

# APPENDIX C



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville MD 20857

NDA 21-223

Novartis Pharmaceuticals Corporation  
Attention: Ms. Eileen Ryan  
Associate Director, Drug Regulatory Affairs  
59 Route 10  
East Hanover, NJ 07936-1080

Dear Ms. Ryan:

Please refer to your new drug application (NDA) dated and received December 21, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zometa (zoledronic acid for injection).

We acknowledge receipt of your submissions dated September 14, 21, and 29, November 6, and December 13 and 21, 2000, and February 19, March 26 and 29, April 2, 9, 11, 25, and 30, May 3, June 1 and 12, July 10, and August 3, 17, and 20, 2001. Your submission of February 19, 2001, constituted a complete response to our September 21, 2000, action letter.

This new drug application provides for the use of Zometa (zoledronic acid for injection) for the treatment of hypercalcemia of malignancy.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed-upon draft labeling text submitted August 20, 2001, vial labels submitted August 3, 2001, and carton labels submitted August 20, 2001, for the treatment of hypercalcemia of malignancy when administered as a 4 mg dose over no less than 15 minutes. Accordingly, the application is approved effective on the date of this letter. The final printed labeling (FPL) must be identical to the submitted draft labeling. Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 21-223." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your postmarketing study commitment in your submission dated August 17, 2001, in which you agree to conduct a pharmacokinetics and pharmacodynamic study of Zometa in patients with impaired renal function. The study may be either single- or multiple-dose. The final study report

should be submitted within one month of the date of this letter.

Submit clinical protocols to your IND for this product. Submit study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of the commitment in your annual report to this NDA. The status summary should include expected study completion and final report submission dates, any changes in plans since the last annual report, and, the number of patients entered into each study. All submissions, including supplements, relating to this postmarketing study commitment must be prominently labeled "Postmarketing Study Protocol", "Postmarketing Study Final Report", or "Postmarketing Study Correspondence."

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

As of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 FR 66632). On November 30, 1999, you requested a waiver from conducting pediatric studies for the indication, treatment of hypercalcemia of malignancy. The waiver was granted for patients ages 0 - 16 years on February 25, 2000.

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

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

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

In addition we have concluded that the proposal to recommend an 8-mg intravenous dose for patients requiring retreatment of hypercalcemia of malignancy is approvable. The similar response rates following single infusions of 4-mg and 8-mg, the lack of a comparison arm in the retreatment portion of the two controlled, multicenter studies, and the increased risk of renal toxicity with the 8-mg dose compared to the 4-mg dose, do not support the safety and efficacy of the 8-mg dose for retreatment. A study demonstrating that the 8-mg dose is superior to the 4-mg dose in patients requiring retreatment and data to support the safety of the 8-mg dose would be necessary to support approval of the 8-mg dose for patients who require retreatment for hypercalcemia of malignancy.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your

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intent to file an amendment, or follow one of your other options under 21 CFR 314.110. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

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

Sincerely,

*(See appended electronic signature page)*

John K. Jenkins, M.D.  
Director  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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

/s/

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John Jenkins  
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