VP, Clin. Dev.
Dirk Reitsma, M.D., Clin. Team Leader
Greg Burke, M.D., Clinical Development
Mathias Hukkelhoven, M.D., US Head Drug Regulatory Affairs

MEETING OBJECTIVES:

1. To discuss the NDA / sNDA submission.

QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

The sponsor had the following questions about the format of materials to be included in the NDA. The following represents the FDA's responses; these issues were discussed at the teleconference, and comments from the sponsor were incorporated into these comments.

1. The information (i.e., 4 bullets) under ISS comments will be included in the ISS for bone mets, even though not outlined in the ISS table of contents.

FDA: This proposal is acceptable.

July 26, 2001 Meeting minutes
Pre-sNDA

2. SAE's from ~~TIH~~ patients will be in the ISS and presented as narratives but not in the body of the ISS.

FDA: This proposal is acceptable.

3. Please refer to your minutes of the FDA Meeting for question 10. It was agreed that types of cancer should be in the table; HCM was not included. Has this changed?

FDA:

The pre-NDA February 13, 2001 meeting minutes read as follows:

"We have the following comments about the ISS tables:

- **The "Organization of the ISS" in the briefing document, page 18, does not include SAEs from trials in TIH. SAEs from these studies should be provided.**
- **While it is acceptable to pool SAEs by treatment, you should also provide data pooled by treatment and disease type (including type of cancer). The table should be organized by disease type vs. treatment group.**
- **The ISS tables listed in Appendix 5 include the category of "Prior type of therapy: hormonal or chemo" but do not include the type of therapy given at the time of randomization.**
- **Proposed table 3.3-3, Appendix 5 includes antineoplastics given prior to the start of study drug. The purpose of this tabulation is unclear, particularly since only a few chemotherapy drugs are listed."**

Please see the answer to question 6.

4. At the pre-NDA meeting (question 41) it was agreed that full reports for the bone mets studies would be included in the NDA but for the TIH studies only the main body of the report and appendix 1. Are you now requesting full reports for the TIH studies be included in either an original NDA or an sNDA?

FDA: No, we are requesting only the main body and appendix I.

The sponsor agrees to submit the study report and a copy of the protocol. The Division agrees that a submission of the text tables, a lengthy section, is not necessary. We do not need a copy of the blank CRFs for the HCM studies.

- 5.

FDA:

After discussion with the sponsor, we agreed that tables organized according to the criteria listed in question 3 are appropriate. A separate table of renal events for HCM patients should be submitted and it will include information about renal events over time (i.e., number of administered doses). We agreed that because the HCM trials used a 5-minute infusion and the bone metastases trials used a 15-minute infusion, it will be difficult to directly compare toxicity.

7. If Novartis decides to submit an sNDA (i.e., HCM is approved) is the Division requesting that Novartis include in the sNDA the 3 HCM trial reports?

FDA: You are not required to submit the abbreviated form of the HCM trial reports if you submit an sNDA (see answer to question 4). However, it is helpful to the reviewer if they are included in the sNDA submission (expedited access to the summaries, instead of filing a request with a separate FDA document room and awaiting delivery).

8. Please note at the pre-NDA meeting we were planning an original NDA and therefore proposed including study reports from other indications. However, if we now submit an sNDA why would TIH reports be necessary if these studies were already reviewed and approved by another Division?

FDA: Please see answer to question 7.

July 26, 2001 Meeting minutes
Pre-sNDA

The meeting was concluded at 4pm. There were no unresolved issues or discussion points.

Ann Staten, RD Date
Project Manager
Minutes preparer

Concurrence Chair: _____
Susan Flamm Honig, MD Date
Medical Officer

**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/

Ann Staten
7/31/01 04:07:52 PM

Susan Honig
8/1/01 07:38:27 AM

**APPEARS THIS WAY
ON ORIGINAL**

QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

Clinical Pharmacology

1. The pharmacokinetics of ZOMETA[®] (zoledronic acid) will be studied in the following patient populations:

Western population, n = 48 - 54 cancer patients with bone metastases:

- Study 503: An open-label, single intravenous infusion dose study to determine the PK and PD of zoledronic acid in cancer patients with bone metastases (n=36)
- Study 503 extension: PK after multiple administrations of zoledronic acid (in a subgroup of study 503 patients)
- Study 506: Single and multiple dose PK and PD of zoledronic acid in cancer patients with varying degrees of renal function (n=12 - 18 patients)

Asian population, n = 9 cancer patients with bone metastases:

- Study ZOLJ001: Open-label, fixed ascending dose ranging safety trial zoledronic acid in cancer patients with bone metastases.

We believe that these studies are adequate to characterize zoledronic acid's pharmacokinetics and pharmacokinetics/pharmacodynamics relationship and support the intended use for treatment of bone metastases. Do you concur?

FDA Response: The plan appears adequate

[Note: Any claim you make in the labeling for zoledronic acid regarding the clinical pharmacology section should be supported by data.]

2. ZOMETA[®] is not metabolized by and does not inhibit human P450 enzymes. In addition, ZOMETA[®] shows low plasma protein binding.

On the basis of these findings, clinical PK drug-drug interaction studies were not considered necessary. Do you concur?

FDA Response: This is a review issue. Please submit data to support this claim.

3. ZOMETA[®] is cleared from the body exclusively via the renal route. Renal clearance is proportional to creatinine clearance as established in a study of zoledronic acid PK in patients with normal and mild to moderately impaired renal function (Studies 503 and 506). The relationship of zoledronic acid renal clearance with creatinine clearance is similar to that seen for pamidronate, a bisphosphonate not requiring dose adjustment in patients with mild to moderate renal impairment.

We believe that on the basis of these findings, dose adjustments of ZOMETA® in patients with mild or moderate renal impairment are not necessary. Do you concur?

FDA Response: This is a review issue. Please submit Study 506 results with the NDA submission.

4. ADME studies have shown that ZOMETA® is not metabolized. Following intravenous administration of zoledronic acid, no drug was found in the feces, indicating no biliary excretion.

We believe that on the basis of these findings, studies of the pharmacokinetics of the drug in patients with hepatic impairment are not necessary. Do you concur?

FDA Response: Yes.

5. ZOMETA® shows no differences in clearance between Caucasian, Afro-American, and Japanese patients.

We believe that no labelling precautions regarding ethnicity are required. Do you concur?

FDA Response: This is a review issue. Please submit data to support this claim.

6. ZOMETA® show no differences in clearance between male and female patients.

We believe that no labelling precautions regarding gender are required. Do you concur?

FDA Response: This is a review issue. Please submit data to support this claim.

7. ZOMETA® clearance is not affected by body weight or body surface area.

We believe that dose adjustments due to interpatient differences in body weight or body surface are not needed. Do you concur?

FDA Response: This is a review issue. Please submit data to support this claim.

8. ZOMETA® clearance is not affected by age in the range studied, 44 y - 79 y.

We believe that dose adjustments on the basis of age are not needed. Do you concur?

FDA Response: This is a review issue. Please submit data to support this claim.

Clinical and Statistical

9. A complete list of all studies conducted will be provided in the NDA. We will submit Clinical Trial Reports for the studies in patients with Paget's Disease (001, 002), tumor induced hypercalcemia (036, 037, CJ/HC1) and osteoporosis (041). We request a waiver for submission of the data listings. Only SAEs narratives will be included in the ISS. Do you concur?

FDA Response:

- **Yes, we do. Data listings are not necessary for the listed studies.**

10. Please advise us as to the suitability of our ISS tables to facilitate your review. (Please note the ISS tables will be provided along with the briefing document in January 2001.)

FDA Response:

- **We have the following comments about the ISS tables:**
- **The "Organization of the ISS" in the briefing document, page 18, does not include SAEs from trials in TIH. SAEs from these studies should be provided.**
- **While it is acceptable to pool SAEs by treatment, you should also provide data pooled by treatment and disease type (including type of cancer).**
- **The ISS tables listed in Appendix 5 include the category of "Prior type of therapy: hormonal or chemo" but do not include the type of therapy given at the time of randomization.**
- **Proposed table 3.3-3, Appendix 5 includes antineoplastics given prior to the start of study drug. The purpose of this tabulation is unclear, particularly since only a few chemotherapy drugs are listed.**

11. We proposed to exclude clinical study reports and SAEs for skin irritation studies conducted with the transdermal patch formulation (020, 017, 029, 004, 018, and 031). Development of this formulation has been terminated due to skin reactions restricted to the application site and lack of systemic biological activity and no relevant safety data can be provided. Only SAEs will be reported. In addition, in the ISS, we will provide a discussion of injection sites and dermatological observations from all trials. Do you concur?

FDA Response: Yes, we concur.

12. Novartis proposes that narratives be provided in the Integrated Summary of Safety (ISS) for the agreed upon criteria (please refer to questions 34 and 35 for details) for the extensions of studies 10 (breast cancer and multiple myeloma) and 11 (solid tumors other than breast and prostate), and for phase 2 of study 039 (prostate cancer). Do you concur?

FDA Response:

- **See questions 34 and 35. The same criteria for narrative submissions should be used for the primary studies and for their extensions.**

13. For study 506, "The pharmacokinetics and pharmacodynamics of zoledronic acid in cancer patients with varying degrees of renal function", Novartis will have pharmacokinetics data and Serious Adverse Events reports at the time of NDA submission. However, Novartis proposes that the safety data will be provided in the 120

day safety update. Narratives for Serious Adverse Events will be provided in the Integrated Summary of Safety (ISS) for the agreed upon criteria (please refer to questions 34 and 35 for details). Do you concur?

FDA Response:

- **No, we do not. Because renal toxicity has been a major concern with zoledronate and because information about the potential for toxicity in patients with underlying renal insufficiency is important for a risk/benefit assessment, all information should be complete at the time of filing.**

14. Efficacy data from patients at _____

_____. Do you concur?

FDA Response:

- **Please document:**
 - ◆ **How many patients were enrolled at this site, what disease did they have, and what percentage of the study population they represent**
 - ◆ **The nature of the violations of good clinical practice**
- **We will respond to this question after reviewing this information.**
- **What are the results at this site?**
- **Please submit results with and without this site.**

15. Per amendment 6 of Study 010, the success criteria for zoledronate is based on the upper limit of the 90% confidence interval for the difference in proportions between zoledronate 4 mg versus Aredia 90 mg is below +8%. Do you concur?

FDA Response:

- **This is a review issue.**
- **FDA reviews non-inferiority applications using a 95% CI or a one-sided CI of 97.5%.**
- **Any demonstration of efficacy will need to be considered in light of the toxicity of the intervention.**
- **In addition, review of the efficacy in important subsets (such as breast cancer patients treated with hormonal therapy and with chemotherapy) will be considered in the approval process.**

16. For Study 010, a per-protocol analysis will be performed only for the primary efficacy variable (proportion of patients experiencing any SRE, excluding hypercalcemia, during the study). Do you concur?

FDA Response:

- We will consider an intent-to-treat analysis of all randomized patients as the primary analysis. A per-protocol analysis will be considered as a secondary analysis.

17. At Dr. Gleason's site in Arizona, the person who prepared the study drug also performed study evaluation on the patients. Novartis will not exclude this site from the intent-to-treat population of study 039. Novartis will provide a sensitivity analysis of the primary efficacy variable excluding patients of Dr. Gleason. Do you concur?

FDA Response:

- In the situation you have described, the study was, in essence, unblinded at this site. The investigator may have been biased in his referral of patients for additional imaging procedures or for evaluation by radiation oncology colleagues.
- Please document how many patients were entered at this site, and what proportion of the study population they represent.
- Whether these data can be considered in support of the application will be a review issue.
- You should submit analyses of the data with and without patients from this site, you should submit an analysis of this data from this site alone, and the Agency will consider all of these factors in its review.

18. Per amendment 6 of Study 11 and 39, the success criteria for zoledronate in these studies is based on the test of zoledronate 4 mg versus placebo at 0.05 significance level. No adjustment of multiplicity is planned. Do you concur?

FDA Response:

- Yes, we concur. Because _____ was eliminated, adjustment for multiplicity is no longer necessary.

19. Patients who did not have radiographic studies of bone lesions before study entry will be excluded from the analysis of bone disease and overall disease. Do you concur?

FDA Response:

- Please clarify this statement. List how many patients did not have baseline radiographic studies of bone, what malignancies these patients had, and in which studies they were enrolled. How were the efficacy endpoints determined in these patients without baseline documentation of disease?

Sponsor should perform both the intent-to-treat analysis on all randomized patients and their proposed analysis excluding those patients without baseline radiographic studies. At whatever time a lesion is seen, this should be called "progressive disease."

20. Novartis will provide samples of the SAS programs used for the inferential analyses dataset creation at the time of submission. SAS programs for summary analysis will be provided upon request. Do you concur?

FDA Response:

- **We would like to have all SAS codes for efficacy analyses.**

FDA would like all the SAS programs for studies 7, 10, 11, and 39. FDA agreed these could be provided on a CD separate from the NDA electronic submission.

21. IMN terms for adverse events were used during studies for the treatment of bone metastases. Novartis proposes that all terms for these studies will be mapped into MEDDRA terms at the end of the studies for the summary tables and listings of adverse events in the clinical study reports and ISS reports. Do you concur?

FDA Response:

- **Yes, this approach is acceptable.**

22. For the ISS, Novartis proposes two tiers of summary tables and listings. The first tier is the primary safety population and consists of data from well-controlled studies for the treatment of bone metastases Studies 007 (core), 010, 011, and 039. The second tier includes the supportive studies (Studies 003, 003 extension, 007 extension, 035 and 035 extension, IA03, 503 and 503 extension). Do you concur?

FDA Response:

- **Yes, this approach is acceptable.**

23. For analysis of efficacy in the phase 3 studies, patients will be analyzed in the treatment group to which they were randomized (intent-to-treat), regardless of actual treatment received. Do you concur?

FDA Response:

- **Yes, we agree.**

24. For analysis of safety in the phase 3 studies, patients will be analyzed in the treatment group which they actually received. Do you concur?

FDA Response:

- **Yes, we agree.**

25. For analysis of efficacy, patients will be analyzed in the stratum which they were randomized regardless of which stratum the patient actually belongs. For the analysis of safety, patients will be assigned to the stratum which they belong. For protocol 011 stratum will be lung cancer and solid tumors other than prostate and breast cancer. Do

you concur?

FDA Response:

- Yes, we agree.
- For protocol 011, we agree that one stratum should be lung cancer. Were significant numbers of patients with any other type of malignancy enrolled? In previous meetings, you mentioned renal cell carcinoma as a potential stratum.

Renal cell cancer should be one of the strata; thus, there would be lung, renal cell, and other solid tumors.

26. For analysis of the proportion of patients with or without events, including primary efficacy variable, the number of patients in the intent-to-treat population will be the denominator of the ratio. Do you concur?

FDA Response:

- Yes, we concur.

27. For analysis of time to first event, patients who did not have post-randomization observations will be censored at day 0. Do you concur?

FDA Response:

- Yes. However, you should perform a sensitivity analysis that includes these patients, since in the majority of patients the first event was probably symptomatic.

FDA requested that sensitivity analyses be performed in the intent-to-treat population with two methods: by censoring patients on day zero as the sponsor proposes, and by censoring patients on the date of last follow-up, including those who didn't take any medication.

**APPEARS THIS WAY
ON ORIGINAL**

28. For analysis of time to the progression of disease, patients with no cancer at study entry will be excluded from the analysis. Do you concur?

FDA Response:

- Yes, we agree.

29. For analysis of change from baseline, only those patients with both baseline and post-baseline values will be included. Do you concur?

FDA Response:

- Yes, we concur.

30. Health economics data will not be included in this submission. Do you concur?

FDA Response:

- Yes.

31. Font sizes of 9 or 10 will be used for the in-text tables and font size of 9 for the post-text and appendix tables and listings. For the purpose of clarity and convenience of review, a font size of 8 will occasionally be used. Do you concur?

FDA Response:

- The "Guidance for Industry: Providing Regulatory Submissions in Electronic Format—General Considerations" reads as follows: "Resizing a document because the contents are too small to read is inefficient. We believe that Times New Roman, 12-point font, the font used for this document, is adequate in size for reading narrative text. Although sometimes tempting for use in tables and charts, fonts smaller than 12 points should be avoided whenever possible."
- Use of 10-point font for tables and charts submitted as paper copies is acceptable to the reviewer, but use of 8 and 9-point font is not.

All study reports will be in 12 font; most tables will be in 9 or 10, but an occasional table will be in 8 font. All tables in 8 font will also be available electronically.

**APPEARS THIS WAY
ON ORIGINAL**

Case Report Tabulations (CRTs)

32. SAS transport files will be provided for the efficacy and safety data for the well controlled studies (Protocols 007, 010, 011 and 039). These will be provided electronically in accordance with 21 CFR Part 11 and the "Guidance for industry: Providing Regulatory Submissions in Electronic Format - General Considerations" (January 1999) and "Providing Regulatory Submissions in Electronic Format - NDAs" (January 1999). An example format of the SAS Transport files and documentation will be provided in the briefing book in January 2001. Data listings for the core phase of the well controlled studies (Protocols 007, 010, 011, and 039) will be provided in Item 11 of the NDA in pdf format. Do you concur?

FDA Response:

- **Data listings in pdf format are acceptable provided that all efficacy and safety data are available in an electronic database format. Use of SAS transport files is the Agency standard. Please re-read the guidance and ask if you have additional questions—you have had difficulty with the electronic format for other recent submissions to the Division.**

Novartis will use version 5 for the export files, which worked at FDA last time. All unscheduled lab values will be included – everything Novartis knows about each patient will be submitted.

Narratives and Case Report Forms (CRFs)

33. Novartis proposes to provide Case Report Forms electronically in accordance with 21 CFR Part 11 and the "Guidance for industry: Providing Regulatory Submissions in Electronic Format - General Considerations" (January 1999) and "Providing Regulatory Submissions in Electronic Format - NDAs" (January 1999). Do you concur?

FDA Response:

- **Yes, we do.**

34. Novartis proposes that narratives and case report forms not be provided for the control arms (placebo, pamidronate) in the well-controlled studies (10, 11 and 39). Narratives and case report forms will be provided for the Zometa® arms only. Do you concur?

FDA Response:

- **No. Narratives and CRFs should be provided for control patients with renal events.**
- **For the sites that DSI selects to inspect (domestic and/or foreign), narratives (for SAEs, premature withdrawals, deaths) and CRFs for all subjects in ALL treatment arms at these sites selected should be provided.**

- Please refer to the attached document for the data DSI requests.

FDA to get back to Novartis re: which CRFs and narratives we would like submitted with the original NDA, with the understanding that others could be provided within a reasonable timeframe of the request.

35. Novartis proposes that narratives and case report forms will be provided for the following categories of events in the well-controlled studies (10, 11 and 39):

a) All elevations of serum creatinine that meet the Renal Advisory Board criteria as significantly elevated, whether or not study drug related, as follows:

- For patients with a baseline serum creatinine < 1.4 mg/dL, an increase of 0.5 mg/dL above baseline,
- For patients with a baseline serum creatinine \geq 1.4 mg/dL, an increase of 1.0 mg/dL above baseline, or
- Any doubling of the baseline serum creatinine.

b) Renal Adverse Events and Serious Renal Adverse Events, whether or not study drug related, meeting the "all terms" criteria from the Renal Board for deterioration of renal function (see list below).

- | | |
|---|---------------------------|
| • Anuria | • Oliguria |
| • Bladder Retention | • Proteinuria |
| • Creatinine blood increased | • Pyelonephritis |
| • Hematuria | • Renal calculus |
| • Hydronephrosis | • Renal failure acute |
| • Hyperuricemia | • Renal function abnormal |
| • Micturition frequency | • Renal insufficiency |
| • Nephritis | • Renal tubular disorder |
| • Nephrolithiasis | • Tumor lysis syndrome |
| • Nephropathy toxic | • Uremia |
| • Nephrotic syndrome | • Urinary retention |
| • Obstructive uropathy, urethral obstruction or urethral disorder | • |

c) All arrhythmia serious adverse events, whether or not study drug related.

d) All ophthalmologic serious adverse events, whether or not study drug related.

- e) All study drug related serious adverse events.
- f) All study drug related notable laboratory abnormalities (Grade 4).
- g) Deaths, if other than from disease progression. Narratives and case report forms will not be provided for those patients that in the judgment of the Novartis Medical Expert expired from either the underlying disease or a complication of the underlying disease, even if the investigator did not specifically note disease progression as the cause of death.

Do you concur?

FDA Response:

- Narratives and CRFs should be provided for all patients with serious adverse events and grade 3-4 laboratory abnormalities, whether or not they are judged to be drug-related.
- Additional narratives and CRFs may be requested by the Division as needed during the NDA review.

FDA to get back to Novartis re: which CRFs and narratives we would like submitted with the original NDA, with the understanding that others could be provided within a reasonable timeframe of the request.

Labeling

36. We have conducted trials to treat bone metastases in patients with osteoblastic, osteolytic and mixed bone metastases across numerous tumor types. We believe that we therefore can apply for _____ . Do you concur?

FDA Response:

- You may do so, if efficacy has been demonstrated in all 3 studies.
- The exact wording of the final indication, if zoledronate is approved, will depend on the results of the FDA review. Considerations will include the types and numbers of cancers studied, the number of patients with representative malignancies, and efficacy trends in subset analyses by cancer type.

Financial Disclosure

37. We propose to submit the appropriate Financial Disclosure certification in accordance with the Final Rule published in the December 31, 1998 Federal Register for all investigators who enrolled patients in Studies 007, 010, 011 and 039. These studies are the basis for establishing the safety and efficacy of zoledronate for the proposed indication. Do you concur?

FDA Response:

- Yes, we concur.

Priority Review

38. Zometa® may provide _____ (010). It may also provide superior treatment over placebo in treatment of bone metastases (011, 039). We believe either of these effects will represent clinically relevant advantage over existing treatment and therefore warrants a priority review. Do you concur?

FDA Response:

- _____
- **Superiority of zoledronate to pamidronate does not automatically warrant priority review status, given the reported renal toxicity of zoledronate.**
- **Whether efficacy in reducing skeletal morbidity in patients with osteoblastic metastases or in patients with non-breast non-prostate malignancies, in light of the reported renal toxicity of zoledronate, warrants a priority review will be determined after the NDA is submitted at the 45-day filing meeting.**

Cross-reference

39. An NDA for Zometa® in the indication of treatment of tumor-induced hypercalcemia, was submitted to the Division of Metabolic and Endocrine Drug Products (HFD-510) on December 21, 1999 (NDA 21-223). This application was determined by the FDA to be approvable on September 21, 2000. We propose to cross-reference Item 4 (CMC) and Item 5 (Nonclinical Pharmacology and Toxicology) of this NDA to NDA 21-223, HFD-510. Do you concur?

FDA Response:

- **Yes, we do.**

Pediatric Labeling

40. In accordance with 21 CFR 314.55 we hereby request a full waiver of the requirements for submission of data that are adequate to assess the safety and effectiveness of Zometa® for the claimed indication of treatment of bone metastases in all relevant pediatric subpopulations. Do you concur?

FDA Response:

- **Yes, we do. The malignancies studied in the adult populations do not exist in children. Also, biphosphonates, agents with avid uptake and retention in the skeleton, would require different safety considerations prior to administration to children.**

New Question:

41. Novartis proposes to *only* submit full study reports for the core studies 007, 010, 011 and 039. Studies in Paget's disease: 001, 002; TIH: CJ/HC1, 036, 037; postmenopausal osteoporosis: 041 will have the main body of the full study report and appendix 1 (Protocol, sample CRFs and informed consent). Do you concur?

FDA Response:

- **Your proposal is acceptable. However, the ISS should include a detailed analysis of renal events in all clinical trials.**

Additional FDA Comments regarding the Pediatric Final Rule and Exclusivity:

- Final Rule – Under 21 CFR 314.55(c), you will be eligible for a waiver since the indication under discussion does not apply to pediatric populations.
- Exclusivity – Under the Food and Drug Administration Modernization Act, you have the opportunity for an exclusivity extension if zoledronate is appropriate for an indication in pediatrics. If you choose to pursue pediatric exclusivity, your plans for a pediatric drug development, in the form of a Proposed Pediatric Study Requirement (PPSR), should be submitted so that we can consider issuing a Written Request.

Please refer to the "Guidance for Industry: Qualifying for Pediatric Exclusivity Under Section 505 A of the Federal Food, Drug and Cosmetic Act".

Additional Comments during Telecon:

1. *FDA inquired if Novartis would be interest in direct E-Mail to the primary reviewers. It was agreed Novartis would pursue this through the secure E-Mail program and that all communications would copy Ann Staten and Eileen Ryan.*
2. *Dr. Honig would like to be able to electronically search the database for subset such as creatinine values within a certain range. Novartis said that this could be done with the database as proposed, but they will confirm this with their statisticians and data managers. Dr. Honig will provide Novartis with a list of other parameters on which she is likely to want to search the database.*

ACTION ITEMS:

1. FDA to provide Novartis with a list of which CRFs and narratives we would like submitted in the original NDA. (Completed. See FDA facsimile dated 2-22-01)

Step I: **Please send DSI the following data, preferably at the time the NDA is submitted to the review division.**

- ◆ NDA number, commercial and generic name of the drug product, chemical classification (whether new molecular entity or not), pharmacologic class (e.g., antiarrhythmic agent), and the indication(s) sought
- ◆ Sponsor's submission date, expected filing meeting date and expected user fee goal date
- ◆ Mention whether the review is standard or priority
- ◆ A copy of Volume 1.1 of NDA
- ◆ Name and phone number of sponsor's contact person for the NDA
- ◆ General list of reportable AEs
- ◆ List of pivotal studies considered "critical" for this NDA. For each pivotal study (include all indications):
 - ◆ Protocol number(s) and title(s)
 - ◆ Copies of protocol(s) and amendments
 - ◆ Blank CRFs
 - ◆ Copy of unsigned consent form
 - ◆ Names and addresses of monitoring organization(s) (e.g., CRO, sponsor's monitoring team) in these pivotal studies
 - ◆ Description of the primary efficacy endpoint(s) considered "critical" for the pivotal protocol study
 - ◆ List of study sites (domestic and/or foreign) for each pivotal study preferably presented in a table, providing the following information for each study site:
 - ◆ name(s) of investigator(s)
 - ◆ addresses
 - ◆ number of subjects enrolled in each study arm
 - ◆ number of evaluable subjects
 - ◆ number of reportable AEs
 - ◆ number of SAEs including deaths
 - ◆ number of premature withdrawals
 - ◆ number of protocol violations
 - ◆ descriptive statistics of primary efficacy parameters (e.g., mean, SD, median, mean change from baseline, etc., or if the endpoint is non-parametric, number of deaths, number of responders, etc.)

Please send a copy of the cover letter, which lists all of the above data sent to DSI, to the application file.

Step II: DSI has determined that some or all of the (US and/or foreign) sites in the attached list may require FDA inspection. Please send DSI the following site-specific data.

For each U.S. site selected for inspection please send the following data:

- Address and phone number of the site
- Investigator's 1572
- List of investigator(s) and sub-investigators on 1572, and their c.v.
- Protocol and amendments approved for the site
- Sample blank CRF and case report data tabulations for the site with coding key
- Copies of completed CRFs of all (or selected number of) subjects enrolled
- Randomization list for the site
 - Total number of subjects entered in each study arm
 - The number of drop outs/discontinued subjects, identified by the subjects' study numbers for the site, together with the reasons for each dropout/discontinuation
 - List by the subject's study numbers all evaluable / inevaluable subjects
 - List by the subject's study numbers all reportable AEs, SAEs and deaths with a narrative for all SAEs and deaths
 - List of protocol violations and protocol deviations for the site
 - Results (by site) of the "critical" primary efficacy parameters (with descriptive statistics: mean, SD, median, range at baseline and at endpoint, or change from baseline at endpoint, etc., or if the endpoint is non-parametric, number of deaths, number of responders, etc.)
 - Data listing of the efficacy endpoint data for each subject for each of the centers
 - IRB names (and SOPs)
 - Names of monitors and monitoring logs

For foreign sites selected for inspection, please send additional data as follows:

- ◆ Name, phone number, fax number and address of contact person from the sponsor
- ◆ List of hotels near the site(s) to be inspected, room rates, etc.
- ◆ Written confirmation by the sponsor of the dates of inspection including names of FDA personnel involved.
- ◆ Written assurance from the sponsor (i.e., sponsor's authorized representative within the US) of free access to the records, right to make copies of needed documents.
- ◆ Availability of Xerox machine in the inspection workroom or in immediate vicinity for our unrestricted use.
- ◆ Sponsor provides a translator who is not affiliated with the sponsor or the study and is acceptable to FDA
- ◆ Additional equipment as needed for the inspection (i.e., X-ray viewer in the room, microscope to evaluate slides, etc.)
- ◆ Someone representing the sponsor should be at site to delete subject identifiers from copied documents (i.e., names, hospital number, etc.)
- ◆ The local equivalent to the PDR should be available in the workroom for FDA use during the inspection.
- ◆ A list of subjects' names, study numbers, hospital identifiers, and drug treatment groups should be available for FDA use during the inspection. This list will remain in the (secure) inspection workroom, must not be copied, and must be returned to the clinical investigator at the conclusion of the inspection (important to protect confidentiality).
- ◆ All source documents including hospital charts and laboratory reports (e.g., biopsy reports, X-rays, ECGs, ultrasonograms, CT scans and reports, biopsy slides, etc.) related to the study should be available in the workroom for FDA review for the duration of the inspection.
- ◆ All CRFs, consent forms, IRB approvals, pharmacy records, drug accountability records, and correspondences related to the study should be available in the workroom for FDA review for the duration of the inspection.

Sample table of data to be presented in list of study sites submitted to DSI

| Site # | C.I. Name/Address | # enrolled in each treatment arm | # evaluable | # reportable AEs | # SAEs and deaths | # Premature withdrawals | # Protocol violations | Primary efficacy data (non-parametric) |
|--------|---|---|-------------|------------------|-------------------|-------------------------|-----------------------|---|
| 007 | Icure Mypatient, MD 123 Research Blvd, Anytown, ZA98765 | Treatment A = 35 Treatment B = 34 Treatment C = 37 Total = 106 | 100 | 12 | 4 | 4 | 2 | Number with disease progression: Treatment A = 5 Treatment B = 4 Treatment C = 9 Total = 18 |
| | | | | | | | | |
| | | | | | | | | |

**APPEARS THIS WAY
ON ORIGINAL**

/s/

Ann Staten

2/28/01 12:54:05 PM

Susan Honig

2/28/01 02:23:05 PM

Dotti Pease

2/28/01 02:18:06 PM

APPEARS THIS WAY
ON ORIGINAL

Fax



DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Ellen Cutler From: Ann Staten, Project Manager

Fax: 973-781-8325 Fax: 301-827-4500

Phone: 973-781-8180 Phone: 301-594-5770

Pages: ~~2~~ 20/47 Date: May 4, 1999

Re: Zoledronate (CGP 42446) for injection; serial no. 017, letter dated January 21, 1999

- Urgent
- For Review
- Please Comment
- Please Reply
- Please Recycle

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• Comments:

Ellen,

Please find attached a copy of the final meeting minutes for the EOP2 meeting for zoledronate.

Please call if you have any questions.

Sincerely,

is
Ann

APPEARS THIS WAY
ON ORIGINAL

MEETING MINUTES

MEETING DATE: April 13, 1999 **TIME:** 2:30pm-4pm **LOCATION:** Conference Room G

IND/NDA

Meeting Request Submission Date: January 21, 1999
Briefing Document Submission Date: March 9, 1999

DRUG: zoledronate for injection

SPONSOR/APPLICANT: Novartis Pharmaceuticals Corporation

TYPE of MEETING:

1. End of Phase 2
2. **Proposed Indication:** For prevention of bone metastases in patients with breast and prostate cancer.

FDA PARTICIPANTS:

Rachel Behrman, MD, MPH, Office Deputy Director, Office of Drug Evaluation I (ODEI)
 Robert Justice, M.D., Acting Director, Division of Oncology Drug Products (DODP)
 Julie Beitz, M.D., Acting Deputy Director, Division of Oncology Drug Products (DODP)
 Susan Honig, M.D., Medical Reviewer
 Grant Williams, M.D., Medical Team Leader
 Paul Andrews, Ph.D., Pharmacology/ Toxicology Team Leader (internal meeting only)
 Wendy Schmidt, Ph.D., Acting Pharmacology/ Toxicology Team Leader (industry meeting only)
 Hua Zheng, Ph.D., Pharmacology/Toxicology Reviewer (internal meeting only)
 Ann Staton, RD, Project Manager
 Gang Chen, Ph.D., Biometrics Team Leader
 Ning Li, Ph.D., Biometrics Reviewer
 Lydia Kieffer, Pharm.D., Clinical Pharmacology and Biopharmaceutics Reviewer (internal meeting only)
 Atiqur Rahman, Ph.D., Clinical Pharmacology and Biopharmaceutics Team Leader (industry meeting only)
 Patty Delaney, Cancer Liaison Program, Office of the Commissioner (industry meeting only)
 George Siedga, M.D., ODAC consultant (internal meeting only)

INDUSTRY PARTICIPANTS:

Bee-Lian Chen, Ph.D., Biostatistics
 Ellen Cutler, Regulatory Affairs
 Andrea Kay, M.D., Clinical Research
 Robert Knight, M.D., Clinical Research
 Beatrice Oberle-Roth, Ph.D., Regulatory Affairs
 Sharon Olmstead, Regulatory Liaison
 Horst Schran, Ph.D., Clinical Pharmacology

MEETING OBJECTIVES:

1. To discuss the proposal for a program to develop zoledronate to prevent bone metastases in patient with breast and prostate cancer.

QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:**Preclinical**

1. On the basis of the preclinical and clinical safety and efficacy data, are trials in the proposed patient populations acceptable in light of the unmet clinical need?

FDA Response:

We are not certain what you are asking.

- Regardless of whether zoledronate provides an unmet clinical need, the preclinical studies and clinical data to date support the dose, schedule, and duration of the proposed trials.
- If your intended indication(s) for an NDA includes adjuvant treatment of patients believed to be disease free, then carcinogenicity studies are likely to be needed to support the NDA.
- Based on the wording of your question, we believe you may desire fast track designation. If this is your intent, a formal request should be made after protocol revisions are complete.
- You should be aware that these trials are not designed to demonstrate clinical benefit in the affected population. It is not clear whether biphosphonate treatment designed to delay bone metastases in a large group of early stage breast cancer patients provides clinical benefit compared to biphosphonate treatment initiated at diagnosis of bone metastases. You will need to demonstrate that prophylactic treatment with zoledronate results in less skeletal-related morbidity and greater patient benefit than treating established bone metastases with zoledronate.
- The proposed trial could be modified to test this hypothesis: after the initial randomization to zoledronate versus placebo, the protocol could specify the use of open-label zoledronate when bone metastases are diagnosed and this would support full approval.
- The Medical Officer's comments from the Phase 3 protocol review (trial 0701) will be attached to your copy of the meeting minutes.

Novartis Response:**Regarding bullet #1:**

- The carcinogenicity study has been completed and will be submitted in December to the Division of Metabolic and Endocrine Drug Products.

Regarding bullet #4:

- Novartis shared their overheads (see attachment 1)

FDA Response:**Regarding bullet #4:**

- The bone metastases-free survival endpoint could serve as an adequate surrogate for accelerated approval.
- Endpoints supporting full approval could be improvements in survival and bone-morbidity.

Breast Cancer Studies

2. Given the available literature for bone sialoprotein (BSP) in breast cancer, Novartis has selected BSP as the surrogate marker to enrich the pivotal trial (0701) for patients at high risk of developing bone metastases. With the validation of BSP as a prognostic indicator for the development of bone metastases in breast cancer, is the proposed population acceptable for evaluation in the adjuvant setting?

FDA Response:

- It is acceptable to use elevated BSP levels in order to attempt to enrich the protocol for women at high risk for bone metastases.
- The indication will be limited to the population studied, i.e., patients with BSP levels ≥ 24 ng/ml. We are concerned about the generalizability of the study.
- We are concerned about the accuracy of the sample size estimation and the power calculations, which are based on the assumption that an elevated BSP level is correlated with both the subsequent development of bone metastases and with bone metastases-free survival.

Novartis Response:**Regarding bullet #3- Novartis shared an overhead (see attachment 2)**

- The predictive value of BSP will be examined in banked sera from patients with follow-up data before the proposed trial is initiated.
3. Overall survival will be a secondary endpoint in the 0701 trial. Given the size of the trial, zoledronate therapy is not expected to provide a statistically significant improvement in the overall survival of adjuvant breast cancer patients. It is likely that zoledronate will delay the occurrence of bone metastases (≥ 12 months). Performance status could be maintained by reducing the disability and symptoms associated with bone metastases. The maintenance of QOL and performance status is supported by trials with pamidronate in patients with lytic bone metastases from breast cancer and myeloma (Hortobagyi, Berenson, and Therisult). Is the primary efficacy endpoint, bone metastasis-free survival, an acceptable endpoint in this proposed adjuvant breast cancer trial?

FDA Response:

Not for traditional approval.

- See question #1 regarding the need to demonstrate clinical benefit
 - Time to development of bone metastases could be a useful secondary endpoint. Bone metastases-free survival is currently defined as the time to death from any cause or the time to the development of bone metastases. This definition creates a composite endpoint. The endpoint should be re-defined as the time to the development of bone metastases; deaths should be censored. If the endpoint is redefined, it could serve as a basis for accelerated approval.
 - Patients should be followed for overall survival and bone morbidity.
 - See Phase 3 protocol review for additional comments
4. The definition of events in the 0701 trial includes death from any cause, recurrent breast cancer (loco-regional or metastatic disease), and any new cancer (except non-melanomatous skin cancer, carcinoma in situ of the uterine cervix, and lobular carcinoma in situ); is this acceptable?

FDA Response:

- Yes, with the following comments:
 - Patients with an in-breast recurrence (IBTR) can be treated with mastectomy and have survivals that are similar to patients treated with initial mastectomy. An in-breast recurrence does not alter survival, although it may be a predictive factor for subsequent systemic relapse. Removing these patients from the study might affect the trial results: patients may still develop an in-breast recurrence (if zoledronate has no effect in the breast), but might have a decreased rate of bone metastases due to continued zoledronate therapy. You may wish to include them and perform several analyses, one with all randomized patients and one without patients with IBTR or patients with IBTR alone.
 - All randomized patients, without counting IBTR as an event, should be included in the primary analysis.
5. Is the IVRS (details in appendix 5) used in the randomization for 0701 with skipping randomization number for institutional balancing acceptable?

FDA Response:

- Please specify how the block size will be determined (random or fixed). If the number of skipping is relatively small, the skipping should have little effect on the randomization. However, it will be problematic if the number of skipping is larger. The sponsor needs to justify the procedure (by simulation or literature) in the latter case.

- Because there is some evidence that taxanes provide a survival benefit when given with anthracycline-based adjuvant chemotherapy, we recommend that you add a stratum for chemotherapy with or without a taxane.

Novartis Response:**Regarding bullet #1**

- Blocksize will be determined as fixed.

Regarding bullet #2

- Novartis shared overhead (see attachment 3)

FDA Response:

- The proposal is acceptable (re: attachment 3)
- Please submit the "audit trail" for randomization.

6. Is 0701 acceptable to support registration and labeling of zoledronate for the following indication: Zoledronate is indicated for the prevention of bone metastases in patients with primary breast cancer and a serum BSP greater than or equal to 24 ng/mL.

FDA Response:

- See question #1 regarding the need to demonstrate clinical benefit
- It is unlikely that the indication will be "prevention" of "X". "Reduction in the incidence 'X' " or "delay of 'X'" will probably describe the results of a positive trial more accurately. The indication would also need to specify the stage of disease of women in the trial (i.e., Stage I, II, and IIIA as written).
- A confirmatory trial will likely be required. However, a positive result from study 0704 or from treatment trials may suffice as confirmatory evidence (see guidances "Providing clinical evidence of effectiveness for human drug and biologic products" and "FDA approval of new cancer treatment uses for marketed drug and biologic products").

7. Is a statistically significant result in bone mineral density favoring the zoledronate arm sufficient to support the claim of relevant clinical benefit in the adjuvant breast population?

FDA Response:

- No, this claim requires a formal osteoporosis study performed in accordance with the standards in effect in HFD-510, the Division of Metabolic and Endocrine drugs.

Prostate Cancer Studies

8. In order to evaluate zoledronate in a prostate cancer population at high-risk of developing bone metastases, Novartis has selected an androgen-independent population without radiologically evident metastases. Is this proposed population acceptable?

FDA Response:

- While PSA is not an accepted surrogate endpoint for efficacy evaluations, serial rising PSA values have been associated with an increased risk of relapse or progression. It is acceptable to use this criterion to enrich the study with patients at high risk of developing bone metastases.
- We would not accept a rising PSA alone as evidence of "androgen independent" disease.

Novartis Response:

- See re-defined population as defined per overhead (see attachment #4)

9. Similar to the breast cancer patients, delaying the onset of bone metastases may be clinically relevant for prostate cancer patients. Is the primary efficacy endpoint, bone metastases-free survival, an acceptable endpoint in the proposed prostate cancer trial?

FDA Response:

- Prostate cancer patients with a rising PSA nearly always develop metastatic disease, but after variable lengths of follow-up. It is not clear that delaying bone scan positivity in asymptomatic patients provides clinical benefit compared to a "watch and wait" approach. You will need to demonstrate that prophylactic treatment with zoledronate results in less skeletal-related morbidity and greater patient benefit than treating established bone metastases with zoledronate. The proposed trial could be modified to test this hypothesis: after the initial randomization to zoledronate versus placebo, the protocol could specify the use of open-label zoledronate when bone metastases are diagnosed.
- Time to development of bone metastases could be a useful secondary endpoint. Bone metastases-free survival is currently defined as the time to death from any cause or the time to the development of bone metastases. This definition creates a composite endpoint. The endpoint should be re-defined as the time to the development of bone metastases; deaths should be censored.
- See comments regarding accelerated approval.

10. Is 0704 acceptable to support the registration and labeling of zoledronate for the following indication: Zoledronate is indicated for the prevention of bone metastases in patients with androgen-independent prostate cancer who do not have radiologically evident metastases?

FDA Response:

- See question #1 regarding the need to demonstrate clinical benefit
 - It is unlikely that the indication will be "prevention" of "X". "Reduction in the incidence 'X' " or "delay of 'X'" will probably describe the results of a positive trial more accurately. The indication would also need to specify the stage of disease of women in the trial (i.e., Stage I, II, and IIIA as written).
 - A confirmatory trial will likely be required. However, a positive result from study 0701 or from treatment trials may suffice as confirmatory evidence (see guidances "Providing clinical evidence of effectiveness for human drug and biologic products" and "FDA approval of new cancer treatment uses for marketed drug and biologic products").
11. Are the following stratification variables in 0704 acceptable:
- a. Type of concomitant therapy, either chemotherapy-based or further hormonal manipulations (but not withdrawal of peripheral androgen blockade, i.e. "flutamide withdrawal")
 - b. Interval between initial diagnosis of prostate cancer and enrollment in the 0704 trial less than or equal to two years and/or failure of anti-androgen therapy within six months of starting it?

FDA Response:

- It will be important to control for androgen withdrawal effect, either by stratification or by waiting a prospectively determined amount of time after stopping androgen therapy, to avoid imbalance between treatment arms.
 - Duration of hormone response is an important prognostic factor
 - Performance status, the most important factor, has been addressed, as patients must have a Karnofsky PS \geq 90% for study entry
12. Is a statistically significant result in bone mineral density favoring the zoledronate arm sufficient to support the claim of relevant clinical benefit in the androgen-independent prostate population?

FDA Response:

- No, it is not. Loss of bone mineral density has not been shown to be associated with symptoms, morbidity, or mortality in this population.

General

13. Bisphosphonate treatment significantly suppresses the serum bone alkaline phosphatase. A central laboratory will be used in studies 0701 and 0704 and the serum alkaline phosphatases will remain blinded unless they are elevated two or more times the upper

limit of normal. However, an individual site may unblind a patient by performing a serum alkaline phosphatase. Does the FDA view this as a problem?

FDA Response:

- The study is strengthened by the double-blind design and maintaining the blind is desirable. However, a clinical investigator always has the option to obtain any laboratory test necessary for the care of the patient, and it is not possible to prevent investigators from unblinding patients in this fashion. Investigators should be encouraged to comply with the protocol as much as possible. Specific descriptions of this potential bias in the protocol may help to increase compliance.
- We recommend that you not evaluate alkaline phosphatase unless the liver enzymes are elevated.

FDA Clinical Pharmacology and Biopharmaceutics comments:

- You have submitted a protocol (submission 019, dated February 1, 1999) to evaluate PK and PD of zoledronate in patients with bone metastases. You will be required to submit assay methodology validation with the final study report.
- You should provide a Clinical Pharmacology and Biopharmaceutics development plan for zoledronate.

Novartis Response:

- Novartis concurs with bullet #1.
- Regarding bullet #2, Novartis will provide an overview development plan for FDA review and comment.

Additional FDA Comments regarding the Pediatric Final Rule and Exclusivity:

- Final Rule - Under 21 CFR 314.55(c), you will be eligible for a waiver since the two indications under discussion do not apply to pediatric populations.
- Exclusivity - Under the Food and Drug Administration Modernization Act, you have the opportunity for an exclusivity extension if zoledronate is appropriate for an indication in pediatrics. If you choose to pursue pediatric exclusivity, your plans for a pediatric drug development, in the form of a Proposed Pediatric Study Requirement (PPSR), should be submitted so that we can consider issuing a Written Request.