

# TELECON MINUTES

**TELECON DATE:** 2-13-01    **TIME:** 10:30    **LOCATION:** Div. Dir. Off.

**IND: —**    **Meeting Request Submission Date:** 12-20-00 (N130)  
**Briefing Document Submission Date:** 1-12-01 (N137)  
**Additional preparation documents:** 1-3-01 (N134) and 2-12-01 (N145)

**DRUG:** Zometa (zoledronate)    **INDICATION:** bone mets

**SPONSOR/APPLICANT:** Novartis

**TYPE of TELECON:** Pre-NDA

## FDA PARTICIPANTS:

Richard Pazdur, M.D., Dir., HFD-150 (internal meeting only)  
Grant Williams, M.D., Med. Team Leader, HFD-150 (internal meeting only)  
Susan Honig, M.D., Medical Officer, HFD-150  
John Leighton, Ph.D., Pharmacologist, HFD-150 (internal meeting only)  
Atik Rahman, Ph.D., Biopharm. Team Leader, HFD-150 (internal meeting only)  
Sophia Abraham, Ph.D., Biopharm Reviewer, HFD-150 (internal meeting only)  
Gang Chen, Ph.D., Statistics Team Leader, HFD-150 (internal meeting only)  
Ning Li, Ph.D., Statistician, HFD-150  
Khin Maung U, M.D., Div. of Scientific Investigations (internal meeting only)  
Dotti Pease, Project Manager, HFD-150 (industry meeting only)  
Ann Staten, Project Manager, HFD-150 (internal meeting only)

## INDUSTRY PARTICIPANTS: Novartis

Eileen Ryan, Drug Reg. Affairs	Beatrice Oberle-Rolle, Ph.D., Drug Reg. Aff.
Bee Chen, Ph.D., Biostat.	David Parkinson, M.D., VP, Clin. Dev.
Dirk Reitsma, M.D., Clin. Team Leader	Horst Schran, Ph.D., Clin. Pharm.
Joanne Machalaba, Proj. Man.	John Seaman, Pharm. D., Clin. Team Leader
Lillian Ng, Pharm. D., Drug Reg. Affairs	Ming Zheng, Ph.D., Stat.
Paul Gallo, Ph.D., Stat.	Sasha Vilimovskij, M.D., Clin. Dev.

**MEETING OBJECTIVES:** Discuss proposed NDA and sponsor's specific questions.

**BACKGROUND:** Following the internal pre-meeting on 2-1-01, FDA's responses were faxed to the sponsor on 2-7-01. Sponsor replied in a 2-12-01 fax (N145) that a telecon would be adequate and noted that they would only need clarification on #19, 20, 31, 32, 34, and 35. Below

are the original questions with FDA's responses as faxed. The additional clarification discussed in the telecon is in italics.

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

### Clinical Pharmacology

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

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

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

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

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

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

**FDA Response: The plan appears adequate**

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

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

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

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

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

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

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

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

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

**FDA Response: Yes.**

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

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

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

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

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

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

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

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

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

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

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

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

#### Clinical and Statistical

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

**FDA Response:**

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

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

**FDA Response:**

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

11. We proposed to \_\_\_\_\_

Development of this formulation has been terminated due to skin reactions restricted to the application site and lack of systemic biological activity and no relevant safety data can be provided. Only SAEs will be reported. In addition, in the ISS, we will provide a discussion of injection sites and dermatological observations from all trials. Do you concur?

**FDA Response: Yes, we concur.**

12. Novartis proposes that \_\_\_\_\_

**FDA Response:**

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

13. \_\_\_\_\_

**FDA Response:**

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

14. Efficacy data from patients at \_\_\_\_\_

\_\_\_\_\_ Do you concur?

**FDA Response:**

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

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

**FDA Response:**

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

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

**FDA Response:**

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

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

**FDA Response:**

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

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

**FDA Response:**

- **Yes, we concur. Because the 8-mg dose was eliminated, adjustment for multiplicity is no longer necessary.**

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

**FDA Response:**

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

*Sponsor should perform* \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

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

**FDA Response:**

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

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

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

**FDA Response:**

- Yes, this approach is acceptable.

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

**FDA Response:**

- Yes, this approach is acceptable.

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

**FDA Response:**

- Yes, we agree.

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

**FDA Response:**

- Yes, we agree.

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

you concur?

**FDA Response:**

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

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

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

**FDA Response:**

- **Yes, we concur.**

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

**FDA Response:**

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

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

**APPEARS THIS WAY  
ON ORIGINAL**

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

**FDA Response:**

- Yes, we agree.

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

**FDA Response:**

- Yes, we concur.

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

**FDA Response:**

- Yes.

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

**FDA Response:**

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

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

**APPEARS THIS WAY  
ON ORIGINAL**

Case Report Tabulations (CRTs)

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

**FDA Response:**

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

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

Narratives and Case Report Forms (CRFs)

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

**FDA Response:**

- **Yes, we do.**

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

**FDA Response:**

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

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

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

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

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

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

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

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

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

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

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

Do you concur?

**FDA Response:**

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

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

Labeling

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

**FDA Response:**

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

Financial Disclosure

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

**FDA Response:**

- **Yes, we concur.**

Priority Review

38.

**FDA Response:**

- Please note that your studies were designed to evaluate the effect of zoledronate on skeletal morbidity and do not provide information on the antitumor activity of zoledronate. "Treatment of bone metastases" does not accurately describe the results of your studies.
- Superiority of zoledronate to pamidronate does not automatically warrant priority review status, given the reported renal toxicity of zoledronate.
- Whether efficacy in reducing skeletal morbidity in patients with osteoblastic metastases or in patients with non-breast non-prostate malignancies, in light of the reported renal toxicity of zoledronate, warrants a priority review will be determined after the NDA is submitted at the 45-day filing meeting.

Cross-reference

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

**FDA Response:**

- Yes, we do.

Pediatric Labeling

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

**FDA Response:**

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

**New Question:**

41.

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

**Additional FDA Comments regarding the Pediatric Final Rule and Exclusivity:**

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

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

**Additional Comments during Telecon:**

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

**ACTION ITEMS:**

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

2. FDA to provide Novartis with a list of parameters on which she might want to search the database. Novartis to clarify that the database as supplied will have this capability.  
(Completed. See FDA facsimile dated 2-22-01)

\_\_\_\_\_  
Dotti Pease for Ann Staten,  
Project Manager

Concurrence Chair: \_\_\_\_\_  
Susan Honig, M.D.  
Medical Reviewer

Attachment: DSI handout for question #34.

**APPEARS THIS WAY  
ON ORIGINAL**

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

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

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

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

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

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

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

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

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

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

APPEARS THIS WAY  
ON ORIGINAL

/s/

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Ann Staten  
2/28/01 12:54:05 PM

Susan Honig  
2/28/01 02:23:05 PM

Dotti Pease  
2/28/01 02:18:06 PM

APPEARS THIS WAY  
ON ORIGINAL



Vause

Food and Drug Administration  
Rockville MD 20857

Feb 11 2002

Dear \_\_\_\_\_

Between December 14, 2001, and January 3, 2002, Messrs. Keith A. Schwartz and Paul L. Figarole Jr., representing the Food and Drug Administration (FDA), met with you to review your conduct of clinical studies (Protocols No. 010 and No. 011) of the investigational drug Zometa® (zoledronic acid), performed for Novartis Pharmaceuticals Corporation. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of these studies have been protected.

We are aware that you conducted the studies as sub-investigators under David Gordon, M.D., of US Oncology, Inc., in Houston, Texas, who signed the Form FDA-1572 as the principal investigator. However, we wish to remind you that each study physician must have his/her own Form FDA-1572 as the principal investigator.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that you did not adhere to pertinent federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects. We note that at the close of the inspection, our personnel presented their inspectional observations (Form FDA 483) and discussed these observations with you and your staff. We concur with their findings and wish to emphasize the following:

1. You failed to follow appropriate informed consent procedures [21 CFR 50.20 and 25] in that:
  - a. Although you stated in the opening interview that you "would generally sign off on the informed consent form within 24 hours *after* the patient signed it," we found that you signed the consent form *prior* to the date the subject signed the consent form for the following subjects:
    - i. Subject \_\_\_\_\_ signed the consent form on 1/21/00; however, you signed this consent form and dated it one day before, on 1/20/00.
    - ii. Subject \_\_\_\_\_ signed the consent form on 7/28/00; however, you signed this consent form and dated it one day before, on 7/27/00.
    - iii. Subject \_\_\_\_\_ signed the consent form on 12/20/99; however, Dr. Paladine signed this consent form and dated it six days before, on 12/14/99.

- b. You did not submit to the IRB the revised consent form for approval to ensure that the requirements pertaining to patients' safety and legal rights were met.
2. You failed to obtain or document IRB approval [21 CFR 312.66] for amendments to the protocols and consent forms that were obtained from the \_\_\_\_\_ web pages.
3. You failed to maintain adequate drug accountability [21 CFR 312.62(a)] in that there are no records of study medications administered to patients, or of the study drug receipt, disposition or destruction by you at the site.

Because of the departures from FDA regulations discussed above, we request that you inform this office, in writing, within thirty (30) working days from the date of receipt of this letter, of the actions you have taken or plan to take to bring your procedures into compliance with FDA regulations and to ensure that the violations are not repeated in any ongoing or future studies.

We plan to monitor your activities to ensure that you have, indeed, implemented appropriate measures to remedy the situation and comply with federal regulations.

We appreciate the cooperation shown our personnel during the inspection. Should you have any questions or concerns about any aspect of the clinical testing of investigational drugs, we invite you to contact me by letter at the address given below.

Sincerely yours,

151

Antoine El Hage, Ph.D.  
Branch Chief  
Good Clinical Practice II, HFD-47  
Division of Scientific Investigations  
Office of Medical Policy  
Center for Drug Evaluation and Research  
7520 Standish Place, Room 125  
Rockville, MD 20855

Page \_\_\_\_\_

bcc:

HFA-224

HFD-150 / Document Room (NDA 21-386 Zometa® (zolendronic acid) injection)

HFD-150 / Review Division - Div. Director: Dr. Richard Pazdur, M.D.

HFD-150 / Medical Officer - Amna Ibrahim, M.D.

HFD 150 / RHPM / CSO - Debra Vause

HFD-45 / Division File

HFD-47 c/r/s GCP II File #10538

HFD-47 / U / Hajarian

HFR-SE250 / DIB (GALLANT)

HFR-SE2585 / BIMO MONITOR (TORRES)

HFR-SE2570/ FIELD INVESTIGATOR (SCHWARTZ AND FIGAROLE)

FEI: 3002873962

FACTS Assignment #255756

Field Classification: OAI

H.Q. Classification:

- \_\_\_\_\_ 1) NAI
- \_\_\_\_\_ 2) VAI - no response requested
- X  3) VAI-R - response requested
- \_\_\_\_\_ 4) VAI-RR - response received
- \_\_\_\_\_ 5) OAI

If the Field and Headquarters classifications are different, reasons for change in classification, if applicable: Information regarding lack of study oversight by the principal investigator of record is forwarded to the Dallas District Office that will be inspecting the principal investigator. Clinical investigators at this site are made aware of the need to sign Form FDA-1572.

Deficiencies Noted:

- X  inadequate informed consent
- X  inadequate drug accountability
- \_\_\_\_\_ deviations from protocol
- \_\_\_\_\_ inaccurate and inadequate records
- \_\_\_\_\_ failure to report ADR's
- X  other: failure to notify IRB of amendments in protocols and consent forms

Deficiency Codes: #3, #4, and #15

O: \ (uk \ HFD150\_2002JanJun' \_\_\_\_\_ \_ AIR.doc)

drafted: KMU/ (02/01/02)

reviewed: AEH / (1/31/02; 2/4/02)

revised: KMU/ (2/4/02)

finalized: MRB / (2/4/02)

**Note to Review Division Medical Officer, HFD 150:**

Zometa® (zoledronic acid) is a third generation bisphosphonate and a potent inhibitor of bone resorption. It is approved for use in the treatment of tumor-induced hypercalcemia in over 40 countries including the U.S., Canada, European Union, Australia and New Zealand.

The sponsor submitted results of 3 studies: Study #039 showed that zoledronic acid was effective in the treatment of bone metastases in hormone-refractory prostate cancer patients. Study #010 showed that zoledronic acid was as effective as pamidronate in preventing skeletal-related events (SRE) in patients with breast cancer and multiple myeloma. Study #011 showed that zoledronic acid significantly reduced the median time to the first SRE by two months compared to placebo in patients with lung cancer and other solid tumors. Zometa® is intended to prevent SRE in prostate cancer, breast cancer, multiple myeloma, and solid tumors other than prostate and breast cancer.

The sponsor requested priority review on the basis that (i) prostate cancer is one of the most common cancers in men, (ii) bone is a preferred or only site for prostate cancer metastases in >80% of men with advanced prostate cancer causing painful, debilitating clinical symptoms, and (iii) Zometa® offers a significant improvement in the treatment of patients with bone metastases compared to marketed products.

Dr. Gordon (the principal investigator) was listed in the NDA with having enrolled 112 subjects: 38 subjects in Study #010 and 43 in Study #011. However, when I communicated with the sponsor to set up an inspection, the sponsor informed me that **there are only five subjects enrolled at this site**. This study was managed by a SMO, with many sites in throughout North America. I arranged for Dr. Gordon to be inspected (for the five subjects he enrolled) and to be made aware that he cannot be a PI and supervise by proxy all other subjects (>100) that were enrolled in other sites physically far away (and in different states), and that he is accountable/liable for all regulatory violations that occur at all sub-investigators' sites, and to determine if Dr. Gordon provided adequate study oversight.

The \_\_\_\_\_, where the CFRs and source documents are available for audit. This site \_\_\_\_\_ This site was inspected to verify data submitted to FDA, and to make the sub-investigators aware that it is not proper to undertake clinical trials as sub-investigators for a principal investigator who is physically far away in a different state; that this, in fact, is like conducting a clinical trial without an IND, and that the sub-investigators should sign their own Form FDA 1572, and to determine if the principal investigator provided adequate study oversight of the subjects enrolled at this site.

There is no documentation of study oversight at the site in \_\_\_\_\_ where a FDA Form 483 was issued to the \_\_\_\_\_. The principal investigator's site is scheduled for inspection on January 28, 2002.

Problems with informed consent procedure include the following:

1. Revisions to informed consent and amendments to the protocols were not reviewed and evaluated by the clinical investigators or submitted to the IRB to ensure that the requirements pertaining to patients' safety and legal rights were met.
2. The clinical investigators signed the consent form prior to the date the subject signed the consent form for subjects \_\_\_\_\_

The investigators did not maintain drug accountability records for study medications administered to patients, or records of the study drug receipt, disposition or destruction at the site. Also, they did not keep packing slips or other records for the receipt of study medications received.

In summary, the audit disclosed that there is adequate documentation that all subjects enrolled did exist and that all enrolled subjects received the assigned study medication, had clinical and laboratory parameters recorded, completed the study, and had their outcome captured as specified in the protocol and amendments. Problems with inadequate drug accountability and inadequate informed consent process were found, which were not of clinical significance to require exclusion of any subject from data analysis. Adequate study oversight by the principal investigator (Dr. Gordon in San Antonio, Texas) was not found at the site inspected. This issue will be addressed during the inspection of Dr. Gordon scheduled on January 28, 2002.

Thus, data from subjects at the \_\_\_\_\_, can be used for evaluation of the Study Protocols #010 and #011 submitted in support of NDA 21-386 for review by FDA.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Vause

J. Thaddeus Beck, M.D.  
Highlands Oncology Group  
3232 North Hills Blvd.  
Fayetteville, Arkansas 72703

Food and Drug Administration  
Rockville MD 20857

JUN 05 2002

Dear Dr. Beck:

Between November 27 and 30, 2001, Ms. Paula J. Perry, representing the Food and Drug Administration (FDA), met with you to review your conduct of a clinical study (Protocols No. No. 011) of the investigational drug Zometa® (zoledronic acid), performed for Novartis Pharmaceuticals Corporation. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of these studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that you did not adhere to pertinent federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects. We are aware that Ms. Perry met with you and your staff at the close of the inspection and presented her findings on a Form FDA 483 and discussed them with you. The findings included protocol violations, i.e., failure to follow protocol-specified procedures for test article infusion, required laboratory tests and obtain vital signs; inadequate record keeping; and failure to re-consent study subject with the most current informed consent. We note your agreement with her findings and your intent to comply with protocol requirements and applicable procedures in future studies.

Please make appropriate corrections/changes in your procedures to ensure that the findings noted above are not repeated in any ongoing or future studies.

We appreciate the cooperation shown Investigator Perry during the inspection. Should you have any questions or concerns about any aspect of the clinical testing of investigational drugs, we invite you to contact me by letter at the address given below.

Sincerely yours,

151

Antoine El Hage, Ph.D.  
Branch Chief  
Good Clinical Practice II, HFD-47  
Division of Scientific Investigations  
Office of Medical Policy  
Center for Drug Evaluation and Research  
7520 Standish Place, Room 125  
Rockville, MD 20855

cc:

HFA-224

HFD-150 / Document Room (NDA 21-386 Zometa® (zolendronic acid) injection)

HFD-150 / Review Division - Div. Director: Dr. Richard Padzur, M.D.

HFD-150 / Medical Officer – Amna Ibrahim, M.D.

HFD 150 / RHPM / CSO – Debra Vause

HFD-45 / Division File

HFD-47 c/r/s GCP II File #10535

HFD-47 / U / Hajarian

HFR-SW150 / DIB (THORNBURG)

HFR-SW1540 / BIMO MONITOR (MARTINEZ)

HFR-SW1590 / FIELD INVESTIGATOR (PERRY)

FEI: 3003530911

FACTS Assignment #255756

Field Classification: VAI

H.Q. Classification:

- 1) NAI
- 2) VAI - no response requested
- 3) VAI-R - response requested
- 4) VAI-RR - response received
- 5) OAI

If the Field and Headquarters classifications are different, reasons for change in classification, if applicable:

Deficiencies Noted:

- inadequate consent form
- inadequate drug accountability
- deviations from protocol
- inaccurate and inadequate records
- failure to report ADR's
- other: failure to notify IRB of changes in research activities

Deficiency Codes: #2, #5 and #6

O: \ (uk \ HFD150\_2002JanJun \ Beck\_VAI.doc)

drafted: KMU/ (01/18/02)

reviewed: AEH / (1/22/02)

revised: KMU/ (1/23/02)

finalized: MRB / (1/23/02)

**Note to Review Division Medical Officer, HFD 150:**

Zometa® (zoledronic acid) is a third generation bisphosphonate and an inhibitor of bone resorption. It is approved for the treatment of tumor induced hypercalcemia in over 40 countries including the U.S. Zometa® is intended to prevent skeletal related events in prostate cancer, breast cancer, multiple myeloma, and other solid tumors.

This inspection was limited to the subjects studied in Protocol #011 entitled: "Safety and efficacy of 4 and 8 mg i.v. in patients with any cancer with bone metastases other than breast cancer or multiple myeloma or prostate cancer (double-blind, multicenter, placebo-controlled)." The district office will submit another EIR after completing a second inspection of this site in January, '01.

Dr. Beck enrolled 21 subjects in study #011. Two subjects remain alive at the time of the inspection. The clinic and study records of seven randomly selected subjects (#11174, #10144, #20134, #10135, #11175, #20133 and #10139) were reviewed during the inspection.

A Form FDA 483 was issued for protocol violations, inadequate record keeping and inadequate informed consent.

**Inadequate informed consent [21 CFR 50.20, 50.27(a)].**

- a. Subject #10135 was not re-consented with amended informed consent dated 7/13/99 until visit 10 (8/23/99) after a previous visit 8 on 8/2/99 had occurred.
- b. Subject #11175 was not re-consented with amended informed consent dated 7/11/00 (visits 9-14, study completion).

**Inadequate/inaccurate record keeping [21 CFR 312.62(b)]**

- a. CRF does not reflect infusion of test article for subject #20133, Visit 2, though Drug Accountability Record does reflect test article was dispensed for this subject.
- b. No documentation of serum chemistry, hematology, and urinalysis lab samples/results for subject #11174.

**Failure to conduct study in accordance with the approved protocol [21 CFR 312.60 and 312.53(c)(1)(vi)(a)].**

- a. Infusion of test article for 5 minutes instead of 15 minutes (as changed by protocol amendment) occurred for subject #10135 (visit 8), and subject #20134 (visits 6, 7 and 11).
- b. Subject #20134 was infused with 50 ml of test article/saline at visit 6 instead of 100 ml (protocol amendment).
- c. Urinalysis sample was not collected for subject #10135 (visit 6).
- d. ECGs were not done for subjects #20133 (visit 1), #10135 (visit 14) and #11175 (visit 14).
- e. Bone scan survey was not done for subject #11174 (visit 6).
- f. Vital signs were not taken for study subject #20133.
- g. Pain score (BPI) CRFs were not completed for subjects #20133 (visits 2 and 4) and #11175 (visit 14).
- h. Blood pressure and pulse readings were not collected for subject #20133 (visit 2).

Overall, there was sufficient documentation at this site to assure that all audited subjects did exist, and were available for the duration of the study and that all enrolled subjects received the assigned study medication, had clinical and laboratory parameters recorded, completed the study, and had their outcome captured as specified in the protocols and amendments.

Thus, all of the subjects at the center in Fayetteville, Arkansas can be used for evaluation of the Study Protocols #010 and #011 submitted in support of NDA 21-386 for review by FDA.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

*Vause*

Food and Drug Administration  
Rockville MD 20857

FEB 4 2002

Dear \_\_\_\_\_

Between January 21 and 25, 2002, Dr. Gerald N. Mcgirl, representing the Food and Drug Administration (FDA), met with you to review your conduct of clinical studies (Protocols No. 010 and No. 011) of the investigational drug Zometa® (zoledronic acid), performed for Novartis Pharmaceuticals Corporation. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of these studies have been protected.

We are aware that you conducted the studies \_\_\_\_\_ under Lee S. Rosen, M.D., of UCLA Community Oncology Research Network who provided oversight of the studies as the principal investigator. From our review of the inspection report and the documents submitted with that report, we conclude that you adhered to pertinent federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects. However, we wish to remind you that each study physician must have his/her own Form FDA-1572 as the principal investigator.

We appreciate the cooperation shown Investigator Mcgirl during the inspection. Should you have any questions or concerns about any aspect of the clinical testing of investigational drugs, we invite you to contact me by letter at the address given below.

Sincerely yours,

*ISI*

Antoine El Hage, Ph.D.  
Branch Chief  
Good Clinical Practice II, HFD-47  
Division of Scientific Investigations  
Office of Medical Policy  
Center for Drug Evaluation and Research  
7520 Standish Place, Room 125  
Rockville, MD 20855

cc:  
Lee Rosen, M.D.  
UCLA Medical Center, PVU Building  
10945 Le Conte Avenue, Suite 2333  
Los Angeles, California 90095



**APPEARS THIS WAY  
ON ORIGINAL**

bcc:

HFA-224

HFD-150 / Document Room {NDA 21-386 Zometa® (zolendronic acid) injection}

HFD-150 / Review Division - Div. Director: Dr. Richard Pazdur, M.D.

HFD-150 / Medical Officer - Amna Ibrahim, M.D.

HFD 150 / RHPM / CSO - Debra Vause

HFD-45 / Division File

HFD-47 c/r/s GCP II File #10541

HFD-47 / U / Hajarian

HFR-PA150 / DIB (MOSS)

HFR-PA150 / BIMO MONITOR (MCGIRL)

HFR-PA150 / FIELD INVESTIGATOR (MCGIRL)

FEI: 3003551992

FACTS Assignment #255756

Field Classification: NAI

H.Q. Classification:

- 1) NAI
- 2) VAI - no response requested
- 3) VAI-R - response requested
- 4) VAI-RR - response received
- 5) OAI

O:\(uk\HFD150\_2002JanJun\ )

drafted: KMU/ (01/31/02)

reviewed: AEH / (2/1/02)

revised: KMU/ (2/1/02)

finald: MRB/ (2/1/02)

**Note to Review Division Medical Officer, HFD 150:**

Zometa® (zoledronic acid) is a third generation bisphosphonate and an inhibitor of bone resorption. It is approved for the treatment of tumor induced hypercalcemia in over 40 countries including the U.S. Zometa® is intended to prevent skeletal related events in prostate cancer, breast cancer, multiple myeloma, and other solid tumors.

This inspection was limited to Protocols #010 and #011.

Dr. Rosen (the principal investigator) was listed in the NDA with having enrolled 118 subjects including 38 subjects in Study #010 and 43 in Study #011. However, when I communicated with the sponsor to set up an inspection, the sponsor informed me that **there are NO subjects enrolled at this site**. This study is managed by a \_\_\_\_\_, with many sites in California. The largest \_\_\_\_\_, where the CFRs and source documents are available for audit. Thus, I arranged for Dr. Rosen to be inspected and made aware that he cannot be a PI and supervise by proxy all other subjects that were enrolled in other sites physically far away, and that he is accountable/liable for all regulatory violations that occur at \_\_\_\_\_, and to determine if Dr. Rosen provided adequate study oversight.

The study site managed by \_\_\_\_\_

Adequate study oversight by Dr. Rosen was documented. No FDA Form 483 was issued to either site.

In general, the study was conducted in accordance with the requirements of the protocol. Minor protocol deviations include the following:

- a. Subject 20881 in study #010 received study drug infusion at visit 19 in error (protocol specifies infusions during visits 2-18 only). This subject continued on the extension protocol but did not sign the informed consent form until two months after the study drug infusion at visit 19.
- b. Subject 10092 in study #011 was on oral Fosamax (a bisphosphonate) from March 16 to April 14, 1999, prior to starting study drug treatment on May 14, 1999. Treatment with bisphosphonates at any time during the 12 months prior to visit 1 was an exclusion criterion. However, an exception was given for patients who have had a single exposure to bisphosphonates  $\geq 30$  days prior to visit 1. The sponsor determined that this one month of oral bisphosphonate the patient received was equivalent to one intravenous treatment and therefore not a protocol violation.

In summary, the audit disclosed that there is adequate documentation that all subjects enrolled did exist and that all enrolled subjects received the assigned study medication, had clinical and laboratory parameters recorded, completed the study, and had their outcome captured as specified in the protocol and amendments. Adequate study oversight by the principal investigator was documented.

Thus, data from subjects a \_\_\_\_\_, can be used for evaluation of the Study Protocols #010 and #011 submitted in support of NDA 21-386 for review by FDA.



*Patdur*

Food and Drug Administration  
Rockville MD 20857

FEB 4 2002

Lee Rosen, M.D.  
UCLA Medical Center  
PVU Building  
10945 Le Conte Avenue, Suite 2333  
Los Angeles, California 90095

Dear Dr. Rosen:

Between December 19, 2001 and January 23, 2002, Mr. Ron Koller, representing the Food and Drug Administration (FDA), met with you to review your conduct of clinical studies (Protocols No. 010 and No. 011) of the investigational drug Zometa® (zoledronic acid), performed for Novartis Pharmaceuticals Corporation. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of these studies have been protected.

We are aware that there were no subjects enrolled at your site. This inspection focussed on your oversight of the studies that enrolled subjects at sub-investigators' sites. From our review of the inspection report and the documents submitted with that report, we conclude that you maintained adequate study oversight and adhered to pertinent federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator Koller during the inspection. Should you have any questions or concerns about any aspect of the clinical testing of investigational drugs, we invite you to contact me by letter at the address given below.

Sincerely yours,

*ISI*  
Antoine El Hage, Ph.D.  
Branch Chief  
Good Clinical Practice II, HFD-47  
Division of Scientific Investigations  
Office of Medical Policy  
Center for Drug Evaluation and Research  
7520 Standish Place, Room 125  
Rockville, MD 20855

cc:

HFA-224

HFD-150 / Document Room {NDA 21-386 Zometa® (zolendronic acid) injection}

HFD-150 / Review Division - Div. Director: Dr. Richard Pazdur, M.D.

HFD-150 / Medical Officer – Amna Ibrahim, M.D.

HFD 150 / RHPM / CSO – Debra Vause

HFD-45 / Division File

HFD-47 c/r/s GCP II File #9982

HFD-47 / U / Hajarian

HFR-PA250 / DIB (KOZICK)

HFR-PA2565 / BIMO MONITOR (KOLLER)

HFR-PA2565 / FIELD INVESTIGATOR (KOLLER)

FEI: 3002914062

FACTS Assignment #255756

Field Classification: NAI

H.Q. Classification:

- 1) NAI
- 2) VAI - no response requested
- 3) VAI-R - response requested
- 4) VAI-RR - response received
- 5) OAI

If the Field and Headquarters classifications are different, reasons for change in classification, if applicable:

Deficiencies Noted:

- inadequate consent form
- inadequate drug accountability
- deviations from protocol
- inaccurate and inadequate records
- failure to report ADR's
- other: failure to notify IRB of changes in research activities

Deficiency Codes: —

O: \ (uk \ HFD150\_2002JanJun \ Rosen \_NAI.doc)

drafted: KMU/ (01/31/02)

reviewed: AEH / (1/31/02)

revised: KMU/ (2/1/02)

finalled: MRB / (2/1/02)

**Note to Review Division Medical Officer, HFD 150:**

Zometa® (zoledronic acid) is a third generation bisphosphonate and an inhibitor of bone resorption. It is approved for the treatment of tumor induced hypercalcemia in over 40 countries including the U.S. Zometa® is intended to prevent skeletal related events in prostate cancer, breast cancer, multiple myeloma, and other solid tumors.

This inspection was limited to Protocols #010 and #011.

Dr. Rosen (the principal investigator) was listed in the NDA with having enrolled 118 subjects including 38 subjects in Study #010 and 43 in Study #011. However, when I communicated with the sponsor to set up an inspection, the sponsor informed me that **there are NO subjects enrolled at this site**. This study is managed \_\_\_\_\_, with many sites in California. The largest \_\_\_\_\_ where the CFRs and source documents are available for audit. Thus, I arranged for Dr. Rosen to be inspected and made aware that he cannot be a PI and supervise by proxy all other subjects that were enrolled in other sites physically far away, and that he is accountable/liable for all regulatory violations that occur at all sub-investigators' sites, and to determine if Dr. Rosen provided adequate study oversight.

The study site managed by \_\_\_\_\_

This study site was inspected to verify \_\_\_\_\_

t

id,

Adequate study oversight by Dr. Rosen was documented. No FDA Form 483 was issued to either site.

In summary, there was sufficient documentation at this site to assure that there was adequate oversight of the study by the principal investigator of record, that all audited subjects did exist and were available for the duration of the study and that all enrolled subjects received the assigned study medication, had clinical and laboratory parameters recorded, completed the study, and had their outcome captured as specified in the protocols and amendments.

Thus, all of the subjects \_\_\_\_\_ can be used for evaluation of the Study Protocols #010 and #011 submitted in support of NDA 21-386 for review by FDA.

## CLINICAL INSPECTION SUMMARY

DATE: January 25, 2002

TO: Debra Vause, Regulatory Health Project Manager  
Amna Ibrahim, M.D., Medical Officer, Clinical Reviewer  
Grant Williams, M.D., Team Leader, Clinical Reviewer  
Division of Oncology Drug Products, HFD-150

THROUGH: Tony El-Hage, Ph.D., Branch Chief, Good Clinical Practice Branch II  
(HFD-47), Division of Scientific Investigations

FROM: Khin Maung U, M.D., Medical Officer, Good Clinical Practice Branch II  
(HFD-47), Division of Scientific Investigations

SUBJECT: Evaluation of Domestic Inspections      FACTS #255756

NDA: 21-386

APPLICANT: Novartis Pharmaceuticals Corporation

DRUG: Zometa® (zoledronic acid for injection)

CHEMICAL CLASSIFICATION: Type 1 P

THERAPEUTIC CLASSIFICATION: Priority Review

INDICATIONS: To prevent skeletal related events in prostate cancer, breast cancer, multiple myeloma, and solid tumors other than prostate cancer and breast cancer

CONSULTATION REQUEST DATE: August 29, 2001

GOAL DATE TO PROVIDE INSPECTION SUMMARY REPORT: February 8, 2002

PDUFA GOAL DATE: February 22, 2002

**I. BACKGROUND**

Zometa® (zoledronic acid) is a third generation bisphosphonate and an inhibitor of bone resorption. It is approved for use in the treatment of tumor induced hypercalcemia in > 40 countries including the U.S.

The sponsor submitted results of 3 studies: Study #039 showed that zoledronic acid was effective in the treatment of bone metastases in hormone-refractory prostate cancer patients. Study #010 showed that zoledronic acid was as effective as pamidronate in preventing skeletal-related events in patients with breast cancer and multiple myeloma. Study #011 showed that zoledronic acid significantly reduced the median time to the first skeletal-related event (SRE) by two months compared to placebo in patients with lung cancer and other solid tumors. Zometa® is intended to prevent skeletal related events in prostate cancer, breast cancer, multiple myeloma, and solid tumors other than prostate cancer and breast cancer.

The sponsor requested priority review on the basis that prostate cancer is one of the most common cancers in men, bone is a preferred or only site for prostate cancer metastases in >80% of men with advanced prostate cancer causing painful, debilitating clinical symptoms, and that Zometa® offers a significant improvement in the treatment of patients with bone metastases compared to marketed products.

II. RESULTS (by site):

NAME	CITY, STATE	COUNTRY	PROTOCOL	INSPECTION DATE	EIR RECEIVED	CLASSN.
Leonard Kalman, MD	Miami, FL	USA	#010, #011	11/19-30/2001	1/11/02	VAI
Thaddeus Beck, MD	Fayetteville, AR	USA	#010, #011	11/27-39/2001	1/17/02	VAI
*David Gordon, MD	San Antonio, TX	USA	#010, #011			
†Lee Rosen, MD	Los Angeles, CA	USA	#010, #011			

- \* This is a SMO with many sites all over the US; enrolled only 5 subjects.
- \*\* Studies at this site are conducted by sub-investigators listed in FDA Form 1572 of David Gordon in San Antonio, TX.
- † This is a SMO with many sites in California; enrolled no subjects
- ‡ Studies at this site are conducted by sub-investigators listed in FDA Form 1572 of Lee Rosen in Los Angeles, CA

**Study Protocols:**

Study #010: Safety and efficacy of 4 and 8 mg i.v. in patients with bone metastases breast cancer or multiple myeloma (double-blind, multicenter, double-dummy, placebo-controlled). It was a Phase III study in 1648 patients with bone metastases and multiple myeloma or breast cancer. Patients had to be ambulatory, at least 18 years old, and with ECOG performance status of 0, 1 or 2. Bone lesions had to be apparent on plain film radiographs. Patients had to be receiving anti-cancer therapy. Breast cancer patients who were receiving hormonal therapy had to be using first- or second-line hormonal therapy. Patients were excluded if they had significant hepatic, renal or cardiac impairment, were hypercalcemic or if they had brain metastases, or (in breast cancer patients) if they had lymphangitic lung metastases. The core phase of the study was of 12 months' duration. Patients received zoledronic acid 4 mg, zoledronic acid 8 mg or pamidronate (Aredia) 90 mg every 3-4 weeks. Following a protocol amendment, all patients on 8 mg zoledronic acid were switched to 4 mg zoledronic acid. Of 1648 patients randomized, all but 8 were included in the analysis of efficacy. About 40% of patients in each treatment group discontinued prematurely – the most common reasons being adverse events and deaths.

Study #011: Safety and efficacy of 4 and 8 mg i.v. in patients with any cancer with bone metastases other than breast cancer or multiple myeloma or prostate cancer (double-blind, multicenter, placebo-controlled). This was a Phase III study in 773 patients aged 18 years or over with bone metastases from solid tumors other than breast or prostate cancers. Patients had to have ECOG performance status of 0, 1 or 2; those with ECOG scores of 2 had to have had their bone metastases diagnosed within 6 weeks of study entry. Patient were excluded from the study if they had significant hepatic, renal or cardiac impairment, were hypercalcemic or had symptomatic brain metastases. The duration of the study was 9 months. Patients received treatment every 3 weeks as a 5-minute infusion of 4 mg or 8 mg zoledronic acid in a total volume of 100 ml normal saline or, in the placebo group, 100 ml normal saline. Following protocol amendments, all patients on 8 mg zoledronic acid were switched to 4 mg zoledronic acid, and the infusion time was changed to 15 minutes. All 773 patients were included in the analysis of efficacy. Approximately 25% of patients completed 9 months of treatment. Adverse events and deaths were the most frequent reasons for discontinuation, followed by withdrawal of consent.

The primary endpoint was the same for the above protocols, namely the proportion of patients with at least one skeletal-related event (SRE), compared between groups using a Cochran-Matell-Haenszel (CMH) test. The SREs included: (1) radiation therapy to bone (either irradiation or use of intravenous radioisotopes), (2) Surgery to bone to set, stabilize or prevent pathologic fractures or spinal cord compression, (3) Pathologic bone fractures, (4) Spinal cord compression, (5) Tumor-induced hypercalcemia of malignancy (TIH) defined as a corrected serum calcium level  $\geq 3.00$  mmol/L (12.0 mg/dL). (N.B. TIH was included only in a secondary analysis.)

The following centers enrolled large number of subjects among the centers in North America. Thus, inspection of these sites is critical for approval of this drug.

- (1) **Leonard Kalman, MD**  
**Oncology/Hematology Group of South Florida**  
**Baptist Medical Arts Bldg**  
**8940 N. Kendall Drive, S 300E**  
**Miami, Florida 33176**  
 Inspection dates: November 19-30, 2001

Basis for Site Selection: Dr. Kalman enrolled a total of 44 subjects in three studies, and obtained a positive response (favoring Zometa®) in all three studies.

**Methodology:** Inspection assignments were issued to the field offices at the respective addresses.

**a. What was inspected**

The clinic and study records of eleven subjects (5 in protocol 010 and 6 in protocol 011) were reviewed in detail to determine the investigator's compliance with the study protocols and applicable regulatory requirements.

**b. Limitations of the inspection**

The audit was limited to two protocols reviewed at this site: namely, Study #010 and Study #011.

**c. General observations/commentary**

A form FDA 483 was issued for protocol violations, and inadequate informed consent process:

1) Records not available

All subjects' medical notes and all laboratory test reports were available.

2) Protocol Violations

In general, the study was conducted in accordance with the requirements of the protocol. The following protocol violations were found during the audit:

- a. For subject 20026, serum creatinine was not measured prior to infusion of study drug on 7/10/00 (visit 7) and 7/28/00 (visit 8) as required by the protocol.
- b. Subjects 10026 and 20027 in study 011 did not receive study drug infusions every three weeks as specified by the protocol.
- c. Subject 20107 received Fosamax® (a bisphosphonate), a prohibited concomitant drug, while on study.
- d. Subject 20115 was enrolled without fulfilling the inclusion criteria that required at least one osteolytic bone metastasis confirmed by conventional bone X-ray.

4) Premature withdrawals

None.

5) Adverse events

No issues reported in EIR.

6) Informed consent/IRBs/protocol amendments

Failure to obtain adequate informed consent in that consent was obtained from subject 20115, who was non-English speaking, through the subject's son as interpreter. The latter concealed from the subject the fact that she had bone metastases from her breast cancer, and that the study drug was intended for treatment of cancer-related bone metastases. (This subject was withdrawn from the study after she developed a large subdural hematoma resulting in expressive aphasia and right hemiparesis.)

7) Record Keeping

There were no record keeping issues observed during the inspection.

8) Drug accountability

There were no drug accountability issues observed during the inspection.

In summary, the audit disclosed that there is adequate documentation that all subjects enrolled did exist and that all enrolled subjects received the assigned study medication, had clinical and laboratory parameters recorded, completed the study, and had their outcome captured as specified in the protocol and amendments. Instances of protocol violations and inadequate informed consent process were found, which were not of clinical significance to require exclusion of any subject from data analysis.

Thus, data from subjects at the center in Miami, Florida can be used for evaluation of the Study Protocols #010 and #011 submitted in support of NDA 21-386 for review by FDA.

(2) **J. Thaddeus Beck, MD**  
**Highlands Oncology Group**  
**3232 North Hills Blvd.**  
**Fayetteville, Arkansas 72703**

Inspection dates: ~~November~~ 27-30, 2001

Basis for Site Selection: Dr. Beck enrolled a total of 48 subjects in three studies, and obtained a positive response in two studies; the third study (#039) where no positive response was found enrolled only 4 subjects.

Methodology: Inspection assignments were issued to the field offices at the respective addresses.

**a. What was inspected**

Dr. Beck enrolled 21 subjects in study #011. Two subjects remain alive at the time of the inspection. The clinic and study records of seven randomly selected subjects were reviewed during the inspection.

**b. Limitations of the inspection**

This inspection was limited to the subjects studied in Protocol #011. The district office will submit another EIR after completing a second inspection of this site in January, '01.

**c. General observations/commentary**

A Form FDA 483 was issued for protocol violations, inadequate record keeping and inadequate informed consent.

1) Records not available

All subjects' medical notes and all laboratory test reports were available.

2) Protocol Deviations

In general, the study was conducted in accordance with the requirements of the protocol. The following protocol violations were found during the audit of study #011:

- a. Infusion of test article for 5 minutes instead of 15 minutes (as changed by protocol amendment) occurred for subject #10135 (visit 8), and subject #20134 (visits 6, 7 and 11).
- b. Subject #20134 was infused with 50 ml of test article/saline at visit 6 instead of 100 ml (protocol amendment).
- c. Urinalysis sample was not collected for subject #10135 (visit 6).
- d. ECGs were not done for subjects #20133 (visit 1), #10135 (visit 14) and #11175 (visit 14).
- e. Bone scan survey was not done for subject #11174 (visit 6).
- f. Vital signs were not taken for study subject #20133.
- g. Pain score (BPI) CRFs were not completed for subjects #20133 (visits 2 and 4) and #11175 (visit 14).
- h. Blood pressure and pulse readings were not collected for subject #20133 (visit 2).

3) Premature withdrawals

There were no issues of premature withdrawals.

4) Adverse events

No issues reported in EIR.

5) Informed consent/IRBs/protocol amendments

- a. Subject #10135 was not re-consented with amended informed consent dated 7/13/99 until visit 10 (8/23/99) after a previous visit 8 on 8/2/99 had occurred.
- b. Subject #11175 was not re-consented with amended informed consent dated 7/11/00 (visits 9-14, study completion).

6) Inadequate/inaccurate Record Keeping

- a. CRF does not reflect infusion of test article for subject #20133, Visit 2, though Drug Accountability Record does reflect test article was dispensed for this subject.

b. No documentation of serum chemistry, hematology, and urinalysis lab samples/results for subject #11174.

7) Drug accountability

There were no drug accountability issues observed during the inspection

In summary, the audit disclosed that there is adequate documentation that all subjects enrolled did exist and that all enrolled subjects received the assigned study medication, had clinical and laboratory parameters recorded, completed the study, and had their outcome captured as specified in the protocol and amendments. Instances of protocol violations, inadequate record keeping and inadequate informed consent process were found, which were not of clinical significance to require exclusion of any subject from data analysis.

Thus, all of the subjects at the center in Fayetteville, Arkansas, can be used for evaluation of the Study Protocols #010 and #011 submitted in support of NDA 21-386 for review by FDA.

(3)

(i) **Lee Rosen, MD (Principal Investigator)**  
UCLA Medical Ctr, PVU Bldg,  
10945 Le Conte Ave, S 2333  
Los Angeles, CA 90095

Inspection dates: Jan 14-23, 2002

(ii)

Basis for Site Selection: Dr. Rosen was reported in the NDA as having enrolled a large number of subjects (118).

Methodology: Inspection assignments were issued to the field offices at the respective addresses.

a. **What was inspected**

The informed consent forms, case report forms, medical history notes (of a random selection of four subjects from each study protocol out of the \_\_\_\_\_ .d

Investigator (Dr. Rosen) providing adequate study oversight of the study performed' \_\_\_\_\_ i. Evidence of the Principal  
at a peripheral site was sought for and documentation of this oversight was reviewed.

b. **Limitations of the inspection**

The audit was limited to two protocols reviewed at these sites: namely, Study #010 and Study #011.

c. **General observations/commentary**

Dr. Rosen (the principal investigator) was listed in the NDA with having enrolled 118 subjects including 38 subjects in Study #010 and 43 in Study #011. However, when I communicated with the sponsor to set up an inspection, the sponsor informed me that there are NO subjects enrolled at this site. This study is managed by \_\_\_\_\_ and source documents are available for audit. Thus, DSI arranged for Dr. Rosen to be inspected and made aware that he cannot be a PI and supervise by proxy all other subjects that were enrolled in other sites physically far away, and that he is accountable/liable for all regulatory violations that occur at all sub-investigators' sites, and to determine if Dr. Rosen provided adequate study oversight.

Adequate study oversight was documented. No FDA Form 483 was issued to either site. During the inspection and at the close of the inspection, the following observations were discussed with the clinical investigators.

1) Records not available

2) Protocol Deviations

In general, the study was conducted in accordance with the requirements of the protocol.

Minor protocol deviations include the following:

- a. Subject 20881 in study #010 received study drug infusion at visit 19 in error (protocol specifies infusions during visits 2-18 only). This subject continued on the extension protocol but did not sign the informed consent form until two months after the study drug infusion at visit 19.
- b. Subject 10092 in study #011 was on oral Fosamax (a bisphosphonate) from March 16 to April 14, 1999, prior to starting study drug treatment on May 14, 1999. Treatment with bisphosphonates at any time during the 12 months prior to visit 1 was an exclusion criterion. However, an exception was given for patients who have had a single exposure to bisphosphonates  $\geq 30$  days prior to visit 1. The sponsor determined that this one month of oral bisphosphonate the patient received was equivalent to one intravenous treatment and therefore not a protocol violation.

3) Premature withdrawals

There were no issues of premature withdrawals.

4) Adverse events

No issues reported in EIR.

5) Informed consent/IRBs/protocol amendments

There were no record keeping issues observed during the inspection.

6) Record Keeping

There were no record keeping issues observed during the inspection.

7) Drug accountability

There were no drug accountability issues observed during the inspection

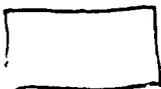
In summary, the audit disclosed that there is adequate documentation that all subjects enrolled did exist and that all enrolled subjects received the assigned study medication, had clinical and laboratory parameters recorded, completed the study, and had their outcome captured as specified in the protocol and amendments. Adequate study oversight by the principal investigator was documented.

(4)

(i) **David Gordon, MD** (*Principal Investigator*)  
8527 Village Drive, S 101,  
San Antonio, TX 78217

Dates of inspection: Inspection will begin at this site on January 28, 2002.

(ii)



**Basis for Site Selection:** Dr. Gordon was reported in the NDA as having enrolled a large number of subjects (114).

**Methodology:** Inspection assignments were issued to the field offices at the respective addresses.

**a. What was inspected**

The informed consent forms, case report forms, medical history notes (of a random selection of subjects from each study protocol out of the \_\_\_\_\_), X-rays and laboratory reports, drug dispensing records and pharmacy records were reviewed. Evidence of the Principal Investigator (Dr. Gordon) providing adequate study oversight of the study performed ' \_\_\_\_\_

**b. Limitations of the inspection**

The audit was limited to two protocols reviewed at these sites: namely, Study #010 and Study #011.

**c. General observations/commentary**

Dr. Gordon (the principal investigator) was listed in the NDA with having enrolled 112 subjects: 38 subjects in Study #010 and 43 in Study #011. However, when I communicated with the sponsor to set up an inspection, the sponsor informed me that **there are only five subjects enrolled at this site.**  
ir

to  
u

8) Other issues

- a. There was no documentation that the clinical studies were personally conducted or supervised by the principal investigator of record – Dr. David Gordon of San Antonio, Texas.
- b. The clinical investigators who conducted and supervised the clinical studies did not sign Form FDA 1572s.
- c. \_\_\_\_\_
- d. The radiology diagnostic sites used by the investigators for evaluating patient status were not included on the FDA Form 1572.

In summary, the audit disclosed that there is adequate documentation that all subjects enrolled did exist and that all enrolled subjects received the assigned study medication, had clinical and laboratory parameters recorded, completed the study, and had their outcome captured as specified in the protocol and amendments. Problems with inadequate record keeping, drug accountability and inadequate informed consent process were found, which were not of clinical significance to require exclusion of any subject from data analysis. Adequate study oversight by the principal investigator (Dr. Gordon in San Antonio, Texas) still needs to be evaluated during the inspection scheduled next week on January 29, 2002.

**III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS**

At all of the US study sites that were inspected, sufficient documentation was found to assure that all audited subjects did exist, and that they were available for the duration of the study, received the assigned study medication, had clinical and laboratory parameters recorded, completed the study, and had their outcome captured as specified in the protocols and amendments. FDA Forms 483 were issued to Dr. Kalman (Miami, FL), Dr. Beck (Fayetteville, AZ) and Dr. \_\_\_\_\_, where instances of protocol violations, inadequate informed consent process, inadequate record keeping and inadequate drug accountability were found, which were not of clinical significance to require exclusion of any subject from data analysis. At the sites in California, adequate study oversight by the principal investigator (Dr. Rosen in UCLA) over the study at the \_\_\_\_\_, was documented.

Overall, I recommend that data from all of the subjects at the centers in the U.S. that were inspected can be used for evaluation of NDA 21-386.

[Note: This Clinical Inspection Summary was based on the inspectional findings (FDA Form 483), EIRs received, and discussions with the FDA field investigators. Should the EIRs and exhibits from the remaining sites, when received, contain additional information that would significantly effect the classification or have an impact on the approval process, I will inform the Review Division in an amendment.]

Khin Maung U, M.D.  
Medical Officer, Good Clinical Practice Branch 2, HFD-47  
Division of Scientific Investigations

CONCURRENCE:  
Supervisory comments

Antoine El-Hage, Ph.D.  
Branch Chief, Good Clinical Practice Branch 2, HFD-47  
Division of Scientific Investigations

DISTRIBUTION:

NDA 21-386  
HFD-45/Division File  
HFD-45/Reading File  
HFD-45/Program Management Staff (electronic copy)  
HFD-47/El-Hage/U/Hajarian                      FACTS #255756  
HFD-47/Balser GCPB2 Files # 10530; #10535 #                      ; #                      ; #                      ; and #

## DSI CONSULT: Request for Clinical Inspections

**Date:** August 29, 2001

**To:** Khin Maung U, GCPB Reviewer/HFD-47

**Through:** Stan Woollen, Ph.D., Acting Director, DSI/HFD-45  
Richard Pazdur, Director, HFD-150

**From:** Debra Vause, HFD-150, PM  
Division of Oncology Drug Products, HFD-150

**Subject:** **Request for Clinical Inspections**  
NDA 21-386  
Novartis Pharmaceuticals Corporation  
Zometa ® (zoledronic acid for 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.

This Supplement provides for a new indication for the treatment of Bone Metastases in patients with Multiple Myeloma, Breast Cancer, or Prostate Cancer, and other solid tumors.

Indication	Protocol #	Site (Name and Address)
To prevent skeletal related events in prostate cancer, breast cancer, multiple myeloma, and solid tumors other than prostate cancer and breast cancer	Protocols 039, 010, 011	Dr Leonard Kallman Miami, Florida
		Dr Thadeus Beck Springdale, AR
		Dr David Gordon San Antonio, TX
		Dr Lee Rosen Los Angeles, CA

**Note: International inspection requests or requests for five or more inspections require sign-off by the ORM Division Director and forwarding through the Director, DSI.**

**Goal Date for Completion:**

We request that the inspections be performed and the Inspection Summary Results be provided by **February 8, 2002**. We intend to issue an action letter on this application by **February 22, 2002**.

Should you require any additional information, please contact Debra Vause at (301) 594-5724.

Concurrence: (if necessary)

Grant Williams, Medical Team Leader  
Amna Ibrahim, Medical Reviewer  
Debra Vause, Regulatory Project Manager

**APPEARS THIS WAY  
ON ORIGINAL**



NDA 21-223/S-003

**PRIOR APPROVAL SUPPLEMENT**

Novartis Pharmaceuticals Corporation  
Attention: Paula E. Rinaldi  
Director, Drug Regulatory Affairs  
One Health Plaza  
East Hanover, NJ 07936-1080

Dear Ms. Rinaldi:

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

Name of Drug Product: Zometa (zoledronic acid) Injection

NDA Number: 21-223

Supplement Number: S-003

Date of Supplement: January 18, 2002

Date of Receipt: January 22, 2002

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 March 23, 2002, in accordance with 21 CFR 314.101(a).

This supplement proposes to add a new indication for the treatment of ~~bone metastases of solid tumors and osteolytic lesions of multiple myeloma~~ bone metastases of solid tumors and osteolytic lesions of multiple myeloma, in conjunction with standard antineoplastic therapy, and make changes relevant to this indication in the Pharmacology, Pharmacokinetics, Warnings, Drug Interactions, Precautions, and Geriatric Use sections. The clinical data in support of the label changes to the package insert are under review in the Division Oncologic Drug Products (NDA 21-386, A Type six NDA).

Please cite the application number listed above at the top of the first page of any communications concerning this application. All communications concerning this supplemental application should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Metabolic and Endocrine Drug Products, HFD-510  
Attention: Division Document Room 14B-19  
5600 Fishers Lane  
Rockville, Maryland 20857

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

**APPEARS THIS WAY  
ON ORIGINAL**

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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.**  
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/s/

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Randy Hedin  
1/30/02 09:03:09 AM

**APPEARS THIS WAY  
ON ORIGINAL**

 **NOVARTIS**

November 21, 2001

NDA 21-386

**ZOMETA<sup>®</sup> (zoledronic acid for injection)**

- **Response to November 20, 2001 FDA email request**

**Richard Pazdur, MD**  
Director  
Division of Oncology Drug Products,  
HFD-150  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, Maryland 20857

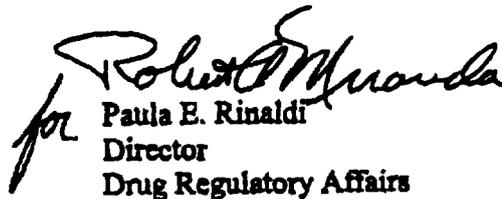
Dear Dr. Pazdur,

Reference is our NDA 21-386 submitted on August 21, 2001. Reference is also made to an email from Debra Vause, Project Manager in which she requested one copy each of the carton and vial label for Zometa.

We are now providing one carton and one vial label for currently marketed Zometa, approved under NDA 21-223 for treatment of hypercalcemia of malignancy.

If you have any questions concerning this submission, or need additional copies of the labeling, please contact me at (973)-781-7712.

Sincerely,



for Paula E. Rinaldi  
Director  
Drug Regulatory Affairs

Attachments: labels  
Submitted in duplicate

**Number of Pages  
Redacted** 2



Draft Labeling  
(not releasable)

 **NOVARTIS**

**DUPLICATE**

**Novartis Pharmaceuticals Corporation**  
Drug Regulatory Affairs  
59 Route 10  
East Hanover, NJ 07936-1080

Tel 973 781 7500  
Fax 973 781 6325

19-SEP-01

**ORIG AMENDMENT**

*BC*

**NDA 21-386**  
**ZOMETA®**  
(zoledronic acid for injection)

**Amendment - Chemistry, Manufacturing and Controls**

**Richard Pazdur, MD**  
Director  
Division of Oncology Drug Products/HFD-150  
Food and Drug Administration  
Woodmont FDA Oncology Drug Group  
Attn: Document Control Room #20N  
1451 Rockville Pike  
Rockville, Maryland 20852-1448



Dear Dr. Pazdur:

Please refer to our pending NDA 21-386 (Type 6) for ZOMETA® for the treatment of Bone Metastases which was submitted on 22-AUG-01. The following amendment contains the documentation requested in a fax received from the Division dated 17-SEP-01. The information has been provided earlier via fax, to the attention of Ms. Debbie Vause at the Agency.

Should you have any comments or questions regarding this submission or any other Chemistry, Manufacturing and Controls issue please contact me directly at (973) 781-3758. If there are any general or Clinical related issues please contact Eileen Ryan, DRA Therapeutic Area representative at (973) 781-7661.

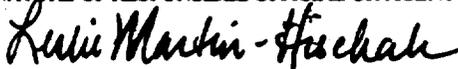
Sincerely,

*Leslie Martin-Hischak*

Leslie Martin-Hischak  
Chemistry, Manufacturing and Controls  
Drug Regulatory Affairs

Submitted in Duplicate  
Attachments



This application contains the following items: (Check all that apply)		
	1. Index	
	2. Labeling (check one)	<input type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))	
X	4. Chemistry section	
X	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50 (d)(1); 21 CFR 601.2)	
	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)	
	C. Methods validation package (e.g., 21 CFR 314.50 (e)(2)(i); 21 CFR 601.2)	
	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50 (d)(2); 21 CFR 601.2)	
	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50 (d)(3); 21 CFR 601.2)	
	7. Clinical Microbiology (e.g., 21 CFR 314.50 (d)(4))	
	8. Clinical data section (e.g., 21 CFR 314.50 (d)(5); 21 CFR 601.2)	
	9. Safety update report (e.g., 21 CFR 314.50 (d)(5)(vi)(b); 21 CFR 601.2)	
	10. Statistical section (e.g., 21 CFR 314.50 (d)(6); 21 CFR 601.2)	
	11. Case report tabulations (e.g., 21 CFR 314.50 (f)(1); 21 CFR 601.2)	
	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)	
	13. Patent information on any patent which claims the drug (21 U.S.C 355 (b) or (c))	
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C 355 (b)(2) or (j)(2)(A))	
	15. Establishment description (21 CFR Part 600, if applicable)	
	16. Debarment certification (FD&C Act 306 (k)(1))	
	17. Field copy certification (21 CFR 314.50 (k)(3))	
	18. User Fee Cover Sheet (Form FDA 3397)	
	19. Financial Information (21 CFR Part 54)	
	20. OTHER (Specify)	
<b>CERTIFICATION</b>		
<p>I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:</p> <ol style="list-style-type: none"> <li>1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.</li> <li>2. Biological establishment standards in 21 CFR Part 600.</li> <li>3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.</li> <li>4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.</li> <li>5. Regulations on making changes in application in FD&amp;C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.</li> <li>6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.</li> <li>7. Local, state and Federal environmental impact laws.</li> </ol> <p>If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.</p> <p>The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.</p> <p>Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.</p>		
SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
	Leslie Martin-Hischak, Assistant Director Drug Regulatory Affairs	19-SEP-01
ADDRESS (Street, City, State, and ZIP Code)	Telephone Number	
One Health Plaza East Hanover, New Jersey 07936-1080	(973) 781-3758	
<p>Public reporting burden for this collection of information is estimated to average 24 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:</p>		
Department of Health and Human Services Food and Drug Administration CBER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448	<p>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.</p>	



**Fax**

Attention Ms. Debbie Vause  
Project Manager

Fax no. 301-594-0499  
Number of pages 4 pages

Date 17-SEP-01

Concerning Type 6 SNDA, FDA fax dated 17-SEP-01, Request for CMC Information

Dear Debbie,

Please refer to the Agency's fax dated today 17-SEP-01 and the request for CMC information.

This response contains a table listing all manufacturing and testing facilities for both the drug substance and drug product. Also included is the Environmental Assessment Information containing a Claim for Categorical Exclusion.

Novartis considers this a full response to both listed requests.

Additionally, in a second fax dated 17-SEP-01 the Division requested confirmation on whether the drug product used in NDA 21-386 was the same as the drug product which was approved in NDA 21-223. Novartis confirms the drug product submitted in NDA 21-386 is the same as the approved drug product.

This information provided above will be filed as a hard copy to the NDA.

Should you require any further CMC information do not hesitate to contact me directly.  
Thank you.

Sincerely,

A handwritten signature in cursive script that reads 'Leslie Martin-Hischak'.

Leslie Martin-Hischak

**CFNs for the sites of manufacture, packaging and control of Zoledronate powder for solution for infusion**

Site	CFN*	Manufacturing	Quality control	Stability	Packaging
<b>Drug substance</b>					
Novartis Pharma Basel AG Lichtstrasse 35 4056 Basel Switzerland	✓ 9611204	X	X	DP X	X
Novartis Pharma Stein AG Schaffhauserstrasse CH-4332 Stein Switzerland	✓ 9692043	X X DP (milling only)	DP X X	X	X DP
Novartis International Pharmaceutical Ltd. Branch Ireland, Ringaskiddy County Cork Ireland	✓ 9612715		X		
				DS DP	
<b>Drug product</b>					
<del>Novartis Pharma Stein AG Schaffhauserstrasse CH-4332 Stein Switzerland</del>	<del>9692043</del>	<del>X</del>	<del>X</del>		X (primary only)
<del>Novartis Pharma Basel AG Lichtstrasse 35 4056 Basel Switzerland</del>	<del>9611204</del>			X (primary stability)	
Novartis Pharmaceuticals Corporation 25 Old Mill Road Suffern, New York 10901 USA	✓ 2416082				X (secondary only)

\*CFN: Central File Number