CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-386
21-223/S003

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-386
NDA 21-223 / S003

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

Dear Ms. Rinaldi:

Please refer to your new drug application (NDA) dated August 21, 2001, received August 22, 2001, 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 August 28, 2001; September 19, 20, 21(2), 24, and 28(2), 2001; October 2, 2001; November 21, 2001; December 5(2), 6, 7, 10, 11(2), 20, and 21, 2001; January 14, 18, and 28, 2002; February 15, and 20, 2002. Finally, we acknowledge your January 18, 2002 submission of a relevant labeling supplement to your approved NDA 21-223.

This new drug application provides for the use of Zometa® (zoledronic acid for injection) 4 mg, for the treatment of patients with multiple myeloma and patients with documented bone metastases from solid tumors, in conjunction with standard antineoplastic therapy. Prostate cancer should have progressed after treatment with at least one hormonal therapy.

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 labeling text. Accordingly, the application and relevant supplement 21-223 / S003 are approved effective on February 22, 2002.

The final printed labeling (FPL) must be identical to the attached labeling text and immediate container and carton labels submitted November 21, 2001. 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 copies of final printed labeling (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 21-386 and supplement 21-223 / S003." Approval of these submissions by FDA is not required before the labeling is used.

We remind you of your postmarketing study commitments in your submission dated February 15, 2002. These commitments are listed below.

1. Conduct a Phase 4 pharmacokinetic, safety and efficacy study in patients with renal dysfunction and serum creatinine $\geq$ 3 mg/dL. The dose of Zometa to be administered should be adjusted to match the AUC 0-24 h in patients with normal renal function, and safety, efficacy and biomarker suppression should be assessed. A suitable patient population may be patients with multiple myeloma.

Protocol Submission:	Within 2 months of the date of this letter
Study Start:	Within 5 months of the date of this letter
Final Report Submission:	Within 29 months of the date of this letter

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

Protocol Submission:	Within 2 months of the date of this letter
Study Start:	Within 5 months of the date of this letter
Final Report Submission:	Within 29 months of the date of this letter

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to NDA 21-223. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled **"Postmarketing Study Protocol", "Postmarketing Study Final Report", or "Postmarketing Study Correspondence."**

Be advised that, 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). We have waived the pediatric study requirement for this action on this application (see minutes of February 13, 2002 telecon).

In addition, 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 submit one copy to this Division 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

We remind you that you must comply with the requirements set forth under 21 CFR 314.80 and 314.81 for an approved NDA. To comply with these regulations, all 3-day and 15-day alert reports, periodic adverse drug experience reports, field alerts, annual reports, supplements, and other submissions should

be addressed to the original NDA for this drug product, not to this NDA. This includes the quarterly periodic adverse drug experience reports required by this new NDA. In the future, no submissions should be made to this NDA except for the final printed labeling, as requested above.

If you have any questions, call Debra Vause, Regulatory Project Manager, at (301) 594-5724.

Sincerely,

{See appended electronic signature page}

Richard Pazdur, M.D.
Director
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure: labeling text

APPEARS THIS WAY
ON ORIGINAL

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

/s/

Richard Pazdur
2/22/02 11:04:53 AM

APPEARS THIS WAY
ON ORIGINAL

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

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

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 deficiences 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

Number of Pages Redacted 11

❖❖❖

Draft Labeling
(not releasable