

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-606

ADMINISTRATIVE
DOCUMENTS/CORRESPONDENCE

EXCLUSIVITY SUMMARY

NDA # 21-606

SUPPL #

HFD # 510

Trade Name Zemplar Capsules

Generic Name paricalcitol

Applicant Name Abbott Laboratories

Approval Date, If Known May 26, 2005

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)1

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 yrs

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

No

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 20-819

Zemplar Injection

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Protocol #s: 95022, 2001013, 2001014, 2001015, 2001019, 2001020, 2001021

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Protocol #s: 95022, 2001013, 2001014, 2001015, 2001019, 2001020, 2001021

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1
IND # 60,672 YES ! NO
! Explain:

Investigation #2
IND # 60,672 YES ! NO
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1
!
! YES NO
! Explain: ! Explain:

Investigation #2
!
! YES NO
! Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES NO

If yes, explain:

Name of person completing form: Patricia Madara
Title: Regulatory Project Manager, Division of Metabolic and Endocrine Drug Products
Date: May 31, 2005

Name of Office/Division Director signing form: David G. Orloff, M.D.
Title: Director, Division of Metabolic and Endocrine Drug Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

Patricia Madara
6/1/05 08:00:56 AM

David Orloff
6/3/05 01:17:50 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 21-606 Supplement Type (e.g. SE5): _____ Supplement Number: _____

Stamp Date: July 30, 2004 Action Date: May 26, 2005

HFD 510 Trade and generic names/dosage form: Zemplar (paricalcitol) Capsules

Applicant: Abbott Laboratories Therapeutic Class: Type 3 (new dosage form); Type 6 (new indication)

Indication(s) previously approved:

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: treatment of secondary hyperparathyroidism in stage 3 and stage 4 chronic kidney disease

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

Yes: Please proceed to Section A.

XX No: Please check all that apply: XX Partial Waiver XX 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:

Min _____ kg _____ mo. _____ yr. 0 Tanner Stage _____
Max _____ kg _____ mo. _____ yr. 11 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
- XX 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:

Min _____ kg _____ mo. _____ yr. 12 Tanner Stage _____
Max _____ kg _____ mo. _____ yr. 16 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: Need data regarding efficacy and safety in adults before starting trials in children

Date studies are due (mm/dd/yy): 12/31/08

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:

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

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Pat Madara
Regulatory Project Manager
Division of Metabolic and Endocrine Drug Products

cc: NDA 21-606
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

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

/s/

Patricia Madara
5/31/05 10:46:59 AM

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information

NDA 21-606	Efficacy Supplement Type SE-	Supplement Number
Drug: Zemplar (paricalcitol) Capsules		Applicant: Abbott Laboratories
RPM: Pat Madara		HFD-510 Phone # 301-827-6416
<p>Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 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.)</p> <p>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.</p> <p><input type="checkbox"/> Confirmed and/or corrected</p>		Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):
❖ Application Classifications:		
<ul style="list-style-type: none"> • Review priority • Chem class (NDAs only) • Other (e.g., orphan, OTC) 		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority 3
User Fee Goal Dates		May 30, 2005
❖ Special programs (indicate all that apply)		<input checked="" type="checkbox"/> None Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2
❖ User Fee Information		
<ul style="list-style-type: none"> • User Fee • User Fee waiver • User Fee exception 		<input checked="" type="checkbox"/> Paid UF ID number <input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other (specify) <input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) <input type="checkbox"/> Other (specify)
Application Integrity Policy (AIP)		
<ul style="list-style-type: none"> • Applicant is on the AIP 		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> 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)	
<ul style="list-style-type: none"> • 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.) 	No
<ul style="list-style-type: none"> • 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. 	<input type="checkbox"/> Yes, Application # _____ <input checked="" type="checkbox"/> No
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	October 12, 2004

General Information

Actions	
• Proposed action	(X) AP () TA () AE () NA
• Previous actions (specify type and date for each action taken)	
• 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 () 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	May 25, 2005
• Original applicant-proposed labeling	
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings (indicate dates of reviews and meetings)	DMETS, 5/6/05; 1/19/05 DMAC, 3/29/05
• 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	May 25, 2005
• Reviews	
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	Deferred peds study
• Documentation of discussions and/or agreements relating to post-marketing commitments	Letters 2/8/02; 3/17/04(2)
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	
❖ Memoranda and Telecons	
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	
• Pre-NDA meeting (indicate date)	23Sept2002; 01March2004
• Pre-Approval Safety Conference (indicate date; approvals only)	
• Other	
❖ Advisory Committee Meeting	
• Date of Meeting	NN
• 48-hour alert	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	

Summary Application Review

Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader).
(indicate date for each review)

Medical team leader, director
concur; 6/3/05

Clinical Information

❖ Clinical review(s) (indicate date for each review)	April 18, 2005
❖ Microbiology (efficacy) review(s) (indicate date for each review)	NN
❖ Safety Update review(s) (indicate date or location if incorporated in another review)	Page 85 of clinical review
❖ Risk Management Plan review(s) (indicate date/location if incorporated in another rev)	NN
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	May 31, 2005
❖ Demographic Worksheet (NME approvals only)	
❖ Statistical review(s) (indicate date for each review)	March 12, 2005
❖ Biopharmaceutical review(s) (indicate date for each review)	May 24, 2005
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	April 4, 2005
• Bioequivalence studies	NN

CMC Information

❖ CMC review(s) (indicate date for each review)	May 18, 2005
❖ Environmental Assessment	NN
• Categorical Exclusion (indicate review date)	Qualifies, 5/18/05
• 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)	NN
❖ Facilities inspection (provide EER report)	Date completed: <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ Methods validation	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested

Nonclinical Pharm/Tox Information

❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	February 4, 2005
❖ Nonclinical inspection review summary	NN
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	NN
❖ CAC/ECAC report	NN

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).



NDA 21-606

DISCIPLINE REVIEW LETTER

Abbott Laboratories
Attention: Steve Hoff, Ph.D.
Associate Director, Global Pharmaceutical Regulatory Affairs
D-389, Building J45-2
200 Abbott Park Road
Abbott Park, IL 60064-6133

Dear Dr. Hoff:

Please refer to your July 28, 2004 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zemplar (paricalcitol) Capsules.

We also refer to your submission dated March 2, 2005.

The Office of Drug Safety, Division of Medication Errors and Technical Support (DMETS) has completed their review of your submission and we have the following comments and recommendations.

A. GENERAL COMMENTS

- 1) We note that you differentiate each strength with the use of different colors (1 mcg = , 2 mcg = , and 4 mcg =). The strength is difficult to read in each color block. It appears the coloring used for each number does not provide sufficient contrast, making the strengths appear washed out and less prominent. Revise the labels and labeling so that the strength is more prominent and legible. We suggest using different color.
- 2) The current presentation of the established name (for Paricalcitol and font for Capsules) increases the prominence of the dosage form rather than the active ingredient. Use one color for the established name and dosage form "Paricalcitol Capsules".
- 3) Relocate or decrease the size of the

B. CONTAINER LABELS (Trade and Professional Samples)

- 1) See General Comments A2 and A3.
- 2) Use contrasting colors for the 1 mcg expression of strength, as the contrast between the — /” strength and ‘ — background appears too light.
- 3) Ensure the established name is at least one half the size of the proprietary name. We refer you to 21 CFR 201.1(g)(2) for guidance.

C. CARTON LABELING (Professional Samples: 1 mcg, 2 mcg, and 4 mcg)

- 1) See General Comments A1 to A3 and Comments B2 and B3.
- 2) Currently, “Professional Sample, Not for Sale” is stated in —

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Pat Madara, Regulatory Project Manager, at (301) 827-6416.

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

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

/s/

Kati Johnson

5/13/05 12:45:30 PM

MEMORANDUM OF TELECON

DATE: May 9, 2005

APPLICATION NUMBER: NDA 21-606, Zemplar (paricalcitol) Capsules

BETWEEN:

Abbott Laboratories:

Steven Hoff, Ph.D.	Associate Director, Global Pharmaceutical Regulatory Affairs (GPRA)-US Area
Jim Segretario	Manager, GPRA-CMC
Steve Laurenz	Associate Director, Global Pharmaceutical Research and Development (GPRD) - PARD
Ji Zhou	Section Manager, GPRD-PARD
Sean Mackey	Process Engineer, GPRD-PARD
Steve Chamberlin	Process Engineer, GPRD-PARD
Mary O'Sullivan	Director, GPRA-Therapeutic Area (TA)
Ellen Holst	Manager, GPRA-TA

Phone: 1-866-819-5631, passcode: 704000

AND

Division of Metabolic and Endocrine Drug Products:

Mamta Gautam-Basak, Ph.D.,	Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II), Office of New Drug Chemistry
Sheldon Markofsky, Ph.D.,	Chemistry Reviewer, DNDC II
David B. Lewis, Ph.D.,	Chemistry Reviewer, DNDC II
Shulin Ding, Ph.D.,	Chemistry Reviewer, DNDC II
Pat Madara, M.S.,	Regulatory Project Manager

SUBJECT: Discussion of CMC information requests sent to the sponsor via email on
May 5, 2005

On July 28, 2004 Abbott Laboratories submitted a new NDA (21-606) for Zemplar (paricalcitol) Capsules. During review of the Chemistry, Manufacturing and Controls sections of this NDA, the chemistry reviewers required additional information. These requests were sent to the firm on May 5, 2005 via email (WORD document attached). Upon receipt of these requests, the firm requested a teleconference to clarify the information needed.

The email to Abbott, the attached document containing the information requests and two explanatory tables submitted by the applicant, prior to the tcon are attached to this document.

DMEDP Chemistry Comments:

- Regarding the drug product specification information requested in question #2, the data supplied in Table 2 is sufficient. No additional information is required.
- Regarding the container quality testing, provide data for the container quality per USP<671>.

The applicant responded that they believed they had this information available and would submit it.

DMEDP Chemistry Comments:

- Regarding the comparability protocol submitted, the ranges (including specific numbers) over which the process parameters will be changed are required for approval – validation is needed.
- This protocol cannot be approved without submission of validated ranges. However, the applicant can resubmit the protocol with the information when it is available.

The applicant expressed understanding of the Agency's comments, noting that the problem would be discussed internally as to the best action to follow. The Agency would be notified shortly as to the decision but the protocol would probably be withdrawn and submitted later.

DMEDP Chemistry Comments:

- Regarding labeling, the following changes were recommended:



The applicant expressed understanding of these requirements.

The meeting was adjourned.

Mamta Gautam-Basak, Ph.D.
Chemistry Team Leader II for the
Division of Metabolic and Endocrine Drug Products
(HFD-510)
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

**Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-420; Parklawn Rm. 6-34
Center for Drug Evaluation and Research**

LABEL AND LABELING REVIEW

DATE OF REVIEW: March 28, 2005

NDA #: 21-606

NAME OF DRUG: **Zemplar®**
(Paricalcitol) Capsules 1 mcg, 2 mcg, and 4 mcg

NDA SPONSOR: Abbott Laboratories

I. INTRODUCTION

This consult was written in response to a request from the Division of Metabolic and Endocrine Drug Products (HFD-510), to review the revised container labels, carton and insert labeling of Zemplar®. The container labels, carton labeling, and package insert labeling for Zemplar Capsules were retrieved from EDR dated March 2, 2005. The container labels, carton and insert labeling for Zemplar Capsules were previously reviewed on December 10, 2004 (ODS consult #04-0243). Zemplar Capsules is an extension of the Zemplar product line. Zemplar Injection 0.005 mg/mL was approved on April 17, 1998 and Zemplar Injection 0.002 mg/mL was approved on February 1, 2000.

PRODUCT INFORMATION

Zemplar® Capsules (Paricalcitol) is indicated for the prevention and treatment of secondary hyperparathyroidism associated with chronic kidney disease stage 3 and 4. The initial dose of Zemplar Capsules is based on baseline intact parathyroid hormone (iPTH) levels. Additionally, dosing must be individualized and based on serum or plasma iPTH levels, with monitoring of serum calcium and serum phosphorus. Zemplar Capsules may be administered daily or three times a week. When dosing three times weekly, the dose should be administered no more frequently than every other day. Zemplar Capsules are available as 1 mcg, 2 mcg, and 4 mcg capsules.

II. ADVERSE EVENT REPORTING SYSTEM (AERS)

DMETS searched the FDA Adverse Event Reporting System for cases of medication errors associated with Zemplar using the preferred terms, "medication error, accidental exposure, accidental overdose, overdose, underdose, treatment noncompliance and pharmaceutical product complaint." Since the previous review on December 10, 2004 (ODS consult #04-0243) one additional medication error report was discovered. The medication error report pertained to look-alike labeling between Zemplar 5 mcg/mL vials and American Pharmaceutical Partners, Inc.'s Oxytocin 10 USP units/mL vials. The report described an actual medication error in which there was a mix-up between the two products, however the error was discovered and corrected before reaching the patient. This medication error report will be reviewed further by DMETS at a later time.

2 Page(s) Withheld

§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling

IV. RECOMMENDATIONS:

DMETS recommends implementation of the container label, carton, and insert labeling revisions outlined in Section III of this review.

DMETS would appreciate feedback of the final outcome of this consult. We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Sammie Beam at 301-827-3242.

Tina M. Tezky, Pharm.D.
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

Alina Mahmud, R.Ph., M.S.
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

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

/s/

Tina Tezky
5/6/05 04:55:43 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
5/6/05 05:00:53 PM
DRUG SAFETY OFFICE REVIEWER
Also signing for Carol Holquist, Director DMETS, in her
absence

Madara, Patricia

From: Madara, Patricia
Sent: Thursday, May 05, 2005 2:31 PM
To: 'steven.hoff@abbott.com'
Subject: CMC information request

Hi Steve;

Please see attached info request. Thanks, Pat

Pat Madara
Regulatory Project Manager
Division of Metabolic and Endocrine Drug
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research



CMC IR.doc
(31 KB)

1. The FDA (ONDC) has some questions/comments regarding the Comparability Protocol (CP) submitted to NDA 21-606, Zemplar (paricalcitol) capsules in the amendment of January 26th, 2005.

For the manufacturing process parameters that are subject to the CP (Table 1, p. 12 of the January 26th, 2005 amendment), provide the range over which these parameters will be changed per the CP. Provide justification for these ranges. In addition, provide, in tabular form, a comparison of the validation range for each of the process parameters subject to the CP alongside the projected range over which they will be changed.

2. The following comments pertain to your proposed drug product release/stability specifications:

- Transfer specification; — from stability to release
- Include — n release specifications;
- Provide clarification – dissolution/disintegration tests are not included in your proposed release specifications, however stability data lists analytical data for dissolution and disintegration at time zero (or initial). Your proposed specifications should be revised accordingly.
- Provide revised release and stability specifications.

Please note the action date for NDA 21-606 is approaching (User Fee Due Date is May 28th, 2005). Provide a timeframe for your response.

B

2 Page(s) Withheld

§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Heather F. Perritano, M.S.
Associate Director, GPRA
Advertising and Promotion Review
Abbott Laboratories
200 Abbott Park Road
Abbott Park, Illinois 60064-6157

RE: NDA 21-606
Zemplar® (paricalcitol) Capsules
MACMIS ID # 13290

Dear Ms. Perritano:

This letter advises Abbott Laboratories (Abbott) of comments for a proposed submitted on April 15, 2005, to the Division of Drug Marketing, Advertising, and Communications (DDMAC).

DDMAC offers the following comments, which apply to this as well as future materials containing the same or similar claims or presentations.

If you have any questions, please direct them to the undersigned by facsimile at (301) 594-6771 or by written communication at the Division of Drug Marketing, Advertising, and Communications, HFD-42, Room 8B-45, 5600 Fishers Lane, Rockville, MD 20857. Please refer to MACMIS ID # 13290 and NDA # 21-606 in all future correspondence relating to this matter. DDMAC reminds you that only written communications are considered official.

Sincerely,

{See appended electronic signature page}

Debi Tran, Pharm.D., LT, USPHS
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications

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

/s/

Debi Tran

4/26/05 01:57:26 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 24, 2005

TO: Pat Madara, Regulatory Project Manager
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 Inspections

NDA: 21-606

SPONSOR: Abbott Laboratories

DRUG: Zemplar™ (paricalcitol) Capsules

CHEMICAL CLASSIFICATION: 3, S

THERAPEUTIC CLASSIFICATION: Vitamin D analog

INDICATIONS: Secondary Hyperparathyroidism

CONSULTATION REQUEST DATE: October 4, 2004

GOAL DATE TO PROVIDE
INSPECTION SUMMARY: April 1, 2005

PDUFA GOAL DATE: May 15, 2005

I. **BACKGROUND:**

Zemplar™ is a vitamin D analog indicated for the prevention and treatment of secondary hyperparathyroidism associated with chronic renal failure. This NDA is for Abbott's new oral dosage form of paricalcitol. It is expected that the introduction of a capsule form of paricalcitol will provide a more convenient dosage form for chronic kidney disease patients.

II. RESULTS (by site):

Name	City, State	Country	Protocol	Insp. Date	EIR Recd.	Classn.
Daniel Batlle, MD	Chicago, IL	USA	2001019	12/21/04- 1/6/05	2/25/05	VAI
Hanna Abboud, MD	San Antonio, TX	USA	2001020	11/22-30/04	2/10/05	NAI
Barton Levine, MD	Los Angeles, CA	USA	2001021	11/29-12/7/04	12/27/04	VAI

Study Protocols:

#2001019, "A Phase III, Prospective, Randomized, Placebo-Controlled, Double-Blind, Multi-Center Study to Determine the Safety and Efficacy of Zemlar Capsule (Dosed Three Times Weekly) in Reducing Elevated Serum Intact Parathyroid Hormone Levels in Subjects with Chronic Kidney Disease"

#2001020, "A Phase III, Prospective, Randomized, Placebo-Controlled, Double-Blind, Multi-Center Study to Determine the Safety and Efficacy of Zemlar Capsule (Dosed Three Times Weekly) in Reducing Elevated Serum Intact Parathyroid Hormone Levels in Subjects with Chronic Kidney Disease"

#2001021, "A Phase III, Prospective, Randomized, Placebo-Controlled, Double-Blind, Multi-Center Study to Determine the Safety and Efficacy of Zemlar Capsule (dosed every day) in Reducing Elevated Serum Intact Parathyroid Hormone Levels in Subjects with Chronic Kidney Disease"

These were multi-center studies conducted in the USA and Poland. Seventy-five subjects were randomized into study 019. The study design encompassed a screening visit, a 1 to 4 week pre-treatment phase, a 24 week treatment phase, and a follow-up phase. For enrollment into the treatment phase, subjects had to have an average of 2 consecutive iPTH values of ≥ 150 pg/mL, 2 consecutive serum calcium levels of ≥ 8.0 to ≤ 10.0 mg/dL, and 2 consecutive serum phosphorus levels of ≤ 5.2 mg/dL. Subjects were randomized to either Zemlar capsule or placebo 3 times weekly. The primary efficacy endpoint was the achievement of 2 consecutive $\geq 30\%$ decreases from baseline in iPTH levels. Seventy subjects were randomized into study 020, the study design was the same as study 019. Seventy-five subjects were randomized into study 021. The study design was the same as studies 019 and 020 except study drug was taken daily.

Sites:

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

1. Daniel C. Batlle, M.D.
Northwestern University/Division of Nephrology
320 E. Superior Avenue, Searle 10-475
Chicago, IL 60611

Methodology: Inspection assignment was issued to the Chicago District Office.

Dates of Inspection: December 21-January 6, 2005

- a. What was inspected: Dr. Batlle randomized 14 subjects into the study. Five 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. Subject 802 had a history of a cardiac graft and a cholecystectomy that were not recorded in the CRF. A 1-item Form FDA 483 was issued for an observation pertaining to the study coordinator, who conducted most of the study, was not listed as a subinvestigator on Form FDA 1572. Data from this site are acceptable.

2. Hanna E. Abboud, M.D.
University of Texas Health Science Center at San Antonio
7703 Floyd Curl Drive
Medicine/Nephrology MSC 7882
San Antonio, TX 78229

Methodology: Inspection assignment was issued to the Dallas District Office.

Dates of Inspection: November 22–30, 2004

- a. What was inspected: Dr. Abboud randomized 16 subjects into the study. Five 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. Data from this site are acceptable.
3. Barton S. Levine, M.D.
West Los Angeles Veterans Medical Center
11301 Wilshire Boulevard
Los Angeles, CA 90073

Methodology: Inspection assignment was issued to the Los Angeles District Office.

Dates of Inspection: November 29-December 7, 2004

- a. What was inspected: Dr. Levine randomized 11 subjects into the study. All 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. A 3-item Form FDA 483 was issued for issues pertaining to protocol deviations: subjects 901, 902 and 905 had dosage changes that were not per protocol. Data from this site are acceptable.

GLOBAL ASSESSMENT

Data submitted by these 3 clinical investigators are acceptable in support of NDA 21-606.

Signature

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 #21-606
HFD-45/Division File
HFD-46/Program Management Staff (electronic copy)
HFD-510/Project Manager/Madara
HFD-46/Slavin
HFD-46/GCP 1 Files # 11365, 11409, 11429
HFD-46/Reading File

O:/Slavin/Summaries/Zemplar Summary

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

/s/

Andrea Slavin
3/28/05 09:29:03 AM
CSO

Ni Aye Khin
4/4/05 02:41:53 PM
MEDICAL OFFICER

C

8 Page(s) Withheld

§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling



NDA 21-606

INFORMATION REQUEST LETTER

Abbott Laboratories
Attention: Steve Hoff, Ph.D.
Associate Director, Global Pharmaceutical Regulatory Affairs
200 Abbott Park Road
RA-76, AP 30-1E
Abbott Park, IL 60064-6157

Dear Dr. Hoff:

Please refer to your July 28, 2004 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zemplar (paricalcitol) Capsules.

We are reviewing the Clinical section of your submission and have the following requests for additional information:

- A. Conduct the following analyses on the combined pivotal studies and by treatment regimen (TIW versus QD), unless otherwise stated or provided in the NDA. Please note the underlined phrases are provided to highlight differences between these analyses and those you have already provided.
1. Mean change and percent change from baseline to final visit in eGFR and serum creatinine by treatment regimen; last on-treatment visit (all subjects).
 2. Mean change and percent change from baseline to final visit and from baseline to last on treatment visit in eGFR and serum creatinine by CKD stage.
 3. Lowest iPTH achieved by CKD stage; define iPTH cutoff as:
 - Less than 35, Stage 3
 - Less than 70, Stage 4
 4. Proportion of subjects who developed one consecutive elevated calcium, phosphorus, and Ca_xP value.
 5. Because diuretic use may alter serum calcium levels, and in study 2001020 there appears to be an imbalance of high-ceiling diuretic use (85% paricalcitol, 65% placebo), please perform the following analyses (studies combined, by treatment regimen, and by individual study):
 - Proportion of subjects who achieved two consecutive $\geq 30\%$ decreases from baseline in iPTH by concomitant high-ceiling diuretic usage.

- Lowest iPTH achieved by concomitant high-ceiling diuretic use. The use of iPTH cutoff of 60 is sufficient for this combined CKD stage analysis.
- Proportion of subjects who achieved one consecutive elevated calcium, Ca_xP, and phosphorus value by concomitant high-ceiling diuretic use.
- Mean change and percent change from baseline to final visit and from baseline to last on-treatment visit in eGFR and serum creatinine by concomitant high-ceiling diuretic usage.

B. Given that vitamin D deficiency is a known cause of secondary hyperparathyroidism, please provide all available data on baseline 25-OH vitamin D levels of subjects in the pivotal studies.

We request a prompt written response in order to continue our evaluation of your NDA.

If you have any questions, call Pat Madara, Regulatory Project Manager, at (301) 827-6416.

Sincerely,

{See appended electronic signature page}

David G. Orloff, M.D.

Director

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/

David Orloff
2/3/05 05:33:32 PM

CONSULTATION RESPONSE
DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)

DATE RECEIVED: August 30, 2004
DOCUMENT DATE: July 28, 2004

DESIRED COMPLETION
DATE: March 30, 2005

ODS CONSULT #: 04-0243

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

THROUGH: Pat Madara
Project Manager
HFD-510

PRODUCT NAME:
Zemplar®
(Paricalcitol Capsules)
1 mcg, 2 mcg, and 4 mcg
NDA #: 21-606

SPONSOR:
Abbott Laboratories

SAFETY EVALUATOR: Linda Y. Kim-Jung, Pharm.D.

RECOMMENDATIONS:

DMETS recommends implementation of the container label, carton, and insert labeling revisions outlined in Section III of this review.

Denise P. Toyer, Pharm.D.
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

Carol Holquist, R.Ph.
Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

**Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-420; Parklawn Rm. 6-34
Center for Drug Evaluation and Research**

LABEL AND LABELING REVIEW

DATE OF REVIEW: December 10, 2004

NDA #: 21-606

NAME OF DRUG: **Zemplar®**
(Paricalcitol Capsules) 1 mcg, 2 mcg, and 4 mcg

NDA SPONSOR: Abbott Laboratories

I. INTRODUCTION

This consult was written in response to a request from the Division of Metabolic and Endocrine Drug Products (HFD-510), to review the container labels, carton and insert labeling of Zemplar®. Zemplar Capsules is an extension of the Zemplar product line. Zemplar Injection 0.005 mg/mL was approved on April 17, 1998 and Zemplar Injection 0.002 mg/mL was approved on February 1, 2000. The container labels, carton labeling for Zemplar Capsules were retrieved from EDR dated July 28, 2004 and package insert labeling from EDR dated October 21, 2004.

PRODUCT INFORMATION

Zemplar® Capsules (Paricalcitol) are indicated for the prevention and treatment of secondary hyperparathyroidism associated with chronic kidney disease stage 3 and 4. The initial dose of Zemplar Capsules is based on baseline intact parathyroid hormone (iPTH) levels. Additionally, dosing must be individualized and based on serum or plasma iPTH levels, with monitoring of serum calcium and serum phosphorus. Zemplar Capsules may be administered daily or three times a week. When dosing three times weekly, the dose should be administered no more frequently than every other day. Zemplar Capsules are available as 1 mcg, 2 mcg, and 4 mcg capsules.

II. ADVERSE EVENT REPORTING SYSTEM (AERS)

DMETS searched the FDA Adverse Event Reporting System for cases of medication errors associated with Zemplar using the preferred terms, "medication error, accidental overdose, overdose, and pharmaceutical product complaint." The search retrieved three medication error reports pertaining to look-alike labeling between Zemplar 5 mcg/mL vials and Abbott's Metoclopramide 5 mg/mL vials. One report described a potential for medication error due to look-alike labeling of the two products, and the other two reports described actual medication errors in which there was confusion or mix-up between the two products. These medication error reports will be reviewed further by DMETS. Upon completion of this review, DMETS will notify the Division of Metabolic and Endocrine Drug Products (HFD-510).

D

2 Page(s) Withheld

 § 552(b)(4) Trade Secret / Confidential

 § 552(b)(5) Deliberative Process

 / § 552(b)(4) Draft Labeling

IV. RECOMMENDATIONS:

DMETS recommends implementation of the container label, carton, and insert labeling revisions outlined in Section III of this review.

DMETS would appreciate feedback of the final outcome of this consult. We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Sammie Beam at 301-827-3242.

Linda Y. Kim-Jung, Pharm.D.
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

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

/s/

Denise Toyer
1/19/05 08:25:05 AM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
1/19/05 02:09:26 PM
DRUG SAFETY OFFICE REVIEWER

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-606

Supplement #

SE1 SE2 SE3 SE4 SE5 SE6 SE7 SE8

Trade Name: Zemplar Capsules
Generic Name: paricalcitol
Strengths: 1 mcg, 2 mcg, 4 mcg

Applicant: Abbott Laboratories

Date of Application: July 28, 2004
Date of Receipt: July 30, 2004
Date clock started after UN: N/A
Date of Filing Meeting: September 16, 2004
Filing Date: September 28, 2004
Action Goal Date (optional):

User Fee Goal Date: May 30, 2004

Indication(s) requested: prevention and treatment of secondary hyperparathyroidism associated with chronic kidney disease Stage 3 and 4.

Type of Original NDA: (b)(1) X (b)(2) _____
OR
Type of Supplement: (b)(1) _____ (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 X P _____
Resubmission after withdrawal? N Resubmission after refuse to file? N
Chemical Classification: (1,2,3 etc.) 3
Other (orphan, OTC, etc.) _____

Form 3397 (User Fee Cover Sheet) submitted: YES

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
If yes, explain: M-31 exclusivity expires March 31, 2007
Ped exclusivity expires October 1, 2007
 - Does another drug have orphan drug exclusivity for the same indication? NO
 - 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)]? N/A
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)? NO
If yes, explain.
 - If yes, has OC/DMPQ been notified of the submission? N/A
 - Does the submission contain an accurate comprehensive index? YES
 - Was form 356h included with an authorized signature? YES
If foreign applicant, both the applicant and the U.S. agent must sign.
 - Submission complete as required under 21 CFR 314.50? YES
If no, explain:
 - If an electronic NDA, does it follow the Guidance? YES
If an electronic NDA, all certifications must be in paper and require a signature.
Which parts of the application were submitted in electronic format?
All parts except for required certifications
- Additional comments:
- If in Common Technical Document format, does it follow the guidance? N/A
 - Is it an electronic CTD? NO
If an electronic CTD, all certifications must be in paper and require a signature.
Which parts of the application were submitted in electronic format?
- Additional comments:

- Patent information submitted on form FDA 3542a? **YES**
- Exclusivity requested? **YES, 3 years** **NO**
NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.

- Correctly worded Debarment Certification included with authorized signature? **YES**
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**
(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**

Refer to 21 CFR 314.101(d) for Filing Requirements

- PDUFA and Action Goal dates correct in COMIS? **YES**
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: 60,672
- End-of-Phase 2 Meeting(s)? **Date: 11Dec2001**
If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s)? **Date(s) 23Sep2002, 01Mar2004**
If yes, distribute minutes before filing meeting

Project Management

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? **YES**
- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? **YES**
- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? **N/A**
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted? **N/A**

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/A
- Has DOTCDP been notified of the OTC switch application? N/A

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? N/A

Chemistry

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

ATTACHMENT

MEMO OF FILING MEETING

DATE:

BACKGROUND:

(Provide a brief background of the drug, e.g., it was already approved and this NDA is for an extended-release formulation; whether another Division is involved; foreign marketing history; etc.)

ATTENDEES:

ASSIGNED REVIEWERS:

<u>Discipline</u>	<u>Reviewer</u>
Medical:	Julie Golden, M.D.
Secondary Medical:	N/N
Statistical:	Japo Choudhury, Ph.D.
Pharmacology:	Karen Davis Bruno, Ph.D.
Statistical Pharmacology:	NN
Chemistry:	Shulin Ding, Ph.D.
Environmental Assessment (if needed):	NN
Biopharmaceutical:	Johnny Lau, Ph.D.
Microbiology, sterility:	NN
Microbiology, clinical (for antimicrobial products only):	NN
DSI:	consulted to Andrea Slavin
Regulatory Project Management:	Pat Madara
Other Consults:	DDMAC, ODS

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

CLINICAL FILE XX REFUSE TO FILE _____

- Clinical site inspection needed: **YES**
- Advisory Committee Meeting needed? **NO**
- 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**

CLINICAL MICROBIOLOGY NA XX FILE _____ REFUSE TO FILE _____

STATISTICS FILE XX REFUSE TO FILE _____

BIOPHARMACEUTICS FILE XX REFUSE TO FILE _____

- Biopharm. inspection needed: **NO**

PHARMACOLOGY NA _____ FILE XX REFUSE TO FILE _____

- GLP inspection needed: **NO**

CHEMISTRY FILE _____ REFUSE TO FILE _____

- Establishment(s) ready for inspection? **YES**
- Microbiology **NN**

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:

_____ The application is unsuitable for filing. Explain why:

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

XX No filing issues have been identified

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

ACTION ITEMS:

1. If RTF, notify everybody who already received a consult request of the RTF action. Cancel the EER.
2. If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
3. Document filing issues/no filing issues conveyed to applicant by Day 74.

Pat Madara
Regulatory Project Manager, HFD-510

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

/s/

Patricia Madara
10/12/04 03:05:29 PM
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 60,672

Abbott Laboratories
Attention: Ellen Holst
Manager, Regulatory Affairs; Hospital Products Division
200 Abbott Park Road; D-389, Building J45-2
Abbott Park, IL 60064-6133

Dear Ms. Holst:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zemplar (paricalcitol) Capsules.

We also refer to the meeting between representatives of your firm and the FDA on March 1, 2004. The purpose of the meeting was to obtain Agency input regarding organization and content of the NDA.

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) 827-6416.

Sincerely,

{See appended electronic signature page}

Pat Madara
Regulatory Project Manager
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

MEETING DATE: March 1, 2004
TIME: 11:00 AM
LOCATION: Teleconference
APPLICATION: IND 60,672 Zemplar (paricalcitol) Capsules
TYPE OF MEETING: Type B; Pre-NDA
MEETING CHAIR: Eric Colman, M.D., Medical Team Leader
MEETING RECORDER: Pat Madara

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION

Division of Metabolic and Endocrine Drug Products, HFD 510

- | | |
|---------------------------|--------------------------------|
| 1. Eric C. Colman, M.D. | Medical Team Leader |
| 2. S.W. Johnny Lau, Ph.D. | Clinical Pharmacology Reviewer |
| 3. Lee-Ping Pian, Ph.D. | Biometrics Reviewer |
| 4. Jon T. Sahlroot, Ph.D. | Biometrics Team Leader |
| 5. Pat Madara, M.S. | Regulatory Project Manager |

Division of New Drug Chemistry II, Office of New Drug Chemistry

- | | |
|------------------------------|-----------------------|
| 1. Eric Duffy, Ph.D. | Division Director |
| 2. Mamta Gautam-Basak, Ph.D. | Chemistry Team Leader |

EXTERNAL CONSTITUENT ATTENDEES AND TITLES:

Abbott Laboratories, Global Pharmaceutical Research and Development Division

- | | |
|--------------------------------|-------------------------------------------------------------|
| 1. William Bracken, Ph.D. | Scientific Director, Global Preclinical Safety |
| 2. Steve Chamberlin, Ph.D. | Project Manager, Renal Project Team |
| 3. G. Richard Granneman, Ph.D. | Divisional Vice President, Center of
Clinical Assessment |
| 4. Alison Hayles | Sr. Regulatory Associate |
| 5. Dean Hickman, Ph.D. | Group Leader, Drug Metabolism |
| 6. Richard Hippensteel, M.S. | Sr. Statistician |
| 7. Ellen Holst | Manager, Regulatory Affairs, Renal Project Team |
| 8. Gerald Leahy, B.A. | Sr. Research Clinical Programmer |
| 9. Joel Melnick, M.D. | Medical Director, Renal Project Team |
| 10. W. Patrick Mulligan | Manager, e-Submission Operations |

11. Mary O'Sullivan, MPH	Global Regulatory Head, Renal Project Team
12. Ramesh Palaparthy, Ph.D.	Sr. Research Pharmacokineticist, Clinical Pharmacokinetics
13. Ping Qiu, M.D.	Associate Medical Director, Renal Project Team
14. Lisa Ruiz	Manager, Regulatory Affairs
15. James Segretario, Ph.D.	Manager, Regulatory Affairs - CMC
16. Dennis Stephens, Ph.D.	Manager, Pharmaceutical Development
17. Laura Williams, M.D., MPH	Global Project Head, Renal Project Team

BACKGROUND:

Zemplar (paricalcitol) Capsules (IND 60,672) is being developed for the prevention and treatment of secondary hyperparathyroidism associated with chronic kidney disease (CKD). The purpose of this meeting was to obtain Agency input regarding the content of the preclinical, clinical and chemistry programs and the proposed format for organizing the submission. This is the second preNDA meeting granted for this IND. The Sponsor submitted 16 specific questions for Agency comment.

DISCUSSION POINTS:

Preclinical

Question #1: Does the Agency agree that the Preclinical Program presented in this package supports the NDA submission for the indication "Prevention and treatment of secondary hyperparathyroidism associated with chronic kidney disease"

- *The Agency has no outstanding (preclinical) issues with the capsule formulation. Any discussions or agreements reached at preNDA #1 remain in effect.*

Clinical

Question #2: Does the Agency agree that the Clinical Pharmacology program presented in this package supports the NDA submission?

- *Per the Phase 4 study reports, paricalcitol is metabolized via CYP3A4 and UGT1A4. Paricalcitol's metabolic enzyme induction potential is unknown. Hence, the sponsor should conduct:*
 - an in vivo study to examine the interaction potential of paricalcitol with CYP3A4 inhibitor*
 - an in vivo study to examine the interaction potential of paricalcitol with UGT1A4 inhibitor*
 - an in vitro study to examine the metabolic enzymes induction potential of paricalcitol with human liver cells*
- *The sponsor should submit raw in vitro dissolution data from 3 different lots (12units/lot) for review as soon as possible. The dissolution data should include descriptive statistics such as range, mean, median, and plots. An agreement should be reached with the Division on the in vitro dissolution method before further development of the dissolution part of the stability program.*

Based on the above information, the sponsor had the following questions and comments:

- *Agency responses are bulleted*

Would it be possible to submit the interaction and metabolic studies as Phase IV commitments?

- *The study reports could be submitted during the review period but not too late in the review cycle. The Agency suggested a follow-up teleconference to discuss the studies.*

Would the Agency comment on protocol design before initiation? If the Agency agreed to comment on design, what was the timeframe for responses?

- *The Agency will provide comments on the protocol design within 45 days.*

Did the Agency know of any specific inhibitors of UGT1A4?

- *The Agency knew of no specific UGT1A4 inhibitors.*

Can the in vitro study be conducted using cryopreserved human hepatocytes?

- *The Agency recommends using primary cultured human liver cells as they are the most accepted method for studying CYP induction (see J Clin Pharmacol 2003; 43: 443)*

The sponsor also noted that a report detailing the dissolution method had been previously submitted to the IND. However, they would resubmit this data.

Question#3: Does the Agency agree that the Clinical Program presented in this package supports the NDA submission?

- *Yes*

Question#4: Does the Agency agree that the Special Populations program presented in this package supports the NDA submission?

- *The Agency finds the program acceptable.*

Question#5: Does the Agency agree with the proposal to provide financial disclosure information for the three Phase 3 pivotal CKD studies?

- *Yes*

Question#6: Does the Agency agree that the Statistical Analysis Plan presented in this package supports the NDA submission?

- *The Agency requested that the proportion of subjects having a single calcium measurement > 10.5 be included in the Primary Safety Analysis. Also, descriptive data should be included.*

CMC

Question#7: Does the Agency agree with the submission of stability data to be included in the NDA and the submission schedule for additional data to be provided during review as presented in this package?

- *Yes*

Administrative/Procedural

Question#8: Does the Agency agree that all previously submitted data to the Zemplar Injection NDA 20-819 may be included by cross-reference throughout the application?

- *Yes*

Question#9: Does the Agency agree with the proposal to provide publications upon request?

- *Yes*

Question#10: Does the Agency agree with the proposed organization of the Integrated Summary of Safety?

- *Yes*

Question#11: Does the Agency agree with the organization and proposed data to be included in the Integrated Summary of Efficacy?

- *Yes*

Question#12: Will the Division consider waiving fully, or in part, the requirement for the paper review copy, or, will the Division require this to facilitate review of this application?

If not waived, how many paper review copies will the Division require of each item?

- *The Agency would like to request the following paper documents:*
 1. *one copy of volume 1, containing all administrative documents requiring signatures*
 2. *one copy of the chemistry section*
 3. *one copy of all clinical pharmacology studies and any appendices that contain detailed PK or PD study reports and bioanalytical reports*
 4. *one copy of the Phase III pivotal study reports*

Question#13: Does the Agency agree with the proposal to not include patient profiles in light of the fact that we are including CRT datasets? If so, will the content and structure of the "analysis-ready" datasets presented in this package and programs facilitate Division review?

- *Yes*

Question#14: Does the Agency agree with the proposal to include case report forms only for deaths and discontinuations due to adverse events?

- *Yes*

Question#15: Does the Agency agree with the overall outline of the NDA?

- *Yes*

Question#16: Does the Agency agree with the proposal to provide an electronic NDA with approximately 40% of the data provided as scanned images, as well as the level of navigation proposed?

- *It is acceptable.*

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

/s/

Patricia Madara
3/31/04 04:14:20 PM



IND 60,672

Abbott laboratories
Attention: Ellen J. Holst
Manager, Regulatory Affairs
200 Abbott Park Rd., D-389, J45-2
Abbott Park, IL 60064-6133

Dear Ms. Holst:

Please refer to the meeting between representatives of your firm and FDA on September 23, 2002. The purpose of the meeting was to discuss the presentation of the data in support of the Zemplar (paricalcitol) Capsules' New Drug Application.

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 301-827-6416.

Sincerely,

{See appended electronic signature page}

Samuel Y. Wu, Pharm.D.
Regulatory Project Manager
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

**MEMORANDUM OF MEETING MINUTES
(TELECONFERENCE)**

MEETING DATE: September 23, 2002

TIME: 10:30 AM – 11:30 AM

LOCATION: Parklawn, Room 14B-45

SPONSOR: Abbott Laboratories

APPLICATION: IND 60,672

DRUG: Zemplar (paricalcitol) Capsules

TYPE OF MEETING: Pre-NDA

MEETING CHAIR: Eric Colman, Medical Team Leader

MEETING RECORDER: Samuel Wu, Regulatory Project Manager

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION

<u>Name of FDA Attendee</u>	<u>Title</u>	<u>Division Name & HFD#</u>
1. Eric Colman, M.D.	Medical Team Leader	DMEDP, HFD-510
2. Yvonne Yang, Ph.D.	Chemistry Reviewer	DMEDP, HFD-510
3. Todd Sahlroot, Ph.D.	Biometrics Team Leader	DMEDP, HFD-510
4. Lee-Ping Pian, Ph.D.	Biometrics Reviewer	DMEDP, HFD-510
5. Gemma Kuijpers, Ph.D.	Pharm/Tox Reviewer	DMEDP, HFD-510
6. Hae Young Ahn, Ph.D.	Biopharmaceutics Team Leader	DMEDP, HFD-510
7. Kenneth Edmunds	IT Specialist	OIT, HFD-073
8. Samuel Wu, Pharm.D.	Regulatory Project Manager	DMEDP, HFD-510

EXTERNAL CONSTITUENT ATTENDEES AND TITLES:

<u>External Attendee</u>	<u>Title</u>	<u>Sponsor/Firm Name</u>
1. Michael Amadahl	Senior Statistician	Abbott Laboratories
2. Mitchell B. Friedman, Ph.D., DABT	Director, Scientific Affairs	Abbott Laboratories
3. Ellen Holst	Manager, Regulatory Affairs	Abbott Laboratories
4. Rich Manski	Manager, Statistics	Abbott Laboratories
5. Bruce McNutt, M.D.	Global Medical Director	Abbott Laboratories

6. W. Patrick Mulligan	Manager, e-Submissions Center of Excellence	Abbott Laboratories
7. Mary O'Sullivan, MPH	Global Regulatory Head, Renal	Abbott Laboratories
8. Rajendra Pradhan, Ph.D.	Section Manager, Center of Clinical Excellence	Abbott Laboratories
9. Ping Qiu, M.D.	Associate Medical Director, Renal Care Clinical Development	Abbott Laboratories
10. James Segretario, Ph.D.	Manager, Regulatory Affairs-CMC	Abbott Laboratories
11. Dennis Stephens, Ph.D.	Manager, Product Development	Abbott Laboratories

BACKGROUND:

Zemlar™ Injection was approved on April 17, 1998, for the prevention and treatment of the secondary hyperparathyroidism associated with chronic renal failure. The sponsor is developing an oral capsule formulation, under IND 60,672, for the prevention and treatment of secondary hyperparathyroidism in patients with chronic kidney disease (CKD). An end-of-phase 2 meeting was held on December 11, 2001, to discuss the adequacy of phase 3 clinical trials to support a marketing application for the aforementioned proposed indications. The sponsor requested a Pre-NDA meeting on June 28, 2002. According to the sponsor, this application will be an electronic submission, to be submitted on March 31, 2003. The meeting package was submitted on August 22, 2002.

MEETING OBJECTIVES:

The objective of this Pre-NDA meeting is to discuss the proposed content and format of the electronic NDA.

DISCUSSION POINTS (Bullet Format):
(Agency responses are in *italics*.)

- Agency comments on clinical studies (special populations) to be submitted in the NDA. *Your proposed submission of special population studies is acceptable. The Agency recommends that you fully characterize the metabolic pathway(s) and the responsible enzyme(s) for paricalcitol metabolism. Please include bioanalytical and validation reports in each clinical pharmacology study report. Please provide raw pharmacokinetic data as well as pharmacokinetic parameters estimates in SAS transport files in your NDA submission. Your proposed in vitro dissolution method and specifications for paricalcitol capsules should be included in the Human Pharmacokinetics and Bioavailability section of the NDA. Please state the relationship between Study M02-437 (pivotal bioequivalence study) and the clinical relevance study to address the bioequivalence among the different strengths of paricalcitol capsules. Please also state the status of both studies.*

- Does the Agency agree with the proposed overall outline of NDA?
Agency agrees.
- Does the Agency agree with the proposed methods for presenting Integrated Summary of Safety (ISS) and Integrated Summary of Efficacy (ISE) data?
Agency agrees.
- Does the Agency agree with the proposed detailed description of electronic NDA navigation?
Agency agrees. The agency requests that you submit one paper copy of the three Phase III pivotal studies reports for the biometrics reviewer.
- Does the Agency agree with the proposed electronic data presentation plan?
Your proposed content and structure of the "analysis-ready" datasets are acceptable. However, please include one additional derived variable – the percent change from baseline in iPTH and the last observation carried forward (LOCF). The Agency agrees with your proposal not to include patient profiles in the submission. Your proposed presentation of Case Report Forms is acceptable. In addition to organizing by study, the Agency recommends that you organize them by site and by individual patient. The Agency agrees that you may submit financial disclosure information only for the three Phase III pivotal studies. Please submit the all of the items requiring original signatures in paper, e.g., certifications, user fee cover sheet, financial disclosure information, and patent information.
- Is the scheduled submission date for the — stability data acceptable for the Agency's review?
Your proposed stability submission date is acceptable.

ADDITIONAL COMMENTS:

- Per SUPAC, the difference between the 2- and 4-µg capsules used in Phase III clinical trials and the to-be-marketed capsules is acceptable.
- For additional information on electronic submission, please refer to the following two guidance documents and the Electronic Regulatory Submissions and Review web site:
 1. Providing Regulatory Submissions in Electronic Format – General Considerations
 2. Providing Regulatory Submissions in Electronic Format – New Drug Applications
 3. www.fda.gov/cder/regulatory/ersr/default.htm
- To avoid any delay in processing your submissions, we have the following recommendations:
 1. Submit only one copy of electronic media to the Agency.
 2. Pay close attention to the guidance description of acceptable formats for each component of the electronic NDA so that you can avoid submitting in a format not listed in the guidance. A common format mistake, for example, is the submission of native SAS data sets instead of SAS transport Version 5. Another common mistake is the submission of Microsoft Word files, other than draft labeling, instead of PDF files.
 3. Please submit the draft labeling in both Microsoft Word and PDF files.

4. Please submit all electronic media to the Central Document Room at the following address:

Central Document Room (HFD-94)
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, MD 20852

5. If you had additional questions regarding electronic NDA submission, please contact the email account at ESUB@CDER.fda.gov.

DECISIONS (AGREEMENTS) REACHED:

- Abbott will provide paper copy of the three pivotal Phase III clinical trials for the biometrics reviewer.

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

None.

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

/s/

Samuel Wu
10/24/02 10:29:41 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 60,672

Abbott Laboratories
Attention: Ms. Ellen Chiodo
Manager, HPD Regulatory Affairs
200 Abbott Park Rd., D-37N, J45
Abbott Park, IL 60064-6133

Dear Ms. Chiodo:

Please refer to the meeting between representatives of your firm and FDA on December 11, 2001. The purpose of the meeting was to discuss the phase 3 clinical development program for Zemplar Capsules, and its adequacy to support a marketing application for the prevention and treatment of secondary hyperparathyroidism associated with —
— chronic kidney disease.

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

Meeting Date: December 11, 2001 Time: 1:00 - 2:30 AM Location: Potomac Conf. Rm.

IND 60,672 Zemplar (paricalcitol) Capsules

Type of Meeting: End-of-Phase 2

External participant: Abbott Laboratories

Meeting Chair: Dr. Eric Colman

External participant lead: Ms. Mary O'Sullivan

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

Karen Davis-Bruno, Ph.D., Pharmacology Team Leader

Gemma Kuijpers, Ph.D., Pharmacology Reviewer

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

Office of New Drug Chemistry:

Yvonne Yang, Ph.D., Reviewer

Sheldon Markofsky, Ph.D., Acting Team Leader

Duu-Gong Wu, Ph.D., Deputy Division Director

Division of Pharmaceutical Evaluation II

Hae-Young Ahn, Ph.D., Team Leader

External participant Attendees and titles:

Michael Amdahl, M.S., Senior Statistician

Leticia Delgado-Herrera, R.Ph., M.S., Program Director, Proprietary Programs

Jonathan Dohnalek, B.D., Manager, Regulatory Affairs-CMC

Maurice G. Emery, Pharm.D., Ph.D.

Mitchell B. Friedman, Ph.D., DABT, Director, Scientific Affairs

Bruce McNutt, M.D., Director, Clinical Development

Mary O'Sullivan, M.P.H., Associate Director, Regulatory Affairs

Rajendra Pradhan, Ph.D., Project Leader, Center of Clinical Assessment

Ping Qiu, M.D., M.S., Associate Medical Director
_____, Abbott Consultant
Aron Stein, Ph.D., Vice President, Medical & Regulatory Affairs
Dennis Stephens, Ph.D., Manager, Pharmaceutical Development

Meeting Objectives:

The meeting was requested by Abbott Laboratories to discuss the phase 3 clinical development program for Zemplar Capsules, and its adequacy to support a marketing application for the prevention and treatment of secondary hyperparathyroidism associated with _____ chronic kidney disease (CKD). Zemplar Injection was approved on April 17, 1998, for the indication, the prevention and treatment of secondary hyperparathyroidism associated with chronic renal failure in end-stage renal disease patients.

Discussion Points and Decisions (agreements) reached:

- The firm submitted the following questions in a background document dated November 29, 2001. The Divisions answers follow the questions in *Italics*.
1. Does the Division agree that the pharmacology/toxicology program presented and performed to date is adequate?

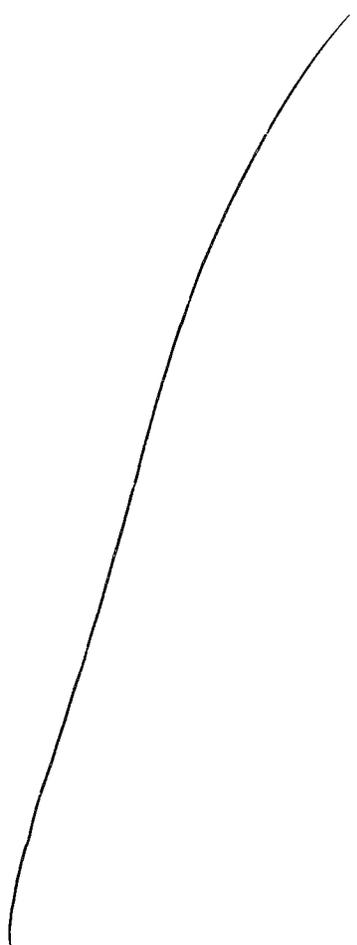
The program appears adequate. Carcinogenicity studies are needed for NDA filing. The firm responded that they will submit carcinogenicity studies to the IND.
 2. Based on dose titration in clinical practice, the bioequivalence differences observed between 1, 2, and 4 ug strengths, does the Division agree that:
 - A. It is acceptable to continue with the Phase III program?

The bioequivalence differences between the strengths may be a problem. For example, patients may substitute two 1 ug doses for a 2 ug dose, and get a different response. In an extreme case a pharmacy may only carry the 1 ug dose and have a patient who is getting 32 ug. If the pharmacist dispensed 1 ug dose capsules vs. 4 ug dose capsules, the patient would get a much different effect.
 - B. It is acceptable to market these dosage strengths?

Data from a phase 1 study indicate that eight 1 ug capsules, four 2 ug capsules, and two 4 ug capsules are not bioequivalent. The eight 1 ug capsules may be as much as 25% less bioavailable than the two 4 ug capsules. The Division is concerned that the differences in bioequivalence between doses may be clinically meaningful. Abbott was advised to propose a study to demonstrate that the difference in bioavailability are not clinically meaningful. The Company stated that they would discuss the issue internally, and propose a study to address the issue.

3. Does the Division agree with the dosing regimens for CKD studies as presented in the dosing rationale section of this package?

This is acceptable if the bioequivalence issue is resolved.

- 4.
- 

This seems acceptable.

The following three Phase III CKD draft protocols were submitted as part of the Special Protocol Assessment to the IND on September 28, 2001, Serial No. 009,

- A. Protocol No. 2001-019: A Phase III, Prospective Randomized, Placebo-Controlled, Double-Blind, Multi-Center Study to Determine the Safety and Efficacy of Zemplar Capsules (Dosed Three times Weekly) in Reducing Elevated Serum Intact Parathyroid Hormone Levels in Subjects with Chronic Kidney Disease”
- B. Protocol No. 2001-020: A Phase III, Prospective, Randomized, Placebo-Controlled, Double-Blind, Multi-Center Study to Determine the Safety and Efficacy of Zemplar Capsule (Dosed Three times Weekly) in Reducing Elevated Serum Intact Parathyroid Hormone Levels in Subjects with Chronic Kidney Disease”
- C. Protocol No. 2001-021: “A Phase III, Prospective Randomized, Placebo-Controlled Double-Blind, Multi-Center Study to Determine the Safety and efficacy of Zemplar Capsules (Dosed Every Day) in Reducing Elevated Serum Intact Parathyroid Hormone Levels in Subjects with Chronic Kidney Disease”

Does the Division agree that this program would support a — indication to include the chronic kidney disease patient population?

This seems acceptable. The Division pointed out that Abbott should not assume that data

- 5. Abbott will defer pediatric studies until the results from the adult clinical trials using the oral formulation and the ongoing intravenous pediatric studies are complete. Does the Division agree with this deferral?

This is acceptable; Abbott Laboratories will propose a date the studies are deferred to.

- 6. Does the Division agree to grant a partial waiver for the 0-11 year age group for the Zemplar capsule program?

The Division cannot give a definite answer at this time. The Division raised the possibility of studying Zemplar in pre-dialysis, or chronic kidney disease patients? Abbott Laboratories will provide additional information on how this patient population can be studied.

7. Does the Division agree with Abbott's procedure to monitor and report the related substances in the drug product?

The proposed analytical method seems reasonable, however we have the following concerns:

A. Potential _____ s may result in degradation products not yet identified within the _____ degradants described in the method.

B. /

Therefore, we cannot give a definitive answer to the above question without looking at the data. Abbott Laboratories said they will provide additional information on related substances in the drug product.

8. Does the Division agree with Abbott's dissolution procedure for the drug product?

The method seems to be reasonable.

Use of the _____ may be high, Abbott Laboratories needs to submit justification.

- *Abbott Laboratories needs to reach agreement with the Division regarding the dissolution study before launching the stability study.*
- *The Division requires three different concentrations of _____*

9. Does the Division accept Abbott's justification for a proposed in-process _____

This is acceptable. The target paricalcitol content should be _____ of labeled product at release.

10. Does the Division accept Abbott's proposed specifications as adequate for controlling quality of the drug product?

- *In addition to the proposed specification, please specify related substances based on retention time, and set limit based on historical stability data.*

Unknown peaks should be identified by their retention time and area %.

- Please justify why the acceptance criterion for paricalcitol is set for _____ and Abbott explained that the current acceptance criterion for potency is _____
- Abbott needs to include a specification for _____
- The Division has no comment regarding the specification for dissolution until after seeing dissolution data.

11. Abbott will file the NDA with _____ stability data on the NDA exhibit batches (3 lots of each strength, 4 strengths). This data would be supported by _____ of stability data on the Phase III batches (1 lot of each strength, 4 strengths). Is this plan for submission of stability data acceptable to the Division?

ICH guidance recommends twelve months of stability data from three lots at the time of submission. We have no problem with receiving updated stability data during the reviewing process. Limited stability data will result only in reduced expiry.

Unresolved or issues requiring further discussion:

- None

Action Items:

- Abbott will submit a draft protocol to the Division for review to address the different capsule strength bioavailability issue.
- Concerning the pediatric rule and request for a waiver, Abbott Laboratories will provide information on how the 0-11 year age group can be studied.
- Abbott Laboratories will provide additional information on related substances in the drug product.

Signature, minutes preparer:

Concurrence Chair:

**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
1/9/02 08:42:34 AM