CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020819

ADMINISTRATIVE DOCUMENTS

5.0 Section G: Patent Information

Paragraph III Certification

Paracalcin for Injection is covered by United States Patent 5246925, expiring 21 September 2010 which claims the method of use, and United States Patent 5587497, expiring 24 December 2013 which claims the drug. Both patents are owned by Wisconsin Alumni Research Foundation.

The undersigned declares that Patent No. 5246925 covers the formulation, composition, and/or method of use of paracalcin for injection. This product is the subject of this application for which approval is being sought.

Gregory Steele
Abbott Laboratories

1/8/96
Date

RECORD OF TELEPHONE CONVERSATION/MEETING	DATE: 9/29/97
I requested clarification of the following question: Why was no maternal toxicity noted in the segment 3 study while toxicity was noted in the segment 2 study and other toxicity studies at similar dose levels and exposures.	**NDA/IND NUMBER:** NDA 20-819
Reply: Here is the information that you requested: Treatment with the product was not expected to produce observable effects in the pregnant dams in the perinatal and postnatal (Segment III) study in rats. In a one-month toxicity study, no gross changes were observed in rats treated with the same dosages (0.3, 3.0 or 20.0 micrograms/kg/dose, three doses per week). Clinical chemistry evaluations revealed elevations in serum calcium, and mineralization of the aorta, stomach and heart and increased incidences of nephrocalcinosis and renal pelvic microliths were observed histologically in the one-month toxicity study. However, these changes could not have been seen in the Segment III study, since the study protocol did not call for clinical pathology or histopathology evaluations. Please call me if any additional details are needed. Tom Willer APPEARS THIS WAY ON ORIGINAL	**PRODUCT NAME:** Paracalcin APPEARS THIS WAY ON ORIGINAL
	FIRM NAME: Abbott
	NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD: Tom Willer, Ph.D.
REVIEWER: Daniel T. Coleman, Ph.D. APPEARS THIS WAY ON ORIGINAL	**TELEPHONE NUMBER:** (847)937-6845
SIGNATURE:	**DIVISION:** DMEDP

RECORD OF TELEPHONE CONVERSATION/MEETING	DATE: 9/12/97
I requested clarification of why the half life estimates were so different in the two dog studies (3 vs. 17 h). Reply- I am enclosing a paragraph to try to explain the differences in the half-life estimates in dogs. The half life of paracalcin in dog plasma was estimated to be approximately 3 hours after administration of paracalcin as [3H] drug (_____), and approximately 17 hours after administration of paracalcin as cold drug (_____). Estimation of the half life of a drug is dependent on the sampling time points during the study and on the lower limit of quantification of the assay. Elimination of paracalcin is biphasic and many of the samples collected during the terminal phase after administration of the cold drug had concentrations below the lower limit of quantification (LLQ=100 ng/mL in Dog Plasma). The calculation of b in this study utilized plasma concentration-time points between 4 and 12 hours post dosing and thus may have included significant portions of the distribution phase. On the other hand, the estimated value of paracalcin half-life using the radioactive detection (approximately 17 hours) may be an overestimate of the true half life since levels of the drug could not be accurately estimated beyond 24 hours post dosing. In general, one needs measurable samples for 3 to 5 half-lives before one can estimate the half-life very well. Most likely, the actual t1/2 in dogs is some where between the two estimates of the half life of the drug in the two studies. Let me know if you have any additional questions. Also, please send me a note and let me know that you received this e-mail. APPEARS THIS WAY ON ORIGINAL	**NDA/IND NUMBER:** NDA 20-819 APPEARS THIS WAY ON ORIGINAL
	PRODUCT NAME: Paracalcin
	FIRM NAME: Abbott
APPEARS THIS WAY ON ORIGINAL	**NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD:** Tom Willer, Ph.D.
REVIEWER: Daniel T. Coleman, Ph.D. APPEARS THIS WAY ON ORIGINAL	**TELEPHONE NUMBER:** (847)937-6845
SIGNATURE:	**DIVISION:** DMEDP

Memorandum of Consultation

NDA#:	20-819	APR 6 1998
Applicant:	Abbott Labs	
Name of Drug:	Capthrol [tradename] Paracalcin Injection / Paricalcitol Injection [generic name] (1α, 3β, 7E, 22E) -19-nor-9,10,-secoergosta-5,7,22-triene-1,3,25-triol abbreviated as 19-NOR	
Indication:	Prevention and treatment of renal osteodystrophy and secondary hyperparathyroidism encountered with chronic renal failure	
Documents Reviewed:	2-10-97 Vol. 39, 65-67; March 20, 1998 fax	
Statistical Reviewer:	Barbara Elashoff, M.S. (HFD-715)	
Medical Input:	Leo Lutwak, M.D. (HFD-510)	

Introduction

Abbott and the Division had a videoconference on March 24, 1998 to discuss the proposed labeling. The only point for which Abbott and the Division did not agree was the dosage recommendations. Abbott's proposed wording is below.

DOSAGE AND ADMINISTRATION

The currently accepted target range for iPTH levels in CRF patients is no more than 1.5 to 3 times the non-uremic upper limit of normal.

The recommended initial dose of Trade Name, depending on the severity of the secondary hyperparathyroidism, is 0.04 mcg/kg to 0.24 mcg/kg _____, administered as a bolus dose no more frequently than every other day at any time during dialysis.

If a satisfactory response is not observed, the dose may be increased by 2 to 4 mcg at 2 to 4 week intervals. During any dose adjustment period, serum calcium and phosphorous levels should be monitored more frequently, and if an elevated calcium level or a Ca x P product greater than 75 is noted, the drug should be immediately reduced or interrupted until these parameters are normalized. Then, Trade Name should be reinitiated at a lower dose. Doses may need to be decreased as the PTH levels decrease in response to therapy. Thus, incremental dosing must be individualized and commensurate with serum PTH, calcium and phosphorous levels.

The following table is a suggested approach in dose titration:

Suggested Dosing Guidelines	
PTH Level	**Trade Name Dose**
the same or increasing	increase
decreasing by <30%	increase
decreasing by >30%, <60%	maintain
decreasing by >60%	decrease
one and one-half to three times upper limit of normal	maintain

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Discard unused portion.

The similarities between the proposed wording dose regimen and the dose regimen used in the clinical trials upon which efficacy is based (Studies 35 and 36) are as follows:

1) range of doses = (0.04 mcg/kg, 0.24 mcg/kg);
2) the dose may be increased at 2 to 4 week intervals;
3) dose is increased if iPTH is not at least 30% lower than baseline;
4) dose is maintained if iPTH is equal to or greater than 30% lower than baseline; and
5) dose is decreased if Ca or Ca x P is elevated above cutoff point.

However, the differences are as follows:

1) initial starting dose in clinical trials was 0.04 mcg/kg;
2) dose decreased in clinical trials if iPTH fell below 100 pg/mL;
3) label recommends maintaining dose if iPTH level is _____ times the upper limit of normal.

The point of contention between the sponsor and the Division was the initial starting dose. The Division did not want the initial starting dose to be dependent on the severity of the secondary hyperparathyroidism, unless the sponsor provided efficacy and safety data to support this dose regimen. The sponsor submitted two studies , #022 and #004, in the original NDA submission to support this dose regimen.

Study 022

Study 022 was a Phase II, double-blind, placebo-controlled, randomized, multi-center study evaluating 4 different starting doses of 19-NOR (0.04,0.08, 0.16, 0.24), with approximately 6 patients per active treatment arm and a total of 13 patients on placebo. The patients were randomized to the different treatment groups. The doses were fixed and not based on the patient's iPTH level. This study does not appear to relate efficacy or safety with an initial dose based on the severity of the patient's secondary hyperparathyroidism. Further, there appears to be some evidence that the higher initial doses may have caused elevated calcium. All instances (n=4) of elevated calcium occurred in the treatment arms that were the highest of the four doses (0.16 and 0.24 mcg/kg).

Study 004

The study report for Study 004 was written on December 31, 1996 and submitted to the FDA on January 17, 1997. The study report states that the study was ongoing and the report includes information for all treated patients as of August 16, 1996. It is not clear why the sponsor did not include data between August 16, 1996 and December 31, 1996. The study is a Phase III, open-label, multi-center study evaluating the long term safety and efficacy of 19-NOR in decreasing iPTH to clinically appropriate levels as determined by the investigator. The total number of patients enrolled, treated and analyzed in the interim analysis was 95. The mean treatment duration was 26 days_____ _____ The study report states that, "The initial starting dose could have ranged from 0.04 to 0.24 mcg/kg according to the Investigator's discretion." This reviewer could not find any statement that described the starting dose as being dependent upon the patient's iPTH level, only wording regarding the starting dose to be decided "according to the investigator's discretion". The sponsor did not analyze any efficacy data in the interim analysis presented in the study report. The safety data presented represent at the most, 52 days (less than 2 months) and at the least, 3 days. On average, the patients were in the study about 1 month (26 days) as of August 16, 1996. The changes in Ca, Phosphorous and Ca x P product levels between baseline and last interim assessment value were statistically significantly different from zero. Eight percent (8/95) of the patients had hypercalcemia at

least once; thirteen percent (12/95) had Ca x P product levels > 75 for at least one period. The sponsor did not present descriptive statistics of the safety variables separately for each initial starting dose.

Conclusions

Study 022 cannot, by design, support the dose regimen in the proposed labeling, because the initial doses were not based on the severity of the individual patient's secondary hyperparathyroidism. Study 004 may support the dose regimen in the proposed labeling if,

1. the initial doses were based on the severity of the individual patient's secondary hyperparathyroidism (the study report did not make this clear); and
2. the completed efficacy and safety results are similar to those upon which the efficacy and safety of this drug was based (results of Studies 35 and 36).

It appears that the results of these two studies do not support the proposed dose regimen recommendations in the labeling.

/S/ 4/6/98

Barbara Elashoff

Mathematical Statistician

cc:
Orig. NDA 20-819
HFD-510 / Division File
HFD-510 / SSobel, GTroendle, LLutwak, DHedin
HFD-715 / Chron
HFD-715/ BElashoff, JMele, Biometrics Division 2

APPEARS THIS WAY
ON ORIGINAL

EXCLUSIVITY SUMMARY for NDA # 20819 SUPPL #_____

Trade Name — **Generic Name** paracalcin inj.

Applicant Name Abbott **HFD-** 510

Approval Date, if known _____

APPEARS THIS WAY ON ORIGINAL

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

   a) Is it an original NDA?

   YES /✓/ NO /___/

   b) Is it an effectiveness supplement?

   YES /___/ NO /___/

   If yes, what type? (SE1, SE2, etc.) _____

   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?

_____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx-to-OTC switches should be answered NO-please indicate as such.)

YES /___/ NO /✓/ OTC Switch /___/

If yes, NDA #_____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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

YES /___/ NO /✓/

IF THE ANSWER TO QUESTION 3 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# _____ _____

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. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S 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:

_____

_____

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"):

_____ _____

_____ _____

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 # _____ YES /___/	NO /___/ Explain: _____
	_____
Investigation #2	
IND # _____ 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 /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____
Investigation #2	
YES /___/ Explain _____	NO /___/ 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: _____

_____

/S/

Signature

4/2/98

Date

Randy Hedlin

Name (type or print)

Senior Reg. Management Officer

Title

/S/

Signature of Division Director

4/9/98

Date

Solomon Sobel

Name (type or print)

cc: Original NDA Division File HFD-93 Mary Ann Holovac

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

(NDA)/BLA # 20-819 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-510 Trade and generic names/dosage form: paracalcin Action: AP AE NA

APPEARS THIS WAY ON ORIGINAL

Applicant Abbott Therapeutic Class 15

Indication(s) previously approved None

Pediatric information in labeling of approved indication(s) is adequate __ inadequate __

Proposed indication in this application Prevention + Treatment of Secondary Hyperparathyroidism in chronic renal failure

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.

IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS? ___Yes (Continue with questions) ___No (Sign and return the form)

WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)

__Neonates (Birth-1month) __Infants (1month-2yrs) __Children (2-12yrs) __Adolecents(12-16yrs)

__ 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

__ 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

✓ 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

__ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

__ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

__ c. The applicant has committed to doing such studies as will be required.

- __ (1) Studies are ongoing,
- __ (2) Protocols were submitted and approved.
- __ (3) Protocols were submitted and are under review.
- __ (4) If no protocol has been submitted, attach memo describing status of discussions.

APPEARS THIS WAY ON ORIGINAL

✓ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

__ 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

__ 5. **If none of the above apply, attach an explanation, as necessary.**

APPEARS THIS WAY ON ORIGINAL

ARE THERE ANY PEDIATRIC PHASE IV COMMITMENTS IN THE ACTION LETTER? ___Yes ✓No

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

This page was completed based on information from _____ (e.g., medical review, medical officer, team leader)

TSI RPM

Signature of Preparer and Title

4/3/98

Date

cc: Orig NDA/BLA # 20-819
HFD-510 Div File
NDA/BLA Action Package
HFD-006/ KRoberts

(revised 10/20/97)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, KHYATI ROBERTS, HFD-6 (ROBERTSK)

ABBOTT

CERTIFICATION REQUIREMENT FOR ALL APPLICATIONS

FOR APPROVAL OF A DRUG PRODUCT

CONCERNING USING SERVICES OF DEBARRED PERSONS

Under the new law, any application for approval of a drug product submitted on or after June 1, 1992, must include:

> "a certification that the applicant did not and will not use in any capacity the services of any person debarred under subsections (a) or (b) [section 306(a) or (b)], in connection with such application."

Abbott Laboratories certifies that it did not and will not use in any capacity the services of any person debarred under subsections (a) or (b) [section 306(a) or (b)], in connection with this application.

Generic Drug Enforcement Act of 1992
Section 306(k) (1) of the act (21 USC 335a(k) (1)).

APPEARS THIS WAY
ON ORIGINAL

Thomas F. Willer

March 5, 1998

Date

Thomas F. Willer, Ph.D
Manager, Regulatory Affairs
Hospital Products Division
D-389, AP30
Abbott Laboratories
200 Abbott Road
Abbott Park, Illinois 60064-3537

APPEARS THIS WAY

3-98f.tfw/13

ABBOTT

LIST OF RELEVANT CONVICTIONS FOR

PERSONS DEBARRED OR NOT DEBARRED

Per letter from the Office of Generic Drugs dated January 15, 1993, abbreviated applications must contain a list of relevant convictions, as described in section 306(a) and (b) of the GDEA*, of the applicant and affiliated persons (i.e., contractors, et. al.) responsible for the development or submission of the application, which have occurred within five years before the date of the application. Firms with no convictions to list should submit a statement to that effect.

Abbott Laboratories states that it has no such convictions to list.

* Generic Drug Enforcement Act of 1992
Section 306(k) (1) of the act (21 USC 335a(k) (1)).

APPEARS THIS WAY ON ORIG

Thomas F. Willer

March 5, 1998
Date

Thomas F. Willer, Ph.D.
Manager, Regulatory Affairs
Hospital Products Division
D-389, AP30
Abbott Laboratories
200 Abbott Road
Abbott Park, Illinois 60064-3537

APPEARS THIS WAY ON ORIG

TFW:tw

3-98F.tfw/14

Memorandum
April 13, 1998
To: the file NDA 20-819,paracalcitol (previously called paracalcin) injection
From: Solomon Sobel M.D. Director, Division of Metabolic and Endocrine Drug Products
Subject: Approval of NDA
Paracalcitol injection (Tradename: Zemplar) is a synthetic vitamin D analog.
The approval is based on 3 placebo controlled studies.
Dosing used in the phase 3 controlled studies was established in dose ranging phase 2 studies performed in patients with chronic renal failure in which the range of dosing was 0.04 mcg to 0.24 mcg per kilogram.
There were several issues which were discussed during the review of this NDA.
The Division recommended that the indication be limited at this time to the "prevention and treatment of secondary hyperparathyroidism encountered with chronic renal failure".
The sponsor had initially asked for wording in the indication which included the treatment of osteodystrophy. However, we believe that bone biopsy data are necessary for granting this indication. Although we recognized that a beneficial effect on bone would be the probable outcome of the effective suppression of hyperparathyroidism, we would like a direct histomorphometric demonstration of this. This analog of vitamin D is a new molecular entity and its actions on bone (both indirect and direct) remain to be verified. There is some evidence that in addition to parathyroid suppression, vitamin D and its analogs may have a direct bone effect.
Also,the issue of the incidence of "adynamic" bone during this treatment should be looked for.
Another issue which arose was the dosing of the drug. The sponsor wished to start patients with higher parathyroid levels on higher initial doses of paracalcitol. Although, there is evidence with other vitamin D drugs for justifying this approach, we believed that starting with higher doses with paracalcitol would have to be demonstrated with that drug specifically. We based this view primarily on safety considerations; that is, the need to show that severe hypercalcemia will not result. The sponsor cited some data from studies presented in the NDA that would indicate that higher initial doses in patients with higher inital levels of parathyroid were justified. However, our reconsideration of these data showed that this was not systematically studied and no conclusions could be drawn in respect to this higher initial dosing approach.

Conclusion:
The Division recommends approval of paracalcitol.

/S/
Solomon Sobel

CC: Arch NDA 20-819
HFD-510
HFD-510/SSobel/GTroendle/RHedin

NDA 20819
Abbott Laboratories
Paracalcitol (Zemplar)
Approval Package
14 April, 1998

Team Leader Response to Dr. Sobel review of NDA

Package Insert, ADVERSE REACTIONS: The title should be changed to ADVERSE EVENTS. The description of early and late signs and symptoms of vitamin D intoxication associated with hypercalcemia should not be in the ADVERSE EVENTS section. It would be more appropriate in PRECAUTIONS, General, after the third sentence: "If clinically significant hypercalcemia develops, the dose should be reduced or interrupted." The digitalis and adynamic bone sentences should then follow as separate paragraphs. ADVERSE EVENTS would then begin with the description of the safety data in the clinical studies. It is meaningless to describe the discontinuations due to any adverse event as "treated with Zemplar up to 0.24 mcg/kg..." That could mean a single patient was titrated to that level and most were only able to tolerate 0.04, which was the initial dose. The sentence might be changed to read: "...62 patients treated with Zemplar as recommended and 2.0% of 51 patients..."

The table of adverse events is based on only 62 Zemplar- and 51 placebo-treated patients. Therefore, using a cut-off of 5 occurrences means that only those events occurring in at least 8% of patients are included. Also, the table contains COSTART terms that are not meaningful, and most of the events occur at a higher rate in drug than in placebo patients. It would be more helpful to include events of possible importance to practitioners. That could be all events occurring in at least 2% of patients, and with a frequency greater in drug than in placebo patients. The COSTART term that is a problem is "vascular disorder." It is more frequent in Zemplar patients, although the category of cardiovascular system events is less frequent in Zemplar patients. Only one other event listed in this table is more frequent in Zemplar patients: nausea. I suppose the sponsor may wish to claim benefit from the lower incidence of pain and chest pain, because they could be related to fractures of spine and other places affected by osteodystrophy. Such a claim would be inappropriate based on the numbers involved.

On page 11 the list of events from all of the 270 patients studied (including non-randomized trials) is again using at least 5 occurrences (2%) for the cut-off, which is more

appropriate now, but why not use 2 or 5% (I am not sure which is preferred)? Some of those COSTART terms should also be removed: infection, pain, vascular disorder, gastrointestinal disorder, lung disorder. I suggest removal of vascular disorder, gastrointestinal disorder, and lung disorder, because many other terms are included that seem to cover the conditions related to those symptoms. They just do not seem helpful. Also, they should be listed into a table with percent of patients. It might be possible to remove those symptoms that commonly result from renal osteodystrophy.

In OVERDOSAGE, the reference for signs and symptoms of vitamin D intoxication should be "See PRECAUTIONS, General" instead of (see ADVERSE REACTIONS."

The Letter, page 2, reminder of Phase 4 commitments:

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