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13 pages Draft Label

TELEFAX

To: Ms. Ellen Cutler
Novartis Pharmaceuticals Corporation

FAX: 973-781-6325
PHONE: 973-781-8180

From: Randy Hedin, R.Ph.

Food and Drug Administration
Division of Metabolism and Endocrine Drug Products
5600 Fishers Lane--HFD-510
Rockville, Maryland 20857-1706

FAX: (301) 443-9282
PHONE: (301) 827-6392

Date: August 14, 2000

Pages: __3__ [inclusive]

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2. In addition, the following data analyses are needed from the

C. Analysis of Protocols 010, 011, 039 cohort for the incidence of Grade 3 and Grade 4 changes in serum creatinine.

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

/S/

8/11/98

Cleared for Faxing:

Dr. Lisa Rarick, Deputy Office Director

NDA 21-223

AUG 15 2000

Novartis Pharmaceuticals Corporation
Attention: Ms. Ellen Cutler
Assistant Director, Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Dear Ms. Cutler:

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

We also refer to your submissions dated February 11 and May 18 and 26, 2000.

Our review of the biopharmaceutics section of your submissions is complete, and we have identified the following deficiencies:

1. Although acceptable, the RIA assays have large precision and accuracy errors which you should minimize through further optimization of the assay.

2. Please re-format the pharmacokinetic section of the labeling into the following sections: Distribution, Metabolism, Excretion, and Special Populations.

3. We recommend the development of dosing guidelines in renally impaired patients. This may be done as a phase 4 study. You should define an exposure (probably AUC-related) that shows efficacy, and develop a dosing regimen based on creatinine clearance that would result in that exposure at different creatinine clearances. All study designs should be submitted for review and approval before proceeding with these studies. This may be required as a phase 4 commitment.

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Sincerely,

/S/

Hae-Young Ahn, Ph.D.
Biopharmaceutics Team Leader
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

RH 8/11/00

cc:
Archival NDA 21-223
HFD-510/Div. Files
HFD-510/R.Hedin
HFD-510/Reviewers and Team Leaders
DISTRICT OFFICE

Drafted by: RH/July 12, 2000
Initialed by: RShore/7.13/HAhn/6.4/EGalliers/8.10.00
final: RHedin/8.11.00
filename: [redacted]

DISCIPLINE REVIEW LETTER (DR)

TELEFAX

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Novartis Pharmaceuticals Corporation

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From: Randy Hedin, R.Ph.

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Division of Metabolism and Endocrine Drug Products
5600 Fishers Lane--HFD-510
Rockville, Maryland 20857-1706

FAX: (301) 443-9282
PHONE: (301) 827-6392

Date: May 25, 2000

Pages: __3__ [inclusive]

Food and Drug Administration
Division of Metabolism and Endocrine Drug Products
5600 Fishers Lane--HFD-510
Rockville, Maryland 20857-1706

NDA 21-223
Zometa (zoledronic acid for injection)

Dear Ms. Cutler:

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

We have completed a preliminary review of renal toxicity and have the following comments and information requests:

1. Please submit the following data tables arranged by type of trial.

HYPERCALCEMIA OF MALIGNANCY (PROTOCOLS 010, 011, 039)

NDA Enumeration	Description
Post-text listing 5.4-1	Serious Adverse Events (SAEs)
Post-text supplement ??	Narratives for SAEs

NDA 21-223
Zometa (zoledronic acid for injection)

Dear Ms. Cutler:

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

We also refer to your February 2, March 21, and April 14 and 20, 2000 submissions.

We have completed the chemistry of these submissions and have the following comments and information requests:

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Cleared for Faxing: 5/25/00
Dr. Duu-Gong Wu, Team Leader

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MESSAGE CONFIRMATION

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Rockville, Maryland 20857-1706

FAX: (301) 443-9282
PHONE: (301) 827-6392

Date: May 5, 2000

Pages: __5__ [inclusive]

TELEFAX

To: Ms. Ellen Cutler
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FAX: 973-781-6325
PHONE: 973-781-8180

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Date: May 5, 2000

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Food and Drug Administration
Division of Metabolism and Endocrine Drug Products
5600 Fishers Lane--HFD-510
Rockville, Maryland 20857-1706

NDA 21-223
Zometa (zoledronic acid for injection)

Dear Ms. Cutler:

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

We are reviewing the microbiology section of your submission and have the following comments:

1. The description and data provided regarding the microbial retention validation of the intended sterilizing filter are too abbreviated for substantive review. Minimally, the following information should be included:
   - The validation test method (i.e. direct inoculation, recirculation, etc.)
   - If applicable, a rationale for use of a recirculation challenge method as opposed to direct inoculation
   - A comparison of process and validation filtration parameters (differential pressure, flow rate, through-put, etc.)
   - Retention validation test results generated with at least three different filter media production lots
   - Pre- and post-challenge integrity test values for the test and control filters
   - Bacterial size control (0.45µ rated) results
   - Duration of exposure of test and control filters to the product solution
   - Duration of the challenge portion of the test
   - The number of organisms in the challenge suspension on a per milliliter basis

   The method(s) used to determine the product-wet integrity test parameters should be provided in greater detail. The data generated during these determinations should also be included.

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load, [redacted] s). Are these the only equipment loads applicable to this drug product sterilized in these units? If not, please provide a comprehensive list of other load configurations including validation data for those load configurations. Alternatively, a rationale for not conducting validation experiments on the other load configurations may be provided.

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b. The illustrations indicating the placement of thermocouples is illegible. Legible illustrations of thermocouple and biological indicator placement should be provided.

c. The description of the requalification indicates that only filling needles for 7.5 mL vials need to be "checked" because they represent "worst case". A rationale for the choice of this equipment as the "worst case" should be provided. Please provide a definition for the term "check" as it is used here (page 4-211, Volume 8).

6. The specified minimum F_0 for the lyophilizer sterilization cycle —— The lowest observed F_0's during qualification studies were —— (AB —— These do not validate sterilization efficacy at the minimum specified F_0. Results of validation/qualification studies conducted at the minimum F_0 specification should be provided.

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

Cleared for faxing /S/

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Hedin

NDA 21-223

FEB 25 2000

Novartis Pharmaceuticals Corporation
Attention: Ellen Cutler
Assistant Director, Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Dear Ms. Cutler:

Reference is made to your new drug application dated December 21, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Zometa (zoledronic acid for injection)

Therapeutic Classification: Priority (P)

Date of Application: December 21, 1999

Date of Receipt: December 21, 1999

In this application you requested a waiver for pediatric studies under 21 CFR 314.55(c). We have reviewed the information you submitted and agree that a waiver is justified for Zometa for the treatment of hypercalcemia of malignancy for the pediatric population. Accordingly, a waiver for pediatric studies for this application is granted under 21 CFR 314.55 at this time.

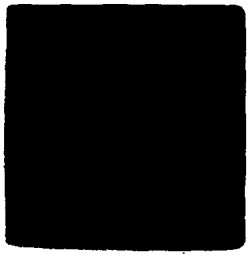
If you have any questions, call Randy Hedin, R.Ph., Senior Regulatory Management Officer, at (301) 827-6392.

Sincerely,

/S/

John K Jenkins, M.D.
Acting Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

RH 2/24/00



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/S/ 8/11/98

Cleared for Faxing:

Dr. Lisa Rarick, Deputy Office Director

NDA 21-223

AUG 15 2000

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Assistant Director, Drug Regulatory Affairs
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Biopharmaceutics Team Leader
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

RH 8/11/00

cc:
Archival NDA 21-223
HFD-510/Div. Files
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HFD-510/Reviewers and Team Leaders
DISTRICT OFFICE

Drafted by: RH/July 12, 2000
Initialed by: RShore/7.13/HAhn/6.4/EGalliers/8.10.00
final: RHedin/8.11.00
filename: [redacted]

DISCIPLINE REVIEW LETTER (DR)

TELEFAX

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FAX: (301) 443-9282
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Date: May 25, 2000

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Cleared for Faxing: 5/25/00
Dr. Duu-Gong Wu, Team Leader

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Date: May 5, 2000

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THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL,

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Assistant Director, Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Dear Ms. Cutler:

Reference is made to your new drug application dated December 21, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Zometa (zoledronic acid for injection)

Therapeutic Classification: Priority (P)

Date of Application: December 21, 1999

Date of Receipt: December 21, 1999

In this application you requested a waiver for pediatric studies under 21 CFR 314.55(c). We have reviewed the information you submitted and agree that a waiver is justified for Zometa for the treatment of hypercalcemia of malignancy for the pediatric population. Accordingly, a waiver for pediatric studies for this application is granted under 21 CFR 314.55 at this time.

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

Sincerely,

/S/

John K Jenkins, M.D.
Acting Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

RH 2/24/00

cc:
Archival NDA 21-223
HFD-102/Office Director
HFD-2/M.Lumpkin
HFD-104/D.Murphy
HFD-002/T.Crescenzi
HFD-510/Div. Files
HFD-510/R.Hedin
HFD-510/Reviewers and Team Leaders/E. Galliers
HFD-510/Pediatric

DISTRICT OFFICE

Drafted by: RH/February 17, 2000
Initialed by: EGalliers/2.17/EColman/2.18.00
final: RHedin/2.23.00

PEDIATRIC WAIVER LETTER

APPEARS THIS WAY
ON ORIGINAL

Hedin

NDA 21-223

FEB - 4 2000

Novartis Pharmaceuticals Corporation
Attention: Ms. Ellen Cutler
Assistant Director, Drug Regulatory Affairs
59 Route 10
East Hanover NJ 07936-1080

Dear Ms. Cutler:

Please refer to your December 21, 1999, new drug application for Zometa (zoledronic acid) Injection.

We are reviewing the Clinical Pharmacology and Biopharmaceutics section of your submission and have the following comments and information requests. We need your prompt written response to continue our evaluation of your NDA.

1. Please submit all data sets used in analyses for studies ZOL503 and ZOLJ001 as well as data sets used for the POP PK analysis. These data sets should be submitted in ——— format and on 3.5" floppy diskettes.

2. According to the index, study DMPK(US) R98-106 (Vol. 57) "In vitro blood to plasma partitioning and plasma protein binding of [14C]ZOL446B in human, dog, and rat blood" and study DMPK(CH) 1997/530 (VOL 57) "Evaluation of ZOL446 (zoledronate) as an inhibitor of human P450 enzymes" have been submitted only to Section 5. Please also submit these studies to Section 6 since they involve human data.

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

Sincerely,

/S/

John K. Jenkins, M.D.
Acting Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

RH 2/4/00

cc:
Archival NDA 21-223
HFD-510/Div. Files
HFD-510/R.Hedin
HFD-510/Reviewers and Team Leaders
DISTRICT OFFICE

Drafted by: RH/February 1, 2000
Initialed by: RShore/HAhn/2.1/EGalliers/2.2/JJenkins/2.3.00
final: RHedin/2.4.00

INFORMATION REQUEST (IR)

NDA 21-223

DEC 27 1999

Novartis Pharmaceuticals Corporation
Attention: Ellen Cutler
Assistant Director, Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Dear Ms. Cutler:

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

Name of Drug Product:	Zometa™(zoledronic acid for injection), 4 mg
Therapeutic Classification:	To be determined at filing meeting
Date of Application:	December 21, 1999
Date of Receipt:	December 21, 1999
Our Reference Number:	NDA 21-223

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 February 19, 2000, in accordance with 21 CFR 314.101(a).

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). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within 120 days of receipt of your pediatric drug development plan, we will notify you of the pediatric studies that are required under section 21 CFR 314.55.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will notify you within 120 days of receipt of your response whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

We note your request for a full waiver of this requirement in your submission and will respond by April 19, 2000.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will proceed with the pediatric drug development plan that you submit and notify you of the pediatric studies that are required under section 21 CFR 314.55. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

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

U.S. Postal Service/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 Randy Hedin, R.Ph., Senior Regulatory Management Officer, at (301) 827-6392.

Sincerely,

/S/ 3.99

Enid Galliers
Chief, Project Management Staff
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

cc:
Archival NDA 21-223
HFD-510/Div. Files
HFD-510/R.Hedin
HFD-510/Reviewers and Team Leaders
DISTRICT OFFICE

Drafted by: ddk/December 23, 1999
Initialed by: Galliers 12/23/99
final: ddk/December 23, 1999
filename: _____

ACKNOWLEDGEMENT (AC)

APPEARS THIS WAY
ON ORIGINAL

SECTION
WAS
TERMINED
NOT
TO BE
RELEASABLE

[redacted]

31 pages Confidential

[redacted]