CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-223

ADMINISTRATIVE DOCUMENTS
CORRESPONDENCE

Patent Submission

Time Sensitive Patent Information

pursuant to 21 C.F.R. 314.53

for

NDA # 21-223

The following is provided in accordance with the Drug Price Competition and Patent Term Restoration Act of 1984:

- Trade Name: Zometa™
- Active Ingredient(s): Zoledronate/Zoledronic Acid
- Strength(s): 4 mg
- Dosage Form: Lyophilized powder for injection
- Approval Date: Pending

A. This section should be completed for each individual patent

U.S. Patent Number: 4,939,130

Expiration Date: November 13, 2007

Type of Patent--Indicate all that apply:

1.	Drug substance (Active Ingredient)	✓ Y	N
2.	Drug Product (Composition/Formulation	✓ Y	N
3.	Method of Use	✓ Y	N

a. If patent claims method(s) of use, please specify approved method(s) of use or method(s) of use for which approval is being sought that are covered by patent: Hypercalcemia of Malignancy.

Name of Patent Owner: Novartis Corporation

U.S. Agent (if patent owner or applicant does not reside or have place of business in the US):

U.S. Patent Number: 4,777,163

Expiration Date: July 24, 2007

Type of Patent--Indicate all that apply:

1.	Drug substance (Active Ingredient)	✓ Y	N
2.	Drug Product (Composition/Formulation	✓ Y	N
3.	Method of Use	✓ Y	N

a. If patent claims method(s) of use, please specify approved method(s) of use or method(s) of use for which approval is being sought that are covered by patent: Hypercalcemia of malignancy.

Name of Patent Owner: Boehringer Mannheim GmbH

U.S. Agent (if patent owner or applicant does not reside or have place of business in the US):

B. The following declaration statement is required if any of the above listed patents have Composition/Formulation or Method of Use claims.

The undersigned declares that the above stated United States Patent Number 4,939,130 covers the composition, formulation and/or method of use of Zoledronate/Zoledronic acid (name of drug product). This product is:

- ____ currently approved under section 505 of the Federal Food, Drug, and Cosmetic Act)

or

- ✓ the subject of this application for which approval is being sought.)

B. The following declaration statement is required if any of the above listed patents have Composition/Formulation or Method of Use claims.

The undersigned declares that the above stated United States Patent Number 4,777,163 covers the composition, formulation and/or method of use of Zoledronate/Zoledronic Acid (name of drug product). This product is:

- ____ currently approved under section 505 of the Federal Food, Drug, and Cosmetic Act)

or

- ✓ the subject of this application for which approval is being sought.)

Signed: Carol A. Loschiavo

Title: Patent Attorney

Date: October 27, 1999

Telephone Number: (908) 522-6932

A copy of the above information should be submitted to the NDA with the original application or as correspondence to an existing NDA. For patents issued after the NDA is filed or approved, the applicant is required to submit the information within 30 days of the date of issuance of the patent.

To expedite publication in the ***The Orange Book,**** a deskcopy should be submitted to:

Mailing address: (US Mail)

U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Division of Data Management and Services
Information Services Team
HFD-93
5600 Fishers Lane
Rockville, MD 20857

OR

Location address: (for FedX deliveries)

U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Division of Data Management and Services
Information Services Team
Building A
HFD-93 Room #235
Nicholson Lane Research Center
5516 Nicholson Lane
Kensington, MD 20895

OR faxed to: (301)-594-6463

* - Please note that patents for unapproved compositions, formulations, or uses will NOT be published in the ***The Orange Book***.

PEDIATRIC PAGE (Complete for all original application and all efficacy supplements)

View as Word Document

NDA Number:	021223	**Trade Name:**	ZOMETA (ZOLEDRONIC ACID FOR INJECTION)(4
Supplement Number:	000	**Generic Name:**	ZOLEDRONIC ACID
Supplement Type:	N	**Dosage Form:**	
Regulatory Action:	AE	**COMIS Indication:**	TREATMENT OF TUMOR INDUCED HYPERCALCEMIA
Action Date:	9/21/00		

Indication # 1 Zometa is indicated for the treatment of tumor-induced hypercalcemia.

Label Adequacy:	Other - See Comments
Formulation Needed:	NO NEW FORMULATION is needed
Comments (if any):	The firm requested a pediatric waiver in their submission dated December 21, 1999. The waiver was granted for the specific indication, the treatment of tumor-induced hypercalcemia on February 25, 2000, because the disease occurs in too few children to study. If additional indications are granted, pediatric studies may be requested. 8/14/01

Ranges for This Indication

Lower Range	Upper Range	Status	Date
0 months	16 years	Waived	

This page was last edited on 8/14/01

Signature /S/ Date 8/14/01

APPEARS THIS WAY ON ORIGINAL

Drug Regulatory Affairs

Zometa™ (zoledronic acid for injection)

Request for Waiver for Pediatric Labeling

Author(s):	Ellen Cutler
Document type:	
Document status:	Final
Release date:	November 30, 1999
Number of pages:	2

APPEARS THIS WAY
ON ORIGINAL

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 effective of Zometa™ (zoledronic acid for injection) for the claimed indication of hypercalcemia of malignancy in all relevant pediatric subpopulations.

The basis for this waiver is 314.55c(2)(ii): necessary studies are impossible or highly impractical because, e.g., the number of such patients is so small.

Zometa™ is a highly potent, new generation bisphosphonate. Aredia® (pamidronate disodium for injection) has been the recognized standard bisphosphonate therapy for hypercalcemia of malignancy. Following the October 31, 1991 approval, we (then Ciba-Geigy) initiated discussions with consultants and with the Pediatric Oncology Group (POG) and Children's Cancer Study Group (CCSG) regarding the feasibility of conducting a clinical trial in children with hypercalcemia of malignancy. It was estimated that approximately ten to 15 patients are available nationally for study each year. We were unable to generate sufficient interest within the NCI's cooperative group network to initiate a pediatric protocol. Given the incidence, we believe it is impractical to initiate a study in this patient population with any hope of generating data. We concluded that it was not feasible to conduct a pediatric hypercalcemia study with Aredia®. This was communicated to FDA in September 30, 1992 correspondence to NDA 20-036 regarding Phase 4 commitments. Additionally, Aredia® was initially on the List of Approved Drugs for Which Additional Pediatric Information May Produce Health Benefits in the Pediatric Population. The FDA subsequently removed Aredia® from the list in May 1999 following its annual review and update of the list as mandated by the regulations. We believe FDA's removal of pamidronate from the "pediatric list" is consistent with the intent of 21 CFR 314.55c(2)(ii) and further substantiates our request for a full waiver of the pediatric requirements under 314.55.

A recent search of the literature yields mostly case reports of individual patients or small groups (≤ 5) of children treated with pamidronate. McKay and Furman[1] report a retrospective analysis of 25 children (median age 9.5 years) treated over a 29-year period (1962-1991) at St. Jude Children's Research Hospital. These 25 cases represented 0.4% of the total number of children treated for cancer at the institution during that period and the authors conclude that hypercalcemia of malignancy is extremely rare in children.

A request for Orphan Drug designation was submitted to FDA's Office of Orphan Drug Products on October 29, 1999. We are awaiting their response.

Reference:

1. McKay C, Furman WL. Hypercalcemia Complicating Childhood Malignancies. Cancer, 1993; 72:256-260.

ZOMETA[TM] (zoledronic acid for injection)

New Drug Application

NOVARTIS CERTIFICATION
IN COMPLIANCE WITH THE
GENERIC DRUG ENFORCEMENT ACT OF 1992

Novartis Pharmaceuticals Corporation certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.

12/17/99
Date

Ellen Cutler
Assistant Director
Drug Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

Hecht

DEPARTMENT OF HEALTH & HUMAN SERVICES

Dcc Rm.

Food and Drug Administration
Rockville MD 20857

Jeremy K. Hon, M.D.
Comprehensive Cancer Institute
201 Sivley Road, SE, Suite 200
Huntsville, Alabama 35801

Dear Dr. Hon:

On April 3 and 4, 2000, Ms. Patricia Smith representing the Food and Drug Administration (FDA), met with you to review your conduct of a clinical study (Protocol #4244604037) of the investigational drug, Zometa™ (zoledronate), performed for Novartis Pharmaceutical 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 those 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 all pertinent Federal regulations and/or good clinical investigational practices governing the conduct of clinical investigations and the protection of human subjects. We note that at the conclusion of the inspection, Ms. Smith presented and discussed with you the items listed on Form FDA 483, Inspectional Observations. We wish to emphasize the following:

1. You failed to conduct your study in accordance with the approved protocol

   A. Five of the twelve subjects in your study were enrolled even though they met protocol-defined exclusion criteria. Specifically:

      1) Subject #s 1262 and 1264 did not have a cancer diagnosis confirmed through cytologic or histologic examination.

      2) Subject #1434 participated in a separate investigational drug study and continued to receive that investigational drug within 30 days of enrollment and treatment in this study.

      3) Subject #1260 was receiving hydrochlorothiazide, a prohibited medication.

      4) Subject #1261 had a serum calcium level of 11.9 mg/dL, a concentration below the specified lower limit of 12.0 mg/dL

B. Two of the twelve subjects received concomitant drugs prohibited by the protocol, specifically:

1) Subject #1431 received Lasix and calcitonin after enrollment into the study.
2) Subject #1435 had chemotherapy initiated within ten days of Visit 1.

We also note that you failed to assure continued IRB review and approval of the conduct of your protocol. We found no documentation that progress or status reports were filed with the IRB even though the IRB renewed the study on two separate occasions, or that a final report stating that the study had been completed was submitted to the IRB.

Because of the nature of the violations of FDA regulations discussed above, we request that you inform us, in writing, of the actions you have taken or plan to take to prevent similar violations in current or future studies.

We appreciate the cooperation shown Ms. Smith during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

/S/

John R. Martin, M.D.
Branch Chief
Good Clinical Practice I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Suite 103
Rockville, MD 20855

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

21-223
Doc. Rm.

Food and Drug Administration
Rockville MD 20857

JUL 12 2000

Furhan Yunus, M.D.
The Boston Cancer Group PLC
1331 Union Avenue, Suite 800
Memphis, Tennessee 38104

Dear Dr. Yunus:

On April 10 and 11, 2000, Ms. Patricia Smith representing the Food and Drug Administration (Agency), inspected your conduct as the investigator of record of a clinical study (Protocol #4244604037) of Zometa™ (zoledronate) that you conducted for Novartis Pharmaceutical Corporation. This inspection is part of the FDA's Bioresearch Monitoring Program. This program includes inspections to determine the validity of clinical drug studies that may provide the basis for drug marketing approval and to assure that the rights and welfare of the human subjects who participated in those studies have been protected.

At the close of the inspection, Ms. Smith presented her inspectional observations (i.e., Form FDA 483) and discussed these observations with you. From our evaluation of the inspection report and your oral responses to the inspectional observations, we conclude that you did not adhere to all pertinent Federal regulations and/or good clinical investigational practices governing the conduct of clinical investigations and the protection of human subjects. In particular, we note that you failed to conduct your study in accordance with the approved protocol in that subject #s 1157 and 1158 were enrolled into the study despite meeting exclusion criteria of low serum calcium levels and high serum creatinine levels, respectively.

Please ensure that corrective actions will be taken to prevent similar problems in your current and future studies.

APPEARS THIS WAY
ON ORIGINAL

We appreciate the cooperation shown Ms. Smith during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

/S/

John R. Martin, M.D.
Branch Chief
Good Clinical Practice Branch, I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place
Rockville, MD 20855

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH HUMAN SERVICES

DOC. Rm.

Food and Drug Administration
Rockville MD 20857

JUN 15 2000

Kelly B. Pendergrass, M.D.
Oncology & Hematology Associates of Kansas City
6400 Prospect Avenue
Suite 546
Kansas City, Missouri 64132

Dear Dr. Pendergrass:

Between April 4 and April 6, 2000, Mr. Carl Montgomery, representing the Food and Drug Administration (FDA), inspected your conduct as the investigator of record of a clinical study (Protocol #4244604037) of Zometa™ (zoledronate) that you conducted for Novartis Pharmaceutical Corporation. From our evaluation of the inspection report prepared by Mr. Montgomery, we conclude that you conducted your study in compliance with applicable Federal regulations and good clinical investigational practices governing the conduct of clinical investigations and the protection of human subjects.

This inspection is part of FDA's Bioresearch Monitoring Program. This program includes inspections to determine the validity of clinical drug studies that may provide the basis for drug marketing approval and to assure that the rights and welfare of the human subjects who participated in those studies have been protected.

We appreciate the cooperation shown Investigator Montgomery during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

/S/

David Lepay, M.D., Ph.D.
Director
Division of Scientific Investigations
Office of Medical Policy, HFD-45
Center for Drug Evaluation and Research
7520 Standish Place, Suite 103
Rockville, Maryland 20855

Public Health Service
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

(1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		
	See attached spreadsheet	

(2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

(3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
David R. Parkinson, MD	V.P., CRD; Head U.S. Oncology
FIRM/ORGANIZATION	
Novartis Pharmaceuticals Corporation	
SIGNATURE	**DATE**
	12/17/99

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

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

Please mark the applicable checkboxes.

☐ any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;

☐ any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;

☐ any proprietary interest in the product tested in the covered study held by the clinical investigator;

☐ any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

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

NAME	TITLE
David R. Parkinson, MD	V.P., CRD; Head U.S. Oncology
FIRM/ORGANIZATION	
Novartis Pharmaceuticals Corporation	
SIGNATURE	**DATE**
	12/17/99

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 4 hours per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

Office of Post-Marketing Drug Risk Assessment

Memo

To: David Orloff, M.D.
Director, Division of Metabolic and Endocrine Drug Products
HFD-510

From: Jerry Phillips, R.Ph.
Associate Director, Office of Post-Marketing Drug Risk Assessment
HFD-400

CC: Randy Hedin
Project Manager, HFD-510

Date: June 8, 2001

Re: OPDRA Consult 01-0112; Zometa (Zoledronic Acid); NDA 21-223

This memorandum is in response to a May 15, 2001, request from your Division for a re-review of the proprietary name, Zometa. The goal date for this application is August 20, 2001.

OPDRA has not identified any additional proprietary or established names that have the potential for confusion with Zometa since we conducted our initial review on September 17, 1999 (OPDRA consult 99-023), that would render the name objectionable. Therefore, we have no objections to the use of this proprietary name.

OPDRA considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary/established names from this date forward.

If you have any questions or need clarification, please contact the medication errors project manager, Sammie Beam at 301-827-3231.

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

/s/

Carol Holquist
6/8/01 10:06:03 AM
PHARMACIST

Jerry Phillips
6/8/01 10:29:35 AM
DIRECTOR

nulldate
DIRECTOR

Martin Himmel
6/8/01 02:43:29 PM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

Electronic Mail Message

Date: 8/23/00 12:08:39 PM
From: Sammie Beam (BEAMS)
To: Randy Hedin (HEDINR)
Subject: Proprietary Name Consult for NDA 21-223

Hello,

Attached is the original proprietary name consult for NDA 21-223 that found the name "Zometa" acceptable by OPDRA. The name was reviewed again on 4/26/00. Since 90 days have past since that date, OPDRA will again review the name against any newly approved proprietary names. OPDRA will e-mail the division the findings of that review in the next 2 weeks.

Thanks,
Sammie Beam

APPEARS THIS WAY
ON ORIGINAL

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE SENT: September 17, 1999	**DUE DATE:** N/A	**OPDRA CONSULT #:** 99-023

TO (Division):

Solomon Sobel, MD
Director, Division of Metabolic and Endocrine Drug Products
HFD-510

PRODUCT NAME: Zometa **IND #:** ——	**MANUFACTURER:** Novartis

CASE REPORT NUMBER(S): Not applicable.

SUMMARY:

In response to a consult from the Division of Metabolic and Endocrine Drug Products, OPDRA conducted a review of the proposed proprietary names Zometa (primary) and —— (alternate) to determine their acceptability based on potential for confusion with approved proprietary and generic names as well as pending names.

OPDRA RECOMMENDATION:

OPDRA has no objection to the use of the proprietary names Zometa or —— at this time. However, these names should be forwarded again to OPDRA within 60 days of NDA approval. This will assure that no newly approved FDA products are similar to this proposed proprietary name.

Jerry Phillips
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3225
Fax: (301) 827-5189

Peter Honig, MD
Deputy Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

Office of Post-Marketing Drug Risk Assessment
HFD-400; Rm 15B03
Center for Drug Evaluation and Research

MEDICATION ERROR REVIEW

DATE OF REVIEW: **September 2, 1999**

IND# ——

NAME OF DRUG: **Zometa (Zoledronic Acid)**

NDA HOLDER: **Novartis**

I. INTRODUCTION:

On August 9, 1999, the Division of Metabolic and Endocrine Drug Products (HFD-510) requested OPDRA evaluate Novartis's proposed proprietary name "Zometa" and alternative name —— for zoledronic acid.

Zoledronic acid was submitted under IND —— Therefore, the container labels, carton and insert labeling were not available for review. According to the chemist this product will be available as a powder for injection ———— The strength is undetermined at this time but could be anything from ——— mg. Zoledronic acid will be indicated for the treatment of tumor-induced hypercalcemia. ————

II. RISK ASSESSMENT:

1. An internal study was conducted within OPDRA to evaluate the proposed proprietary names and determine their potential for confusion with currently marketed drug products due to handwritten or verbal communication. This exercise was conducted to simulate an actual practice setting. Many medication errors are due to the misinterpretation of handwriting as well as verbal pronunciation of the drug name.

   Methodology:

   The firm proposed Zometa as the primary name and —— as their alternate. The Zometa study involved nine health care practitioners within OPDRA and the —— study involved seven. The participants were comprised of pharmacists, physicians and nurses. For each proposed name, OPDRA staff wrote one inpatient order and one outpatient prescription. Each written order contained two known drugs and a prescription for either Zometa or —— Written prescriptions were scanned and randomly sent to the participants via e-mail. The participants were instructed to respond with their interpretation of what they "saw" via e-

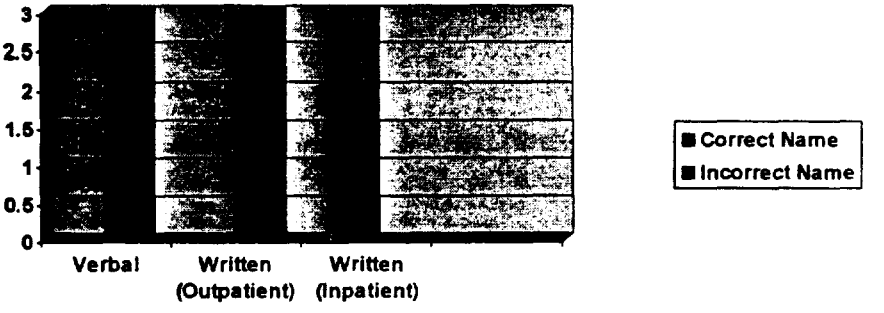
mail. In addition, three verbal outpatient prescriptions containing two know drugs and a prescription for either Zometa or [redacted] were recorded on voice mail. These prescriptions were then forwarded to the participants. Once again, the participants were requested to respond with their interpretations with what they "heard" via e-mail. After receiving the participants interpretations of the various orders, the correct spelling of the proposed proprietary names were sent to the participants with a request for them to furnish handwriting samples of each name. The medication error staff then reviewed each sample to determine the possibility of any look-alike drugs.

Results:

a) Zometa:

OPDRA received responses from nine individuals. Three out of nine participants correctly responded with the appropriate drug name "Zometa". The remainder of interpretations were spelled incorrectly and therefore counted as incorrect responses. All three orders that were interpreted correctly were written inpatient prescriptions. The following represents the incorrect responses:

1 verbal - Zumada	1 outpatient - Zomita
1 verbal - Zemada	1 outpatient - Zemeta
1 verbal - Zameda	1 outpatient - No guess



b) [redacted]

Analysis:

The majority of participants interpreted the drug names incorrectly. However, the responses were counted as incorrect because the drug names were spelled incorrectly. Most participants wrote the drug name phonetically. We recognize that low scores of correct interpretations would be common for all unapproved drug product names because health care professionals are not familiar with the name. However, none of the responses represent potential confusion with any currently approved and marketed drug products. Most participants stated they would have contacted the physician prior to filling the prescription.

2. A search of the American Drug Index (43rd Edition), Physicians' Desk Reference [53 Edition; 1999] and Drug Facts and Comparisons (Updated Monthly) for potential sound-alike or look-alike names to approved drugs revealed the following:

Sabin	Zantac	Zyban
Sabril	Zofran	
Soma	Zoloft	
Zagam	Zovia	
Zonite	Zemalo	
Zenate	Zebeta	
Zentil	Zantryl	
Zestril	Zebeta	

In OPDRA's opinion none of the names listed above represent a potential problem with sound-alike/look-alike issues.

3. A search of the Agency's internal databases, Establishment Evaluation System (EES), Drug Product Reference File (DPR), and the Labeling and Nomenclature Committee database (LNC) for potential sound-alike or look-alike names to unapproved/approved drugs revealed the following:

[redacted]

Zanosar

[redacted]

Zantac

[redacted]

Zomig

In OPDRA's opinion none of the names listed above represent a potential problem with sound-alike/look-alike issues.

4. The CDER Labeling and Nomenclature Committee reviewed the name on August 31, 1999. To date, we have not received their comments. As soon as the comments are sent to OPDRA
we will forward them to your Division.

III. RECOMMENDATIONS:

OPDRA has no objection to the use of the proposed proprietary name, Zometa, or the alternate name [redacted] at this time. However, we would request that your Division provide us with a follow-up consult 60 days before the expected approval date of the NDA because many products may be approved in the interim and OPDRA would appreciate the opportunity for a second review.

If you have any questions concerning this review please contact Carol Holquist at 301-827-3244.

Carol Holquist, RPh.
Safety Evaluator
Office of Post-Marketing Drug Risk Assessment

Concur:

Jerry Phillips, RPh
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment

CC:

Office Files
HFD-510; Lanh Green, Safety Evaluator, DDRE II, OPDRA
HFD-400; Jerry Phillips, Associate Director, OPDRA
HFD-400; Peter Honig, Deputy Director, OPDRA
HFD-002; Murray Lumpkin, Acting Director, OPDRA

Memorandum

Date September 21, 2000

From Steven R. Koepke, /S/
Deputy Director, Division of New Drug Chemistry II,
Office of New Drug Chemistry

Subject NDA ——
Zometa
(zoledronic acid for injection)
Novartis Pharmaceuticals Corporation

Zometa is a sterile powder for infusion drug product containing zoledronic acid (4 mg), manntiol and sodium citrate. The drug substance used for this drug product is actually a monohydrate. There are adequate specifications to control the known polymorphs. An initial expiry of 2 years was justified based on 36 months of supportive data along with 18 month data on three full scale production lots form the Basel facility.

Overall recommendation from CMC: This application is recommended for approval from CMC as of CMC review #1 (9/11/00). The Division concurs with this recommendation with a very minor comment (on labeling).

EER: Compliance overall recommendation was acceptable 8/25/00

Microbiology: Satisfactory May 22, 2000

DMFs: Rubber Stopper, adequate 5/23/00.

EA: Firm requested categorical exclusion in original submission.

Nomenclature: OPDRA consult indicates that trade name Zometa is acceptable 9/8/00.

Labeling: The labeling is acceptable from a CMC standpoint. The submitted label has no spaces in several lines. This will need to be corrected on the final printing.

Package Insert: Satisfactory.

APPEARS THIS WAY
ON ORIGINAL

Meeting Date: June 22, 1999 Time: 1:00 - 1:30 am Location: PKLN 14-56

[redacted]	zoledronate for injection
Type of Meeting:	Pre-NDA (chemistry)
External participant:	Novartis Pharmaceuticals Corporation
Meeting Chair:	Dr. Duu-Gong Wu
External participant lead:	Ms. Ellen Cutler
Meeting Recorder:	Mr. Randy Hedin

FDA Attendees and titles:

Dr. Duu-Gong Wu, Chemistry Team Leader II, ONDC
Dr. Sheldon Markosky, Chemistry Reviewer, ONDC
Mr. Randy Hedin, PM, DMEDP

External participant Attendees and titles:

Ms. Ellen Cutler, Drug Regulatory Affairs
Ms. Leslie Martin-Hischak, Drug Regulatory Affairs
Dr. Robert Spaet, Pre-clinical Safety
Dr. Rolf Loeffler, Pharmaceutical Analytical Development
Dr. Susanne Braunhofer, Technical CMC Documentation
Dr. Joan Materna, Drug Regulatory Affairs
Ms. Sharon Olmstead, Regulatory Liaison

Meeting Objectives:

This meeting was requested by Novartis Pharmaceuticals Corporation to discuss their proposals regarding the content and format of the CMC section of their proposed new drug application

Discussion Points and Decisions (agreements) reached:

- The following questions were submitted by Novartis Pharmaceuticals Corporation in their background package dated May 27, 1999. The Divisions answers follow the questions in bolded type.

Drug Substance

1. ***Drug substance synthesis/Impurities:*** CGP 42446 (zoledronic acid), Modified D Synthesis was filed to the [redacted] in Serial # 090 on 29-Jul-98. In anticipation of the NDA filing for-

Zoledronate, the synthesis was scaled up and manufacture moved from the pilot plant to Chemical Production. Analysis of [redacted] batches manufactured in Chemical Production according to Modified D synthesis resulted in the detection of an additional polymorphic form, trihydrate and a synthetic [redacted] batches.

The dimer is not a degradation product, as retainer samples over 10 years old show no evidence of the dimer forming over time. The characterization for the safety profile of this impurity and proposed toxicology qualification studies were discussed at the Pre-NDA meeting held on 15-Apr-99. The proposal for an acute comparative i.v. rat study followed by a 2-week repeat dose i.v. rate study was found acceptable for qualification assuming no significant unique toxicology findings are detected.

Based on the fact that the dimer could be removed to a level below LOD and that no amount of dimer could be detected in previous batches of drug substance, we do not intend to include impurity specifications for release or stability.

In an attempt to remove the trihydrate the launch batches were recrystallized with a second ethanol/water purification step. This purification step resulted in drug substance in the desired monohydrate form and additionally reduced the dimer to levels below the Limit of Detection. Hence, a second and final recrystallization step using the same solvents, ethanol and water, as the first recrystallization step has been added and this synthesis is labeled Synthesis E. A detailed description and flow diagram of Synthesis E and individual discussions of the trihydrate and Dimer can be found in Sections 2.7 and 2.8, on pages 9 through 12 of the attached briefing book.

Does the Agency have any concerns about this approach and the additional recrystallization step?

This is acceptable; however we feel this is a problem and you should continue to monitor for both the dimer and trihydrate. At a later date when you get more information we may allow you to drop it.

2. *Stability* Novartis considers the providing of three (3) month stability data on Synthesis E at time of submission to be sufficient based on the availability of the twelve (12) month registration stability on Modified Synthesis D.

   At the time of NDA filing, twelve (12) months of registration/primary stability according to ICH guidelines will be available for three (3) batches of drug substance representative of the material used in the clinical studies. (Batches 97901, 97903, 97905, Modified Synthesis D)

We anticipate three (3) months of accelerated and long term stability data generated according to Stability Commitment (SC No. 99-087.01) for three (3) recrystallized drug substance batches (400198, 400298 and 400598; Synthesis E) at the time of submission. The Stability Commitment (SC No. 99-087.01) is Attachment 3 to the briefing book.

For a complete discussion see Section 2.10, ***Stability*** on page 13 in the attached briefing book.

Is the Stability Commitment (SC N0. 99-087.01) as submitted and the proposed data acceptable for NDA filing?

This is acceptable; however, we don't make commitments on fileability until the application is submitted.

Will it be acceptable to the Agency to receive a nine (9) month stability update during the NDA review cycle with additional data from the recrystallized drug substance batches?

This is acceptable.

3 ***Heavy Metals***: Zoledronic acid is an aminobisphosphonate, a strong chelating agent. Traces of sodium (Na) and calcium (Ca) may result from the active substances' contact to glass-lined equipment while the traces of transition metals as chromium (Cr), iron (Fe), nickel (Ni), molybdenum (Mo) may result from the active substance's contact to stainless steel in the equipment.

Twenty three (23) batches of Zoledronic acid drug substance (including batches used for preclinical toxicological studies) were analyzed. For a complete discussion see Section 2.8.3, ***Heavy Metals*** on page 11 in the attached briefing book.

The following are the specifications for Heavy Metals with individual limits for lead (Pb) and Nickel (Ni) for the drug substance.

Heavy metals and other elements	
By ICP-OES	
Fe, Cu, Ni, Pb, Zn in sum	Not more than 20 µg/g
Pb	Not more than 2 µg/g
Ni	Not more than 5 µg/g
Cr	Not more than 10 µg/g
Mo	Not more than 20 µg/g

The United States Pharmacopoeia sets a general limit of 20 ppm of heavy metals (USP<231>) and for single metals limits of 10 ppm for iron (USP<241>) and of 10 ppm for lead (USP<251> in drug substances.

Are these specifications for heavy metals and other elements acceptable for the drug substance at the time of filing?

This is acceptable.

Drug Product

1. ***Stability*** Until recently the manufacturing site for zoledronate drug product was Novartis Basel. However, the final manufacturing site will be moved to Novartis Stein and the manufacturing process was revalidated. Drug product manufactured at Novartis Stein is equivalent to the Novartis Basel(previous site of manufacture) material.

   The equipment used at Novartis, Stein is the same class and sub-class as that used at Novartis Basel. The Complete equipment comparison is in Section 3.2.3, **Manufacturing Equipment**, on page 21 of the attached briefing book.

   The environmental conditions at Stein are the same or more restricted than those at Basel. For a detailed comparison of the two sites see **Table, 3.2.2.1** on page 19 of the attached briefing book.

   During the site change to Novartis Stein, the same three (3) batches of drug substance (97001, 97003, and 97005) were used at both sites to manufacture three (3) comparative batches of drug product.

   At the time of NDA submission, there will be at least twelve (12) months long term and six (6) months accelerated registration stability data for drug product manufactured at Novartis Basel to be used to establish product expiration date. Additionally, there will be at least six (6) months of accelerated and long term stability data available for the Novartis Stein manufactured drug product to demonstrate comparability. The drug product is tested according to an updated Primary Stability Protocol (PSP) which was previously filed as PSP 1/98 to l ——— is Serial #090 on July 29, 1998. Attachment V to the briefing book.

   Is the Primary Stability Protocol, PSP 3/99 as submitted and the proposed data acceptable for NDA filing?

   This is acceptable; however, we don't make commitments on fileability until the application is submitted.

Discussion: **The Division asked what degradation products are seen, and the firm replied that they didn't find any.**

- The Division stated that a glossary of terms should be included in the submission.
- The Division asked when the NDA would be submitted, and the firm responded that the target date for submission is in December, 1999.

Unresolved or issues requiring further discussion:

- None

Action Items:

- None

Signature, minutes preparer: /S/

Concurrence Chair: /S/ 7/14/99

cc: NDA Arch
HFD-510
Attendees
HFD-510/EGalliers
HFD-511/RHedin/7.7.99/I43240.MN1
Concurrence: SMarkofsky/7.14.99

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ON ORIGINAL

Meeting Date: April 15, 1999 Time: 10:00 - 11:30 am Location: Conf. Rm. "L"

zoledronate for injection

Type of Meeting: Pre-NDA

External participant: Novartis Pharmaceuticals Corporation

Meeting Chair: Dr. Troendle

External participant lead: Ms. Ellen Cutler

Meeting Recorder: Mr. Randy Hedin

FDA Attendees and titles:

Dr. Gloria Troendle, Deputy Director, DMEDP
Dr. Leo Lutwak, Medical Reviewer, DMEDP
Dr. Eric Colman, Medical Reviewer, DMEDP
Dr. Joanna Zawadzki, Medical Reviewer, DMEDP
Dr Bruce Stadel, Medical Reviewer, DMEDP
Dr Gemma Kuijpers, Pharmacology Reviewer, DMEDP
Dr Jagobrata Choudhury, Reviewer, Division of Biometrics 2
Dr. Hae-Young Ahn, Team Leader, Division of Biopharmaceutics
Mr Randy Hedin, CSO, DMEDP

External participant Attendees and titles:

Dr. BeeLian Chen, Biostatistics
Ms. Ellen Cutler, Drug Regulatory Affairs
Dr Andrea Kay, Oncology Clinical Research
Dr Robert Knight, Oncology Clinical Research
Dr. Beatrice Oberle-Rolle, Drug Regulatory Affairs
Dr Horst Schran, Clinical Pharmacology
Dr Robert Spaet, Preclinical Safety
Mr John Ketchum, Global Project Management
Mr Russ Hume, Regulatory Liaison

Meeting Objectives:

This meeting was requested by Novartis Pharmaceuticals Corporation to discuss their proposals regarding the content and format of a new NDA for zoledronate for injection.

Discussion Points and Decisions (agreements) reached:

- The following questions were submitted by Novartis Pharmaceuticals Corporation in their background package dated March 15, 1999. The Divisions answers follow the questions in bolded type. Discussion at the meeting follows the Division's answers.

Preclinical

1. Are the studies conducted as outlined in the NDA Index Item 5 adequate to characterize the preclinical effects of zoledronate to support the labeling in TIH?

We need more information, particularly regarding comparability of findings in subcutaneous vs intravenous studies. To support a single dose administration in humans for an NDA, there should be toxicology studies in at least 2 species of 2 weeks duration by the clinical route of administration. There appear to be sufficient data in the dogs, but the maximum IV rat study is 10 days. If you have data to permit comparison of SC studies in rats of longer duration (e.g., exposure or PK data), this may be sufficient to cover the NDA.

Discussion: The firm stated it is planning a 2-week or 4-week repeat dose i.v. study in rats to be carried out with the launch batch containing the highest dimer concentration. The Division agreed that, together with the chronic i.v. dog studies, this would be sufficient to support a single dose administration in humans

compound from the launch batch containing the highest concentration of the dimer by-product. The results of the 2-week repeat-dose rat tox study will be included in the NDA submission.

Does this proposal provide adequate characterization for the safety profile of this manufacturing by-product?

We need more information. The 2 week study in rats should cover the single dose use in humans assuming that no significant unique toxicology findings are detected. Is there any suitable information from the chronic toxicology studies that might help determine relative exposures to the dimer during longer term studies?

Discussion: The firm stated that exposure data for the dimer are currently not available, but may be acquired in the future.

Clinical PK

3. We believe that the studies described in Section 2.2.3 of this briefing book are adequate to characterize zoledronate's pharmacokinetics and the pharmacokinetic/pharmacodynamic relationship and support the intended patient population? Do you concur?

Yes.

Discussion: The firm stated it is revising its program, and asked whether only a Japanese study will be sufficient for submitting and NDA, and the Division stated no, that a second study will be needed to submit an NDA. The firm further stated it will submit a revised protocol for review.

4. As ZOL J001 includes only 9 Japanese patients (3 patients per 2, 4, or 8 mg zoledronate dose) we propose to submit an abbreviated study report covering safety and efficacy (bone markers) and request a waiver for submission of the corresponding data listings. Do you concur with this proposal?

We need to look at the raw data in order to make a determination.

Discussion: The firm stated that all raw PK data would be submitted, and the Division replied that it concurred with the proposal.

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Clinical/Statistical

5

Yes.

6.

Please report all adverse events.

7 The enrollment in the two TIH trials has been much slower than anticipated due to the prominent use of Aredia® in the treatment of TIH and bone lesions of breast cancer and multiple myeloma. We are concerned that the accrual goal of 288 patients may not be attainable within a reasonable timeframe. On the basis of the extensive data obtained to date with the use of zoledronate in the cancer setting and the broad experience with this class of compounds, Novartis proposes that if enrollment does not improve, the data from the first 144 patients in both Protocol 036 and 037 be combined and submitted for the initial filing. Maintenance of the blinding should be conserved in most centers. The analysis of the second cohort of 144 patients will be provided with the 120-day Safety Update if available. Do you concur with this proposal?

No, please submit NDA when both studies are completed.

Discussion. The firm stated it will submit two trials (36/37) of 108 patients each instead of the 144 patients originally planned. The firm further stated that it will continue to recruit until it has the full sample size of 288 patients for both studies. The Division stated that if you fail with the analysis of 108 patients; you will not get another chance to show efficacy with the 144 patients. In the event the original submission is approved the completed study with 144 patients may be used for a labeling supplement.

8. The combined analysis for the two 144-patient cohorts for Protocols 036/037 (see section 2.2.3) will be submitted to the FDA if available at the time of filing, otherwise this analysis will be included in the 120-day Safety Update since FDA does not require an assessment of the non-inferiority of zoledronate to Aredia® for approval. Is this acceptable?

No, submit the NDA when both studies are complete, and a separate analysis for each study should be done.

Discussion: The firm stated it will submit two trials (36/37) of 108 patients each. The firm will submit a revised data analysis plan for the interim look that will be used for registration in the US.

9. Please advise us as to the suitability of our ISS tables to facilitate your review. (Section 2.2.3 and Appendix 8)

The tables are adequate.

10. The medical terminology used for adverse events in the ISS is based on WHO. However, for the 120-day Safety Update the new MEDDRA dictionary may be used. This decision depends upon the availability of the new version of the MEDDRA dictionary and the implementation schedule within Novartis. The switch would be required because it is not possible to map MEDDRA terms to our current dictionary, whereas we can map our current dictionary to a MEDDRA term.

If necessary, is it acceptable to the agency to submit the 120-day Safety Update using the MEDDRA dictionary?

No, please use the same dictionary throughout the application.

Discussion: The Division stated is will be acceptable to use MEDDRA; however, if the resulting data look different then more analysis with WHO terminology may be needed

Case Report Tabulations (CRTs)

11. Do you concur with our presentation of CRTs as described in Section 2.2.5. to satisfy the requirements of 21 CFR 314.50(f)(1)?

Yes.

Narratives and Case Report Forms (CRFs)

12. Is the proposal for submission of narratives and CRFs described in Section 2.2.6 acceptable?

Yes

Labeling

13. Is the proposed TLH registration program, (two) randomized, controlled clinical trials [redacted] acceptable to support registration for the following:

Indication

"Zoledronate is indicated for the treatment of tumor-induced hypercalcemia

This topic requires further discussion.

Discussion: The firm agreed to delete the following partial sentence from question number 13, "([redacted])." The Division then found the question acceptable.

Dosage and Administration

"The recommended dose of zoledronate is (4[redacted]) administered as a 5-minute intravenous infusion. Patients should be adequately hydrated."

"A limited number of patients have received more than one treatment with zoledronate for hypercalcemia. Retreatment with zoledronate, in patients who show complete or partial response initially, may be carried out if serum calcium does not return to normal or remain normal after initial treatment. It is recommended that a minimum of 4 days elapse before retreatment to allow for full response to the initial dose. The dose for retreatmen[redacted]

This is not adequate. A study needs to be submitted to show that retreatment is effective.

Discussion: The Division stated that the partial sentence "safe and" should be placed before effective in the above answer. The Division also objected to the procedure in the protocol that retreats all failures with zoledronate. The

Division stated that patients treated with Aredia should be retreated with Aredia.

14. In addition to the major advantages of zoledronate compared to pamidronate (potency and rapid infusion), we anticipate that zoledronate will provide a longer duration of normocalcemia than Aredia® and may provide successful retreatment for relapsed/refractory Aredia® patients. We believe either of these effects would represent a clinically relevant advantage over existing treatment and would request a priority review. Does the Division agree that the prolongation of duration of effect or the successful retreatment of relapsed/refractory patients would justify a priority review? In case no positive effects on duration and/or retreatment could be shown, would the rapid infusion only be sufficient to qualify for priority review?

No.

Discussion. The Division stated that the question of a priority review will be addressed when the application is submitted.

Financial Disclosure

15. 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 036 and 037 as of February 2, 1999. These studies are the basis for establishing the safety and efficacy of zoledronate for the proposed indication. Is this acceptable?

Please submit all information requested under the Final Rule for Financial Disclosure certification published in the December 31, 1998 Federal Register.

Pediatric Exclusivity

16 We intend to request a full waiver for the provision of pediatric data for the intended population on the basis that zoledronate is not likely to be used in a substantial number of pediatric patients. Based on a review of the literature and discussions with the NCI's Pediatric Oncology Group and Children's Cancer Study Group following the approval of Aredia®, it is estimated that approximately ten to fifteen pediatric patients with TIH are available in the US for study each year.

Please clarify the estimated number of pediatric patients.

Alternatively, we propose to request a Written Request for zoledronate in the treatment of pediatric Osteogenesis Imperfecta, a severely debilitating disorder characterized by osteopenia,

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frequent fractures, progressive deformity, loss of mobility, and chronic bone pain for which there is no effective therapy. It is believed that information on the pediatric use of zoledronate for this unapproved indication would provide health benefits in the pediatric population. Would a six-month extension to the patent and exclusivity be granted?

We will consider this after an action letter is sent concerning the original NDA.

Unresolved or issues requiring further discussion:

- None

Action Items:

- None

Signature, minutes preparer: /S/

Concurrence Chair: /S/

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NDA 21-223
Zometa (zoledronic acid for injection)
Novartis Pharmaceuticals Corp.

This section is not applicable at this time.

NDA 21-223
Zometa (zoledronic acid for injection)
Novartis Pharmaceuticals Corp.

This section is not applicable at this time.

NDA 21-223
Zometa (zoledronic acid for injection)
Novartis Pharmaceuticals Corp.

Advertising material is requested in letter..

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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: June 22, 2001

To: Eileen Ryan	**From:** Randy Hedin
Company: Novartis Pharmaceuticals Corporation	Division of Division of Metabolic and Endocrine Drug Products
Fax number: 973-781-6325	**Fax number:** 301-827-6392
Phone number: 973-781-7661	**Phone number:** (301) 827-6392

Subject: Labeling comments from the clinical review.

Total no. of pages including cover: 14

Comments: The following pages contain labeling comments. Additions are underlined, and deletions are struck through. Comments are bracketed, bolded and in 14 pt. font. These are preliminary comments, and additional changes may be requested. If you have any questions please contact me.

Document to be mailed: ☐ YES ☑ NO