

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Is this an orphan indication?

- ☐ Yes. PREA does not apply. Skip to signature block.
- ☐ No. Please proceed to the next question.

Is there a full waiver for this indication (check one)?

- ☐ Yes: Please proceed to Section A.
- ☐ No: Please check all that apply: ____ Partial Waiver ____ Deferred ____ Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below)::

Min _____	kg _____	mo. _____	yr. _____	Tanner Stage _____
Max _____	kg _____	mo. _____	yr. _____	Tanner Stage _____

Reason(s) for partial waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Adult studies ready for approval
- ☐ Formulation needed
- ☐ Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is

complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below)::

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Adult studies ready for approval
- ☐ Formulation needed
- ☐ Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 10/10/2006)

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/s/

Randy Hedin

4/16/2007 05:35:45 PM

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA 21-817	Efficacy Supplement Type SE-	Supplement Number	
Drug: Reclast (zoledronic acid) Injection		Applicant: Novartis Pharmaceuticals Corporation	
RPM: Randy Hedin		HFD- 510	Phone # 301-796-1224
Application Type: ☒ 505(b)(1) ☐ 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.) If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct. ☐ Confirmed and/or corrected		Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):	
❖ Application Classifications:			
Review priority			☐ Standard ☒ Priority
Chem class (NDAs only)			3
Other (e.g., orphan, OTC)			
❖ User Fee Goal Dates			
			April 16, 2007
❖ Special programs (indicate all that apply)			
			☐ None ☐ Subpart H ☐ 21 CFR 314.510 (accelerated approval) ☐ 21 CFR 314.520 (restricted distribution) ☐ Fast Track ☐ Rolling Review ☐ CMA Pilot 1 ☐ CMA Pilot 2
❖ User Fee Information			
User Fee			☒ Paid UF ID number 4803
User Fee waiver			☐ Small business ☐ Public health ☐ Barrier-to-Innovation ☐ Other (specify)
User Fee exception			☐ Orphan designation ☐ No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) ☐ Other (specify)
❖ Application Integrity Policy (AIP)			
Applicant is on the AIP			☐ Yes ☒ No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

() Yes () No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).

If "No," continue with question (5).

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?

() Yes () No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).

If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).

If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.

❖ Exclusivity (approvals only)	
- Exclusivity summary - Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)	April 16, 2007
Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.	() Yes, Application # _____ (X) No
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	November 29, 2004

General Information	
❖ Actions	
• Proposed action	(X) AP () TA () AE () NA
• Previous actions (specify type and date for each action taken)	AE, March 18, 2005 AE, February 22, 2006
• Status of advertising (approvals only)	(X) Materials requested in AP letter () Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	() Yes (X) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(X) None () Press Release () Talk Paper () Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling	April 13, 2007
• Original applicant-proposed labeling	September 21, 2004
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings (indicate dates of reviews and meetings)	DMETS, September 1, 2004 DMETS, December 1, 2005
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	
• Applicant proposed	April 13, 2007
• Reviews	
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	April 12, 2007
• Documentation of discussions and/or agreements relating to post-marketing commitments	April 13, 2007
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	X
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	None
• Pre-NDA meeting (indicate date)	None
• Pre-Approval Safety Conference (indicate date; approvals only)	
• Other	
❖ Advisory Committee Meeting	
• Date of Meeting	None
• 48-hour alert	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	None

Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	Deputy Director: April 11, 2007
Clinical Information	
❖ Clinical review(s) (indicate date for each review)	March 18, 2005 February 22, 2006 April 16, 2007
❖ Microbiology (efficacy) review(s) (indicate date for each review)	None
❖ Safety Update review(s) (indicate date or location if incorporated in another review)	Clinical Review March 18, 2005 Clinical Review February 22, 2006 Clinical Review April 16, 2007
❖ Risk Management Plan review(s) (indicate date/location if incorporated in another rev)	N/A
❖ Pediatric Page (separate page for each indication addressing status of all age groups)	Draft
❖ Demographic Worksheet (NME approvals only)	N/A
❖ Statistical review(s) (indicate date for each review)	March 8, 2005
❖ Biopharmaceutical review(s) (indicate date for each review)	March 15, 2005
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	March 18, 2005
• Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) (indicate date for each review)	March 18, 2005 March 19, 2007
❖ Environmental Assessment	
• Categorical Exclusion (indicate review date)	March 18, 2005
• Review & FONSI (indicate date of review)	
• Review & Environmental Impact Statement (indicate date of each review)	
❖ Microbiology (validation of sterilization & product sterility) review(s) (indicate date for each review)	February 17, 2005
❖ Facilities inspection (provide EER report)	Date completed: January 31, 2005 (X) Acceptable () Withhold recommendation
❖ Methods validation	(X) Completed () Requested () Not yet requested
Nonclinical Pharmacology Information	
❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	February 23, 2005
❖ Nonclinical inspection review summary	None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	None
❖ CAC/ECAC report	None

Appendix A to NDA/Efficacy Supplement Action Package Checklist

An application is likely to be a 505(b)(2) application if:

- (1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
- (2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
- (4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

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/s/

Randy Hedin

4/16/2007 04:19:25 PM

From: Hedin, Durand M
Sent: Thursday, April 05, 2007 12:03 PM
To: 'lynn.mellor@pharma.novartis.com'
Subject: NDA 21-817, Reclast (zoledronic acid) Injection

Contacts: Lynn Mellor

Hi Lynn,

If Reclast is approved, you should devise a plan that would monitor concomitant administration of these products and adverse events associated with the use of both drug products in postmarketing pharmacovigilance monitoring. We recommend the following to minimize potential user error.

A. EDUCATION

1. We recommend the circulation of a dear health care practitioner letter regarding the existence of the two drug products, their dual tradename status, different concentrations, and associated indications. This could help practitioners to become aware of the existence of both drug products.

2. We also recommend a public education campaign, including professional journal advertisements. This campaign will inform the public that Reclast is the same drug as Zometa, but a different concentration and indication. This would provide global information to the community that the same safety concerns (i.e. renal toxicities) that are seen with Zometa would be expected to be seen with Reclast. This will also aid to alleviate confusion between the two drug products and their indications.

B. CONTAINER AND CARTON LABELS

1 Page(s) Withheld

 Trade Secret / Confidential

X Draft Labeling

 Deliberative Process

Withheld Track Number: Administrative 1



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-817

Novartis Pharmaceuticals Corporation
Attention: Lynn Mellor
Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Ms. Mellor:

We acknowledge receipt on October 16, 2006 of your October 13, 2006 resubmission to your new drug application for Reclast (zoledronic acid) Injection.

We consider this a complete, class 2 response to our February 22, 2006 action letter. Therefore, the user fee goal date is April 16, 2006.

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. We note that you have not fulfilled the requirement. We are waiving the requirement for pediatric studies for this application.

If you have any questions, call me at (301) 796-1224.

Sincerely,

{See appended electronic signature page}

Randy Hedin, R.Ph.
Senior Regulatory Management Officer
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Randy Hedin

10/31/2006 01:49:23 PM

CONSULTATION RESPONSE

**DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; White Oak 22, Mail Stop 4447)**

DATE RECEIVED: September 15, 2005	DESIRED COMPLETION DATE: November 23, 2005	ODS CONSULT #: 04-0133-1
DATE OF DOCUMENT: August 23, 2005	PDUFA DATE: February 26, 2006	

TO: David Orloff, MD
Director, Division of Metabolism and Endocrinology Products
HFD-510

THROUGH: Randy Hedin
Project Manager, Division of Metabolism and Endocrinology Products
HFD-510

FROM: Kimberly Pedersen, RPh, Safety Evaluator
Alina Mahmud, RPh, MS, Team Leader

PRODUCT NAME: Reclast (Zoledronic Acid Injection) 5 mg/100 mL	NDA SPONSOR: Novartis Pharmaceuticals
NDA #: 21-817	

RECOMMENDATIONS:

1. Although we have not identified any proprietary names that would render the name "Reclast" objectionable from a look-alike or sound-alike perspective, we do not recommend the use of a second proprietary name for Zoledronic Acid Injectable marketed by Novartis Pharmaceuticals. If approved as Reclast, we recommend implementation of the educational suggestions and label and labeling revisions as described in section III of this review in order to minimize product confusion.
2. DDMAC finds the proprietary name "Reclast" acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Diane Smith, project manager, at 301-796-5038.

Denise P. Toyer, PharmD
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety

Carol Holquist, RPh
Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 796-2360 Fax: (301) 796-9865

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts^{1,2}, as well as several FDA databases³ for existing drug names which sound-alike or look-alike to Reclast to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted⁴. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study that involved health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name "Reclast." Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff with representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and professional experiences in addition to a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC finds the name Reclast acceptable from a promotional perspective.
2. The Expert Panel identified one proprietary name that was thought to have the potential for confusion with Reclast. This product is listed in table 1 (see below), along with the dosage forms available and FDA approved usual dosage.

Table 1: Potential Sound-Alike/Look-Alike Names for Reclast Identified by DMETS Expert Panel and Independent Review

Product Name	Established name, Dosage Form(s), Strength(s)	Usual adult dose*	Other**
Reclast	Zoledronic Acid Injection, 5 mg/100 mL	5 mg in 100 mL aqueous solution IV via vented infusion line. The infusion rate must be 15 minutes or greater. Should be administered as a single IV solution.	
Prefest™ (1 mg)	Estradiol/Norgestimate Tablets 1 mg estradiol (15 pink tabs) 1 mg estradiol/0.09 mg norgestimate (15 white tabs)	One pink tablet/day for 3 days, followed by 1 white tablet/day for 3 days. This regimen is repeated continuously without interruption.	LA/SA
*Frequently used, not all-inclusive. **L/A (look-alike), S/A (sound-alike)			

¹ MICROMEDEX Integrated Index, 2005 MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

² Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

³ AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-05 and the electronic online version of the FDA Orange Book.

⁴ WWW location <http://www.uspto.gov/tmdb/index.html>.

B. PHONETIC and ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. The phonetic search module returns a numeric score to the search engine based on the phonetic similarity to the input text. Likewise, an orthographic algorithm exists which operates in a similar fashion. All names considered to have significant phonetic or orthographic similarities to Reclast were discussed by the Expert Panel (EPD).

C. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion with Reclast and other marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 119 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Reclast (see below). These prescriptions were optically scanned and delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail, which were sent to a random sample of the participating health professionals for their interpretation and review. After receiving either the written or verbal prescription orders, the participants sent their interpretation of the order via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
<u>Outpatient RX:</u> Reclast 10 mg 2 bags For use by home health care	Reclast 10 mg Dispense two bags for home use by the home health care nurse
<u>Inpatient RX:</u> Reclast 10mg In 100ml ampules IV over 15 min	

2. Results:

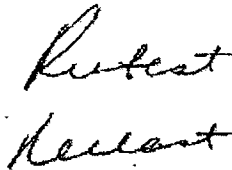
One respondent in the verbal study interpreted the proposed name as "Replax." Replax is similar to a currently marketed U.S. product, Relpax. In addition, another verbal study participant noted the interpretation of "reflux", which looks and sounds similar to the medical term, "reflux." See appendix A for the complete listing of interpretations from the verbal and written studies.

D. SAFETY EVALUATOR RISK ASSESSMENT

1. Sound-Alike/Look-Alike Assessment

In reviewing the proprietary name Reclast, the primary concerns related to look-alike and sound-alike confusion with Prefest. Additionally, DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was suggestion that Reclast could be confused with the marketed product "Relpax" as one verbal study respondent interpreted the order as "Replax." In addition, another verbal study respondent misinterpreted the name as "Reflax", which is similar to the medical term of "reflux." Upon further review of these names with potential for confusion, DMETS will not review Relpax due to a lack of convincing sound-alike similarities with Reclast. This, is in addition to the numerous differentiating product characteristics such as strength (20 mg and 40 mg compared to 5 mg), indication for use (migraine compared to Paget's Disease), route of administration (oral compared to intravenous administration), and dosage formulation (tablets compared to solution for infusion). Furthermore, DMETS could not ascertain a clinical situation where the medical term of "reflux" could result in confusion with the proposed name of Reclast. The majority of remaining misinterpretations were misspelled/phonetic variations of the proposed name, Reclast. However, negative findings are not predicative as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to a small sample size.

Prefest may look and sound similar to Reclast when scripted and spoken. Prefest is a hormonal supplement for the treatment of menopausal symptoms and osteoporosis prevention. Prefest contains fifteen tablets of 1 mg estradiol and another fifteen tablets of 1 mg estradiol/0.09 mg norgestimate. The patient should take one tablet of the 1 mg estradiol days one through three of therapy with the combination estradiol/norgestimate tablets taken on days four through six with the cycle repeated thereafter. The orthographic similarities stem from the shared concluding "st" with the similarly placed central upstroke ("f" of Prefest and "l" of Reclast) and potential for the leading "P" of Prefest to appear similar to the "R" of Reclast when the practitioner does not lift the pen.

The image shows two handwritten words, "Prefest" and "Reclast", written in cursive. The "Prefest" is written above "Reclast". Both words are written in a way that highlights their orthographic similarities, particularly the shared concluding "st" and the central upstroke of the "f" in Prefest and "l" in Reclast.

The auditory similarities stem from the shared two syllable count, leading hard "e, ē" and concluding "st." However, the leading "P" compared to "R" and central "f" of Prefest compared to "cl" of Reclast should distinguish the two in speech. The products are both single strengths; thus, an order does not need an indication of strength for accurate completion. However, in light of the numerous differing product characteristics such as indication for use (menopausal symptoms compared to Paget's Disease), primary areas of use (outpatient compared to inpatient/infusion clinics), route of administration (oral compared to intravenous), packaging/dosage form (blister cards containing tablets compared to 100 mL bottle for infusion), and dosing frequency (daily compared to one use to be repeated after evaluation), DMETS believes the possibility for confusion to be minimal.

2. Dual Tradename Concerns

The sponsor proposes to market zoledronic acid injection with two proprietary names (approved NDA #21-223 Zometa and the pending application NDA #21-817 with a proposed name "Reclast") for two different indications. DMETS generally discourages the use of two different proprietary names for the same active ingredient by the same manufacturer due to the potential for confusion in proprietary and established name association and the conceivable patient ingestion of both drug products. Reference is made to the previous DMETS review (ODS consult # 04-0133) in 2004, as those comments remain applicable at this time. This current analysis will focus on any safety repercussions from potential confusion with two tradenames for the same chemical moiety.

a. Lack of Proprietary Name, Established Name, and Concentration Association with Reclast

In essence, if approved, zoledronic acid injectable will be available from the same manufacturer with two different names (Zometa and Reclast). DMETS suspects confusion may arise if practitioners are not aware that Zometa and Reclast are the same drug product. This is especially true in the first six months to one year of approval. From post-marketing reporting, DMETS identified two cases that noted confusion with two bisphosphonate drug products (Aredia and Zometa) marketed by this sponsor.

The first case (2001) involved a patient who received both Aredia and Zometa for hypercalcemia of malignancy. The physician had ordered to administer either Aredia or Zometa, but both were infused. The patient's hospitalization was prolonged for monitoring of laboratory values; however the laboratory values were noted to have mild decreases (hypocalcemia).

One could assume the confusion was due to a lack of familiarity with Zometa due to the recent approval in August of 2001 (Aredia was approved Oct 1991). This is the same situation that DMETS proposes could occur with Reclast and Zometa, which will have the additional problem of different strengths and the same established name/chemical moiety.

The second case (2005) noted confusion with the nursing and pharmacy staff as to if the patient had received therapy with pamidronate. This resulted in the patient receiving both pamidronate and Zometa, which resulted in a worsening renal function, severe hypocalcemia and hypophosphatemia.

Confusion with the dose, dosing frequency, and concentration may also be problematic. The products contain the same active moiety, but differ in concentration by one milligram (4 mg compared to 5 mg); thus, the concern would result from what harm could occur with an increase or decrease of one milligram from the suggested dosing. Two post-marketing cases were found that suggest renal dysfunction could result from errors in dosing.

The first case (2002) involved a patient who received two doses of Zometa accidentally over 3 days with resultant creatinine increase from 1 to 3.8.

The second case (2003) noted a patient received Zometa 4 mg for two days for the treatment of osteoporosis. Subsequently, the patient's electrolytes were monitored, TUMS administered and intravenous hydration initiated; and the patient did not experience adverse reactions.

If Reclast is approved, the sponsor should devise a plan that would monitor concomitant administration of these products and adverse events associated with the use of both drug products in postmarketing pharmacovigilance monitoring.

b. Confusion with Reclast labeling and/or the labels/labeling of other Novartis products

Post-marketing reporting noted two cases (2003, 2004) for Zometa where the infusion times were shorter than the recommended fifteen minutes (both around seven minutes); both were poorly documented and could provide no additional information. As this information on infusion timing is prominent in the package insert and on the carton and container labels and labeling, DMETS believes the possibility for this medication error to be minimal. Another reporter described that the Aredia and Zometa packaging were similar, but did not indicate that this resulted in error just the potential for confusion. After evaluating the labels, DMETS believes the labels and labeling are distinct in color and style to alleviate possible confusion between Zometa and Reclast.

c. Use for Other Indications

Currently, the sponsor is conducting clinical trials for the use of zoledronic acid in the treatment of various osteoporosis conditions. This leads to additional concern for the proposal and introduction of another proprietary name for zoledronic acid in the treatment of osteoporosis. This introduction into a broader patient population could potentiate more confusion and increase the possibility for overdose or accidental infusion of the same medication multiple times.

III. COMMENTS TO THE SPONSOR:

DMETS does not recommend the use of the tradename "Reclast." Rather than the use of a dual tradename, DMETS recommends use of the single tradename "Zometa" for all Zoledronic Acid Injection marketed by the sponsor.

Dual Tradename Concerns

The sponsor proposes to market zoledronic acid injection with two proprietary names (approved NDA #21-223 Zometa and the pending application NDA #21-817 with a proposed name "Reclast") for two different indications. DMETS generally discourages the use of two different proprietary names for the same active ingredient by the same manufacturer due to the potential for confusion in proprietary and established name association and the conceivable patient ingestion of both drug products. Reference is made to the previous DMETS review (ODS consult # 04-0133) in 2004, as those comments remain applicable at this time. This current analysis will focus on any safety repercussions from potential confusion with two tradenames for the same chemical moiety.

a. Lack of Proprietary Name, Established Name, and Concentration Association with Reclast

In essence, if approved, zoledronic acid injectable will be available from the same manufacturer with two different names (Zometa and Reclast). DMETS suspects confusion may arise if practitioners are not aware that Zometa and Reclast are the same drug product. This is especially true in the first six months to one year of approval. From post-marketing reporting, DMETS identified two cases that noted confusion with two biphosphonate drug products (Aredia and Zometa) marketed by this sponsor.

The first case (2001) involved a patient who received both Aredia and Zometa for hypercalcemia of malignancy. The physician had ordered to administer either Aredia or Zometa, but both were infused. The patient's hospitalization was prolonged for monitoring of laboratory values; however the laboratory values were noted to have mild decreases (hypocalcemia).

One could assume the confusion was due to a lack of familiarity with Zometa due to the recent approval in August of 2001 (Aredia was approved Oct 1991). This is the same situation that DMETS proposes could occur with Reclast and Zometa, which will have the additional problem of different strengths and the same established name/chemical moiety.

The second case (2005) noted confusion with the nursing and pharmacy staff as to if the patient had received therapy with pamidronate. This resulted in the patient receiving both pamidronate and Zometa, which resulted in a worsening renal function, severe hypocalcemia and hypophosphatemia.

Confusion with the dose, dosing frequency, and concentration may also be problematic. The products contain the same active moiety, but differ in concentration by one milligram (4 mg compared to 5 mg); thus, the concern would result from what harm could occur with an increase or decrease of one milligram from the suggested dosing. Two post-marketing cases were found that suggest renal dysfunction could result from errors in dosing.

The first case (2002) involved a patient who received two doses of Zometa accidentally over 3 days with resultant creatinine increase from 1 to 3.8.

The second case (2003) noted a patient received Zometa 4 mg for two days for the treatment of osteoporosis. Subsequently, the patient's electrolytes were monitored, TUMS administered and intravenous hydration initiated; and the patient did not experience adverse reactions.

If Reclast is approved, the sponsor should devise a plan that would monitor concomitant administration of these products and adverse events associated with the use of both drug products in postmarketing pharmacovigilance monitoring.

b. Confusion with Reclast labeling and/or the labels/labeling of other Novartis products

Post-marketing reporting noted two cases (2003, 2004) for Zometa where the infusion times were shorter than the recommended fifteen minutes (both around seven minutes); both were poorly documented and could provide no additional information. As this information on infusion timing is prominent in the package insert and on the carton and container labels and labeling, DMETS believes the possibility for this medication error to be minimal. Another reporter described that the Aredia and Zometa packaging were similar, but did not indicate that this resulted in error just the potential for confusion. After evaluating the labels, DMETS believes the labels and labeling are distinct in color and style to alleviate possible confusion between Zometa and Reclast.

c. Use for other Indications

Currently, the sponsor is conducting clinical trials for the use of zoledronic acid in the treatment of various osteoporosis conditions. This leads to additional concern for the proposal and introduction of another proprietary name for zoledronic acid in the treatment of osteoporosis. This introduction into a broader patient population could potentiate more confusion and increase the possibility for overdose or accidental infusion of the same medication multiple times.

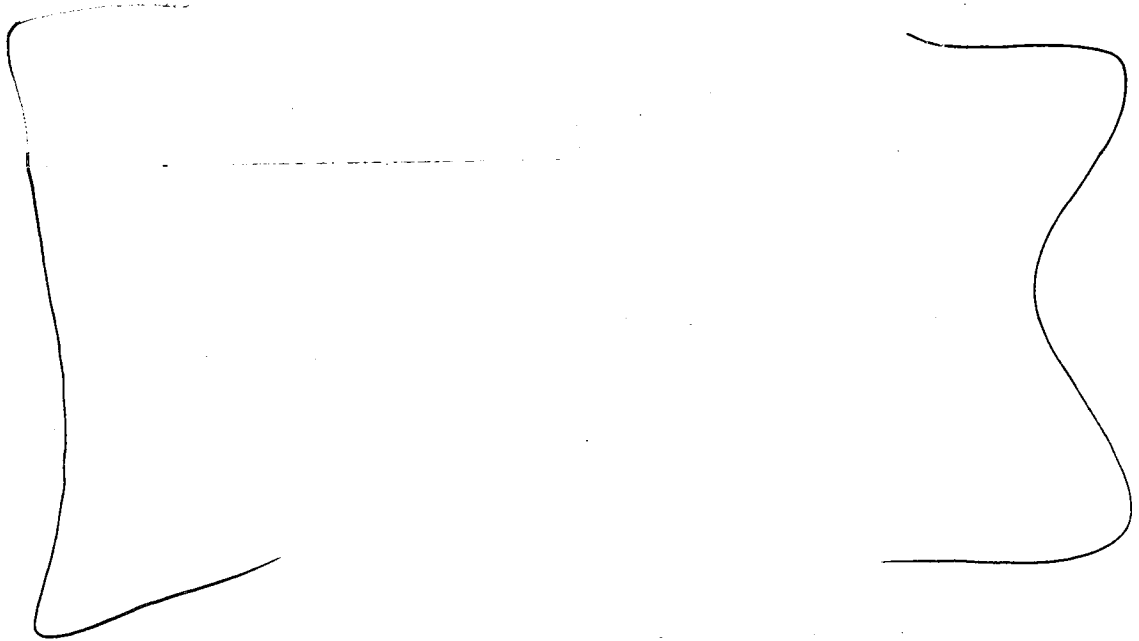
If approved with two proprietary names, then we recommend the following to minimize potential user error.

A. EDUCATION

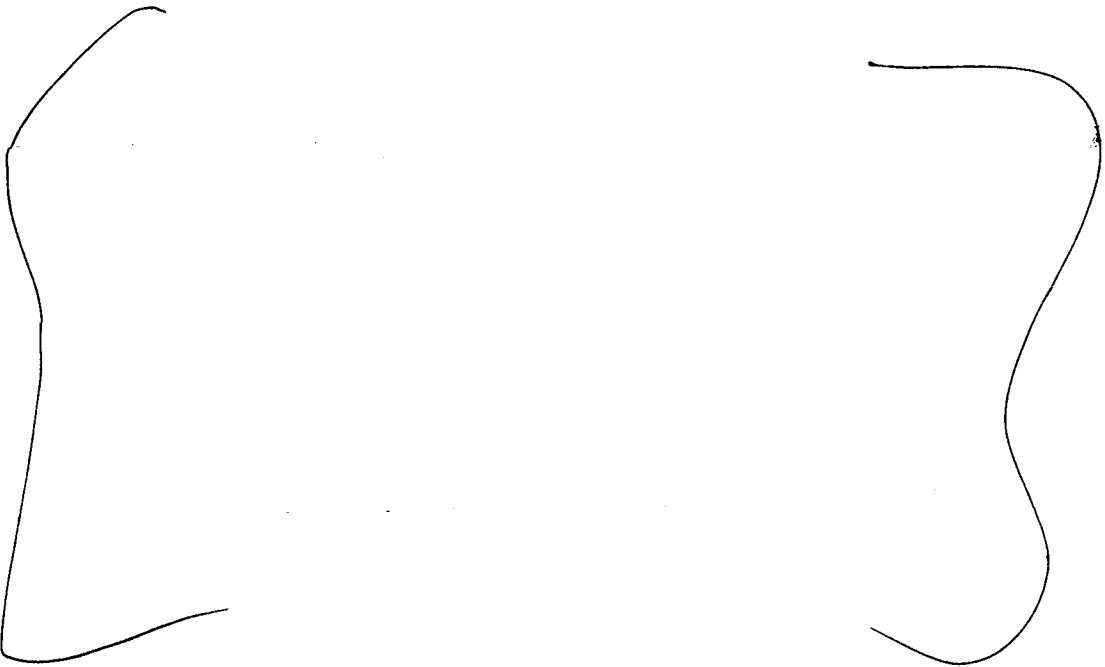
1. DMETS recommends the circulation of a dear health care practitioner letter regarding the existence of the two drug products, their dual tradename status, different concentrations, and associated indications. This could help practitioners to become aware of the existence of both drug products.

2. DMETS also recommends a public education campaign, including professional journal advertisements. This campaign will inform the public that Reclast is the same drug as Zometa, but a different concentration and indication. This would provide global information to the community that the same safety concerns (i.e. renal toxicities) that are seen with Zometa would be expected to be seen with Reclast. This will also aid to alleviate confusion between the two drug products and their indications.

B. CONTAINER AND CARTON LABELS



C. INSERT LABELING



**APPEARS THIS WAY
ON ORIGINAL**

Attachment A: DMETS Prescription Study Results

Inpatient	Outpatient	Voice
Reclast	Reclast	Replax
Reclast	Reclast	Replast
Reclast	Reclast	Reclass
Reclast	Reclast	Reclass
Reclant	Reclast	Reclass
Reclast	Reclast	Reclass
Reclast	Reclast	Reclass
Reclast	Reclast	Reclass
Reelast	Reclast	Reclass
Reclast	Reclast	Reclass
Reelast	Reclast	reclast
Reclast	Reclast	Reclasp
Reelast	Restast	Reclass
Reclast	Reelast	Reflax
Reclast	Reclast	
Reclast	Reclast	
Reclast	Reclast	
Reclast	Reclast	
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/s/

Kimberly Culley-Pedersen
12/1/2005 09:18:45 AM
DRUG SAFETY OFFICE REVIEWER

Alina Mahmud
12/1/2005 11:23:38 AM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
12/1/2005 01:14:34 PM
DRUG SAFETY OFFICE REVIEWER
Also signing for Carol Holquist, DMETS Director, in her
absence.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-817

Novartis Pharmaceuticals Corporation
Attn: Lynn Mellor
Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Ms. Mellor:

We acknowledge receipt on August 23, 2005 of your August 25, 2005 resubmission to your new drug application for Reclast (zoledronic acid) Injection.

We consider this a complete, class 2 response to our March 18, 2005 action letter. Therefore, the user fee goal date is February 25, 2006.

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. We note that you have not fulfilled the requirement. We are waiving the requirement for pediatric studies for this application.

If you have any questions, call me at (301) 827-6392.

Sincerely,

{See appended electronic signature page}

Randy Hedin, R.Ph.
Senior Regulatory Management Officer
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research and Research

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/s/

Randy Hedin

9/14/2005 10:34:47 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-817

Novartis Pharmaceuticals Corporation
Attention: Lynn Mellor
Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Ms. Mellor:

Please refer to the meeting between representatives of your firm and FDA on May 25, 2005. The purpose of the meeting was to discuss the approvable letter for zoledronic acid 5 mg to treat Paget's Disease of bone.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 827-6392.

Sincerely,

{See appended electronic signature page}

Randy Hedin
Senior Regulatory Management Officer
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

- Novartis stated that they collected data from the study sites concerning compliance with the dosing of calcium and vitamin D for patients with a serum calcium less than the lower limit of normal (LLN). The Division asked if collecting data in this manner would introduce bias into the results, and Novartis agreed that bias could influence the results. The Division stated that, optimally, the protocol for collecting the data should have been submitted for review by the Division before data were collected. The Division also stated that data on all patients, not just those who developed low calcium levels, should be collected to lessen the chance of error being introduced into the procedure. Novartis stated that the data collected indicates that administration of supplemental calcium to patients treated with zoledronic acid for Paget's Disease attenuates the decline in serum calcium. Novartis asked if the data presented were adequate for a complete response to the approvable letter, and the Division responded that the decision on a complete response would be made when the data are reviewed. In addition, Novartis should state in a complete response why an additional study is not warranted, and whether additional phase 4 studies would be useful to clarify the role of supplemental calcium and vitamin D in mitigating the risk for developing hypocalcemia following Zometa administration.
- Novartis stated that they would introduce labeling that would stress the need for adequate calcium supplementation in a complete response to the approvable letter. The Division stated that educational efforts to communicate the need for calcium supplementation when zoledronic acid 5 mg is administered should also be discussed in the complete response.
- Novartis stated that an analysis shows that the majority of the patients with day-10 serum calcium values below the LLN were just below the LLN (2.1 mmol/L), and didn't present with clinical symptoms of hypocalcemia.
- The Division asked why the 5 mg dose was selected and not the 4 mg dose that is currently marketed, and Novartis responded that the 5 mg dose is the dose being studied for osteoporosis. Also, Novartis stated that in the complete response to the approvable letter it would expand on its rationale for selecting the 5 mg dose to treat Paget's Disease.
- The Division asked if an additional study would be warranted, and Novartis responded that it believes the currently available data on calcium supplementation are sufficient to support approval, and further stated that the package insert can be strengthened to stress that adequate calcium supplementation is very important.
- Novartis asked if a safety update will need to be submitted with the complete response to the approvable letter, and the Division stated that it would, and that Novartis should submit a proposal on what would be required in the safety update.
- The Division stated it would communicate with Novartis any other issues it felt

should be included in the complete response to the approvable letter.

Unresolved or issues requiring further discussion:

- None

Action Items:

- The Division will communicate with Novartis issues to be included in the complete response to the approvable letter.
- Novartis will submit a proposal as to what information will be included in the safety update.

Signature, minutes preparer: Randy Hedin

Concurrence Chair: Eric Colman

APPEARS THIS WAY
ON ORIGINAL

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/s/

Randy Hedin

6/23/05 11:09:40 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-817

Novartis Pharmaceuticals Corporation
Attention: Lynn Mellor
Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Ms. Mellor:

Please refer to the teleconference between representatives of your firm and FDA on May 10, 2005. The purpose of the meeting was to discuss the trade name "Aclasta," and Novartis' request to have two trade names for zoledronic acid, "Aclasta" and "Zometa."

The official minutes of that teleconference are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 827-6392.

Sincerely,

{See appended electronic signature page}

Randy Hedin
Senior Regulatory Management Officer
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

Meeting Date: May 10 , 2005 Time: 3:30 - 4:30 PM Location: Teleconference

NDA 21-817 Zoledronic Acid Injection

Type of Meeting: Guidance Teleconference

External participant: Novartis Pharmaceuticals Corporation

Meeting Chair: Dr. Eric Colman

External participant lead: Ms. Lynn Mellor

Meeting Recorder: Mr. Randy Hedin

FDA attendees and titles:

Division of Metabolic and Endocrine Drug Products:

David Orloff, M.D., Director

Eric Colman, M.D., Clinical Team Leader

Randy Hedin, R.Ph., Senior Regulatory Management Officer

Office of Drug Safety

Kristina Arnwine, Pharm.D., Safety Evaluator, DMETS

Denise Toyer, Pharm.D., Deputy Director, DMETS

Linda Kim-Jung, Pharm.D., Lead Pharmacist, DMETS

Carol Holquist, Ph.D., R.Ph., Director, DMETS

Parivash Nourjah, Ph.D., Epidemiologist, DDRE

External participant Attendees and titles:

Kevin Carl, Pharm.D., Assistant Director, Regulatory

John Cutt, Ph.D., V.P, Global Head ABGHI, Regulatory

Lynn Mellor, Director, Drug Regulatory Affairs

Joel Krasnow, M.D., Sr. Director, Clinical Program Leader, ABH

John Orloff, M.D., V.P. Therapeutic Area Head, ABHI

Theresa Rosario-Jansen, Ph.D., Director, Clinical Research & Development

Audrey Kriegman M.D., Clinical Development

Judith Sills, Pharm.D., Clinical Safety and Epidemiology

Steven Hartman, Global Head of Trademarks

Paul McGinley, U.S. Brand Director, zoledronic acid

Meeting Objectives:

Novartis requested to meet with the Division to discuss the trade name "Aclasta," and to discuss having two trade names for zoledronic acid, "Aclasta" and "Zometa." Zometa was approved on August 20, 2001, for the treatment of hypercalcemia of malignancy, and has subsequently been approved for the treatment of patients with multiple myeloma and

patients with documented bone metastases from solid tumors, in conjunction with standard antineoplastic therapy. This NDA is for the indication, Paget's Disease of bone.

Discussion Points and Decisions (agreements) reached:

- 
- The Division stated that its opinion is that dual trade names have a greater tendency to increase errors because of doubling up of doses. Novartis stated that it did not agree and that dual trade names will maximize the correct and safe use of zoledronic acid for both the oncology and non-oncology metabolic bone disease indications. Novartis further stated that a label that contains both oncology and non-oncology indications with a different dose and dosing frequency, and dose titration by creatinine clearance for oncology patients adds complexity to the label. This complexity will increase the number of medication errors. The Division did not agree, and stated that the possibility of doubling doses was of greater concern. Both parties agreed to disagree on this issue at this time.
- The Division did acknowledge that one's belief about the clinical risks of medication errors with one or two trade names is hypothetical, and is based on opinion rather than data. The Division will internally re-review the issues and take into consideration the points in Novartis's presentation. The Division stated it may send a consult to General Council to get their opinion regarding setting conditions for reversion to one label, if dual trade names are allowed and errors arise that indicate allowing two trade names is more hazardous than one. The Division stated that there is no set timeframe for an opinion; however, the Division will try to expedite the review of this issue.

Unresolved or issues requiring further discussion:

- None

Action Items:

- Consider sending a consult to General Council to get their opinion regarding setting conditions for reversion to one trade name, if dual trade names are allowed and errors arise that indicate allowing two trade names is more hazardous than one.

Signature, minutes preparer: Randy Hedin

Concurrence Chair: Eric Colman

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/s/

Randy Hedin
6/9/05 02:11:49 PM

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: March 18, 2005

TO: Randy Hedin, Senior Regulatory Management Officer
Eric Colman, M.D., Medical Reviewer
Division of Metabolic & Endocrine Drug Products, HFD-510

THROUGH: Ni A. Khin, M.D., Branch Chief
Good Clinical Practice Branch 1, HFD-46
Division of Scientific Investigations

FROM: Andrea Slavin, RN, Consumer Safety Officer
Good Clinical Practice Branch 1, HFD-46
Division of Scientific Investigations

SUBJECT: Evaluation of Domestic & Foreign Inspections

NDA: 21-817

SPONSOR: Novartis Pharmaceuticals, Inc.

DRUG: Aclasta ® (zoledronic acid injection)

CHEMICAL CLASSIFICATION: 3, P (New Formulation, Therapeutic Gain)

THERAPEUTIC CLASSIFICATION: Bone/Calcium-Phosphorus Metabolism

INDICATIONS: Paget's Disease

CONSULTATION REQUEST DATE: December 8, 2004

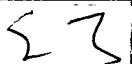
GOAL DATE TO PROVIDE
INSPECTION SUMMARY: March 1, 2005

PDUFA GOAL DATE: March 21, 2005

I. BACKGROUND:

Zoledronic acid is a representative of the nitrogen containing bisphosphonates and is the most potent bisphosphonate in development. Bisphosphonates are analogues of pyrophosphate and exhibit marked effects on bone metabolism. Paget's disease of the bone is characterized by accelerated bone remodeling. Excessive osteoclastic bone resorption coupled with increased osteoblastic activity leads to the formation of new bone, which is structurally flawed and may lead to deformity, pain, and fractures.

II. RESULTS (by site):

Name	City, State	Country	Protocol	Insp. Date	EIR Recd.	Classn.
		Canada	CZOL446H2304	2/28-3/4/2005	pending	pending
		Canada	CZOL446H2304	3/7-11/2005	pending	pending
		USA	CZOL446H2304	3/14-16/2005	pending	pending

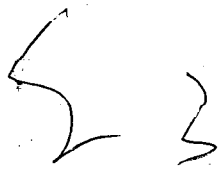
Study Protocol: #CZOL446H2304, "Randomized, Double-Blind, Safety and Efficacy Trial with Intravenous Zoledronic Acid for the Treatment of Paget's Disease of Bone Using Risedronate as a Comparator"

This was a multicenter, multinational study conducted in Australia, Canada, United Kingdom, United States and Spain. A total of 172 subjects were randomized. The primary objective was to show non-inferiority of zoledronic acid to risedronate, with respect to the proportion of subjects who achieved therapeutic response. Subjects randomized to receive zoledronic acid 5 mg received a single 15-minute intravenous infusion and 60 days of oral placebo capsules while subjects randomized to receive risedronate received 60 days of oral risedronate 30 mg/day and a single 15-minute intravenous placebo infusion. The primary efficacy variable was the proportion of subjects who achieved therapeutic response. A therapeutic response was defined as a reduction of at least 75% from baseline in serum alkaline phosphatase (SAP) excess (difference between measured level and midpoint to the normal range) or normalization of SAP.

Sites:

Basis for site selection: Sites were selected by the medical reviewer.

1.



Methodology: Inspection assignment was issued to the Associate Director, International Operations Branch, DFI.

Dates of Inspection: February 28-March 4, 2005

a. What was inspected:  randomized 19 subjects into the study; eight subjects' records were audited in-depth for data integrity.

b. General observations/commentary: In general, data in sponsor provided data listings were supported by data in source documents and case report forms at the site. No objectionable conditions were noted. Form FDA 483 was not issued. Final classification of this inspection pending receipt of the EIR and exhibits by the Center.

2.



Methodology: Inspection assignment was issued to the Associate Director, International Operations Branch, DFI.

Dates of Inspection: March 7-11, 2005

a. What was inspected:  randomized 9 subjects into the study; five subjects' records were audited in-depth for data integrity.

- 3.

Dates of Inspection: March 14-16, 2005

- It was noted that the same firm that was utilized as the central laboratory- was also the firm that managed the IVR system and shipped the study drugs to the sites.

Data submitted by these 3 clinical investigators are acceptable in support of NDA 21-817.

Andrea Slavin, RN

CONCURRENCE:

Ni A. Khin, M.D., Branch Chief
Good Clinical Practice Branch 1
Division of Scientific Investigations
Office of Medical Policy

DISTRIBUTION:

NDA #21-817
HFD-45/Division File
HFD-46/Program Management Staff (electronic copy)
HFD-510/Project Manager/Hedin
HFD-46/Slavin
HFD-46/GCP 1 Files
HFD-46/Reading File

O:/Slavin/Summaries/Aclasta Summary

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/s/

Andrea Slavin
3/18/05 02:45:14 PM
CSO

Joseph Salewski
3/18/05 02:54:10 PM
CSO

18 Page(s) Withheld

X Trade Secret / Confidential

 Draft Labeling

 Deliberative Process

Withheld Track Number: Administrative- 2

From: Hedin, Durand M
Sent: Friday, January 07, 2005 1:02 PM
To: 'robert.clark@pharma.novartis.com'
Subject: NDA 21-817, Aclasta (zoledronic acid) Injection

Dear Ms. Materna:

We have the following comments and requests for information concerning the chemistry review of NDA 21-817.

1. The analytical method for the identity and determination (assay) of zoledronic acid by HPLC should be demonstrated to be stability-indicating. This may be demonstrated by reference to _____ In addition, HPLC response factors should be determined for degradation products generated by the _____ studies. This data may be supplied by reference to the approved application NDA 21-223, Zometa® (zoledronic acid) for injection.
2. Identify the solvents contained in the _____ adhesive (used to affix the label to the container) and the chemical composition of the dyes (colorants, solvents, etc.).

Please provide a timeline as to when you will be able to respond to these issues. If you have any questions, contact me at 301-827-6392.

Sincerely,

Randy Hedin, R.Ph.
Senior Regulatory Management Officer
Division of Metabolic and Endocrine Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
Parklawn 14B-45, HFD-510
5600 Fishers Lane
Rockville MD 20857

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/s/

Randy Hedin
1/7/05 01:56:45 PM
CSO

From: Hedin, Durand M
Sent: Monday, December 27, 2004 1:32 PM
To: 'lynn.mellor@pharma.novartis.com'
Subject: Aclasta (zoledronic acid) Injection, NDA 21-817

Dear Ms. Mellor

We have the following requests for information concerning the biopharm review of Aclasta Injection, NDA 21-817.

Sincerely,

Randy Hedin, R.Ph.
Senior Regulatory Management Officer
Division of Metabolic and Endocrine Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
Parklawn 14B-45, HFD-510
5600 Fishers Lane
Rockville MD 20857

Reference the appropriate NDA section(s) that contain the following, or provide the Division with the following:

- Evidence that 5 mg zoledronic acid intravenously administered over 15 minutes does not cause QT prolongation.
- Files (model building, model validation, control file for the final model, and data sets) for the population pharmacokinetic covariate analyses in SAS transport files.

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/s/

Randy Hedin
12/27/04 01:43:27 PM
CSO

MEMORANDUM OF TELECON

DATE: December 22, 2004

APPLICATION NUMBER: NDA 21-817

BETWEEN:

Name: Lynn Mellor
Phone: _____
Representing: Novartis Pharmaceuticals Corporation

AND

Name: Randy Hedin
Division of Metabolic and Endocrine Drugs, HFD-510

SUBJECT: Aclasta (zoledronic acid) Injection

I called Ms. Mellor and requested, on her voice-mail, that the following information be submitted to NDA 21-817:

Provide the rationale behind the selection of the proposed dose of zoledronic acid 5 mg infused over 15-minutes in patients with Paget's disease of bone.

I stated that she should telephone me, and confirm that she got the message, and give me a timeline as to when we can expect a response.

Randy Hedin
Senior Regulatory Management Officer

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/s/

Randy Hedin
12/22/04 04:01:37 PM
CSO



NDA 21-817

FILING COMMUNICATION

Novartis Pharmaceuticals Corporation
Attention: Lynn Mellor
Director, Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Ms. Mellor:

Please refer to your September 21, 2004 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Aclasta (zoledronic acid) Injection.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application was filed under section 505(b) of the Act on November 20, 2004 in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

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

Sincerely,

{See appended electronic signature page}

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

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/s/

Randy Hedin
11/29/04 03:56:21 PM
Signing for Kati Johnson

NDA REGULATORY FILING REVIEW

NDA # 21-817	Supplement #	SE1	SE2	SE3	SE4	SE5	SE6	SE7	SE8
--------------	--------------	-----	-----	-----	-----	-----	-----	-----	-----

Trade Name:	Aclasta Injection
Generic Name:	zoledronic acid
Strengths:	5 mg

Applicant: Novartis Pharmaceuticals Inc.

Date of Application: September 21, 2004

Date of Receipt: September 21, 2004

Date clock started after UN: NA

Date of Filing Meeting: November 17, 2004

Filing Date: November 20, 2004

Action Goal Date (optional): _____ User Fee Goal Date: March 21, 2005

Indication(s) requested: Treatment of Paget's disease of bone.

Type of Original NDA: (b)(1) (b)(2)

Type of Supplement: (b)(1) X (b)(2)

NOTE:

- (1) *If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2), complete Appendix B.*

- (2) *If the application is a supplement to an NDA, please indicate whether the NDA is a (b)(1) or a (b)(2) application:*

____ NDA is a (b)(1) application OR ____ NDA is a (b)(2) application

Therapeutic Classification: S P X

Resubmission after withdrawal?	NA	Resubmission after refuse to file?	NA
--------------------------------	----	------------------------------------	----

Chemical Classification: (1,2,3 etc.) 3

Other (orphan, OTC, etc.)	NA
---------------------------	----

Form 3397 (User Fee Cover Sheet) submitted: YES X NO

User Fee Status: Paid X Exempt (orphan, government) _____
 Waived (e.g., small business, public health) _____

NOTE: If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx to OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling.

If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the user fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application?

YES X NO

If yes, explain: NDA 21,223, Zometa (zoledronic acid) Injection has exclusivity. This application is also owned by Novartis.

- Does another drug have orphan drug exclusivity for the same indication? YES NO X

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?

YES NO

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES NO X
If yes, explain.

- If yes, has OC/DMPQ been notified of the submission? YES NO

- Does the submission contain an accurate comprehensive index? YES X NO

- Was form 356h included with an authorized signature? YES X NO

If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES X NO

If no, explain:

- If an electronic NDA, does it follow the Guidance? N/A YES X NO

If an electronic NDA, all certifications must be in paper and require a signature.

Which parts of the application were submitted in electronic format? Only labeling.

Additional comments:

- If in Common Technical Document format, does it follow the guidance? N/A X YES NO

- Is it an electronic CTD? N/A YES NO X

If an electronic CTD, all certifications must be in paper and require a signature.

Which parts of the application were submitted in electronic format? All

Additional comments:

- Patent information submitted on form FDA 3542a? YES X NO

- Exclusivity requested? YES, X years NO

Note: The application didn't specify the number of years.

NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.

- Correctly worded Debarment Certification included with authorized signature? YES X NO
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby 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." Applicant may not use wording such as "To the best of my knowledge . . ."

- Financial Disclosure forms included with authorized signature? YES X NO
(Forms 3454 and 3455 must be used and must be signed by the APPLICANT.)
- Field Copy Certification (that it is a true copy of the CMC technical section)? YES X NO

Refer to 21 CFR 314.101(d) for Filing Requirements

- PDUFA and Action Goal dates correct in COMIS? YES X NO
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections.
- List referenced IND numbers: 43,240
- End-of-Phase 2 Meeting(s)? Date(s) NO X
If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s)? Date(s) NO X
If yes, distribute minutes before filing meeting.

Project Management

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? YES NO X
- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? YES X NO
- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A YES NO X
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted? N/A X YES NO

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/A X YES NO
- Has DOTCDP been notified of the OTC switch application? YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?
N/A X YES NO

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES X NO
If no, did applicant submit a complete environmental assessment? YES NO
If EA submitted, consulted to Florian Zielinski (HFD-357)? YES NO
- Establishment Evaluation Request (EER) submitted to DMPQ? YES X NO
- If a parenteral product, consulted to Microbiology Team (HFD-805)? NA YES X NO

APPEARS THIS WAY
ON ORIGINAL

ATTACHMENT

MEMO OF FILING MEETING

DATE: November 17, 2004

BACKGROUND:

Zoledronic acid injection is currently approved as Zometa Injection for oncologic indications, and is being studied to treat postmenopausal osteoporosis. The indication in this NDA is the treatment of Paget's disease of bone. The firm is requesting a different trade name for the Paget's disease indication to differentiate it from Zometa and the oncologic indications.

ASSIGNED REVIEWERS:

Discipline

Medical:
Secondary Medical:
Statistical:
Pharmacology:
Statistical Pharmacology:
Chemistry:
Environmental Assessment (if needed):
Biopharmaceutical:
Microbiology, sterility:
Microbiology, clinical (for antimicrobial products only):
DSI:
Regulatory Project Management:
Other Consults:

Reviewer

Eric Colman
NA
Todd Sahlroot
Gemma Kuijpers
NA
David Lewis
David Lewis
Johnny Lau
Consult
NA
Andrea Slavin
Randy Hedin

Per reviewers, are all parts in English or English translation?
If no, explain:

YES X NO

CLINICAL

FILE X

REFUSE TO FILE

The clinical reviewer did not attend the meeting; however, he stated the application is fileable, and that an advisory committee meeting is not needed.

- Clinical site inspection needed: YES X NO
- Advisory Committee Meeting needed? YES, date if known NO X
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?

N/A X YES NO

CLINICAL MICROBIOLOGY

NA X

FILE

REFUSE TO FILE

STATISTICS

NA

FILE X

REFUSE TO FILE

BIOPHARMACEUTICS

FILE X

REFUSE TO FILE

- Biopharm. inspection needed:

YES NO X

PHARMACOLOGY

NA FILE X

REFUSE TO FILE

- GLP inspection needed:

YES NO X

CHEMISTRY

FILE X

REFUSE TO FILE

- Establishment(s) ready for inspection?
- Microbiology
- Filing review comments: None

NA YES X NO
 YES X NO

ELECTRONIC SUBMISSION: The NDA is an electronic submission.
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:

 The application is unsuitable for filing. Explain why:

 X The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.

 X No filing issues have been identified.

 Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

- Goal to finish reviews with team leader sign-off is February 14, 2005.
- Action package should start circulating on February 21, 2005.
- Action package should go to the Division Director on February 28, 2005.

Randy Hedin

Regulatory Project Manager, HFD-510

Appendix A to NDA Regulatory Filing Review

An application is likely to be a 505(b)(2) application if:

- (1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
- (2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
- (4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

**Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications**

1. Does the application reference a listed drug (approved drug)? YES NO

If "No," skip to question 3.

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):

3. The purpose of this and the questions below (questions 3 to 5) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval and that should be referenced as a listed drug in the pending application.

- (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?

YES NO

(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

If "No," skip to question 4. Otherwise, answer part (b).

- (b) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES NO
(The approved pharmaceutical equivalent(s) should be cited as the listed drug(s).)

If "Yes," skip to question 6. Otherwise, answer part (c).

- (c) Have you conferred with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007)?

YES NO

If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.

4. (a) Is there a pharmaceutical alternative(s) already approved? YES NO

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

If "No," skip to question 5. Otherwise, answer part (b).

- (b) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES NO
(The approved pharmaceutical alternative(s) should be cited as the listed drug(s).)

NOTE: If there is more than one pharmaceutical alternative approved, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007) to determine if the appropriate pharmaceutical alternatives are referenced.

If "Yes," skip to question 6. Otherwise, answer part (c).

- (c) Have you conferred with the Director, Division of Regulatory Policy II, YES NO
ORP?

If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.

5. (a) Is there an approved drug product that does not meet the definition of "pharmaceutical equivalent" or "pharmaceutical alternative," as provided in questions 3(a) and 4(a), above, but that is otherwise very similar to the proposed product?

YES NO

If "No," skip to question 6.

If "Yes," please describe how the approved drug product is similar to the proposed one and answer part (b) of this question. Please also contact the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007), to further discuss.

- (b) Is the approved drug product cited as the listed drug? YES NO

6. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

7. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). YES NO

8. Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 21 CFR 314.101(d)(9)). YES NO

9. Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application should be refused for filing under 21 CFR 314.101(d)(9). YES NO

10. Are there certifications for each of the patents listed for the listed drug(s)? YES NO

11. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

_____ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

_____ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

_____ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

_____ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)

*IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must **subsequently** submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)].*

_____ 21 CFR 314.50(i)(1)(ii): No relevant patents.

_____ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

_____ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).

_____ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.

12. Did the applicant:

- Identify which parts of the application rely on information (e.g. literature, prior approval of another sponsor's application) that the applicant does not own or to which the applicant does not have a right of reference?

YES NO

- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

YES NO

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

N/A YES NO

- Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv)).?

N/A YES NO

13. If the (b)(2) applicant is requesting 3-year exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

- Certification that at least one of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

YES NO

- A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

YES NO

- EITHER

The number of the applicant's IND under which the studies essential to approval were conducted.

IND # _____ NO

OR

A certification that the NDA sponsor provided substantial support for the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

YES NO

14. Has the Associate Director for Regulatory Affairs, OND, been notified of the existence of the (b)(2) application?

YES NO

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

/s/

Randy Hedin
11/29/04 03:28:36 PM
CSO

From: Hedin, Durand M
Sent: Monday, November 08, 2004 4:56 PM
To: 'lynn.mellor@pharma.novartis.com'
Subject: Aclasta (zoledronic acid) Injection, NDA 21-817

Dear Ms. Mellor

We have the following requests for information concerning the biopharm review of Aclasta Injection, NDA 21-817.

Please respond before November 15, 2004.

Sincerely,

Randy Hedin

In page 5 of the 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods section (1 Background and Overview, 1.1 General Overview), this statement exists: "The presence of mannitol in the formulation (approx ~~100~~ is not expected to influence the renal excretion of zoledronic acid, as osmotic diuresis does not increase glomerular filtration rate, the main mechanism for renal excretion, and will not be induced by such small amounts of ~~mannitol~~."

- Please reference the appropriate section(s) of the NDA that contain data to substantiate the above claims, or provide the Division with evidence to substantiate that:
 1. An osmotic diuretic does not change glomerular filtration rate.
 2. The amount of mannitol in the to-be-marketed zoledronic acid injection does not change the glomerular filtration rate.
- Please also substantiate that the ~~100~~ g mannitol in the to-be-marketed zoledronic acid injection (intravenously administered over 15 minutes) will not alter the pharmacokinetic parameters for zoledronic acid's renal clearance:

$$CL_R = f_P GFR + CL_S - CL_{Ra}$$

The above equation is per: J.H. Lin. Bisphosphonates: a review of their pharmacokinetic properties. *Bone* 18:75-85 (1996).

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

/s/

Randy Hedin
11/16/04 03:03:37 PM
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-817

Novartis Pharmaceuticals Corporation
Attn: Lynn Mellor
Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Ms. Mellor:

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:	Aclasta® (zoledronic acid) Injection
Review Priority Classification:	Priority (P)
Date of Application:	September 21, 2004
Date of Receipt:	September 21, 2004
Our Reference Number:	NDA 21-817

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on November 20, 2004 in accordance with 21 CFR 314.101(a). If we file the application, the user fee goal date will be March 21, 2005.

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. We note that you have not fulfilled the requirement. We are waiving the requirement for pediatric studies for this application.

NDA 21-817

Page 2

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

U.S. Postal Service/Courier/Overnight Mail:

Food and Drug Administration

Center for Drug Evaluation and Research

Division of Metabolic & Endocrine Drug Products, HFD-510

Attention: Fishers Document Room, 8B45

5600 Fishers Lane

Rockville, Maryland 20857

If you have any questions, call me at (301) 827-6392.

Sincerely,

{See appended electronic signature page}

Randy Hedin, R.Ph.

Senior Regulatory Management Officer

Division of Metabolic and Endocrine Drug Products

Office of Drug Evaluation II

Center for Drug Evaluation and Research

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

/s/

Randy Hedin
10/7/04 01:56:38 PM

MEMORANDUM
DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: September 30, 2004

FROM: Parivash Nourjah, Ph.D., Epidemiologist
Division of Drug Risk Evaluation I, HFD-430

THROUGH: Mark Avigan, M.D., C.M., Division Director
Division of Drug Risk Evaluation, HFD-430

TO: Carol Holquist, Ph.D.
Division of Medication Errors and Technical Support (DMETS),
HFD-420

SUBJECT: Review of Drug Safety Expert Panel Consensus on Dual trademarks for
Zoledronic Acid (NDA 21-817)

PID#: D040435

EXECUTIVE SUMMARY

Zoledronic acid (Zometa, Novartis) is currently indicated for treatment of hypercalcemia of malignancy, multiple myeloma, and bone metastases of solid tumors. In support of new proposed indications for the treatment of Paget's disease and osteoporosis (with a different dose and dose regimen), Novartis sponsored a modified Delphi survey to measure the extent of consensus of experts on preventable drug-related morbidity (PMRM) for selecting one of the two different strategies on trade name nomenclature. The study concludes that two separate and distinctive names, two indication-specific trademarks, two trade packages and separated prescribing information would likely reduce the risk of both dose amount and dose regimen errors associated with zoledronic acid. However, a lack of sufficient information to adequately assess quality of the experts, the small number of experts, low survey response rates, and the narrow scope of the content of the questionnaire raise concerns about the validity of the Sponsor's conclusions.

INTRODUCTION

This consult is in response to a request by the ODS Division of Medication Errors and Technical Support (DMETS) to review a study conducted by _____ on behalf of Novartis in order to study the new tradename "Aclasta" for zoledronic acid injection to treat Paget's disease and osteoporosis. A zoledronic acid injection is currently marketed as "Zometa" to treat hypercalcemia of malignancy, multiple myeloma, and bone metastases of solid tumors. The sponsor has proposed a dose and regimen for zoledronic acid to treat Paget's disease and osteoporosis indications _____. The recommended dose for cancer treatment (Zometa) is 4 mg per year. [As stated in approved product labeling, zoledronic acid is associated with renal toxicity among patients with hypercalcemia of cancer. This information is included within a warning which states that single doses of Zometa should not exceed 4 mg and dosed over an interval > 15 minutes. In the mock package insert for the "L" product, the dose limit has been increased from _____. This change does not effect review of the design questions that are the purview of the review. It is assumed that this is an error, oversight, or rationalized in other documentation supporting the supplemental NDA.]

Background / Overview

There are two possible nomenclature strategies to market one drug product (i.e., zoledronic acid injection) for two indications: (1) two separate trademarks, two trade packages, and two sets of prescribing information, or (2) one trademark, one trade package, and one product label (prescribing information) containing both (or all) indications. To determine which strategy introduces the lesser likelihood of confusion around dose and regimen, the Sponsor commissioned a Delphi survey of experts on **preventable drug-related morbidity (PDRM)**. These data were conducted by _____ and submitted in a report to the Division of Metabolism and Endocrine Drug Products (DMEDP), which subsequently requested review of the study by DMETS.

Protocol Synopsis

Objectives: To measure the extent of consensus found among a panel of experts regarding the relative safety of two different product nomenclatures strategies.

Methodology: A two-round Delphi technique was used to elicit the collective views of a panel of 11 PDRM experts.

The Delphi technique is an interactive group procedure without face to face meetings to achieve consensus among experts for an issue. The procedure involves multiple, self-administered questionnaires interspersed by controlled feedback. Often in a first Delphi round, an unstructured questionnaire with few open-end questions is administered to identify issues to be addressed in subsequent questionnaires. Subsequent questionnaires can be highly structured based on information drawn from the unstructured questionnaires, the medical literature, or identified in a focus groups.

Selection of the panelists: Panelists were identified by computer searches of various biomedical data bases and websites (e.g., MEDLINE, MEDSCAPE, IOM, FDA, CDER), major schools of pharmacy and medicine, and leading US and international patient and medication safety organizations. The investigators noted an *a priori* intention to have diversity in respect of region as well as the affiliation of the experts, and representation of various disciplines.

From a total of 52 “potential” experts were identified by the search criteria. These 52 “qualified” experts were then stratified as Tier 1 experts or Tier 2 experts, with Tier 1 experts defined as “highly acknowledged thought leaders on PDRM, specifically, those most generally recognized as experts on risk management of medication errors.” 40 were determined to be qualified “experts” for the purpose of this study. Only 11 out of 40 qualified experts (21% of invitees) agreed to participate in Delphi survey after being contacted by phone or email. The investigator’s targeted sample size was 15.

Comment: *It is indisputable that the selection of experts is an important key in validity of results derived from a study based upon the Delphi method. Therefore, the experience and informed knowledge of experts about the root cause of medication errors, particularly in the area of nomenclature and packaging, should be a criteria for selection. From the report of sponsor, it is not clear what criteria the investigators used to classify one as "highly acknowledged thought leaders on PDRM, specifically, those most generally recognized as experts on risk management of medication errors." In another words, what criteria were used to define: (1) "highly acknowledged thought leaders," or (2) "expert on risk management of medication errors." Since errors due to packaging and nomenclature contribute to a fraction of all medication errors, did the investigators attempt to select more of this sub-specialty?*

Also, rational for stratification into Tier 1 expert and Tier 2 expert is not given. Although there were 40 individuals who were classified as either a Tier1 expert or a Tier 2 expert, only 11 out of these 40 individuals agreed to participate in the study. Given 21% of "qualified" experts participated in the study, it would be useful to know what percent of final panelists (n=11) were classified as Tier1 experts.

Similar to any other research methodology, response rate and sample size are key aspects for assessing the quality of the results. Although not always true, higher response rates are usually assumed to suggest better study validity. In this study, the response rate is 21%, which raises concerns about the validity of the study. Clearly, if the level of expertise among those who did not participate is higher (i.e., have a higher percent of individuals classified as Tier1 expert) than those who participated in this study, the result of this study cannot be viewed as a consensus of "experts."

Although there is no empirical evidence about the relationship of the size of panel and its reliability of consensus building, it is intuitive that the larger the sample size the more likely a wider range of issues would be covered and examined. The sample size in this study was 11 while the investigator's targeted sample size was 15. This suggests additional concern about validity of the consensus.

Delphi questionnaires

In Round I, a questionnaire sent via email to panelists without reference to the name of the product or its precise recommended dose. The questionnaire consisted of two parts. Part I (questions 1a through 4b) assessed the panelist's view on which strategy reduces errors related to dose or dosage regiment. Part II (questions 5 through 10), assessed the panelist's view on which strategy would reduce errors associated with the administration of an IV drug. [All questions, except for question 7 or 10, were multiple choice; question 7 and 10 were open-ended questions.]

The Round I package included a) explicit clarification of the precise nature of "Strategy A" consisting of two separate trademarks ("J" and "L"), two trade packages, and two sets of prescribing information). Mockups of the full-text prescribing information for products "J" and "L" were included. Round I also included "Strategy B," consisting of one trademarks ("P"), one trade package, and one package insert listing both indications. Mockups of the full-text prescribing information for products "P" were included.

In Round II, essentially the same questionnaires as used in Round I were sent to the panelists. However, some of the questions were modified to ensure further clarification of information obtained from responses to the Round I questionnaire. In Round II, the packages sent to each expert included a) collective, anonymous Round I results, b) Round II questionnaires, c) Round II prescribing information comparison charts, and d) mockups of the full-text prescribing information for all products.

Comment:

The questionnaire used in Round I was structured and limited in scope. For example, the questionnaire deals with errors that may be made by prescribers of this product (physicians); however, and it does not deal with errors which could be made by staff (e.g., nurses, hospital pharmacists). The questionnaire refers only to the package insert. It does not address errors that could arise by confusion between these two products when they are stored next to each other on some pharmacy's shelves because of their identical

generic names/.* In order to ensure an adequate survey of all possible errors resulting from this product, it would have been preferable to begin with a few open-ended questions such that all the issues would be further examined in subsequent rounds with more structured questionnaires. In addition, it would be useful to identify concerns of physicians, nurses, and pharmacists who will use this product. Pharmacists in particular may provide other perspectives that may not have been identified initially by the experts included in this study. One approach to obtain the perspectives of all of the health providers of this product is to conduct focus groups. By health providers, we mean the nurses who may administer these products, the pharmacist, and the physicians who may likely prescribe these products. Issues raised by such groups could have been added to the questionnaire for expert responses.

Results

Table 1 displays the table reported by sponsor. The sponsor summarized the result as follows:

“For osteoporosis patients, the consensus was that a product nomenclature strategy employing two separate product trademarks, trade packages, and prescribing information would be preferable. The consensus that this strategy would reduce the likelihood of a dose amount error was 73% in Round I and 100% in Round II. The consensus that this strategy would reduce the likelihood of a dose regimen error was 73% in Round I and 90% in Round II.

For cancer patients, the consensus was that a product nomenclature strategy employing two separate product trademarks, trade packages, and prescribing information also would be preferable. The consensus that this strategy would reduce the likelihood of both a dose amount and a dose regimen error was 82% in Round I and 90% in Round II.”

Comment

Experts believed that Strategy A, consisting of two separate tradenames, reduced the likelihood of error more than Strategy B, consisting of a single tradename. However, it is

difficult without predefined criteria to interpret some of the results derived from this methodology. For example, although the expert opinions favored Strategy A, 8 out of 10 experts in Round II reported that Strategy A would yield the same or lower rate of error than a new IV drug (Table 1). Of these 8 individuals, 6 were "Somewhat confident" about their opinions. This reviewer interprets "somewhat confident" as an expression of ambiguity or reservation. Since a large proportion of participating experts were not very confident about their opinions the error rates with Strategy A would be the same or lower than with any new IV, thus, it is important to further examine their reasons for such reservations.

Conclusion

Based upon views expressed by members of the PDRM expert panel in the two-round modified Delphi process, two separate and distinctive, indication-specific trademarks, trade packages, and prescribing information for zoledronic acid would likely reduce the risk of both dose amount and dose regimen errors. This conclusion was derived from the opinion of a panel, and therefore, it is not based on evidence derived from an empirical study.

Since the Delphi method is not an evidence-based approach, it is difficult to evaluate its quality systematically. However, the validity and its reliability can be qualified by the method of identifying and selecting the expert panel, sample size and response rate, and the content of questions.

The report provided by the Zometa sponsor lacks sufficient information to adequately assess the quality and appropriate distribution of the participating experts. The study is further limited since there was a small number of experts and the survey had a low response rate. Moreover, the questionnaires were characterized by a narrow scope of content. Because of these limitations, this reviewer has concerns about the validity of sponsor's conclusions.

Table 1: Round 1 and Round 2 responses to multiple choice questions.

Question	Strategy A Two Trademarks Product J & Product L		Strategy B One Trademark Product P	
	Round I N=11	Round II N=10 (11)*	Round I N=11	Round II N=10 (11)*
1.a: More Likely to reduce Dose Regimen Error in a Cancer Patient	9	9(10)	2	1
1b: Degree of Certainty				
<i>Very</i>	5	6(6)	0	0
<i>Somewhat</i>	4	3 (4)	2	1
<i>Little/Not at All</i>	0	0 (0)	0	0
2a: More likely to Reduce Dose Amount Error in a Cancer patient	9	9 (10)	2	1
2b: Degree of Certainty				
<i>Very</i>	3	6 (5)	1	0
<i>Somewhat</i>	6	3 (5)	0	1
<i>Little</i>	0	0	1	0
<i>Not at All</i>	0	0	0	0
3a: More Likely to Reduce Dose Regimen Error in an Osteoporosis Patient	8	9 (10)	3	1
3b: Degree of Certainty				
<i>Very</i>	4	6 (6)	1	0
<i>Somewhat</i>	4	3 (4)	2	1
<i>Little/Not at All</i>	0	0 (0)	0	0
4a: More likely to Reduce Dose Amount Error in an Osteoporosis Patient	8	10(11)	3	0
4b Degree of Certainty				
<i>Very</i>	3	6(6)	0	0
<i>Somewhat</i>	5	4(5)	2	0
<i>Little</i>	0	0(0)	1	0
<i>Not at All</i>	0	0(0)	0	0
5: Likelihood of Dosing Errors for Strategy A compared to a New IV drug			NA	
<i>More</i>	4	2(2)		
<i>Same</i>	5	6(7)		
<i>Less</i>	2	2 (2)	NA	
6: Degree of Confidence				
<i>Very</i>	1	2 (2)		
<i>Somewhat</i>	10	9 (9)		
<i>Little/Not at All</i>	0	0 (0)		
8: Likelihood of Dosing Errors for Strategy B compared to a New IV Drug	NA			
<i>More</i>			7	7 (8)
<i>Same</i>			4	3 (3)
<i>Less</i>	NA		0	0 (0)
9: Degree of Confidence				
<i>Very</i>			6	4(5)
<i>Somewhat</i>			4	6 (6)
<i>Little</i>			1	0 (0)
<i>Not at All</i>			0	0 (0)

* Round 2 values in parentheses include the R-2 non-respondent's answers from Round 1, e.g., for Q1a, 9 of the 10 R-2 respondents chose A but this number becomes 10 of 11 when the R-2 non-respondent's R-1 answer is included.

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/s/

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