

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-080

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

**PATENT INFORMATION SUBMITTED WITH THE
FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**
*For Each Patent That Claims a Drug Substance
(Active Ingredient), Drug Product (Formulation and
Composition) and/or Method of Use*

NDA NUMBER

22-080

NAME OF APPLICANT / NDA HOLDER

Novartis Pharmaceuticals Corporation

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)

RECLAST

ACTIVE INGREDIENT(S)

Zoledronic acid

STRENGTH(S)

5 mg in 100 ml solution

DOSAGE FORM

Injectable, IV (Infusion)

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number

4,939,130

b. Issue Date of Patent

07/03/1990

c. Expiration Date of Patent

09/02/2012

d. Name of Patent Owner

Novartis AG

Address (of Patent Owner)

Lichtstrasse 35

City/State

CH-4056 Basel, Switzerland

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.96 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)



General Counsel

Novartis Pharmaceuticals Corporation

Address (of agent or representative named in 1.e.)

One Health Plaza

City/State

East Hanover, NJ

ZIP Code

07936

FAX Number (if available)

Telephone Number

(862) 778-8300

E-Mail Address (if available)

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No

2.6 Does the patent claim only an intermediate? Yes No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No

3.2 Does the patent claim only an intermediate? Yes No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2 Claim Number (as listed in the patent) 5 Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)
Treatment of Osteoporosis

5. No Relevant Patents

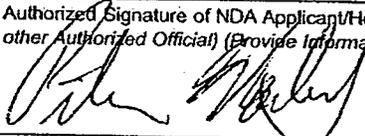
For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

6. Declaration Certification

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide information below)



Date Signed

09/13/2006

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

Peter J. Waibel

Address

One Health Plaza

City/State

East Hanover, NJ

ZIP Code

07936

Telephone Number

(862) 778-7951

FAX Number (if available)

E-Mail Address (if available)

The public reporting burden for this collection of information has been estimated to average 9 hours 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:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

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.

INFORMATION AND INSTRUCTIONS FOR FORM 3542a
PATENT INFORMATION SUBMITTED WITH THE FILING
OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplemental approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book Publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. An additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of July 2003) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: <http://forms.psc.gov/forms/fdahtml/fdahtm.html>.

First Section

Complete all items in this section.

I. General Section

Complete all items in this section with reference to the patent itself.

- 1c) Include patent expiration date, including any Hatch-Waxman patent extension already granted. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.
- 1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

- 1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

- 2.4) Name the polymorphic form of the drug identified by the patent.
- 2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.
- 2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

- 3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement.

- 4.2) Identify by number each claim in the patent that claims the use(s) of the drug for which approval is being sought. Indicate whether or not each individual claim is a claim for a method(s) of use of the drug for which approval is being sought.
- 4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

- 6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

**PATENT INFORMATION SUBMITTED WITH THE
FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**
*For Each Patent That Claims a Drug Substance
(Active Ingredient), Drug Product (Formulation and
Composition) and/or Method of Use*

NDA NUMBER

22-080

NAME OF APPLICANT / NDA HOLDER

Novartis Pharmaceuticals Corporation

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)

RECLAST

ACTIVE INGREDIENT(S)

Zoledronic acid

STRENGTH(S)

5 mg in 100 ml solution

DOSAGE FORM

Injectable, IV (Infusion)

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

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FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number

4,777,163

b. Issue Date of Patent

10/11/1988

c. Expiration Date of Patent

07/24/2007

d. Name of Patent Owner

Boehringer Mannheim GmbH (Roche Holding, AG)

Address (of Patent Owner)

Sandhofer Strasse 112-132, Postfach 31 01 20

City/State

68305 - Mannheim, Germany

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address (of agent or representative named in 1.e.)

One Health Plaza

City/State

East Hanover, NJ

ZIP Code

07936

FAX Number (if available)

Telephone Number

(862) 778-8300

E-Mail Address (if available)



General Counsel

Novartis Pharmaceuticals Corporation

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No

2.6 Does the patent claim only an intermediate? Yes No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No

3.2 Does the patent claim only an intermediate? Yes No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2 Claim Number (as listed in the patent) 17, 19, 20, and 21 Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)
Treatment of osteoporosis

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

6. Declaration Certification

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide information below)

Date Signed

09/13/2006

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

Peter J. Waibel

Address

One Health Plaza

City/State

East Hanover, NJ

ZIP Code

07936

Telephone Number

(862) 778-7951

FAX Number (if available)

E-Mail Address (if available)

The public reporting burden for this collection of information has been estimated to average 9 hours 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:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

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.

INFORMATION AND INSTRUCTIONS FOR FORM 3542a

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplemental approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book Publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. An additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of July 2003) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: <http://forms.psc.gov/forms/fdahtm/fdahtm.html>.

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

- 1c) Include patent expiration date, including any Hatch-Waxman patent extension already granted. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.
- 1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

- 1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

- 2.4) Name the polymorphic form of the drug identified by the patent.
- 2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.
- 2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

- 3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement.

- 4.2) Identify by number each claim in the patent that claims the use(s) of the drug for which approval is being sought. Indicate whether or not each individual claim is a claim for a method(s) of use of the drug for which approval is being sought.
- 4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

- 6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

EXCLUSIVITY SUMMARY

NDA # 22-080

SUPPL # N/A

HFD # 510

Trade Name Reclast

Generic Name zoledronic acid

Applicant Name Novartis Pharmaceuticals, Inc.

Approval Date, If Known August 17, 2007

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy 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 a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(1)

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 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

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

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

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

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (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

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

NDA# 21-223 Zometa (zoledronic acid) Injection
NDA# 21-386 Zometa (zoledronic acid) Injection
NDA# 21-817 Reclast (zoledronic acid) Injection

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 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs 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 NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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.

(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 8:

(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:

Study ZOL446H2301

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

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

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

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

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

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"):

Study ZOL446H2301

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 # 43,240 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:

Name of person completing form: Julie Marchick

Title: Regulatory Project Manager

Date: August 17, 2007

Name of Office/Division Director signing form: Mary Parks, M.D.

Title: Director, Division of Metabolism and Endocrinology Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

Theresa Kehoe
8/20/2007 04:19:51 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 22-080 Supplement Type (e.g. SE5): N/A Supplement Number: N/A

Stamp Date: October 17, 2006 PDUFA Goal Date: August 17, 2007

HFD-510 Trade and generic names/dosage form: Reclast (zoledronic acid) Injection

Applicant: Novartis Pharmaceuticals, Inc. Therapeutic Class: Bone/Calcium-Phosphorous Metabolism

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? *

- Yes. Please proceed to the next question.
 No. PREA does not apply. Skip to signature block.

* SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.

Indication(s) previously approved (please complete this section for supplements only): Treatment of Paget's disease of bone

Each indication covered by current application under review must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: Treatment of postmenopausal osteoporosis

Is this an orphan indication?

- Yes. PREA does not apply. Skip to signature block.
 No. Please proceed to the next question.

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
 No: Please check all that apply: Partial Waiver Deferred Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
 Disease/condition does not exist in children
 Too few children with disease to study
 There are safety concerns
 Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

NDA 22-080

Page 3

This page was completed by:

Julie Marchick, MPH

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 10/10/2006)

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/

Julie Marchick

8/8/2007 02:42:26 PM

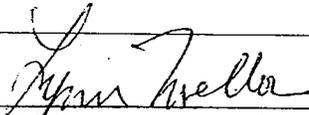
Drug Regulatory Affairs

Reclast[®] (zoledronic acid) Injection

NDA 22-080

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.


Lynn Mellor
Director
Drug Regulatory Affairs

Date Sept 8, 2006

Property of Novartis Pharmaceuticals Corporation
Confidential
May not be used, divulged, published or otherwise disclosed
without the consent of Novartis Pharmaceuticals Corporation

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

The following information concerning _____, who participated as a clinical investigator in the submitted study _____, is submitted in accordance with 21 CFR part 54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Name of clinical investigator
CZOL446H2301
Name of clinical study

Please mark the applicable checkboxes.

- any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;
- any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;
- any proprietary interest in the product tested in the covered study held by the clinical investigator;
- any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME Patrice Matchaba, MD	TITLE Therapeutic Area Head of Arthritis and Bone
FIRM / ORGANIZATION Novartis Pharmaceuticals Corporations	
SIGNATURE 	DATE 8/4/06

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 4 hours 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:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14-72
Rockville, MD 20857

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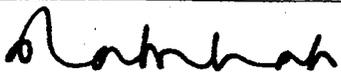
The following information concerning _____, who participated as a clinical investigator in the submitted study _____, is submitted in accordance with 21 CFR part 54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Name of clinical investigator
Name of clinical study

Please mark the applicable checkboxes.

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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	_____ (Study CZ0446H2301)	
	_____ Study CZ0446H2301	

- (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 Patrice Matchaba, MD		TITLE Therapeutic Area Head of Arthritis and Bone	
FIRM / ORGANIZATION Novartis Pharmaceuticals Corporations			
SIGNATURE 		DATE 8/4/06	

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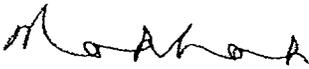
Please mark the applicable checkbox.

- (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	see attached	

- (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)).

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NAME Patrice Matachaba, MD		TITLE Arthritis/Bone Therapeutic Area Head	
FIRM / ORGANIZATION Novartis Pharmaceuticals			
SIGNATURE 		DATE 30 May 2006	

Paperwork Reduction Act Statement

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TO BE COMPLETED BY APPLICANT

The following information concerning _____, who participated as a clinical investigator in the submitted study _____, is submitted in accordance with 21 CFR part _____.

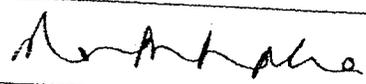
Name of clinical investigator CZOL446H2407
Name of clinical study _____

54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Please mark the applicable checkboxes.

- any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;
- any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;
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NAME Patrice Matchaba, MD	TITLE Arthritis/Bone Therapeutic Area Head
FIRM / ORGANIZATION Novartis Pharmaceuticals	
SIGNATURE 	DATE 30 May 2006

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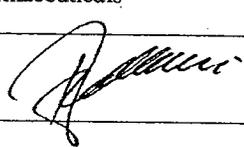
With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the 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 Tomasz Sablinski	TITLE VP US Clinical Development & Medical Affairs ABGU Therapeutic Area
FIRM / ORGANIZATION Novartis Pharmaceuticals	
SIGNATURE 	DATE 5/16/06

Paperwork Reduction Act Statement

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Clinical Investigators	Please see attached list (of 12 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)).

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NAME Tomasz Sablinski	TITLE VP, USCDMA, Novartis Pharmaceutical Corp.
FIRM/ORGANIZATION Novartis Pharmaceutical Corp.	
SIGNATURE 	DATE 5/16/06

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Rockville, MD 20857

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The following information concerning _____, who participated
Name of clinical investigator
as a clinical investigator in the submitted study _____
Name of
clinical study _____ is submitted in accordance with 21 CFR part 54. The
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NAME Tomasz Sablinski, MD	TITLE VP, USCDMA, Novartis Pharmaceutical Corp
FIRM/ORGANIZATION Novartis Pharmaceutical Corp	
SIGNATURE 	DATE 5/16/06

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Rockville, MD 20857

ACTION PACKAGE CHECKLIST

Application Information		
BLA # N/A NDA # 22-080	BLA STN# N/A NDA Supplement # N/A	If NDA, Efficacy Supplement Type N/A
Proprietary Name: Reclast Established Name: zoledronic acid Dosage Form: 5 mg/100 mL solution for intravenous infusion		Applicant: Novartis Pharmaceuticals Corporation
RPM: Julie Marchick		Division: DMEP (HFD-510) Phone # (301) 796-1280
NDAs: NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) (A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)		505(b)(2) NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s): N/A Provide a brief explanation of how this product is different from the listed drug. N/A <input type="checkbox"/> If no listed drug, check here and explain: Review and confirm the information previously provided in Appendix B to the Regulatory Filing Review. Use this Checklist to update any information (including patent certification information) that is no longer correct. <input checked="" type="checkbox"/> Confirmed <input type="checkbox"/> Corrected Date: July 24, 2007
❖ User Fee Goal Date		August 17, 2007
❖ Action Goal Date (if different)		August 17, 2007
❖ Actions		
• Proposed action		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA <input type="checkbox"/> CR
• Previous actions (specify type and date for each action taken)		<input checked="" type="checkbox"/> None
❖ Advertising (approvals only) Note: If accelerated approval (21 CFR 314.510/601.41), advertising must have been submitted and reviewed (indicate dates of reviews)		<input checked="" type="checkbox"/> Requested in AP letter <input type="checkbox"/> Received and reviewed

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❖ Application Characteristics	
Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only): 6	
NDAs, BLAs and Supplements: <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2 <input type="checkbox"/> Orphan drug designation	
NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies	BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies
NDAs and NDA Supplements: <input type="checkbox"/> OTC drug	
Other: Other comments:	
❖ Application Integrity Policy (AIP)	
<ul style="list-style-type: none"> Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> This application is on the AIP <ul style="list-style-type: none"> Exception for review (<i>file Center Director's memo in Administrative Documents section</i>) OC clearance for approval (<i>file communication in Administrative Documents section</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> Not an AP action
❖ Public communications (approvals only)	
<ul style="list-style-type: none"> Office of Executive Programs (OEP) liaison has been notified of action 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Press Office notified of action 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 	<input type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

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notice of certification?

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced

<p>within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application; if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.</i></p>	
Summary Reviews	
❖ Summary Reviews (e.g., Office Director, Division Director) (indicate date for each review)	August 17, 2007
❖ BLA approvals only: Licensing Action Recommendation Memo (LARM) (indicate date)	N/A
Labeling	
❖ Package Insert	
<ul style="list-style-type: none"> • Most recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	N/A
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version) 	August 17, 2007
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	October 16, 2006
<ul style="list-style-type: none"> • Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 	N/A
❖ Patient Package Insert	
<ul style="list-style-type: none"> • Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	N/A
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version) 	August 17, 2007
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	October 16, 2006
<ul style="list-style-type: none"> • Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 	N/A
❖ Medication Guide	
<ul style="list-style-type: none"> • Most recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	N/A
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version) 	N/A
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	N/A
<ul style="list-style-type: none"> • Other relevant labeling (e.g., most recent 3 in class, class labeling) 	N/A
❖ Labels (full color carton and immediate-container labels)	
<ul style="list-style-type: none"> • Most-recent division-proposed labels (only if generated after latest applicant submission) 	
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling 	N/A – same as approved
❖ Labeling reviews and minutes of any labeling meetings (indicate dates of reviews and meetings)	<input type="checkbox"/> DMETS <input checked="" type="checkbox"/> DSRCS August 16, 2007 <input checked="" type="checkbox"/> DDMAC August 10, 2007 <input checked="" type="checkbox"/> SEALD August 9, 2007 <input type="checkbox"/> Other reviews <input type="checkbox"/> Memos of Mtgs

Administrative Documents	
❖ Administrative Reviews (RPM Filing Review/Memo of Filing Meeting; ADRA) (<i>indicate date of each review</i>)	December 1, 2006
❖ NDA and NDA supplement approvals only: Exclusivity Summary (<i>signed by Division Director</i>)	<input checked="" type="checkbox"/> Included
❖ AIP-related documents <ul style="list-style-type: none"> Center Director's Exception for Review memo If AP: OC clearance for approval 	N/A N/A
❖ Pediatric Page (all actions)	<input checked="" type="checkbox"/> Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent. (<i>Include certification.</i>)	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Postmarketing Commitment Studies	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> Outgoing Agency request for post-marketing commitments (<i>if located elsewhere in package, state where locate d</i>) Incoming submission documenting commitment 	
❖ Outgoing correspondence (letters including previous action letters, emails, faxes, telecons)	October 26, 2006; December 1, 2006
❖ Internal memoranda, telecons, email, etc.	N/A
❖ Minutes of Meetings	
<ul style="list-style-type: none"> Pre-Approval Safety Conference (<i>indicate date; approvals only</i>) Pre-NDA/BLA meeting (<i>indicate date</i>) EOP2 meeting (<i>indicate date</i>) Other (e.g., EOP2a, CMC pilot programs) 	N/A <input type="checkbox"/> No mtg August 21, 2003; February 2, 2006 <input type="checkbox"/> No mtg August 30, 2001 N/A
❖ Advisory Committee Meeting	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> Date of Meeting 48-hour alert or minutes, if available 	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A
CMC/Product Quality Information	
❖ CMC/Product review(s) (<i>indicate date for each review</i>)	June 26, 2007
❖ Reviews by other disciplines/divisions/Centers requested by CMC/product reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ BLAs: Product subject to lot release (APs only)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Environmental Assessment (check one) (original and supplemental applications)	
<ul style="list-style-type: none"> <input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>) <input type="checkbox"/> Review & FONSI (<i>indicate date of re view</i>) <input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>) 	June 26, 2007
❖ NDAs: Microbiology reviews (sterility & apyrogenicity) (<i>indicate date of each review</i>)	February 16, 2007 <input type="checkbox"/> Not a parenteral product
❖ Facilities Review/Inspection	
<ul style="list-style-type: none"> NDAs: Facilities inspections (include EER printout) 	Date completed: November 16, 2006 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation

❖ BLAs: Facility-Related Documents <ul style="list-style-type: none"> • Facility review <i>(indicate date(s))</i> • Compliance Status Check (approvals only, both original and supplemental applications) <i>(indicate date completed, must be within 60 days prior to AP)</i> 	<input type="checkbox"/> Requested <input type="checkbox"/> Accepted <input type="checkbox"/> Hold
❖ NDAs: Methods Validation	<input checked="" type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed
Nonclinical Information	
❖ Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	July 18, 2007
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	N/A
❖ Nonclinical inspection review Summary (DSI)	<input checked="" type="checkbox"/> None requested
Clinical Information	
❖ Clinical review(s) <i>(indicate date for each review)</i>	August 16, 2007
❖ Financial Disclosure reviews(s) or location/date if addressed in another review	August 16, 2007, Page 17
❖ Clinical consult reviews from other review disciplines/divisions/Centers <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> None
❖ Microbiology (efficacy) reviews(s) <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> Not needed
❖ Safety Update review(s) <i>(indicate location/date if incorporated into another review)</i>	August 16, 2007, Page 80
❖ Risk Management Plan review(s) (including those by OSE) <i>(indicate location/date if incorporated into another review)</i>	N/A
❖ Controlled Substance Staff review(s) and recommendation for scheduling <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> Not needed
❖ DSI Inspection Review Summary(ies) <i>(include copies of DSI letters to investigators)</i>	<input type="checkbox"/> None requested
• Clinical Studies	June 15, 2007
• Bioequivalence Studies	N/A
• Clin Pharm Studies	N/A
❖ Statistical Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None August 1, 2007
❖ Clinical Pharmacology review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None August 10, 2007

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Appendix A to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.

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/s/

Julie Marchick
8/31/2007 01:54:56 PM

MEMORANDUM

To: Julie Marchick
Division of Metabolism and Endocrinology Products

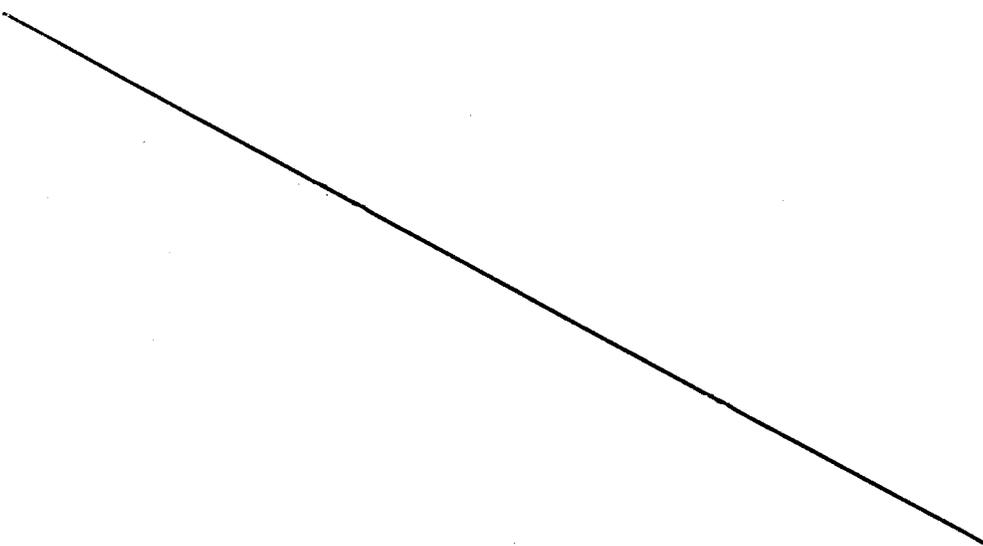
From: Iris Masucci, PharmD, BCPS
Division of Drug Marketing, Advertising, and Communications
for the Study Endpoints and Label Development (SEALD) Team, OND

Date: August 9, 2007

Re: Comments on draft labeling for Reclast (zoledronic acid)
NDA 22-080

We have reviewed the proposed label for Reclast (FDA version dated 8/6/07 and the sponsor's response of 8/7/07) and offer the following comments. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, labeling Guidances, and FDA recommendations to provide for labeling quality and consistency across review divisions. We recognize that final labeling decisions rest with the review division after a full review of the submitted data.

GENERAL COMMENTS



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✓ Draft Labeling

 Deliberative Process

Withheld Track Number: Administrative-1

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/s/

Iris Masucci
8/14/2007 09:22:59 AM
DDMAC REVIEWER

Laurie Burke
8/14/2007 05:24:50 PM
INTERDISCIPLINARY

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

Memorandum

PRE-DECISIONAL AGENCY INFORMATION

Date: August 10, 2007

To: Julie Marchick
Regulatory Project Manager
Division of Metabolism and Endocrinology Products

From: Kanika Vij, Pharm.D.
Division of Drug Marketing, Advertising, and Communications

Subject: Drug: Reclast® (zoledronic acid) injection
NDA: 22-080

DDMAC has reviewed the proposed product labeling (PI) and proposed patient labeling (PPI) for Reclast® (zoledronic acid) injection and we offer the following comments in the track changed format below with each of our comments specified with "DDMAC" before them.

If you have any questions or concerns regarding my comments, please contact me at 301.796.0580 or Kanika.Vij@fda.hhs.gov.

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✓ Draft Labeling

 Deliberative Process

Withheld Track Number: Administrative-2

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/s/

Kanika Vij
8/10/2007 02:37:28 PM
DDMAC REVIEWER



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: August 15, 2007

To: Mary Parks, M.D., Director
Division of Metabolic and Endocrine Products

Thru: Toni Piazza-Hepp, Pharm. D., Deputy Director
Division of Surveillance, Research and Communication
Support

From: Sharon R. Mills, BSN, RN, CCRP
Patient Product Information Specialist
Division of Surveillance, Research and Communication
Support

Subject: DSRCs review of Patient Labeling (PPI)

Drug Name(s): Reclast (zoledronic acid) Injection

Application Type/Number: N22-080

Applicant/sponsor: Novartis Pharmaceuticals Corporation

OSE RCM #: 2007-1746

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1 INTRODUCTION

Novartis Pharmaceuticals Corporation received an Approval Action on April 16, 2007 for Reclast (zoledronic acid) Injection, NDA 21-817 and "is indicated for the treatment of Paget's disease of bone in men and women."

Novartis Pharmaceuticals Corporation submitted an Original New Drug Application, NDA 22-080, for Reclast (zoledronic acid) Injection on October 16, 2006 for the proposed indication: "for the treatment of postmenopausal osteoporosis." Submitted labeling includes Full Prescribing Information (FPI) in PLR format, including Patient Information in the form of a Patient Package Insert (PPI).

Novartis Pharmaceuticals Corporation submitted an Amendment to Pending New Drug Application: Updated Draft Labeling, on June 20, 2007. The updated draft labeling incorporates text approved by the review division for Paget's disease under NDA 21-817, into the PLR format label for the proposed postmenopausal osteoporosis indication. The draft labeling has been further revised by the review division on August 10, 2007

2 MATERIAL REVIEWED

August 10, 2007 review division revision of the draft Professional Information, including Patient Information (PPI).

3 DISCUSSION

See the attached document for our suggested revisions to the sponsor's proposed PPI. We have simplified wording where possible, made it consistent with the Professional Information (PI) and removed unnecessary information.

Formatting issues with the submitted Word copy of the PPI would not allow us to check readability scores.

Comments to the review division are ***bolded, underlined and italicized*** in the attached document.

4 CONCLUSIONS AND RECOMMENDATIONS

- To enhance comprehension, patient materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60% (60% Flesch Reading Ease score corresponds to an 8th grade reading level).
- Reclast will be given to patients as an intravenous infusion. There are no distribution requirements for PPIs and therefore, patients are unlikely to receive the Reclast PPI.

We are providing to the review division a marked-up and clean copy of the revised PPI. We recommend using the clean copy as the working document.

Please let us know if you have any questions.

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✓ Draft Labeling

 Deliberative Process

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/s/

Sharon Mills
8/15/2007 04:31:55 PM
DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp
8/16/2007 08:33:48 AM
DRUG SAFETY OFFICE REVIEWER

From: Markofsky, Sheldon B
Sent: Thursday, May 31, 2007 1:23 PM
To: Seymour, Haley
Cc: Fraser, Blair
Subject: NDA 22080 phone call-

The essence of today's phone call to Novartis for NDA 22-080 can be summarized by the following comment:

Comment

Your stability protocol to support post-approval changes is deficient since it might allow for post-approval changes, related to sterility or endotoxin considerations, without appropriate or sufficient stability testing for sterility or endotoxins. Amend your protocol to address these sterility and endotoxin concerns.

Shelly Markofsky

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/s/

Haley Seymour
7/19/2007 11:00:25 AM
CSO

DSI CONSULT: Request for Clinical Inspections

Date: January 31, 2007

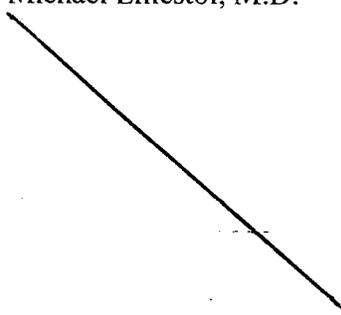
To: Constance Lewin, M.D., M.P.H., Branch Chief, GCP1, HFD-46
Leslie Ball, M.D., Branch Chief, GCP2, HFD-47

From: Randy Hedin, Senior Regulatory Management Officer, HFD-510
Division of Metabolism and Endocrinology Products

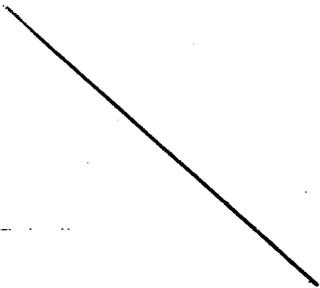
Subject: Request for Clinical Inspections
NDA 22-080
Novartis Pharmaceuticals, Inc.
Reclast (zoledronic acid) Injection

Protocol/Site Identification:

As discussed with you, the following protocols/sites essential for approval have been identified for inspection. These sites are listed in order of priority.

Indication	Protocol #	Site (Name and Address)	Number of Subjects
Treatment of Postmenopausal Osteoporosis	ZOL446H230 I	Site 540 Michael Lillestol, M.D. 	-48 randomized subjects

Request for Clinical Inspections

Treatment of Postmenopausal Osteoporosis	ZOL446H230 1		-84 enrolled subjects
--	-----------------	--	-----------------------------

Goal Date for Completion:

We request that the inspections be performed and the Inspection Summary Results be provided by (inspection summary goal date) **June 29, 2007**. We intend to issue an action letter on this application by (action goal date) **August 17, 2007**.

Should you require any additional information, please contact Randy Hedin.

Concurrence: (if necessary)

Theresa Kehoe, Medical Team Leader
William Lubas, Medical Reviewer

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/s/

Randy Hedin
1/31/2007 09:15:57 AM

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: July 19, 2007

TO: Haley Seymour, Regulatory Project Manager
William Lubas, M.D., Clinical Reviewer
Division of Metabolism and Endocrinology Products

THROUGH: Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

FROM: Andrea Slavin, RN
Consumer Safety Officer

SUBJECT: Evaluation of Clinical Inspections

NDA: 22-080

APPLICANT: Novartis Pharmaceuticals Corporation

DRUG: Reclast® (zoledronic acid) Injection

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: Treatment of postmenopausal osteoporosis

CONSULTATION REQUEST DATE: January 31, 2007

DIVISION ACTION GOAL DATE: August 17, 2007

PDUFA DATE: August 17, 2007

I. BACKGROUND:

Bisphosphonates exhibit marked effects on bone metabolism. Zoledronic acid is a representative of a third generation bisphosphonate and is the most potent bisphosphonate in development. This NDA is for a new indication of postmenopausal osteoporosis. The drug is not a new molecular entity.

The goals of the inspections were to assess adherence to FDA regulatory requirements, specifically, investigator oversight, protocol compliance, verification of primary efficacy endpoint data, adequacy of study records and protection of subjects' rights, safety, and welfare. Site selection was based on subject enrollment.

The inspections audited protocol #CZOL446H2301, "A Multicenter, Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Zoledronic Acid in the Treatment of Osteoporosis in Postmenopausal Women Taking Calcium and Vitamin D."

Summary Report of Inspections

II. RESULTS (by protocol/site):

Name of CI and site #, if known	City, State	Protocol	Inspection Date	EIR Received Date	Final Classification
Michael Lillestol, MD/540	Fargo, ND	CZOL446H2301		5/16/07	NAI
		CZOL446H2301			

Key to Classifications

NAI = No deviations from regulations. Data acceptable.

VAI-No Response Requested= Deviation(s) from regulations. Data acceptable.

VAI-Response Requested = Deviation(s) from regulations. See specific comments below for data acceptability

OAI = Significant deviations from regulations. Data unreliable.

A. Protocol #CZOL446H2301

1. Michael Lillestol, M.D. (site #540)

- _____
- a. What was inspected: At this site, 48 subjects were randomized, 46 subjects received study drug, and 42 subjects completed the study. Sixteen subjects' records were audited for data integrity.
 - b. Limitations of inspection: None
 - c. General observations/commentary: No significant deviations from FDA regulations were observed.
 - d. Data appear acceptable.

- _____
- a. What was inspected: At this site, 151 subjects were screened, 84 subjects were randomized, and 66 subjects completed the study. Twenty-six subjects' records were audited for data integrity.
 - b. Limitations of inspection: None
 - c. General observations/commentary: These observations are based on Form FDA 483 and communication from the field investigator. The establishment inspection report (EIR) with supporting exhibits has not been received.

Seven subjects did not meet the washout requirements for subjects who had taken other osteoporosis therapies in the past, but who are not using any therapies at randomization (Stratum I). The subjects are: 0580-00004 (did not meet washout requirement for SERMS), 0580-00006 (did not meet washout requirement for HRT), 0580-00010 (did not meet washout requirements for bisphosphonates, HRT, and calcitonin), 0580-00012 (did not meet washout requirement for HRT), 0580-00019 (did not meet washout requirement for calcitonin), 0580-00022 (did not meet washout requirement for calcitonin), and 0580-00023 (did not meet washout requirement for SERMS). Subject 0580-00100 initiated the use of a prohibited concomitant medication (a bisphosphonate) during the study. Subjects 0580-00128 and 0580-00129 were infused with the wrong study treatments in May 2004.

- d. Acceptability of data: For the seven out of 84 subjects who did not meet washout requirements for participation in Stratum I, the review division should evaluate the impact, if any, on the overall data acceptability.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

Overall, data from these sites appear acceptable in support of NDA 22-080.

As stated above, no significant deviations from FDA regulations were observed at Dr. Michael Lillestol's site. _____ enrolled 7 subjects who did not meet washout requirements for previous osteoporosis therapy required for Stratum I participation. Observations noted for _____ site are based on the Form FDA 483 and communication from the field investigator; an inspection summary addendum will be generated if conclusions change significantly upon receipt and review of the final EIR.

{See appended electronic signature page}

Andrea Slavin, RN
Consumer Safety Officer

CONCURRENCE:

{See appended electronic signature page}

Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations



NDA 22-080

FILING COMMUNICATION

Novartis Pharmaceuticals Corporation
Attention: Lynn Mellor
Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Ms. Mellor:

Please refer to your October 16, 2006 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Reclast (zoledronic acid) Injection.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application will be filed under section 505(b) of the Act on December 16, 2006 in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

If you have any questions, call Randy Hedin, Senior Regulatory Management Officer, at (301) 796-1224.

Sincerely,

{See appended electronic signature page}

Kati Johnson
Chief, Project Management Staff
Division of Metabolism and Endocrinology Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES NO
If yes, explain: NDA 21-223 received 5 years of exclusivity when approved.

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES NO
- 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 yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES NO
If yes, explain:
- If yes, has OC/DMPQ been notified of the submission? YES NO
- Does the submission contain an accurate comprehensive index? YES NO
If no, explain:
- Was form 356h included with an authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. agent must sign.
- Submission complete as required under 21 CFR 314.50? YES NO
If no, explain:

- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA YES
2. This application is an eNDA or combined paper + eNDA YES
This application is: All electronic Combined paper + eNDA
This application is in: NDA format CTD format
Combined NDA and CTD formats

Does the eNDA, follow the guidance?
(<http://www.fda.gov/cder/guidance/2353fnl.pdf>) YES NO

If an eNDA, all forms and certifications must be in paper and require a signature.

If combined paper + eNDA, which parts of the application were submitted in electronic format?

Additional comments:

3. This application is an eCTD NDA. YES
If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments:

- Patent information submitted on form FDA 3542a? YES NO
- Exclusivity requested? Firm requested exclusivity, however did not state the number of years requested. Years NO

NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.

- Correctly worded Debarment Certification included with authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] 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." Applicant may not use wording such as "To the best of my knowledge"

- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included? YES NO
- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES NO
- Is this submission a partial or complete response to a pediatric Written Request? YES NO

If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? YES NO
(Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)

NOTE: Financial disclosure is required for bioequivalence studies that are the basis for approval.

- Field Copy Certification (that it is a true copy of the CMC technical section) YES NO
- PDUFA and Action Goal dates correct in tracking system? YES NO
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

- List referenced IND numbers: 43,240

- Are the trade, established/proper, and applicant names correct in COMIS? YES NO
If no, have the Document Room make the corrections.

- End-of-Phase 2 Meeting(s)? Date(s) October 11, 2001 NO
If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) May 18, 2005 NO
If yes, distribute minutes before filing meeting.

- Any SPA agreements? Date(s) _____ NO
If yes, distribute letter and/or relevant minutes before filing meeting.

Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES NO
If no, request in 74-day letter.
- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
Was the PI submitted in PLR format? YES NO
If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:
- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES NO
- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES NO
- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS?
N/A YES NO
- Risk Management Plan consulted to OSE/IO? N/A YES NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA YES NO

If Rx-to-OTC Switch or OTC application: Not Applicable

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES NO
- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? Not Applicable
YES NO

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES NO
If no, did applicant submit a complete environmental assessment? YES NO
If EA submitted, consulted to EA officer, OPS? YES NO
- Establishment Evaluation Request (EER) submitted to DMPQ? YES NO

- If a parenteral product, consulted to Microbiology Team? YES NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: December 1, 2006

NDA #: 22-080

DRUG NAMES: Reclast (zoledronic acid) Injection

APPLICANT: Novartis Pharmaceuticals Corporation

BACKGROUND: Zoledronic acid is a third-generation nitrogen-containing bisphosphonate. Anti-resorptive therapy with bisphosphonates, calcitonins, hormone replacement therapy, or raloxifene has been used to maintain or increase bone mass and to reduce excessive bone turnover, with the ultimate goal to reduce the risk of osteoporotic vertebral, hip, and other non-vertebral fractures. Clinical studies have consistently shown that nitrogen containing bisphosphonates provide effective therapy for osteoporotic patients who are at a high risk of fracture. Most bisphosphonates have been developed as oral compounds; however, orally administered bisphosphonates have low bioavailability. A few bisphosphonates, such as clodronate, pamidronate, ibandronate, and zoledronic acid can be given by infusion, which can improve compliance and clinical outcomes. The purpose of the current submission for zoledronic acid is to seek approval for the treatment of postmenopausal osteoporosis. Zoledronic acid will be administered annually as a single intravenous infusion of 5 mg, in a 100 mL ready to infuse solution, over at least 15 minutes.

ATTENDEES: Randy Hedin, Theresa Kehoe, William Lubas, Karen Davis-Bruno, Cynthia Liu, Ronald Wange, Johnny Lau, and Suong Tran

ASSIGNED REVIEWERS (including those not present at filing meeting) :

<u>Discipline/Organization</u>	<u>Reviewer</u>
Medical:	William Lubas
Secondary Medical:	Theresa Kehoe
Statistical:	Cynthia Liu
Pharmacology:	Karen Davis-Bruno
Statistical Pharmacology:	None
Chemistry:	Suong Tran
Environmental Assessment (if needed):	Suong Tran
Biopharmaceutical:	Johnny Lau
Microbiology, sterility:	To be determined
Microbiology, clinical (for antimicrobial products only):	None
DSI:	Andrea Slavin
OPS:	None
Regulatory Project Management:	Randy Hedin
Other Consults:	

Per reviewers, are all parts in English or English translation? YES NO
If no, explain:

CLINICAL		FILE <input checked="" type="checkbox"/>	REFUSE TO FILE <input type="checkbox"/>
• Clinical site audit(s) needed? If no, explain:		YES <input checked="" type="checkbox"/>	NO <input type="checkbox"/>
• Advisory Committee Meeting needed?	YES, date if known _____		NO <input checked="" type="checkbox"/>
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?		N/A <input checked="" type="checkbox"/>	YES <input type="checkbox"/> NO <input type="checkbox"/>
CLINICAL MICROBIOLOGY	N/A <input checked="" type="checkbox"/>	FILE <input type="checkbox"/>	REFUSE TO FILE <input type="checkbox"/>
STATISTICS	N/A <input type="checkbox"/>	FILE <input checked="" type="checkbox"/>	REFUSE TO FILE <input type="checkbox"/>
BIOPHARMACEUTICS		FILE <input checked="" type="checkbox"/>	REFUSE TO FILE <input type="checkbox"/>
• Biopharm. study site audits(s) needed?		YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
PHARMACOLOGY/TOX	N/A <input type="checkbox"/>	FILE <input checked="" type="checkbox"/>	REFUSE TO FILE <input type="checkbox"/>
• GLP audit needed?		YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
CHEMISTRY		FILE <input checked="" type="checkbox"/>	REFUSE TO FILE <input type="checkbox"/>
• Establishment(s) ready for inspection?		YES <input checked="" type="checkbox"/>	NO <input type="checkbox"/>
• Sterile product?		YES <input checked="" type="checkbox"/>	NO <input type="checkbox"/>
If yes, was microbiology consulted for validation of sterilization?		YES <input checked="" type="checkbox"/>	NO <input type="checkbox"/>

ELECTRONIC SUBMISSION: Yes
Any comments:

**REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)**

- The application is unsuitable for filing. Explain why:
- The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.
 - No filing issues have been identified.
 - Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

- Goal to finish reviews with team leader sign-off, June 29, 2007.
- Action Package should start circulating on July 20, 2007.

- Action Package should go to the Division Director on July 27, 2007
- User Fee Date: August 17, 2007

Randy Hedin
Regulatory Project Manager

Appendix A to NDA Regulatory Filing Review

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and,
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the

original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.

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**Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications**

1. Does the application reference a listed drug (approved drug)? YES NO

If "No," skip to question 3.

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):
3. Is this application for a drug that is an "old" antibiotic (as described in the draft guidance implementing the 1997 FDAMA provisions? (Certain antibiotics are not entitled to Hatch-Waxman patent listing and exclusivity benefits.)

YES NO

If "Yes," skip to question 7.

4. Is this application for a recombinant or biologically-derived product?

YES NO

If "Yes" contact your ODE's Office of Regulatory Policy representative.

5. The purpose of the questions below (questions 5 to 6) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

- (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?

YES NO

(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

If "No," to (a) skip to question 6. Otherwise, answer part (b and (c)).

- (b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

- (c) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)?

YES NO

If "Yes," (c), list the pharmaceutical equivalent(s) and proceed to question 6.

If "No," to (c) list the pharmaceutical equivalent and contact your ODE's Office of Regulatory Policy representative.

Pharmaceutical equivalent(s):

6. (a) Is there a pharmaceutical alternative(s) already approved? YES NO

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

If "No," to (a) skip to question 7. Otherwise, answer part (b and (c)).

- (b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval? YES NO

- (c) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES NO

If "Yes," to (c), proceed to question 7.

NOTE: If there is more than one pharmaceutical alternative approved, consult your ODE's Office of Regulatory Policy representative to determine if the appropriate pharmaceutical alternatives are referenced.

If "No," to (c), list the pharmaceutical alternative(s) and contact your ODE's Office of Regulatory Policy representative. Proceed to question 7.

Pharmaceutical alternative(s):

7. (a) Does the application rely on published literature necessary to support the proposed approval of the drug product (i.e. is the published literature necessary for the approval)? YES NO

If "No," skip to question 8. Otherwise, answer part (b).

(b) Does any of the published literature cited reference a specific (e.g. brand name) product? Note that if yes, the applicant will be required to submit patent certification for the product, see question 12.

8. 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").

9. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA may refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)).) YES NO

10. Is the application for a duplicate of a listed drug whose only difference is that 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)? (See 314.54(b)(1)). If yes, the application may be refused for filing under 21 CFR 314.101(d)(9)). YES NO

11. Is the application for a duplicate of a listed drug whose only difference is YES NO

that the rate at which the product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application may be refused for filing under 21 CFR 314.101(d)(9).

12. Are there certifications for each of the patents listed in the Orange Book for the listed drug(s) referenced by the applicant (see question #2)? YES NO
(This is different from the patent declaration submitted on form FDA 3542 and 3542a.)

13. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

- Not applicable (e.g., solely based on published literature. See question # 7)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):
- 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. (Paragraph IV certification)
Patent number(s):

NOTE: IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must **subsequently** submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]. OND will contact you to verify that this documentation was received.

- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):
- Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):
- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is 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 as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s):

14. Did the applicant:

- Identify which parts of the application rely on the finding of safety and effectiveness for a listed drug or published literature describing a listed drug or both? For example, pharm/tox section of application relies on finding of preclinical safety for a listed drug.

YES NO

If "Yes," what is the listed drug product(s) and which sections of the 505(b)(2) application rely on the finding of safety and effectiveness or on published literature about that listed drug

Was this listed drug product(s) referenced by the applicant? (see question # 2)

YES NO

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

N/A YES NO

15. (a) Is there unexpired exclusivity on this listed drug (for example, 5 year, 3 year, orphan or pediatric exclusivity)? Note: this information is available in the Orange Book.

YES NO

If "Yes," please list:

Application No.	Product No.	Exclusivity Code	Exclusivity Expiration

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

/s/

Randy Hedin
12/1/2006 02:53:12 PM
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-080

Novartis Pharmaceuticals Corporation
Attention: Lynn Mellor
Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Ms Mellor:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Reclast (zoledronic acid) Injection

Review Priority Classification: Standard (S)

Date of Application: October 16, 2006

Date of Receipt: October 17, 2006

Our Reference Number: NDA 20-080

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on December 16, 2006, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be August 17, 2006.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. We are waiving the requirement of pediatric studies for this application.

NDA 22-080

Page 2

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Send all submission, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, call me at (301) 796-1224.

Sincerely,

{See appended electronic signature page}

Randy Hedin, R.Ph.
Senior Regulatory Management Officer
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

**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

10/26/2006 09:20:18 AM

Form Approved: OMB No. 0910 - 0297 Expiration Date: December 31, 2006 See instructions for OMB Statement.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

**PRESCRIPTION DRUG USER FEE
COVERSHEET**

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: <http://www.fda.gov/cder/pdufa/default.htm>

<p>1. APPLICANT'S NAME AND ADDRESS</p> <p>NOVARTIS PHARMACEUTICALS CORP Angie Young One Health Plaza East Hanover NJ 07936 US</p>	<p>4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER</p> <p>22-080</p>
<p>2. TELEPHONE NUMBER</p> <p>862-778-8685</p>	<p>5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p>IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. 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 type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:</p>

<p>3. PRODUCT NAME</p> <p>Reclast (zoledronic acid)</p>	<p>6. USER FEE I.D. NUMBER</p> <p>PD3006778</p>
---	---

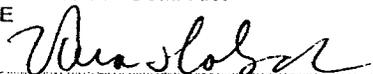
7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

<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 (Self Explanatory)	<input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
<input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act	<input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? YES NO

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:

Department of Health and Human Services Food and Drug Administration CBER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448	Food and Drug Administration CDER, HFD-94 12420 Parklawn Drive, Room 3046 Rockville, MD 20852	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.
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<p>SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE</p> 	<p>TITLE</p> <p>Director</p>	<p>DATE</p> <p>10-10-06</p>
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9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION
\$896,200.00

Form FDA 3397 (12/03)

(IBE PRMT CLOSE G) (Print Cover sheet)



IND 43,240

Novartis Pharmaceuticals Corporation
Attention: Mathias Hukkelhoven, Ph.D.
Global Head, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Hukkelhoven:

Please refer to the meeting between representatives of your firm and FDA on February 2, 2006. The purpose of the meeting was to discuss submitting an NDA for zoledronic acid injection dosed once-yearly for the treatment of post-menopausal osteoporosis based on safety data and fracture efficacy interim analyses data.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 976-1224.

Sincerely,

{See appended electronic signature page}

Randy Hedin
Senior Regulatory Management Officer
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

Meeting Date: February 2, 2006 Time: 3:00 - 4:00 PM Location: Teleconference

IND 43,240 Zoledronic Acid Injection

Type of Meeting: Guidance

External participant: Novartis Pharmaceuticals Corporation

Meeting Chair: Dr. Theresa Kehoe

External participant lead: Dr. Mathias Hukkelhoven

Meeting Recorder: Mr. Randy Hedin

FDA attendees and titles:

Division of Metabolic and Endocrine Drug Products:

Mary Parks, M.D., Acting Director

Eric Colman, M.D., Clinical Team Leader

Theresa Kehoe, M.D., Clinical Team Leader

William Lubas, M.D., Clinical Reviewer

Randy Hedin, R.Ph., Senior Regulatory Management Officer

Division of Biometrics II

Todd Sahlroot, Ph.D., Team Leader

Cynthia Liu, Ph.D., Reviewer

External participant Attendees and titles:

Mathias Hukkelhoven M.D., Global Head, Drug Regulatory Affairs

John Orloff, M.D., V.P. Therapeutic Area Head, ABGU

Paul Gallo, Ph.D., Director Biostatistics

Steffen Roellinger, Head Global Project Management

Meeting Objectives:

Novartis requested to meet with the Division to discuss submitting an NDA for zoledronic acid 5mg injection dosed once-yearly for the treatment of post-menopausal osteoporosis based on safety data and fracture efficacy data based on the 2-year interim analyses of the three-year pivotal fracture trial. Zoledronic acid 4mg injection (Zometa) was approved on August 20, 2001, for the treatment of hypercalcemia of malignancy, and has subsequently been approved for the treatment of patients with multiple myeloma and patients with documented bone metastases from solid tumors, in conjunction with standard antineoplastic therapy. Zoledronic acid 5mg injection is also being developed to treat Paget's Disease of bone.

Discussion Points and Decisions (agreements) reached:

- Novartis submitted a background document dated January 24, 2006 seeking concurrence that they could proceed with the planned new drug application submission based on interim data, as originally agreed during the preNDA meeting on April 18, 2005. After review of the submitted background document which included an efficacy results overview based on the 2-year interim data, a safety results overview and the data safety monitoring board (DSMB) conclusions regarding safety issues in study 2301, the Division sent the following comments to the firm via Email on January 31, 2006, concerning the information submitted to the Division:

“The Division feels that, in order to allow an adequate risk – benefit analysis, submission of the complete 3 year safety and efficacy data is required. Therefore, we do not endorse submission of the application based on interim data. We do not recommend early study close-out. Any final decision regarding early study close-out should occur after the DSMB has adjudicated the relevant cardiovascular safety data and rendered an opinion regarding drug causality.

Long-term safety data may be required to answer questions raised by the DSMB. You should consider prolonging the time-course of the three-year extension study (2301E1). “

Teleconference meeting discussion:

- The firm stated that anti-fracture efficacy has been established with the interim analysis and this was the original requirement for a new drug application submission based on the interim analysis of the pivotal fracture trial. The Division agreed that anti-fracture efficacy appeared to be supported by the current data but a final decision would depend on a complete review of the data which has yet to be submitted. However there are safety issues concerning cardiovascular mortality, cardiac arrhythmias, and ophthalmic disorders that were not apparent in the information provided for the preNDA meeting. These issues are not yet resolved. Resolution of these concerns will require review of the adjudicated data on adverse events (AEs), serious adverse events (SAEs), and deaths by the DSMB.

The Division stated that this is not acceptable. Given the safety concerns, the most complete safety database with fully adjudicated cardiovascular data should be submitted with the original new drug application.

- This would involve no early closure and completion of the trial with last patient last visit scheduled for approximately June 6, 2006. The initial submission of the new drug application will contain the interim 2-year analysis for efficacy as well as all safety data including adjudicated cardiovascular safety data, for all subjects up to and including March 31, 2006 visits, which will equate to approximately 3200 patients with 3-year safety data and 3-year bone histomorphometry data on all 100 subjects. The 120-day safety update will also include the small amount of remaining safety data on subjects with visits from April 1, 2006 to June 6 2006.

Unresolved or issues requiring further discussion:

- None

Action Items:

- None

Signature, minutes preparer: Randy Hedin

Concurrence Chair: Theresa Kehoe

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/s/

Randy Hedin
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 43,240

Novartis Pharmaceuticals Corporation
Attention: Lynn Mellor
Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Ms. Mellor:

Please refer to the meeting between representatives of your firm and FDA on August 21, 2003. The purpose of the meeting was to discuss your proposal to submit a supplemental NDA for once-yearly dosing of Zometa _____

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 827-6392.

Sincerely,

{See appended electronic signature page}

Randy Hedin R.Ph.
Senior Regulatory Management Officer
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

Meeting Date: August 21, 2003 Time: 1:00 - 2:30 PM Location: Conf. Rm. "B"

IND 43,240 Zometa (zoledronic acid)

Type of Meeting: Guidance

External participant: Novartis Pharmaceuticals Corporation

Meeting Chair: Dr. Eric Colman

External participant lead: Ms. Lynn Mellor

Meeting Recorder: Mr. Randy Hedin

FDA Attendees and titles:

Division of Metabolic and Endocrine Drug Products:

Eric Colman, M.D., Clinical Team Leader

Gemma Kuijpers, Ph.D., Pharmacology Reviewer

Randy Hedin, R.Ph., Senior Regulatory Management Officer

Division of Biometrics II:

Todd Sahlroot, Ph.D., Team Leader

Jopo Choudhury, Ph.D. Reviewer

External participant Attendees and titles:

John Orloff, M.D., Global Section Head, Executive Director, Clinical Research, Bone

John Caminis, M.D., Director Clinical Research, Bone

Peter Mesenbrink, Ph.D., Sr. Associate Director of Biostatistics Program Statistician

Jonathan Green, Ph.D., Distinguished Scientist, Bone Research Unit

Peter Freund, Ph.D., Global Project Leader, Project Management

Linda Carter, Executive Director, Drug Regulatory Affairs

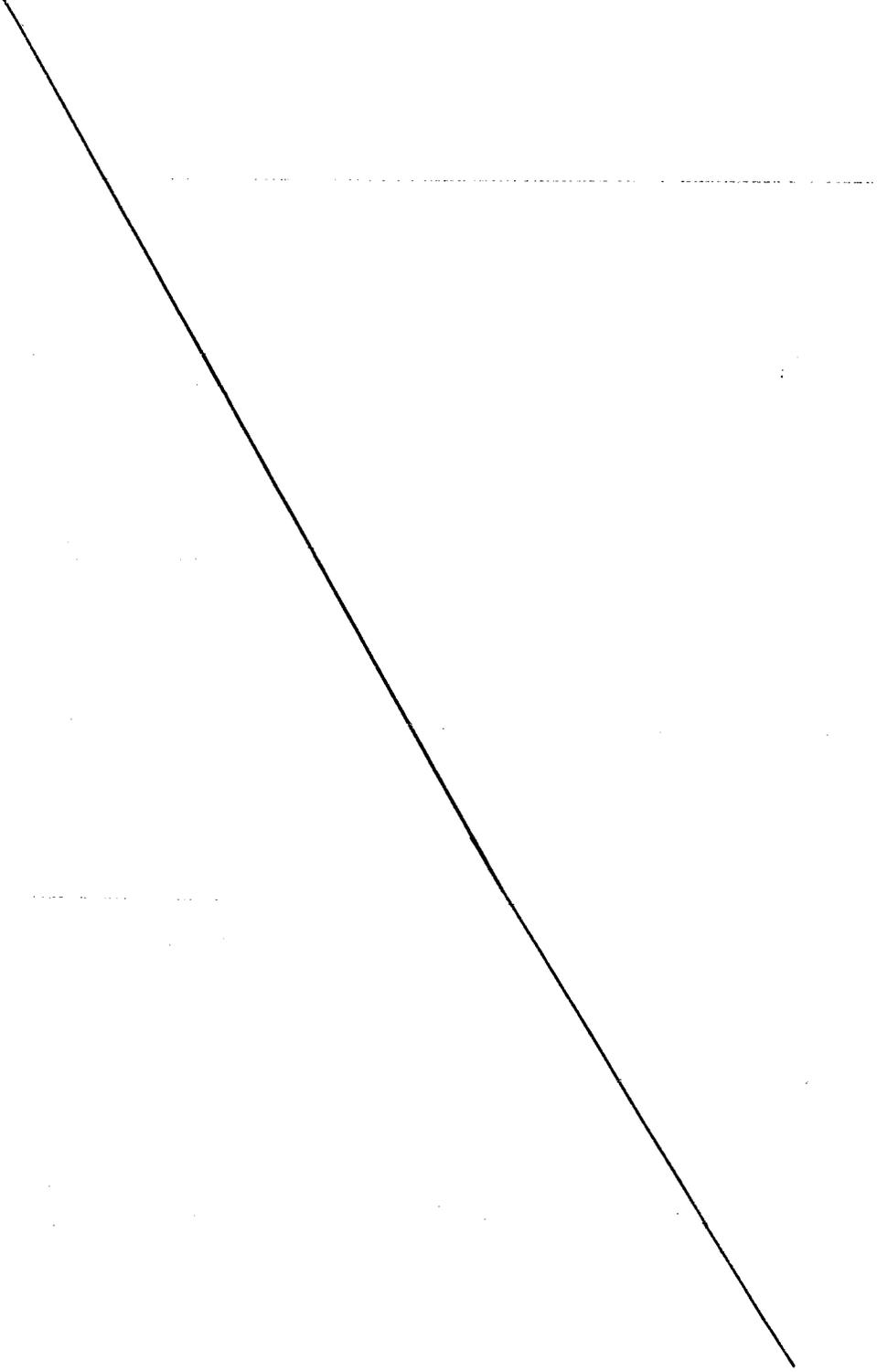
Lynn Mellor, Director, Drug Regulatory Affairs

Meeting Objectives:

The meeting was requested by Novartis Pharmaceuticals Corporation to discuss their proposal to submit a supplemental NDA for once-yearly dosing of Zometa with two year fracture data.

Discussion Points and Decisions (agreements) reached:

- The firm submitted the following 7 questions in a background document dated August 1, 2003. The Division's answers follow the questions in *italics*.

- 
3. Reference is made to the teleconference held with Dr. Eric Colman, Medical Team Leader from the Division of Endocrine and Metabolic Drugs, held on

May 19, 2003, where it was agreed that the 400 ECGs which were originally planned to be done in Study CZOL446H2310 were to be shifted to Study CZOL446H2301. It is proposed that the post-dose ECG evaluations be conducted 9-11 days post-dose in the renal safety cohort in Study CZOL446H2301.

Is this acceptable to the Agency?

This is acceptable.

-
5. Reference is made to the end-of-phase II meeting on 30-Aug-2001 at which the FDA requested a full statistical analysis plan for Study CZOL446H2301, which is provided as Appendix 4.

Does the Agency have any general questions on the Detailed Statistical Analysis Plan for Study CZOL446H2301?

The Division stated that Novartis should pre-specify a multiple comparison adjustment procedure for any secondary efficacy variables that Novartis wishes to include in the labeling. In general, any set of secondary hypotheses to be tested statistically with the possibility of inclusion in the labeling needs a pre-specified multiple comparison adjustment to maintain the overall Type 1 error rate for the trial at no more than 5%..

6. For the analyses of the proportion of subjects with new morphometric vertebral fractures, it is proposed that subjects be required to have both a baseline and at least one post-baseline vertebral x-ray to be included in any of the primary analyses of this efficacy variable (modified ITT population). To evaluate the sensitivity that missing data has on this approach, excluded patients will have their missing x-ray data imputed using a multiple imputation method to simulate the efficacy outcome data for those subjects who do not provide post-baseline x-rays. This data can then be used to estimate what the treatment effect would have been had these subjects provided data.

Is this strategy acceptable to the Agency for handling those subjects excluded from the analysis of morphometric vertebral fractures?

The proposal is acceptable.

The Division requested that in addition to the multiple imputation method for analysis for handling patients without any post-vertebral morphometric data, Novartis should also perform an alternative analysis. The alternative analysis should consider patients that are missing all post-baseline x-rays as not having a fracture. Novartis agreed to these changes in the data analysis plan (DAP), and will submit an updated DAP.

Unresolved or issues requiring further discussion:

- None

Action Items:

- Novartis will submit an updated DAP.

Signature, minutes preparer: Randy Hedin

Concurrence Chair: Eric Colman

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this page is the manifestation of the electronic signature.**

/s/

Randy Hedin

10/24/03 03:45:08 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 43,240

Novartis Pharmaceuticals Corporation
Attention: Lynn Mellor
Associate Director, Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Dear Ms. Mellor:

Please refer to the meeting between representatives of your firm and FDA on August 30, 2001. The purpose of the meeting was to discuss a development program for a once-a-year dosing of Zometa.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 827-6392.

Sincerely,

{See appended electronic signature page}

Randy Hedin
Senior Regulatory Management Officer
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

Meeting Date: August 30, 2001 Time: 11:00 - 12:00 AM Location: Conf. Rm. "C"

IND 43,240 Zometa (zoledronic acid)

Type of Meeting: End-of-Phase 2

External participant: Novartis Pharmaceuticals Corporation

Meeting Chair: Dr. Eric Colman

External participant lead: Ms. Lynn Mellor

Meeting Recorder: Mr. Randy Hedin

FDA Attendees and titles:

Office of Drug Evaluation II:

John Jenkins, M.D., Director

Division of Metabolic and Endocrine Drug Products:

David Orloff, M.D., Director,

Eric Colman, M.D., Clinical Team Leader

Gemma Kuijpers, Ph.D., Pharmacology Reviewer

Randy Hedin, R.Ph., Senior Regulatory Management Officer

Division of Biometrics II:

Todd Sahlroot, Ph.D., Team Leader

Jopo Choudhury, Ph.D. Reviewer

Division of Pharmaceutical Evaluation II:

Hae-Young Ahn, Ph.D., Team Leader

Office of the Inspector General:

Ms. Genevieve Nowolinski

Mr. Mark Yessian

Mr. Steve Keenan

Ms. Elizabeth Tong

Ms. Aimee Golbitz

External participant Attendees and titles:

Zeb Horowitz, M.D., International Clinical Leader, Executive Director Clinical Research

Ulrich Trechsel, M.D., Senior Clinical Research Physician

Peter Richardson, MRCP, Vice President Clinical Research

Irene Ferreira, Ph.D., Senior Biostatistician II, Biostatistics

Andrej Skerjanec, Ph.D., Senior Clinical Pharmacokineticist

Robert Spaet, Fellow, Pre-clinical Research

Jonathan Green, Ph.D., Distinguished Scientist, Pre-clinical Research

Peter Freund, Ph.D., International Project Team Leader, Project Management

Math Hukkelhoven, Ph.D., Vice President, US Head Drug Regulatory Affairs

Lynn Mellor, Associate Director, Drug Regulatory Affairs

Steve Cummings, M.D., Consultant, University of San Francisco

Dennis Black, Aph.D., Consultant, University of San Francisco

Ken Lyles, M.D., Consultant, Duke University
Carl Pieper, DPh, Consultant, Duke University

Meeting Objectives:

The meeting was requested by Novartis Pharmaceuticals Corporation to discuss phase three trials for the submission of a supplement to NDA 21-223, Zometa (zoledronic acid for Injection) for once a year dosing for the prevention and treatment of postmenopausal osteoporosis (PMO). Zometa is currently approved for the treatment of hypercalcemia of malignancy. The dose for this indication is 4 mg given as a single-dose intravenous infusion over no less than 15 minutes.

Discussion Points and Decisions (agreements) reached:

- The firm submitted the following 13 questions in a background document dated July 12, 2001, and one "New Question" submitted in a background document dated August 22, 2001. The Division's answers follow the questions.
 - 1a. The sponsor requests a waiver from the Pediatric Rule for the provision of pediatric data for the intended population of the adult program (the prevention and treatment of postmenopausal osteoporosis, Paget's Disease, male osteoporosis) because these conditions do not occur in the pediatric population. Does the Agency agree?

Division's response: Yes.
 - 1b. The Sponsor also request a waiver from the Pediatric Rule for the provision of pediatric data for the intended populations of the adult program (the prevention and treatment of corticosteroid-induced osteoporosis [CIO]) because sufficient data will be obtained from the adult CIO trials to provide guidance for once per year dosing in pediatric conditions characterized by loss of normal bone. We will be able to extrapolate efficacy, safety and pharmacokinetics data to the general pediatric age group from data from one pediatric trial in osteogenesis imperfecta. Does the Agency agree?

Division's response: No, we will not give a waiver from the Pediatric Rule; however, we will issue a deferral for these studies.
 - 1c. A partial waiver is requested in children less than 3 years old, because data from a protocol in children ≥ 3 years old with osteogenesis imperfecta will be available to guide dosing in younger children. Does the Agency agree?

Division's response: Yes, this is acceptable.
 2. The Sponsor believes that the existing pre-clinical results adequately fulfill regulatory requirements for pre-clinical demonstration of bone safety and bone quality and no additional pre-clinical studies are needed for this purpose. Does the Agency agree?

Division's response: Yes, this is acceptable.
 3. A comprehensive pre-clinical (toxicology and pharmacokinetic) safety package was submitted in support of use of zoledronic acid in the treatment of Tumor Induced

Hypercalcemia (see below). We believe that this pre-clinical safety data and the ongoing program of pre-clinical studies are sufficient to support the current clinical program. Does the Agency agree?

Division's response: Yes; however, the firm needs to provide information that the design of the carcinogenicity studies was adequate for the intended indication, dose, and treatment regimen (5 mg/year).

The firm stated it would provide justification for the highest dose.

4. No additional pharmacokinetic evaluations in the Phase 3 program are planned, apart from _____ Do you agree?

Division's response: Yes, this is acceptable.

5. Does the Agency agree with the Sponsor's conclusion that the results of the Phase II postmenopausal osteoporosis trial 041, summarized below, support i.v. once-a-year dosing, _____ for Phase III, treatment of postmenopausal osteoporosis?

Division's response: Yes, the phase II data support continued study of once-yearly dosing of zoledronate in a population of osteoporotic adults.

6. The Sponsor proposes to conduct Phase III trials with zoledronic acid 5 mg i.v. in administered over 15 minutes once-per-year for all clinical studies to support registration in all adult indications. Is the use of one dose once-per-year acceptable for all adult indications? Is the Sponsor's proposal to administer zoledronic acid 5 mg i.v. in volume, administered in 15 minutes acceptable?

Division's response: Once-per-year dosing is acceptable for the adult indications. However, please justify why infusion over 15 minutes is the optimal administration rate?

The firm stated that the 15-minute infusion rate was selected because it is safe, has not been associated with renal toxicity in the osteoporosis trial to date, and patient compliance should be good. The Division recommended that other dosing regimens should be studied and compared to the 15-minute infusion rate.

- 7a. Does the Committee agree with the proposal to conduct a single large global trial for registration and promotion for the indication of "Treatment of Postmenopausal Osteoporosis?"

Division's response: Yes, this is acceptable.

- 7b. Does the Committee agree with the Sponsor's proposal to assess hip fracture as the primary endpoint in the 3-year fracture trial?

Division's response: Yes, this is acceptable.

- 7c. The _____ efficacy endpoint is the rate of new and/ or worsening vertebral fractures at 3-years. Does the committee agree that a labeling claim for reduction in the rate of vertebral fracture at 3 years can be obtained by the _____ efficacy analysis of vertebral fracture restricted to patients in Stratum I only?

Division's response: The Division agreed that a labeling claim for reduction in the rate of vertebral fracture at 3 years can be obtained by the _____ efficacy analysis of vertebral fracture. However, all hypotheses (arising from multiple efficacy variables, subgroups, etc.) to be tested have to be identified in advance. The sponsor then needs to pre-specify whether to follow a closed testing procedure (i.e. will test the next hypothesis, only if the previous hypothesis were significant) or apply multiple comparison adjustments considering all possible hypotheses to be tested. The final data analysis plan should be submitted during the first year of the study.

- 7d. Does the committee agree that the labeling claim for reduction in the rate of vertebral fracture at 3 years can be obtained, if statistically significant, even if the primary endpoint does not attain statistical significance?

Division's response: No, the primary endpoint must be significant.

- 7e. Does the Committee agree with the proposed 0.05 level of significance in the secondary vertebral fracture analyses?

Division's response: See the answer to 7c.

8a.

8b. Sponsor withdrew question.

-
9. Is the Sponsor's proposal for monitoring of renal safety in the 3-year fracture trial (Protocol 2301) acceptable?

Division's response: No. A 7-10 day post-dose follow-up may not be adequate. Renal toxicity is the Division's major safety concern. Therefore renal function should be analyzed at a variety of time-points after administration and perhaps in all study participants. The firm agreed to submit a revised proposal for renal toxicity monitoring.

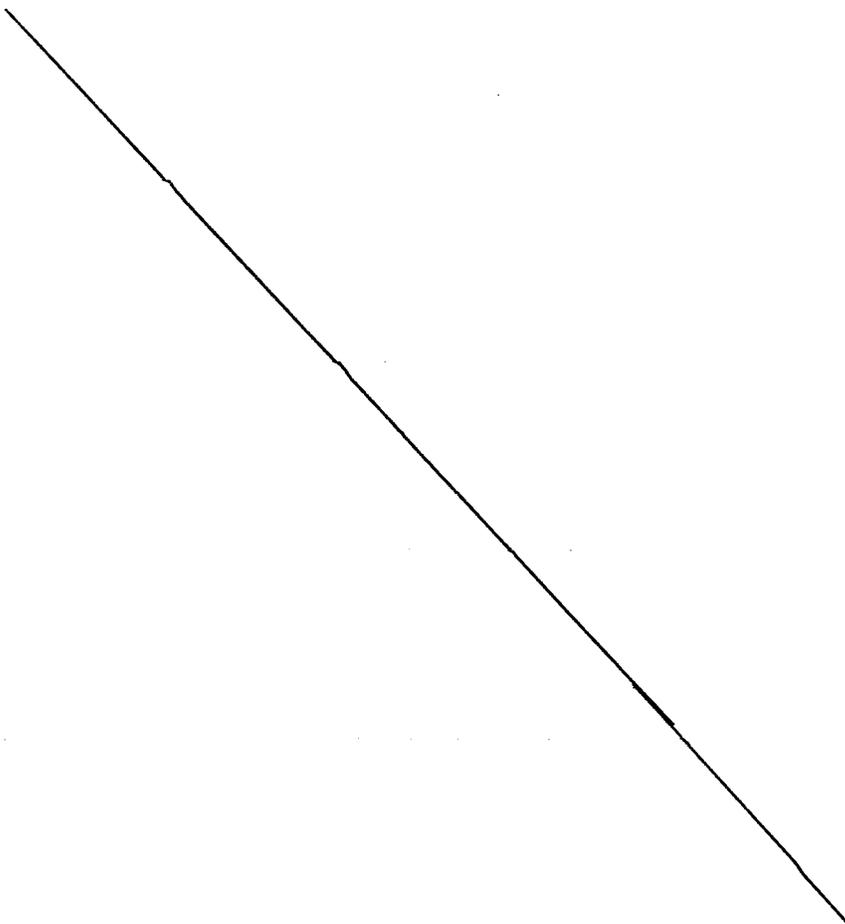
- 11b. Does the Agency agree with the proposed primary efficacy variable and its analysis?

Division's response: We cannot comment at this time. The issue needs to be clarified.

Division's response: Yes, this is acceptable.

- 11d. Does the Agency agree with the composition of the Data Safety Monitoring Board?

The composition of the Data Safety Monitoring Board seems adequate.



New Question:

Would the Agency consider granting registration for the indication Treatment of post-menopausal osteoporosis based on an early vertebral fracture endpoint and BMD/bone turnover markers (or for Treatment of Osteoporosis in post-menopausal women _____)

Division's response:

This question appears to be the result of the Division's review of the teriparatide NDA which contains 18-month fracture data in a trial of postmenopausal women. The Division made it clear that the teriparatide NDA is a unique situation and that at this time we still consider 3-year fracture data optimal for

evaluating the efficacy of drugs used to treat postmenopausal osteoporosis.

Unresolved or issues requiring further discussion:

- None

Action Items:

- The firm stated it will provide the following:
 1. Justification that the design of the carcinogenicity studies is adequate for the 5 mg/year dose.
 2. Justification that the 15-minute infusion rate is safe.
 3. Submit a proposal for renal toxicity monitoring.
-

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/s/

Randy Hedin
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