

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-320

Correspondence



NDA 21-320

INFORMATION REQUEST LETTER

Praecis Pharmaceuticals, Inc.
Attention: J.D. Bernardy, J.D.
Vice President, Regulatory Affairs & Quality Assurance
830 Winter Street
Waltham, MA 02451-1420

Dear Mr. Bernardy:

Please refer to your December 11, 2000 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Plenaxis (abarelix suspension for injection).

We also refer to your February 25, 2003 submission that constituted a completed response to our Not Approvable letter dated June 11, 2002. In addition, we also refer to your submission dated November 21, 2003, containing your proposed labeling.

We are reviewing the Clinical section of your Package Insert (PI) and the Patient Information (PPI) and have the following suggestions for revisions, as attached. We request a prompt written response in order to continue our evaluation of your NDA.

If you have any questions, please call Nenita Crisostomo, R.N., Regulatory Project Manager, at 301-827-4260.

Sincerely,

{See appended electronic signature page}

Margaret Kober, R.Ph.
Chief, Project Management Staff
Division of Reproductive and Urologic Drug
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosures/nic

30 pages redacted from this section of
the approval package consisted of draft labeling

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/s/

Margaret Kober
11/25/03 08:59:28 AM
Chief, Project Management Staff



NDA 21-320

INFORMATION REQUEST LETTER

Praecis Pharmaceuticals, Inc.
Attention: J.D. Bernardy, J.D.
Vice President, Regulatory Affairs & Quality Assurance
830 Winter Street
Waltham, MA 02451-1420

Dear Mr. Bernardy:

Please refer to your December 11, 2000 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Plenaxis (abarelix suspension for injection).

We also refer to your February 25, 2003 submission that constituted a completed response to our Not Approvable letter of June 11, 2001. In addition, we also refer to your submissions, Amendment 080 dated November 7, 2003, and Amendment 081 dated November 10, 2003, following our teleconference dated November 4, 2003.

We are reviewing your submissions and have the following suggestions to revise the Physician Package Insert, Physician Attestation Form, Patient Information Form, and Hospital Pharmacies' Responsibilities Form as enclosed. We request a prompt written response in order to continue our evaluation of your NDA.

If you have any questions, please call Nenita Crisostomo, R.N., Regulatory Project Manager, at 301-827-4260.

Sincerely,

{See ~~/s/~~ appended electronic signature page}

Margaret Kober, R.Ph.
Chief, Project Management Staff
Division of Reproductive and Urologic Drug
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosures

26 pages redacted from this section of
the approval package consisted of draft labeling

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/s/

Margaret Kober
11/14/03 01:47:21 PM
Chief, Project Management Staff



SEP 30 2003

Steven N. Gange, M.D.
Salt Lake Research
4252 South Highland Drive, Suite 201
Salt Lake City, Utah 84124

Dear Dr. Gange:

Between July 11 and 16, 2003, Mr. Blake R. Jensen, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of a clinical investigation (Protocol #149-98-04 entitled: "A Multi-Center Study of Abarelix-Depot in Patients with Prostate Cancer in Whom GnRH Agonists are Contraindicated") of the investigational drug Plenaxis™ (abarelix), performed for Praecis Pharmaceuticals Incorporated. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of the study have been protected.

From our evaluation of the establishment inspection report and the documents submitted with that report, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects. We are aware that at the conclusion of the inspection, Mr. Jensen presented and discussed with you Form FDA 483, Inspectional Observations. We wish to emphasize the following:

1. You did not follow the protocol [21 CFR 312.60] in that:
 - a. The study drug was administered outside of the protocol-specified days for subject 4734019: 6 days after day 57, 6 days prior to day 85 and 2 days prior to day 225.
 - b. Subject — was consented and screened, but declined enrollment in the study. However, no data on this subject was reported to the sponsor.
 - c. You did not complete "Study Summary/Termination (Treatment Day 169 and Beyond)" section of the case report forms for subjects 4734065 and 4734071, and "SWOG 9039" and "EQ-5D Health Questionnaire" sections of the case report forms for subject 4734003 for days 15 and 57, and for subject 4734031 for day 1.

Page 2 – Steven N. Gange, M.D.

2. You did not maintain adequate and accurate records [21 CFR 312.62] in that:
 - a. The Drug Accountability Record showed that the investigational drug was administered to subject 4734074 on 5/16/00 whereas, according to the source data and case report form, the investigational drug was administered on 5/17/00.
 - b. Subject 4734019's number appeared as 4734009 on various case report forms.

Please make appropriate corrections in your procedures to assure that the findings noted above are not repeated in any ongoing or future studies.

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

Sincerely yours,


Joseph P. Salewski
Acting Director
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

Page 3 – Steven N. Gange, M.D.

FEI: 3004029904

Field Classification: VAI

Headquarters Classification: VAI

Deficiencies noted:

failure to adhere to protocol (05)

inadequate and inaccurate records (06)

cc:

HFA-224

HFD-580 Doc.Rm. NDA 21-320

HFD-580 Division Director Shames

HFD-580 MO Monroe

HFD-580 PM Crisostomo

HFD-46/47 c/r/s/ GCP File #10960

HFD-46/47 Blay/Hajarian

HFR-SW250 DIB Miller

HFR-SW250 BIMO Monitor Smith

HFR-SW250 Investigator Jensen

GCF-1 Seth Ray

r/d:GRH:8/15/03

reviewed:KMU:8/15/03

f/t:ML:8/19/03

revised:JPS:8/22/03

f/t:GRH:9/5/03

O:\GRH\GANGE VAL.DOC

Reviewer's Note to Review Division Medical Officer

Seven subjects were enrolled in this open-label, single-arm study. The records of all 7 subjects were reviewed in detail. Informed consents were on file for all subjects.

Several protocol and recordkeeping deficiencies were observed:

For subject 4734019, doses were administered outside of the protocol required days 57, 85 and 225. The P.I. did not report to the sponsor the withdrawal of subject — who was consented and screened. The P.I. did not complete "Study Summary/Termination (Treatment Day 169 and Beyond)" case report forms for subjects 4734065 and 4734071 and "SWOG 9039" and "EQ-5D Health Questionnaire" case report forms for subject 4734003 for days 15 and 57 and for subject 4734031 for day 1.

The Drug Accountability Record showed that the investigational drug was administered to subject 4734074 on 5/16/00 whereas the investigational drug was administered on 5/17/00, according to the source data and case report form. For subject 473019, the subject's number appears as 4734009 on various case report forms.

Although minor protocol and recordkeeping deficiencies were noted, the data from subjects at this site can be used for evaluation of Protocol #149-98-04 submitted in support of NDA 21-320 for review by FDA.

**APPEARS THIS WAY
ON ORIGINAL**

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/s/

Joseph Salewski
10/7/03 03:57:05 PM

Food and Drug Administration
Rockville MD 20857

AUG 11 2003

Arthur S. Centeno, M.D.
Urology San Antonio Research
7090 Fredericksburg Road, Suite 115
San Antonio, Texas 78229

Dear Dr. Centeno:

Between July 7 and 15, 2003, Mr. Joel Martinez, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of a clinical investigation (Protocol #149-98-04 entitled: "A Multi-Center Study of Abarelix-Depot in Patients with Prostate Cancer in Whom GnRH Agonists are Contraindicated") of the investigational drug Plenaxis™ (abarelix), performed for Praecis Pharmaceuticals Incorporated. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of the study have been protected.

From our evaluation of the establishment inspection report and the documents submitted with that report, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects. We are aware that at the conclusion of the inspection, Mr. Martinez presented and discussed with you Form FDA 483, Inspectional Observations. We acknowledge the receipt of your July 21, 2003 letter to FDA's Dallas District Office. We wish to emphasize the following:

1. You did not follow the protocol [21 CFR 312.60].
 - a. You did not perform bone scans on subjects 4024018, 4024027 and 4024073 within the protocol required screening period/baseline (study days -14 to 1). For subject 4024072, the bone scan was done after the initial dose of study drug.
 - b. The case report form for subject 4024027 noted disease progression on day 169, but the subject was not discontinued from the study, as required by the protocol.

Please make appropriate corrections in your procedures to assure that the findings noted above are not repeated in any ongoing or future studies.

Page 2 – Arthur S. Centeno, M.D.

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

Sincerely yours,

A handwritten signature in black ink, appearing to be 'K. Maung U.', written over a horizontal line.

Khin Maung U, M.D.
Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

Page 3 – Arthur S. Centeno, M.D.

FEI: 3004029903

Field Classification: VAI

Headquarters Classification: VAI

Deficiencies noted:

 X failure to adhere to protocol (05)

cc:

HFA-224

HFD-580 Doc.Rm. NDA 21-320

HFD-580 Division Director Shames

HFD-580 MO Scott

HFD-580 PM Crisostomo

HFD-46c/r/s/ GCP File #10963

HFD-46 Blay

HFR-SW150 DIB Thornburg

HFR-SW1540 BIMO Monitor and Investigator Martinez

GCF-1 Seth Ray

r/d:GRH:8/7/03

reviewed: KMU:8/8/03

f/t:ml:8/11/03

O:\GRH\CENTENO VAL.DOC

Reviewer's Note to Review Division Medical Officer

Nine subjects were enrolled in this open-label, single-arm study. The records of all 9 subjects were reviewed in detail. Informed consents were on file for all subjects. There were no significant discrepancies between case report forms and source documents.

Several protocol violations were observed:

1. Bone scans for subjects 4024018, 4024027 and 4024073 were not done within the protocol required screening period/baseline (study days -14 to 1). For subject 4024072, the bone scan was done after the initial dose of study drug.
2. The case report form for subject 4024027 noted disease progression on day 169, but the subject was not discontinued from the study, as required by the protocol.
P.I.'s response: The P.I. and another urologist concluded that the bone scan on 2/14/99, which showed bone involvement, represented sphenoid sinusitis and, with a decreasing PSA level, the P.I. elected to continue the subject in the protocol. No mention of the bone involvement was seen on a subsequent bone scan from 2/22/00.

Although minor protocol violations were noted, the data from subjects at this site can be used for evaluation of Protocol #149-98-04 submitted in support of NDA 21-320 for review by FDA.

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/s/

Joseph Salewski
8/19/03 08:55:10 AM



Food and Drug Administration
Rockville MD 20857

William Friedel, M.D.
8851 Center Drive, Suite 501B
La Mesa, California 91942

JUL 21 2003

Dear Dr. Friedel:

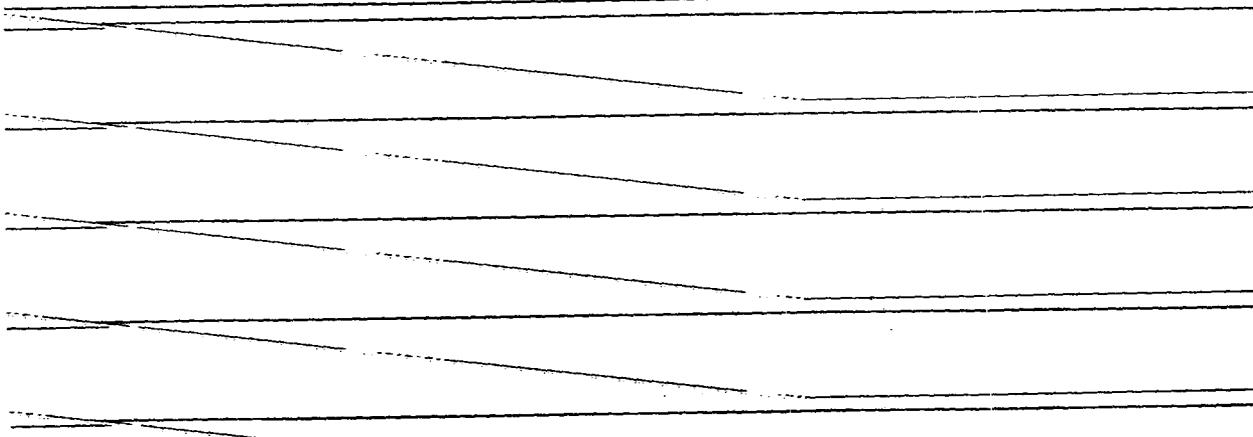
Between June 23 and 25, 2003, Mr. Allen Hall, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of a clinical investigation (Protocol #149-98-01 entitled: "A Multi-Center Study of Abarelix-Depot in Patients with Prostate Cancer in Whom GnRH Agonists are Contraindicated) of the investigational drug Plenaxis™ (abarelix for injectable suspension), performed for Praecis Pharmaceuticals, Inc. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of the study have been protected.

From our evaluation of the establishment inspection report and the documents submitted with that report, we conclude that you adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects.

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

Sincerely yours,

Khin Maung U, M.D.
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855



Page 2 – William Friedel, M.D.

FEI: 3003289554

Field Classification: NAI

Headquarters Classification:

- 1)NAI
- 2)VAI- no response required
- 3)VAI- response requested
- 4)OAI

cc:

HFA-224

HFD-580 Doc.Rm. NDA #21-320

HFD-580/Division Director/Shames

HFD-580/MO/Monroe

HFD-580/PM/Crisostomos

HFD-46/c/r/s/ GCP File #010356

HFD-46 Blay

HFR-PA252/DIB/Tucker

HFR-PA2565/BIMO Monitor/Koller

HFR-PA2535/Field Investigator/Hall

GCF-1 Seth Ray

r/d:rab/6.19.03

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Reviewer's Note to Review Division's Medical Officer

Records for all seven subjects at this site were reviewed in detail for inclusion criteria, adverse events, consent forms, IRB approval and dosing/sampling times. No significant discrepancies were observed. The data appear acceptable in support of the relevant submission.

PRAECIS

21 November 2003

Daniel Shames, M.D.
Director
Division of Reproductive and Urologic Drug Products
Food and Drug Administration
5600 Fishers Lane (HFD-580) Room 17B30
Rockville, Maryland 20857-1706

Re: NDA 21-320: Amendment 091
Plenaxis™, abarelix for injectable suspension
Risk Management Plan
Second Acceptance of Phase 4 Commitments

Dear Dr. Shames:

Reference is made to PRAECIS PHARMACEUTICALS INCORPORATED's NDA No. 21-320 resubmitted in Amendment 042 on 25 February 2003. Reference is also made to a 20 November 2003 teleconference with members of DRUDP and ODS.

Pursuant to 21 CFR 314.85, with this submission PRAECIS accepts the following Phase 4 commitments:

1. Conduct studies of a random sample of all enrolled prescribers as part of your risk management evaluation program to survey physician knowledge and understanding of risks and benefits of Plenaxis™ and responsibilities under the prescribing program. Praecis Pharmaceuticals Incorporated and FDA will review study findings and agree to educational and/or other activities that may be needed to address observations.

Protocol Submission: by February, 2004
Study Start: by 3rd Quarter 2004
Final Report Submission: by 3rd Quarter 2008

Plenaxis™ PLUS Program, Amendment 090 of 21 November 2003, Item D, Risk Management Evaluation Program, Compliance #4, "Physician Knowledge Survey".

2. Conduct a study ancillary to the 2000 patient "Plenaxis™ Experience Study" (see commitment #5) as part of the risk management evaluation program to evaluate use of Plenaxis™ by physicians in the approved, indicated population. Provide an assessment of the frequency of signed Patient Information signature pages being placed in the patient's medical record, frequency of serum testosterone testing, and other physician responsibilities accepted as part of the Plenaxis™ Prescribing Program. Praecis

Pharmaceuticals Incorporated and FDA will review study findings and agree to educational and/or other activities that may be needed to address observations.

Protocol Submission: by January, 2004
Study Start: by 2nd Quarter 2004
Final Report Submission: by 3rd Quarter 2008

Plenaxis™ PLUS Program, Amendment 090 of 21 November 2003, Item D, Risk Management Evaluation Program, Compliance #5, "Physician Compliance Audits" (a part of Item D, Risk Management Evaluation Plan, Evaluation of the Risk #1; see also Attachment 6, protocol concept sheet for "Plenaxis™ Experience Study").

3. Conduct a study involving use of Plenaxis™ through a case claims survey performed by a managed care organization. The survey will provide an assessment of whether Plenaxis™ is being used in the indicated population (eg, review of formulary restrictions and patient information concerning age, sex, diagnosis). Praecis Pharmaceuticals Incorporated and FDA will review study findings and agree to educational and/or other activities that may be needed to address observations.

Protocol Submission: by February, 2004
Study Start: by 3rd Quarter 2004
Final Report Submission: by 3rd Quarter 2008

Plenaxis™ PLUS Program, Amendment 090 of 21 November 2003, Item D, Risk Management Evaluation Program, Compliance #7, "Managed Care Review of Plenaxis™ Case Claims".

4. Conduct a study as part of the risk management evaluation program to evaluate adherence to attested responsibilities of the prescribing program for hospital pharmacies. Praecis Pharmaceuticals Incorporated and FDA will review study findings and agree to educational and/or other activities that may be needed to address observations.

Protocol Submission: by February, 2004
Study Start: by 3rd Quarter 2004
Final Report Submission: by 3rd Quarter 2008

Plenaxis™ PLUS Program, Amendment 090 of 21 November 2003, Item D, Risk Management Evaluation Program, Compliance #6, "Pharmacy Compliance Audits".

5. Conduct a study of 2,000 patients to estimate the incidence of immediate-onset systemic allergic reactions (anaphylaxis, hypotension and/or syncope) in the indicated population receiving Plenaxis™ and to determine whether the hazard rate changes over time.

Protocol Submission: by January, 2004
Study Start: by 2nd Quarter 2004
Final Report Submission: by 3rd Quarter 2008

PlenaxisTM PLUS Program, Amendment 090 of 21 November 2003, Item D, Risk Management Evaluation Program, Evaluation of the Risk #1 (see also Attachment 6, protocol concept sheet for "Plenaxis Experience Study").

6. Conduct a clinical study to characterize PlenaxisTM-induced immediate-onset system allergic reactions by evaluating skin test reactivity to PlenaxisTM and determining anti-abarelix IgG and IgE antibody levels in patients experiencing immediate-onset systemic allergic reactions.

Protocol Submission: by January, 2004
Study Start: by 2nd Quarter 2004
Final Report Submission: by 3rd Quarter 2008

PlenaxisTM PLUS Program, Amendment 090 of 21 November 2003, Item D, Risk Management Evaluation Program, Evaluation of the Risk #2 (see also, Attachment 7, protocol concept sheet).

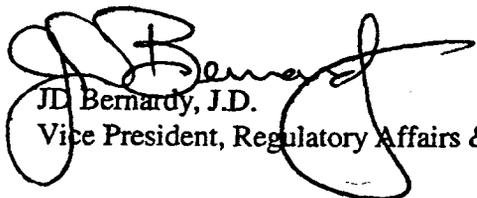
7. Conduct a clinical study to assess the effectiveness of pre-treatment with oral anti-histamine with and without oral steroids in patients who experience PlenaxisTM-induced urticaria and/or pruritis within 2 hours of drug administration and continue PlenaxisTM therapy.

Protocol Submission: by January, 2004
Study Start: by 2nd Quarter 2004
Final Report Submission: by 3rd Quarter 2008

PlenaxisTM PLUS Program, Amendment 090 of 21 November 2003, Item D, Risk Management Evaluation Program, Evaluation of the Risk #3 (see also Attachment 8, protocol concept sheet).

Please direct all communications regarding this submission to my attention. If you require any additional information, please do not hesitate to call me at (781) 795-4100, ext. 4282, or Dr. Marc Garnick, Chief Medical Officer, ext. 4350.

Sincerely,



JD Bernardy, J.D.
Vice President, Regulatory Affairs & Quality Assurance

PRAECIS

3 June 2003

Daniel Shames, M.D.
Director
Division of Reproductive and Urologic Drug Products
Food and Drug Administration
5600 Fishers Lane (HFD-580) Room 17B30
Rockville, Maryland 20857-1706

Re: NDA 21-320: Amendment 050
Plenaxis™, abarelix for injectable suspension
Response to Request for Carton Labeling Copy

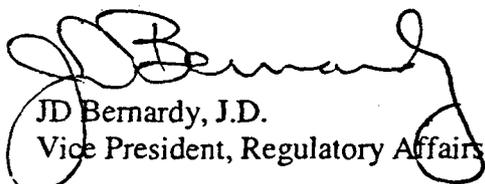
Dear Dr. Shames:

PRAECIS PHARMACEUTICALS INCORPORATED resubmitted NDA 21-320 on 25 February 2003 NDA 21-320. Reference is made to a phone conversation of 30 May 2003 from Ms. Eufrecina DeGuia at DRUDP requesting an electronic version of the proposed Plenaxis™ carton (interior and exterior).

An pdf file was forwarded to Ms. DeGuia on 30 May 2003. In response to a second phone message of 3 June 2003 from Ms. N. Chrisostomo, please find enclosed hard copy of the proposed Plenaxis™ carton (interior and exterior).

Please direct all communications regarding this submission to my attention. If you require any additional information, please do not hesitate to call me at (781) 795-4100, ext. 4282, or Dr. Marc Garnick, Chief Medical Officer, ext. 4350.

Sincerely,



JD Bernardy, J.D.
Vice President, Regulatory Affairs & Quality Assurance

Enclosures

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,
OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT
PRAECIS PHARMACEUTICALS INCORPORATED

DATE OF SUBMISSION
3 June 2003

TELEPHONE NO. (Include Area Code)
(781)-795-4100

FACSIMILE (FAX) Number (Include Area Code)
(781)-890-7015

APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code,
and U.S. License number if previously issued):

830 Winter Street
Waltham, MA 02451-1420

AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State,
ZIP Code, telephone & FAX number) IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 021-320 Amendment 050

ESTABLISHED NAME (e.g., Proper name, USP/USAN name)
abarelix for injectable suspension

PROPRIETARY NAME (trade name) IF ANY
Plenaxis™

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any)

CODE NAME (If any)
PPI-149

DOSAGE FORM: Injectable

STRENGTHS: 100 mg abarelix

ROUTE OF ADMINISTRATION: Intramuscular

(PROPOSED) INDICATION(S) FOR USE:

The of advanced symptomatic carcinoma of the prostate where immediate androgen suppression is appropriate

APPLICATION INFORMATION

APPLICATION TYPE

(check one) NEW DRUG APPLICATION (21 CFR 314.50) ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
 BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE

505 (b)(1) 505 (b)(2)

IF AN ANDA, or 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug Holder of Approved Application

TYPE OF SUBMISSION (check one)

ORIGINAL APPLICATION AMENDMENT TO A PENDING APPLICATION RESUBMISSION

PRESUBMISSION

ANNUAL REPORT

ESTABLISHMENT DESCRIPTION SUPPLEMENT

EFFICACY SUPPLEMENT

LABELING SUPPLEMENT

CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT

OTHER

IF A SUBMISSION OR PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY

CBE CBE-30 Prior Approval (PA)

REASON FOR SUBMISSION Response to request for Carton Labeling Copy

PROPOSED MARKETING STATUS (check one)

PRESCRIPTION PRODUCT (Rx)

OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED

1

THIS APPLICATION IS

PAPER

PAPER AND ELECTRONIC

ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g., Final dosage form, Stability/testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

SEE ATTACHED CONTINUATION SHEETS.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

IND 51.710 Prostate Cancer
IND _____

DMF
DMF
DMF
DMF

DMF _____ & DMF
DMF _____

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pages of trade

secret and/or

confidential

commercial

information



NDA 21-320

INFORMATION REQUEST LETTER

Praecis Pharmaceuticals, Inc.
Attention: J.D. Bernardy, J.D.
Vice President, Regulatory Affairs & Quality Assurance
830 Winter Street
Waltham, MA 02451-1420

Dear Mr. Bernardy:

Please refer to your December 11, 2000 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Plenaxis (abarelix suspension for injection).

We also refer to your February 25, 2003 submission that constituted a completed response to our Not Approvable letter of June 11, 2002. In addition, we also refer to your submission dated October 30, 2003 containing clarifications to your Risk Management Program as a response to our Information Request letter to you dated October 27, 2003. We request a prompt written response to the items below in order to continue our evaluation of your NDA.

In addition to the standard events requiring post-marketing 15-day "Alert reports" under 21 CFR 314.80(c)(1), we seek your agreement that your Risk Management Program will include your commitment to report the following events under 15-day alert reporting procedures to FDA:

1. All spontaneous reports of anaphylaxis, anaphylactic reaction, anaphylactoid (or reaction), anaphylactic shock, angioedema of throat, angioedema of tongue, laryngeal obstruction, laryngeal angioedema, upper respiratory tract obstruction, systemic allergic reaction, immediate hypersensitivity reaction, acute bronchospasm or wheezing.
2. All spontaneous reports of syncope, near-syncope, loss of consciousness, shock, or hypotension.
3. All spontaneous reports involving treatment with epinephrine, parenteral antihistamine, inhaled bronchodilator, parenteral corticosteroids, intubation, tracheostomy, or cricothyroidotomy.
4. All spontaneous reports of hospitalizations or emergency room visits for urticaria or angioedema.
5. All spontaneous reports of death, regardless of causality.

We also remind you that should we find your revisions to the Risk Management Program acceptable and we agree upon labeling documents and Plenaxis is approved under 21 CFR 314.500 Subpart H, all promotional materials must be submitted to our Division of Drug Marketing, Advertising and Communications (DDMAC) as outlined in 21 CFR 314.550.

If Praecis Pharmaceuticals, Incorporated anticipates a press statement on the day of the action letter, we recommend that you provide a draft of your press statement to DDMAC for FDA review and comments.

If you have any questions, please call Nenita Crisostomo, R.N., Regulatory Project Manager, at 301-827-4260.

Sincerely,

{See ~~appended~~  electronic signature page}

Margaret Kober, R.Ph.
Chief, Project Management Staff
Division of Reproductive and Urologic Drug
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Margaret Kober
11/7/03 04:28:10 PM
Chief, Project Management Staff

PRAECIS

7 November 2003

Daniel Shames, M.D.
Director
Division of Reproductive and Urologic Drug Products
Food and Drug Administration
5600 Fishers Lane (HFD-580) Room 17B30
Rockville, Maryland 20857-1706

Re: NDA 21-320: Amendment 080
Plenaxis™, abarelix for injectable suspension
Electronic Submission
Response to Risk Management Plan Discussions and Recommendations

Dear Dr. Shames:

Reference is made to PRAECIS PHARMACEUTICALS INCORPORATED's NDA No. 21-320 resubmitted in Amendment 042 on 25 February 2003. Reference is also made to Agency teleconferences on 18, 21 and 31 July, correspondence regarding PRAECIS' Risk Management Plan received from the Division on 10, 28 and 31 October 2003 and subsequent teleconference discussions with DRUDP and ODS on 14 and 24 October and 4 November 2003.

In the resubmission Amendment 042, PRAECIS submitted a communication-based Risk Management Plan. The original plan was significantly modified in submissions 066, 074 and 76 of 8 August, 20 and 30 October, respectively, to integrate a restricted distribution program and approval under Subpart H, at the Agency's request. In this submission, PRAECIS has further described and re-assembled all the elements of the current proposed Risk Management Plan as a complete and comprehensive revision embodying all earlier discussions and revisions.

The CD included with this submission contains an overview of the **PLUS** Program (Plenaxis™ User Safety) and the following attachments:

1. Physician Attestation
2. Hospital Pharmacy Agreement
3. Model Distributor Contract
4. Patient Information Form
5. SENTRX (Registry Administrator)
- 6.-8. Protocol Concepts

PRAECIS
PHARMACEUTICALS
INCORPORATED

830 Winter Street
Waltham, MA 02451-1420

Tel 781 795 4100
www.praecis.com

The requisite NDA 21-320 folder on the CD includes PDF files of the cover letter and FDA form 356h as well as the following:

Folder entitled "Risk Management Plan" contains PDF files:

Risk Management Plan Overview

Model Distributor Contract

SENTRX (Registry Administrator)

Protocol Concepts

Folder entitled "Labeling – Risk Management Plan", contains both WORD® and PDF files:

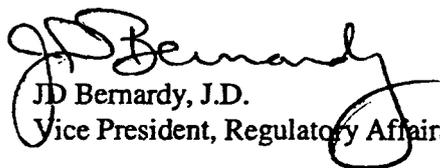
Physician Attestation

Hospital Pharmacy Agreement

Patient Information form

Please direct all communications regarding this submission to my attention. If you require any additional information, please do not hesitate to call me at (781) 795-4100, ext. 4282, or Dr. Marc Garnick, Chief Medical Officer, ext. 4350.

Sincerely,



JD Bernardy, J.D.
Vice President, Regulatory Affairs & Quality Assurance

Enclosure

33 pages redacted from this section of
the approval package consisted of draft labeling

NDA 21-320

Plenaxis (abarelix for injectable suspension)

Praecis Pharmaceuticals, Inc.

Risk Management Plan submitted with revisions on August 8, 2003.

APPEARS THIS WAY
ON ORIGINAL

PRAECIS

4 November 2003

Daniel Shames, M.D.
Director
Division of Reproductive and Urologic Drug Products
Food and Drug Administration
5600 Fishers Lane (HFD-580) Room 17B30
Rockville, Maryland 20857-1706

Re: NDA 21-320: Amendment 079
Plenaxis™, abarelix for injectable suspension
Response to Labeling Discussions of 4 November 2003

- Approval Under 21 CFR §314.520 (Subpart H)
- Immediate-onset Systemic Allergic Reaction Reporting
- Proposed Labeling: Black Box Warning and WARNINGS Sections

Dear Dr. Shames:

Reference is made to PRAECIS PHARMACEUTICALS INCORPORATED's NDA No. 21-320 resubmitted in Amendment 042 on 25 February 2003 and to discussions with FDA on 18, 21 and 31 July and 4 November 2003, respectively.

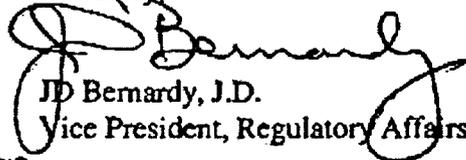
Pursuant to the above discussions, whereby . . . "FDA determines that a drug, effective for the treatment of a disease, can be used safely only if distribution or use is modified or restricted", PRAECIS requests FDA review of NDA 21-320 under 21 CFR 314.520 (Subpart H).

Pursuant to the 4 November 2003 discussion, PRAECIS agrees to report "Risk Management Plan SAEs", ie, anaphylaxis, hypotension and/or syncope along with SAEs reportable under 21 CFR §314.80. These events will be submitted using FDA MedWatch form 3500A or by calling 800-FDA-1088 and will adhere to the 15-day reporting requirements detailed in §314.80(c).

Finally, pursuant to labeling discussion on 4 November 2003, PRAECIS offers its understanding of the likelihood of experiencing an immediate-onset systemic allergic event and consequent labeling changes (Black Box Warning and WARNINGS) in Attachment 1. Supporting data is found in Attachment 2.

Please direct all communications regarding this submission to my attention. If you require any additional information, please do not hesitate to call me at (781) 795-4100, ext. 4282, or Dr. Marc Garnick, Chief Medical Officer, ext. 4350.

Sincerely,



JD Bernardy, J.D.
Vice President, Regulatory Affairs & Quality Assurance

PRAECIS

PHARMACEUTICALS

INCORPORATED

Enclosures

830 Winter Street
Waltham, MA 02451-1420

Tel 781 795 4100
www.praecis.com



NDA 21-320

INFORMATION REQUEST LETTER

Praecis Pharmaceuticals, Inc.
Attention: J.D. Bernardy, J.D.
Vice President, Regulatory Affairs & Quality Assur
830 Winter Street
Waltham, MA 02451-1420

Dear Mr. Bernardy:

Please refer to your December 11, 2000 New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Plenaxis (abarelix suspension for injection).

We also refer to your submissions dated February 25, September 12 and October 3, 2003.

We are reviewing the Clinical portion of the Physician Insert, boxed WARNING, INDICATIONS AND USAGE, CONTRAINDICATIONS, and WARNINGS sections, of your submission and have the following suggestions as attached. We request a prompt written response in order to continue our evaluation of your NDA.

Please note that as our Clinical and Clinical Pharmacology reviews are still ongoing, additional revisions to this labeling may be necessary.

If you have any questions, please call Nenita Crisostomo, R.N., Regulatory Project Manager, at 301-827-4260.

Sincerely,

{See appended electronic signature page}

Daniel Shames, M.D.
Director
Division of Reproductive and Urologic Drug
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Attachment

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the approval package consisted of draft labeling

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/s/

Daniel A. Shames
11/4/03 09:41:01 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-320
Praecis Pharmaceuticals, Inc.
Attention: J.D. Bernardy, J.D.
Vice President, Regulatory Affairs & Quality Assurance
830 Winter Street
Waltham, MA 02451-1420

Dear Mr. Bernardy:

Please refer to your New Drug Application (NDA) submitted in December 11, 2003 under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Plenaxis (abarelix suspension for injection).

We also refer to our Information Request letter to you dated October 28, 2003, containing comments and requests regarding your Risk Management Program.

We have reviewed the Physician Attestation section and we have included our recommendations as attached.

If you have any questions, please call Nenita Crisostomo, R.N., Regulatory Project Manager, at 301-827-4260.

Sincerely,


{See appended electronic signature page}

Donna Griebel, M.D.
Deputy Director
Division of Reproductive and Urologic Drug
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Attachment

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/s/

Donna Griebel
10/31/03 05:14:51 PM



NDA 21-320

INFORMATION REQUEST LETTER

Praecis Pharmaceuticals, Inc.
Attention: J.D. Bernardy, J.D.
Vice President, Regulatory Affairs & Quality Assurance
830 Winter Street
Waltham, MA 02451-1420

Dear Mr. Bernardy:

Please refer to your December 11, 2000 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Plenaxis (abarelix suspension for injection).

We also refer to your February 25, 2003 submission that constituted a complete response to our Not Approvable letter of June 11, 2002. Additionally, we also refer to your submission dated October 20, 2003 containing your response to our Information Request letter dated October 10, 2003, regarding your risk management plan (RMP) that incorporates your restricted distribution program.

The Division of Reproductive and Urologic Drug Products is reviewing your risk management submission and has enclosed our comments and requests for additional information. We request a prompt written response in order to continue our evaluation of your NDA.

1. Prescriber Program

- a. FDA will provide you with extensive edits on the Prescriber's attestation form. The Prescriber Agreement should be re-titled as suggested previously: Prescriber Attestation of Qualifications and Acceptance of Responsibilities. The Prescriber Attestation form will reflect qualifications, skills, and equipment needed to prescribe Plenaxis and responsibilities physicians will be accepting for prescribing Plenaxis. It will include a statement that the prescriber may deactivate prescribing by sending in written notification and that Praecis may deactivate prescribing if there is non-adherence to agreements. It will include the information regarding adverse drug reporting (ADR) as part of the condition of use in the bullet format. Contraindications for use of this product will be included in the prescriber agreement.

- b. The prescribing program needs additional elements to ensure only the indicated population is prescribed Plenaxis. Please propose additional steps you will take to ensure this.
- c. Specify which specialty is likely to check the "other" box on the prescriber attestation. Provide further details on a mechanism to ensure that unusual specialties (e.g., OB/GYN) will not use this product.
- d. Educational materials for prescribers and patients will need more detailed information about the patient observation period and the fact that an allergic event can occur after any dose, not just the first dose.
- e. Provide more details on the deactivation process and the criteria for deactivation for physicians (and also for pharmacists and distributors). Specify criteria to be used and ways to monitor the program to determine whether a physician or pharmacist should be deactivated. A statement indicating that failure to comply with the conditions of use will result in deactivation should be included in the prescriber attestation. Specify mechanisms for reinstatement in the program.
- f. Will there be any mechanism to check if the Medical License Number is valid and current?
- g. All materials used by the field force for educating prescribers on Plenaxis and the prescribing program must be reviewed by FDA prior to use.

2. Audits

- a. Provide time-lines for the various audits proposed.
- b. Provide additional details of the audits' target information. For instance, what kind of information is going to be captured in the audits to ensure that compliance with the conditions of use for the indicated population, by registered physicians or pharmacies or distributors, are being followed?
- c. What are the risk management goals of the proposed audits? Define your level of success for each audit action.

3. Buyer/Pharmacies

- a. Define _____ and "authorized buyer."
- b. Define "group manager."
- c. The pharmacist/buyer agreement is not clear in that it could be interpreted that the buyers and pharmacies may act as secondary distributors. Please clarify.
- d. Will there be any mechanism to check if the Pharmacy State License Number is valid and current?
- e. What risk management program education will be provided to target the dispensing pharmacists, not just the enrolled (chief/buyer) pharmacists?

4.

5. Adverse Drug Reporting

- a. See relevant comments under #1a.
- b. Prescriber educational efforts should emphasize reporting ADRs as soon as possible, to include providing as complete information as possible, such as type of event,

patient demographics, number of initial or subsequent doses at which the ADR took place, treatment provided, etc.

- c. Field force training must include their reinforcing the requirement to forward adverse drug event (ADE) data to Praecis through a specific mechanism. You might consider requiring the field force to record for each physician or pharmacy visit if they did or did not become aware of ADE data during the visit, and if the minimum data set was not obtained, forwarding reporter contact information for Praecis to use for followup.
- d. Include a list of clinically relevant adverse event terms and coding [e.g., MedDRA] terms associated with anaphylactic reactions to be submitted as 15-day type reports.

6. Evaluation

- a. The evaluation plan is not adequate to ensure that only the indicated population, where benefits exceed risk, gets Plenaxis. . Propose one or more means of monitoring the program so that this is ensured. How will the sponsor detect if the product is being used outside the target population of patients? For example, how will the sponsor determine if women are receiving the drug?
- b. Indicate the frequency of the "periodic review" and if the sponsor was going to share the results of the review with the Agency. *The Agency would suggest that quarterly progress reports be submitted.*
- c. How does the sponsor propose to detect unusual or inappropriate use of drug without detailed denominator data?
- d. Tie these evaluation studies on use with deactivation criteria.

7. Survey

- a. Specify the goals of the survey. How is the survey going to capture the success of the RMP program? Define "acceptable levels of knowledge, attitude and practice?"
- b. How will the survey data reflect the experience of all users, not just urologists and oncologists?

8. Distributors

- a. How will the distributor notify Praecis of attempts by un-enrolled physicians and pharmacies to obtain product?
- b. Other than sending enrollment materials, how will Praecis address attempts (both successful and unsuccessful) by un-enrolled physicians and pharmacies to obtain product?

9. Other

Include the approved indication (to be determined) in order forms and reordering procedures (on website or through telephone prompting).

If you have any questions, please call Nenita Crisostomo, Regulatory Project Manager,
at 301-827-4260.

Sincerely,


{see appended electronic signature}

Daniel Shames, M.D.

Director

Division of Reproductive and Urologic Drug
Products (HFD-580)

Office of Drug Evaluation III

Center for Drug Evaluation and Research



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-320

Praecis Pharmaceuticals, Inc.
Attention: J.D. Bernardy, J.D.
Vice President, Regulatory Affairs & Quality Assurance
830 Winter Street
Waltham, MA 02451-1420

Dear Mr. Bernardy:

Please refer to your new drug application (NDA) dated December 11, 2000 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Plenaxis (abarelix for injectable suspension).

We also refer to your February 25, 2003 submission that constituted a completed response to our Not Approvable letter of June 11, 2002. Additionally, we also refer to your submission dated June 3, 2003 containing the copy of the carton labeling.

We are reviewing the Chemistry, manufacturing and controls section of your submission and have the following recommendations. We request a prompt written response in order to continue our evaluation of your NDA.

DESCRIPTION section:

The last paragraph of description section should be read as follows:

“ The single-dose vial contains 113 mg abarelix-CMC. Each vial contains XX mg of anhydrous free base abarelix peptide and 19.1 to 31 mg of CMC. After the vial is reconstituted with 2.2 mL of 0.9% sodium chloride injection, 2 mL is administered to deliver a dose of 100 mg abarelix-CMC.”

HOW SUPPLIED section:

Storage statement should be changed from _____ to “Store at 25°C (77°F), excursions permitted to 15-30°C (59-86 °F) [see USP Controlled Room Temperature]”

CONTAINER LABEL:

1. The strength is currently presented on the labels and labeling as "Provides a 100 mg dose". The statement should be changed as follows:
Plenaxis
(abarelix for injectable suspension)
100 mg abarelix-CMC*
*(Actual content 113 mg to deliver 100 mg abarelix-CMC)
2. Relocate the expression of strength so that it appears immediately following the established and proprietary name as shown above.
3. If space permits, include directions for reconstitution and resultant concentration (mg/mL). For example, once reconstituted with 2.2 mL of Sodium Chloride injection, the resultant solution contains xx mg/mL.

CARTON LABELING:

1. Relocate the "Contents:....." statement from the side panel to the front panel.
2. Relocate the "Dosage and Administration" statement to the side panel.
3. Number each step and the corresponding pictorial under the Reconstitution and Administration of Plenaxis section.
4. Include the resulting concentration (mg/mL) once reconstituted with 2.2 mL of Sodium Chloride Injection
5. The statement _____
_____ " is ambiguous and confusing. Revise the statement to read "... withdraw 2 mL by positioning the needle at a 45 degree angle as shown in the pictorial." Additionally, numbering the steps along with the pictorials will assist health care practitioners in properly reconstituting the drug.
6. The color of the print for the statement "observe the patient after injection for any sign of an allergic-type response" should appear in red rather than black to alert the healthcare professional of its importance.
7. A statement "keep out of reach of children" should be included in the exterior carton labeling.

INSERT LABELING:

1. Revise the statement _____
_____ " to read "Plenaxis Must be Administered Under the Supervision of a Physician". The current presentation is misleading because it presents the proprietary name as "Plenaxis 100 mg" rather than "Plenaxis". This revision should be applied to the two subsequent sentences as well.
2. Please include a recommended dose statement. For example, the statement _____
_____ should be revised to read, " The recommended dose of Plenaxis is 100 mg on day 1, day 15, day 29 (week 4), and every 4 weeks thereafter".

NDA 21320
Page 3

If you have any questions, please call Nenita Crisostomo, R.N., Regulatory Project Manager,
at 301-827-4260.

Sincerely,

{see electronic ended signature}

Daniel Shames, M.D.
Director
Division of Reproductive and Urologic Drug
Products (HFD-580)
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Daniel A. Shames
10/17/03 05:21:24 PM



NDA 21-320

INFORMATION REQUEST LETTER

Praecis Pharmaceuticals, Inc.
Attention: J.D. Bernardy, J.D.
Vice President, Regulatory Affairs & Quality Assurance
830 Winter Street
Waltham, MA 02451-1420

Dear Mr. Bernardy:

Please refer to your new drug application (NDA) dated December 11, 2000 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Plenaxis (abarelix for injectable suspension).

We also refer to your February 25, 2003 submission that constituted a complete response to our Not Approvable letter of June 11, 2002. Additionally, we also refer to your submission dated August 8, 2003 containing your risk management plan that incorporates your restricted distribution program.

The Division of Reproductive and Urologic Drug Products is reviewing your risk management submission and has enclosed our comments and requests for additional information. We have scheduled a teleconference call with you on Tuesday October 14, 2003 at 8:10am Eastern Time to discuss the contents of this letter.

General Questions to Sponsor:

1. How will your proposed system of a central electronic Prescriber's Registry work with all the distributed sites? Why are you proposing distribution to pharmacies, distributors, and central pharmaceutical depositories? Provide a list of pharmacies, chains, distributors, etc., that you are proposing to utilize. Are there privacy issues or will all physicians agree to identification in the registry?
2. The Agency is concerned that your proposal is not feasible. Provide us with details of how all the distribution sites will ensure restrictions are adhered to. For example, list the electronic specifications you are using, whether sites agree to be audited by you and FDA, provide operating procedures they will be told to use, provide agreement or contract language that will be used to establish that these entities will follow restrictions in distribution, what consequences are there if restrictions or operating procedures are not followed, etc.
3. Your plan states you will limit distribution to urologists, oncologists, and internists: how do you plan to do this and verify enrollment?

4. What evaluation program are you planning to develop to monitor achievement of objectives? What is your definition of a successful risk management program for Plenaxis? How and what will you be auditing to ensure compliance with the risk management plan? What studies are needed to help refine safe use?
5. How large is the indicated population?
6. How do you plan to monitor appropriate use in the patient population?
7. Do you think a Medication Guide is needed? Do you think a written acknowledgement from the patient that they have received the risk/benefit information (Patient Attestation) is needed?
8. What is your plan if physicians use the drug outside of the indicated population? How will you learn this and what actions will you take?
9. How do you anticipate reimbursement for this drug in hospital versus the outpatient setting?

FDA believes the following are the goals of the risk management plan for Plenaxis:

1. Use of drug in indicated population where benefits exceed risk;
2. Use by physicians who are knowledgeable and skilled in managing advanced prostate cancer, complications of advanced prostate cancer, anaphylaxis and allergic reactions, as well as are equipped to manage these adverse events.

Risk management program objectives:

1. Develop a program that ensures only appropriately qualified physicians prescribe Plenaxis to indicated population
2. Develop education program for physicians, patients, and other health care providers to understand the risks and benefits of the drug
3. Develop a system to collect post-marketing adverse events along with numbers and characteristics of patients to whom the drug has been administered to monitor safety
4. Develop an evaluation program to monitor achievement of goals and objectives and to guide improvements in the risk management plan

Prescribing Program

Praecis will enroll in the prescribing program physicians who meet all the following qualifications:

- i. Ability to diagnose and manage the treatment of patients with advanced symptomatic prostate cancer.
- ii. Ability to diagnose and manage anaphylaxis and allergic reactions
- iii. Access to medication, equipment and facilities necessary to treat anaphylaxis and allergic reactions
- iv. Understand the risks and benefits of Plenaxis treatment for its approved indication, including the package insert, Medication Guide, Physician Attestation to Qualifications and Responsibilities

Physicians may attest to meeting these qualifications.

Praecis will enroll in the prescribing program those physicians who agree to each of the following:

- i. Educate patients about the risks and benefits of Plenaxis therapy and give the Medication Guide (or other patient-directed risk/benefit information such as a Patient Attestation).
- ii. Report serious adverse events to Praecis or to the FDA MedWatch Program.
- iii. Participate in a system that will identify for the distributor (or central pharmacy) the physicians who are enrolled in your prescribing program.

FDA Information Request

FDA will need the following prior to approval:

- 1) Outline of procedures for enrolling qualified physicians and submitting names into a central electronic file to be accessed by distributors to allow only enrolled physicians to have orders for Plenaxis filled, including procedures for audit of records from the distributors and central pharmacy by Praecis for compliance with the procedures.
- 2) Complete description of software, platform, security, and performance specifications of central electronic file.
- 3) Copy of actual or proposed agreement or contract with distributor or other entity that document adherence to restrictions of distribution and agreement to Praecis and FDA inspection.
- 4) Revisions of the Prescriber's Agreement to Physician Attestation of Qualifications and Acceptance of Responsibilities. Specifically, add: physicians will agree to educate patients, report adverse events, and be part of the prescribing program. More revisions will follow based on the labeling changes to be made, and will include adding contraindications.

Educational Program

Praecis will implement a program to educate physicians and patients about the risks and benefits of Plenaxis.

FDA Information Request

FDA will need the following prior to approval:

1. Statement that Praecis will be complying with 314.550 for DDMAC to review all materials in advance.
2. Revisions to the labeling. FDA has substantial revisions to your proposed labeling and will request teleconferences to come to agreement on labeling. Labeling includes the package insert, the Medication Guide, the Physician Attestation of Qualifications and

Acceptance of Responsibilities forms. Further discussion will be required to ensure that patients will be given appropriate risk/benefit information, including whether a Patient Attestation is necessary.

Adverse Event Reporting

FDA Information Request

FDA will need the following prior to approval:

1. Agreement to report specific adverse events within 15 day events, despite being labeled, such as anaphylaxis, immediate systemic allergic reactions, hypotension, syncope, failure of testosterone suppression.
2. Study proposals to conduct surveillance studies to estimate frequency of anaphylaxis and immediate systemic allergic reactions. Protocols must be approved prior to initiation.

Risk Management Evaluation

There is no program evaluation proposed in your August 8, 2003 submission. This is not acceptable.

FDA Information Request

FDA will need the following prior to approval:

1. Provide an outline of your process evaluation to ensure operating procedures are being followed such as:
 - A study or audit to evaluate whether physicians enrolled in the prescribing program are writing prescriptions and whether pharmacies and distributors are filling prescriptions by physicians not enrolled in the prescribing program
 - Plans to evaluate distributor's (e.g. central pharmacy's) compliance with prescribing program
 - Plan to ensure Medication Guides (or other patient-directed risk/benefit information such as a Patient Attestation) are distributed to patients
2. Provide proposals for studies to evaluate use of product in appropriate population and estimate frequency of adverse events. Propose other studies that may assist in further managing the risk of the drug, such as a study of pre-medication to lower risk of anaphylaxis. Describe how education program will be evaluated. Full protocols will be needed and agreed to prior to implementation.

If you have any questions, please call Nenita Crisostomo, R.N., Regulatory Project Manager,
at 301-827-4260.

Sincerely,

{See ~~appended~~ electronic signature page}

Donna Griebel, M.D.
Deputy Director
Division of Reproductive and Urologic Drug
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Donna Griebel
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NDA 21-320

INFORMATION REQUEST LETTER

Praecis Pharmaceuticals, Inc.
Attention: J.D. Bernardy, J.D.
Vice President, Regulatory Affairs & Quality Assurance
830 Winter Street
Waltham, MA 02451-1420

Dear Mr. Bernardy:

Please refer to your December 11, 2000 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Plenaxis (abarelix suspension for injection).

We also refer to your February 25, 2003 submission that constituted a completed response to our Not Approvable letter of June 11, 2002.

We are reviewing the Clinical section of your submission and have the following information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Please provide the following missing and/or new information before the close of business on October 3, 2003.

1. For Clinical Trial 149-01-05:
 - a. Listing 15.12.3 appears to be missing.
 - b. Adverse Event Listing 15.15 does not include the "toxicity values" (i.e., severity of the AE) for patients who subsequently received Lupron.
 - c. Provide the actual SAE report and additional narrative information for Pt. 6-1004 who experienced a ventricular arrhythmia and died.
 - d. Provide additional information about Pt. 3-1008 who experienced "severe (or serious) hypotension" on Day 85.
2. For the ABACUS1 Clinical Trial:
 - a. It does not appear that efficacy was assessed (reported or calculated) as it was in the pivotal U.S. clinical trials.
 - b. If we have not overlooked the following analysis, please provide them. If we have overlooked them, please refer us to their location in the Final Clinical Report.
 1. Provide for both treatment groups, the percentages of patients who achieved medical castration by Day 29 and who maintained medical castration through Day 85. If such analyses were not provided in the Study report, provide analyses using two

consecutive values > 50 ng/dL as a treatment failure if data were obtained every 14 days. Also provide calculations using any value > 50 ng/dL as a failure. For all calculations, do not consider a premature termination as a failure unless the termination was secondary to a drug related Adverse Event other than hot flashes.

2. Provide similar calculations for the treatment periods through (a) 6 doses of study drug (Day 169) and (b) 12 or 13 doses of study drug.

If you have any questions, please call Nenita Crisostomo, R.N., Regulatory Project Manager, at 301-827-4260.

Sincerely,

/s/
{See appended electronic signature page}

Margaret Kober, R.Ph.
Chief, Project Management
Division of Reproductive and Urologic Drug
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Margaret Kober
9/24/03 04:45:52 PM
Chief, Project Management Staff



NDA 21-320

INFORMATION REQUEST LETTER

Praecis Pharmaceuticals, Inc.
Attention: J.D. Bernardy, J.D.
Vice President, Regulatory Affairs & Quality Assurance
830 Winter Street
Waltham, MA 02451-1420

Dear Mr. Bernardy:

Please refer to your new drug application (NDA) dated December 11, 2000 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Plenaxis (abarelix for injectable suspension).

We also refer to your February 25, 2003 submission that constituted a completed response to our Not Approvable letter of June 11, 2002.

We are reviewing the Chemistry, manufacturing and controls (CMC) section of your submission and have the following information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Please revise the "Marketed Product Post-Approval Stability Commitment" to include the following commitments.
 - a. Praecis Pharmaceuticals Inc. commits to place the first three production batches of PLENAXISTM on stability per the approved commercial protocol, followed by a minimum of one batch per year. The generated data will be submitted to the agency periodically in the annual reports.
 - b. Praecis Pharmaceuticals Inc. commits to withdraw from the market any lot that falls out of specification during shelf life of the drug product. If the applicant has evidence that the deviation is a single occurrence that does not affect the safety and efficacy of the drug product, Praecis Pharmaceuticals Inc. will immediately discuss it with the agency.
 - c. Where future changes to the CMC for the PLENAXISTM drug product requires support of stability evaluation, representative batches will be placed on stability per the approved protocol.
 - d. The expiration dating period for the product may be extended in an annual report if the first three production batches tested by the approved protocol meets established specifications.

2. It is unclear how the — study is performed on drug product batches # 1744311, 1744321 and 1744341. Provide detailed information on the — sources and procedures used. They should be consistent with the recommendations in the ICH Q1B guidance.
3. We recommend that the acceptance criterion for the drug product dissolution specification to be revised to Q % at 45 minutes.
4. Please submit three copies of method validation packages, including a list of samples and equipment that will be provided for the analysis of the methods.

If you have any questions, please call Nenita Crisostomo, R.N., Regulatory Project Manager, at 301-827-4260.

Sincerely,

{see ed electronic signature page}

Moo-Jhong Rhee, Ph.D.
Chemistry Team Leader for
Division of Reproductive and Urologic Drug
Products, HFD-580
Division of New Drug Chemistry II, Office of New
Drug Chemistry
Center for Drug Evaluation and Research

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/s/

Moo-Jhong Rhee
8/27/03 03:48:43 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-320

Praecis Pharmaceuticals, Inc.
Attention: J.D. Bernardy, J.D.
Vice President, Regulatory Affairs & Quality Assurance
830 Winter Street
Waltham, MA 02451-1420

Dear Mr. Bernardy:

Please refer to your December 11, 2000 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Plenaxis (abarelix for injectable suspension). We also refer to your February 25, 2003 submission of a complete response to our June 11, 2002, Not Approvable letter.

On July 16, 2003, we received your major amendment, dated July 14, 2003, to this application. The receipt date is within three months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is November 26, 2003.

If you have any questions, please call Nenita Crisostomo, R.N., Regulatory Project Manager, at 301-827-4260.

Sincerely,

{See appended electronic signature page}

Daniel Shames, M.D.
Director
Division of Reproductive and Urologic Drug
Products (HFD-580)
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Daniel A. Shames
8/8/03 04:54:26 PM

PRAECIS

8 August 2003

Daniel Shames, M.D.
Director
Division of Reproductive and Urologic Drug Products
Food and Drug Administration
5600 Fishers Lane (HFD-580) Room 17B30
Rockville, Maryland 20857-1706

Re: NDA 21-320: Amendment 066
Plenaxis™, abarelix for injectable suspension
Amended Risk Management Plan: Restricted Distribution

Dear Dr. Shames:

Reference is made to PRAECIS PHARMACEUTICALS INCORPORATED's NDA No. 21-320 resubmitted in Amendment 042 on 25 February 2003.

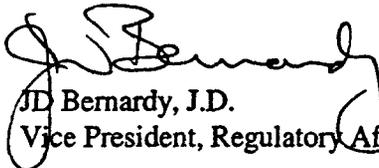
On 31 July 2003, PRAECIS submitted NDA Amendment 065 indicating intent to submit a revised risk management plan containing a restricted distribution program. PRAECIS also agreed that a 90-day extension of the review clock may be necessary in order for the Agency to review the new plan and additional clinical data submitted in Amendment 060 of 14 July 2003.

On 8 August 2003, FDA notified PRAECIS of intent to reset the review clock as a result of the 14 July 2003 submission. The new action date is 26 November 2003.

This submission contains PRAECIS' revised Risk Management Plan (Attachment A) including a proposal for restricted distribution of Plenaxis™.

Please direct all communications regarding this submission to my attention. If you require any additional information, please do not hesitate to call me at (781) 795-4100, ext. 4282, or Dr. Marc Garnick, Chief Medical Officer, ext. 4350.

Sincerely,



JD Bernardy, J.D.
Vice President, Regulatory Affairs & Quality Assurance

Enclosures

PRAECIS
PHARMACEUTICALS
INCORPORATED

830 Winter Street
Waltham, MA 02451-1420

Tel 781 795 4100
www.praecis.com

3 pages redacted from this section of
the approval package consisted of draft labeling

NDA 21-320

INFORMATION REQUEST LETTER

Praecis Pharmaceuticals, Inc.
Attention: J.D. Bernardy, J.D.
Vice President, Regulatory Affairs & Quality Assurance
830 Winter Street
Waltham, MA 02451-1420

Dear Mr. Bernardy:

Please refer to your December 11, 2000 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Plenaxis® (abarelix for injectable suspension).

We also refer to your February 25, 2003 submission that constituted a completed response to our Not Approvable letter of June 11, 2002.

We are reviewing the Chemistry, manufacturing and controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. The stability profile of the drug product is based on the data provided to the NDA. Therefore, we recommend that the acceptance criterion for the drug product specification be revised to NMT — %.
2. The dose delivery level acceptance criterion should be consistent with the — (assay) acceptance criterion and therefore, should be revised from the proposed — %.
3. For a controlled release product, it is recommended that the drug product dissolution specification include a minimum of three time points. These time points should cover the early, middle and late stages of the dissolution profile. In addition, acceptance criteria should be proposed for each of the time points.
4. The — manufactured drug product batches do not meet the — acceptance criteria at release. In addition, the — results for these batches differ from those batches manufactured by —. The — data for — manufactured batches were out of specification at —. Provide an

explanation for these observations and the impact on drug product quality as it relates to safety and efficacy.

If you have any questions, please call Nenita Crisostomo, R.N., Regulatory Project Manager, at 301-827-4260.

Sincerely,


{See appended electronic signature page}

David T. Lin, Ph.D.
Chemistry Team Leader for
Division of Reproductive and Urologic Drug
Products (HFD-580)
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

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/s/

Moo-Jhong Rhee
7/14/03 05:29:53 PM



NDA 21-320

INFORMATION REQUEST LETTER

Praecis Pharmaceuticals, Inc.
Attention: J.D. Bernardy, J.D.
Vice President, Regulatory Affairs & Quality Assurance
830 Winter Street
Waltham, MA 02451-1420

Dear Mr. Bernardy:

Please refer to your February 27, 2003 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for PLENAXIS[®], abarelix for injectable suspension.

In order to facilitate the review of your submission, we are requesting the following clinical information. Please provide the requested information no later than the close of business on July 17, 2003. Provide the requested information both to the document room and directly to the medical reviewer (Dr. Monroe) as a desk copy.

1. The following requests apply to patients enrolled in Clinical Trial 149-99-04 (open-label, rollover study). For each patient treated in Trial 149-99-04, provide all information in an integrated fashion that includes data obtained from both the patient's initial clinical trial with abarelix and the roll-over study. Provide electronic data sets in SAS transport (.xpt). Arrange data sets/listings in the following order: (1) initial clinical trial; (2) dose group if more than 1 dose was used; and (3) patient ID number. For each data set, provide a clear and easy to understand listing/explanation for all conventions used in both a paper and electronic format (PDF). The explanations must be clear to the reader without the need to understand SAS.
 - A. Demographic Information. For each patient in Trial 149-99-04, provide the following information in SAS transport format. Arrange the data sets so that there is 1 line per patient.
 1. Protocol number of initial clinical trial
 2. Dose of abarelix
 3. Patient ID number
 4. Age at entry into initial study
 5. Race
 6. Reason for initial treatment
 7. Stage of prostate cancer
 8. Calendar date for first dose of abarelix in initial study
 9. Duration of treatment (in days) in initial study
 10. Calendar date for first dose of abarelix in rollover study

11. Duration of treatment (in days) in rollover study
 12. Total duration of treatment (in days) for both studies
 13. Date of last dose of abarelix
 14. Primary reason for termination
 15. If reason is "other", specify what other is.
- B. Adverse Event Information. For each patient in Trial 149-99-04, provide the following AE information in SAS transport format. Arrange the data sets so that there is one line for each reported AE. Within each patient, arrange the AEs in order of onset date.
1. Protocol number of initial clinical trial
 2. Dose of abarelix
 3. Patient ID number
 4. Total duration of treatment in days (both initial and rollover study combined)
 5. Preferred term for AE
 6. Verbatim term for AE
 7. Onset date (calendar date)
 8. Onset day (actual study/treatment day) based on first day of dosing in initial study
 9. Onset day (actual study day) relative to Day 1 of the rollover study
 10. Date of cessation
 11. Duration of AE in days
 12. AE continuing (yes if continuing)
 13. Toxicity or severity level
 14. Relationship to treatment
 15. Action taken (e.g., none, hospitalized, discontinued)
 16. Outcome
 17. Classified as serious (Yes if serious)
- C. Liver Function Lab Tests. For each patient in Trial 149-99-04, provide the following liver function lab values in SAS transport format (AST/ALT/Alkaline phosphatase, and bilirubin). Arrange the data sets by initial study, dose level (if more than one dose level), and patient. Within each patient, arrange the lab values by date of collection. The general format of data listing 15.17.2.2 (Vol. 32, pg. 350) should be followed.
1. Protocol number of initial clinical trial
 2. Dose of abarelix
 3. Patient ID number
 4. Total duration of treatment in days (both initial and rollover study combined)
 5. Date of last day of treatment (28 days after final dose of abarelix)
 6. Date of sample (Calendar)
 7. Actual study day of sample (number of days from first dose of abarelix in the initial clinical trial)
 8. Lab value (separate columns for each of AST/ALT/Alkaline phosphatase, and bilirubin)
 9. For each lab value, in a separate column adjacent to the value, place an H (high) if value is above the ULN
 10. For each lab value, in a separate column adjacent to item 9 above, provide the ratio of the value to the ULN (i.e., Value/ULN)
 11. For each lab value, in a separate column, indicate if the value is clinically notable by your definitions

2. The following requests apply to patients enrolled in Clinical Trial 149-99-04 (open-label, rollover study). For each requested analysis listed below, base the analysis on the integrated data obtained from both the patient's initial clinical trial with abarelix and the roll-over study (i.e., the entire abarelix treatment period). The Table numbers cited below refer to the analyses provided in the Final Report for Study 149-99-04. Provide the new analyses in both paper format and PDF format.
 - A. Table 12.4 (Exposure to Study Drug)
 - B. Table 12.5.1 (All AEs)
 - C. Table 12.5.2 (All AEs Related to Treatment)
 - D. Table 12.5.3 (All Serious AEs)
 - E. Table 12.5.4 (Adverse Events by Severity)
 - F. Table 12.6.4 (Shifts to Values outside of the Normal Range for LFTs). Table to be based on the baseline/screening value prior to first dose of abarelix in INITIAL clinical trial.
 - G. Table 10-2 (In Text Table: Summary of Adverse Events)
 - H. Table 10-5 (In Text table: Severe or Life Threatening AEs)
 - I. Table 10-6 (In Text Table: Severe, Treatment Related AEs)
3. The following requests apply to ALL Patients in ALL ABARELIX CLINICAL TRIALS. To better assess the clinical risk associated with the prolongation of the QTc, please provide a listing of all patients who experienced an AE that may have been secondary to such a change. To obtain this listing, search the reported AEs for all patients treated with study drugs in ALL clinical trials conducted with abarelix. The search should be based on preferred AE terms using the following (or closely related) terms:
 - A. Torsade de Pointes, electrocardiogram QT corrected interval prolonged, electrocardiogram QT prolonged, QT prolongation, arrhythmia (not otherwise specified [NOS]), cardiac arrest, cardiac death, cardiac fibrillation NOS, cardio-respiratory arrest, convulsions NOS, death NOS, death sudden, death unexplained, loss of consciousness, sudden cardiac death, sudden death unexplained, syncope, ventricular arrhythmia, ventricular fibrillation, ventricular flutter, ventricular tachycardia, ventricular trigeminy, and hypotension
 - B. Any other terms that you believe may be associated with a prolongation of the QT interval.
 - C. Provide the listing in a format similar to that requested for Item 1B above modified appropriately. List each AE on a separate line. Provide the listing in both SAS transport (.xpt) format and paper format. The listing should include the following information for each AE.
 1. Study number
 2. Study Drug
 3. Patient ID number
 4. Preferred term for AE
 5. Verbatim term for AE
 6. Onset date (calendar date)
 7. Onset day (actual study/treatment day) based on first day of dosing
 8. Date of cessation
 9. Duration of AE in days
 10. AE continuing (mark Yes if continuing)
 11. Toxicity or severity level

12. Relationship to treatment
 13. Action taken (e.g., none, hospitalized, discontinued)
 14. Outcome
 15. Classified as serious (mark Yes if serious)
- D. Any information concerning patients listed above that would be helpful to the medical reviewer in assessing whether the AE may have been secondary to QT prolongation. References (volume and page number) to patient narratives previously provided, if relevant, would be helpful.
4. The following questions refer to the Final Report for Study 149-99-04.
- A. Are the analyses presented in the Shift Tables based on laboratory values at screening/baseline for the initial study or on values at entry to Study 149-99-04?
 - B. If a patient (1) had an AE in their initial study that resolved but recurred in Study 149-99-04 and/or (2) continued into Study 149-99-04, would it have been included in the AE Summary Tables for Study 149-99-04?

If you have any questions, please call Nenita Crisostomo R.N., Regulatory Project Manager, at 301-827-4260.

Sincerely,


{See appended electronic signature page}

Margaret Kober, R.Ph.
Chief, Project Management Staff
Division of Reproductive and Urologic Drug
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Margaret Kober
7/10/03 08:14:08 AM
Chief, Project Management Staff



NDA 21-320

Praecis Pharmaceuticals, Inc.
Attention: JD Bernardy, J.D.
Vice President, Regulatory Affairs & Quality Assurance
830 Winter Street
Waltham, MA 02451-1420

Dear Mr. Bernardy:

We received your June 5, 2003 correspondence on June 5, 2003 requesting a meeting to discuss status of the resubmission of the new drug application (Amendment 042) dated February 25, 2003. The guidance for industry titled *Formal Meetings with Sponsors and Applicants for PDUFA Products* (February 2000), describes three types of meetings:

- Type A: Meetings that are necessary before a company can proceed with a stalled drug development program.
- Type B: Meetings described under drug regulations [e.g., Pre-IND, End of Phase 1 (for Subpart E or Subpart H or similar products), End of Phase 2, Pre-NDA].
- Type C: Meetings that do not qualify for Type A or B.

The guidance can be found at <http://www.fda.gov/cder/guidance/2125fnl.htm>.

You requested a type C meeting. We have determined that this qualified as a Type B meeting. The meeting is scheduled for:

Date: June 10, 2003
Type: Telephone Conference
Time: 3:30—4:00 P.M.
CDER participants: Mark Hirsch, M.D., Medical Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP)
Scott Monroe, M.D., Clinical Reviewer, DRUDP
Krishan Raheja, D.V.M., Ph.D., Pharmacologist, DRUDP
Badrul Chowdhury, M.D., Medical Team Leader, Division of Pulmonary Drug Products, (DPDP)

NDA 21-320
Page 2

Charles Lee, M.D., Medical Officer, DPDP
Margaret Kober, R.Ph., Chief, Project Management Staff
Nenita Crisostomo, R.N., Project Manager

If you have any questions, please call Nenita Crisostomo, R.N., Regulatory Project Manager, at 301-827-4260.

Sincerely,

{See appended electronic signature page}

Margaret Kober, R.Ph.
Chief, Project Management Staff
Division of Reproductive and Urologic Drug
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Margaret Kober
6/9/03 04:51:44 PM
Chief, Project Management Staff



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-320

Praecis Pharmaceuticals, Inc.
Attention: JD Bernardy, J.D.
Vice President, Regulatory Affairs and Quality Assurance
830 Winter Street
Waltham, MA 02451-1420

Dear Mr. Bernardy:

We acknowledge receipt on February 27, 2003 of your February 25, 2003 resubmission to your new drug application for Plenaxis™ (abarelix for injectable suspension).

We consider this a complete, class 2 response to our June 11, 2002 action letter. Therefore, the user fee goal date is August 27, 2003.

If you have any question, please call Eufrecina DeGuia, Regulatory Health Project Manager, at (301) 827-4260.

Sincerely,


{See appended electronic signature page}

Margaret Kober, R.Ph.
Chief, Project Management Staff
Division of Division of Reproductive and
Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Margaret Kober
3/18/03 11:20:28 AM
Chief, Project Management Staff



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-320

Praecis Pharmaceuticals Incorporated
Attention: JD Bernardy, J.D.
Vice President, Regulatory Affairs & Quality Assurance
830 Winter Street
Waltham, MA 02451-1420

Dear Mr. Bernardy:

We received your October 25, 2001, correspondence on October 26, 2001, requesting a meeting to discuss your response to the September 10, 2001, End of Review Meeting. The guidance for industry titled *Formal Meetings with Sponsors and Applicants for PDUFA Products* (February 2000), describes three types of meetings:

- Type A: Meetings that are necessary before a company can proceed with a stalled drug development program.
- Type B: Meetings described under drug regulations [e.g., Pre-IND, End of Phase 1 (for Subpart E or Subpart H or similar products), End of Phase 2, Pre-NDA].
- Type C: Meetings that do not qualify for Type A or B.

The guidance can be found at <http://www.fda.gov/cder/guidance/2125fnl.htm>.

You did not indicate the type of meeting requested. However, based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type C. The meeting is scheduled for:

Date: November 30, 2001
Time: 10:00-11:00 AM
Location: Teleconference
CDER participants: Drs. Daniel Shames, Mark Hirsch, Scott Monroe, Badrul Chowdhury, and Charles Lee, and Ms. Jeanine Best.

NDA 21-320

Page 2

If you have any questions, call Jeanine Best, M.S.N., R.N., Senior Regulatory Associate, at (301) 827-4260.

Sincerely,

{See ~~appendix~~ electronic signature page}

Terri Rumble, B.S.N.
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Terri F. Rumble
10/31/01 03:56:02 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-320

Praecis
Attention: JD Bernardy, J.D.
830 Winter Street
Waltham, MA 02451-1420

Dear Mr. Bernardy:

We acknowledge receipt on August 3, 2001, of your August 2, 2001, correspondence requesting an End of Review meeting to discuss the not approvable letter you received for Plenaxis. FDA categorizes meetings into three types:

- Type A: A meeting that is necessary for an otherwise stalled drug development program to proceed.
- Type B: A meeting described under drug regulations (e.g., Pre-IND, End of Phase 1 (for Subpart E or Subpart H or similar products), End of Phase 2/Pre-Phase 3, Pre NDA).
- Type C: All meetings other than those that qualify for Type A or B.

Your correspondence indicated this to be a Type A meeting, and we concur. This meeting has been scheduled for:

Date: September 10, 2001
Time: 3:30 pm
Location: Parklawn Building, Conference Center, Room "Chesapeake"
CDER participants: Drs. Allen, Shames, Hirsch, Benson, Batra, Monroe, Jordan, Raheja, Rhee, De, Parekh, Chatterjee, Welch, Meaker, Raczdowski, Lee, Chowdhury, Langille, Mann, Ms. Best and Rumble

The background information for this meeting should be received by the Agency at least two weeks prior to the meeting. If we do not receive it by August 31, 2001, rescheduling of the meeting may be necessary.

If you have any questions, contact Jeanine Best, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

Terri Rumble, B.S.N.
Chief, Project Management Staff
Division of Reproductive and
Urologic Drug Products (HFD-580)
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Terri F. Rumble
8/13/01 04:01:57 PM

B231

Food and Drug Administration
Rockville MD 20857

JUN - 5 2001

Donald Gleason, M.D.
5300 East Erickson Dr., Suite 106
Tucson, Arizona 85712

Dear Dr. Gleason:

Between March 27 and April 2, 2001, Mr. Armando Chavez representing the Food and Drug Administration (FDA), met with you to review your conduct of a clinical study (Protocol #149-98-02) of the investigational drug, abarelix, performed for Praecis Pharmaceuticals. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that you adhered to all U.S. Federal regulations and/or good clinical investigational practices governing the conduct of clinical investigations and the protection of human subjects.

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

Sincerely yours,



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

cc:

HFA-224

HFD-580/Doc. Rm.: NDA 21-320

HFD-580/Best

HFD-580/Monroe

HFD-580/Hirsch

HFD-45/Reading File

HFD-46/Chron File

HFD-46/GCP file #10381

HFD-46/Molchan

HFR-PA2540/Chavez

HFR-PA2565/Conder

HFR-PA250/Kozick

Field Classification: Referred to Center

Headquarters Classification: NAI

1)NAI
 2)VAI no response required)
 3)VAI-R (30 day response requested)
 4)VAI-RR (adequate response received)
 5)OAI-WL

Deficiencies noted:

inadequate consent form
 inadequate drug accountability
 deviation from protocol
 inadequate records
 failure to report ADRs
 failure to obtain IRB approval
 failure to personally conduct or supervise study
 other

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r/d: drafted/sem/06.04.01

reviewed:jrm:

final type:jau:

Note to Review Division:

Our review of the information provided to us regarding the inspection of this clinical investigator concludes that the data at this site appears to be acceptable for use in support of the NDA submission. Twenty-two subjects were enrolled at this site; all completed the study. The inspector reviewed all records for the presence of signed informed consent forms and reviewed medical records and case report forms of 10 subjects. Our final classification of this inspection is NAI.

**APPEARS THIS WAY
ON ORIGINAL**



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-320

Praecis Pharmaceuticals Inc.
Attention: JD Bernardy, J.D.
830 Winter Street
Waltham, MA 02452-7015

Dear Mr. Bernardy:

We acknowledge receipt on May 9, 2001 of your May 8, 2001 correspondence to the following new drug application (NDA) notifying the Food and Drug Administration that the corporate address has been changed from:

to:

Praecis Pharmaceuticals Inc.
830 Winter Street
Waltham, MA 02452-7015

for the following new drug application:

NDA 21-320 for Plenaxis™ (abarelix for injectable suspension).

Our records have been revised to reflect this change.

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

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

Sincerely,
{See appended electronic signature page}

Terri Rumble
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Terri F. Rumble
5/10/01 05:39:28 PM.



Rest

MAY - 2 2001

Food and Drug Administration
Rockville MD 20857

Norman Zinner, M.D.
23441 Madison St., Suite 130
Torrance, California 90505

Dear Dr. Zinner:

Between April 5-11, 2001, Mr. Ronald Koller representing the Food and Drug Administration (FDA), met with you to review your conduct of a clinical study (Protocol #149-98-02, NDA 21-320) of the investigational drug, Abarelix performed for Praecis Pharmaceuticals. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that you adhered to all U.S. Federal regulations and/or good clinical investigational practices governing the conduct of clinical investigations and the protection of human subjects. At the conclusion of the inspection, Mr. Koller discussed his findings with you.

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

Sincerely yours,

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

cc:

HFA-224

HFD-580/Doc. Rm.: NDA 21-320

HFD-580/Best

HFD-580/Monroe

HFD-580/Hirsch

HFD-45/Reading File

HFD-46/Chron File

HFD-46/GCP file #10345

HFD-46/Molchan

HFR-PA250/Kozick

HFR-PA2565/Koller

Field Classification: Referred to Center

Headquarters Classification: NAI

- 1)NAI
- 2)VAI (no response required)
- 3)VAI-R (30 day response requested)
- 4)VAI-RR (adequate response received)
- 5)OAI-WL

Deficiencies noted:

- inadequate consent form
- inadequate drug accountability
- deviation from protocol
- inadequate records
- failure to report ADRs
- failure to obtain IRB approval
- failure to personally conduct or supervise study
- other

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r/d: drafted/sem/04.30.01

reviewed:jrm:5/1/01

final type:jau:5/2/01

Note to Review Division:

Note that data concerning the primary efficacy measure, testosterone levels during drug treatment, was not inspected at the clinical trial sites, as investigators were blinded to this information. Our review of the information provided to us regarding the inspection of this clinical investigator concludes that the data at this site appears to be acceptable for use in support of the NDA submission. Twenty-five subjects were enrolled at this site; there were 2 drop-outs. The inspector reviewed all records for the presence of signed informed consent forms and reviewed medical records and case report forms for 12 subjects. Our final classification of this inspection is No Action Indicated (NAI).

**APPEARS THIS WAY
ON ORIGINAL**



DEPARTMENT OF HEALTH & HUMAN SERVICES

MAY 22 2001

Food and Drug Administration
Rockville MD 20857

Winston E.I. Barzell, M.D.
Urology Treatment Center
1921 Waldemere St., Suite 310
Sarasota, Florida 34239

Dear Dr. Barzell:

Between April 18 and 19, 2001, Mr. Paul Figarole representing the Food and Drug Administration (FDA), met with you to review your conduct of a clinical study (Protocol #149-98-03, NDA 21-320) of the investigational drug, Abarelix performed for Praecis Pharmaceuticals. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected. At the conclusion of the inspection, Mr. Figarole discussed his findings with you.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that you adhered to all U.S. Federal regulations and/or good clinical investigational practices governing the conduct of clinical investigations and the protection of human subjects. We appreciate the cooperation shown Mr. Figarole during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

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

cc:

HFA-224
HFD-580/Doc. Rm.: NDA 21-320
HFD-580/Best
HFD-580/Monroe
HFD-580/Hirsch
HFD-45/Reading File
HFD-46/Chron File
HFD-46/GCP file #10357
HFD-46/Molchan
HFR-SE250/Gallant
HFR-SE2585/Torres
HFR-SE2585/Figarole

Field Classification: Referred to Center
Headquarters Classification: NAI

1)NAI
 2)VAI (no response required)
 3)VAI-R (30 day response requested)
 4)VAI-RR (adequate response received)
 5)OAI-WL

Deficiencies noted:

inadequate consent form
 inadequate drug accountability
 deviation from protocol
 inadequate records
 failure to report ADRs
 failure to obtain IRB approval
 failure to personally conduct or supervise study
 other

C:/molchan/barzell.sem
r/d: drafted/sem/05.10.01
reviewed:jrm:5/21/01
final type:jau:5/22/01

Note to Review Division:

Note that data concerning the primary efficacy measure, testosterone levels during drug treatment, was not inspected at the clinical trial sites, as investigators were blinded to this information. Our review of the information provided to us regarding the inspection of this clinical investigator concludes that the data at this site appears to be acceptable for use in support of the NDA submission. Twenty-six subjects were enrolled at this site; there were 2 drop-outs. The inspector reviewed all records for the presence of signed informed consent forms and reviewed medical records and case report forms for 6 subjects. Our final classification of this inspection is No Action Indicated (NAI).

APPEARS THIS WAY
ON ORIGINAL



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

MAY 22 2001

William E. Friedel, M.D.
8851 Center Drive, Suite 501-B
La Mesa, California 91942

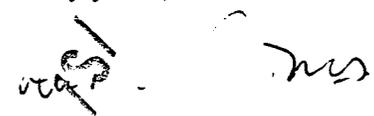
Dear Dr. Friedel:

Between March 26 and April 3, 2001, Mr. Thomas Beilke representing the Food and Drug Administration (FDA), met with you to review your conduct of a clinical study (Protocol #149-98-03, NDA 21-320) of the investigational drug, Abarelix performed for Praecis Pharmaceuticals. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected. At the conclusion of the inspection, Mr. Beilke discussed his findings with you.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that you adhered to all U.S. Federal regulations and/or good clinical investigational practices governing the conduct of clinical investigations and the protection of human subjects.

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

Sincerely yours,



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

cc:

HFA-224

HFD-580/Doc. Rm.: NDA 21-320

HFD-580/Best

HFD-580/Monroe

HFD-580/Hirsch

HFD-45/Reading File

HFD-46/Chron File

HFD-46/GCP file #10356

HFD-46/Molchan

HFR-PA250/Kozick

HFR-PA2565/Koller

HFR-2535/Beilke

Field Classification: Referred to Center

Headquarters Classification: NAI

- 1)NAI
- 2)VAI (no response required)
- 3)VAI-R (30 day response requested)
- 4)VAI-RR (adequate response received)
- 5)OAI-WL

Deficiencies noted:

- inadequate consent form
- inadequate drug accountability
- deviation from protocol
- inadequate records
- failure to report ADRs
- failure to obtain IRB approval
- failure to personally conduct or supervise study
- other

C:/molchan/friedel.sem

r/d: drafted/sem/05.10.01

reviewed:jrm:5/21/01

final type:jau:5/22/01

Note to Review Division:

Note that data concerning the primary efficacy measure, testosterone levels during drug treatment, was not inspected at the clinical trial sites, as investigators were blinded to this information. Our review of the information provided to us regarding the inspection of this clinical investigator concludes that the data at this site appears to be acceptable for use in support of the NDA submission. Twenty-five subjects were enrolled at this site; there were 2 drop-outs. The inspector reviewed all records for the presence of signed informed consent forms and reviewed medical records and case report forms for 9 subjects. Our final classification of this inspection is No Action Indicated (NAI).

**APPEARS THIS WAY
ON ORIGINAL**



FEB 20 2001

J.D. Bernardy, J.D.
Vice President, Regulatory Affairs
Praecis Pharmaceuticals Inc.
One Hampshire Street
Cambridge, MA 02139

**RE: Praecis Pharmaceuticals Inc., New Drug Application 21-320
Small Business Waiver Request 2001.004**

Dear Mr. Bernardy:

This responds to your letter of September 21, 2000, requesting a waiver of the human drug application fee for new drug application (NDA) 21-320 under the small business waiver provision of section 736d(1)(E)¹ of the Federal Food, Drug, and Cosmetic Act (the Act)² (Waiver Request 2001.004). For the reasons described below, the Food and Drug Administration (FDA) grants the request from Praecis Pharmaceuticals Inc. (Praecis) for a small business waiver of the application fee.

According to your waiver request, Praecis currently employs fewer than 500 individuals and has no affiliates. You also state that the NDA for the product, abarelix for suspension, is the first human drug application Praecis will submit to the Agency for review.

Under the Act, a waiver of the application fee shall be granted to a small business for the first human drug application that a small business or its affiliate³ submits to the FDA for review. The small business waiver provision entitles a qualified small business to a waiver when the business meets two criteria: (1) a business must employ fewer than 500 persons, including employees of its affiliates, and, (2) the marketing application must be the first human drug application, within the meaning of the Act, that a company or its affiliate submits to FDA.

¹21 U.S.C. 379h(d)(1)(E).

²Sections 735 and 736 of the Act (21 U.S.C. 379g and 379h).

³"The term 'affiliate' means a business entity that has a relationship with a second business entity if, directly or indirectly - (A) one business entity controls, or has the power to control, the other business entity; or (B) a third party controls, or has the power to control, both of the business entities" (21 U.S.C. 379g(9)).

FDA's decision to grant a small business waiver to Praecis is based on the following findings. First, the Small Business Administration (SBA) determined and stated in its letter dated January 24, 2001, that Praecis has fewer than 500 employees, and has no affiliates. Second, according to FDA records, the marketing application for abarelix for [redacted] suspension, NDA 21-320, is the first human drug application, within the meaning of the Act, to be submitted to FDA by Praecis or its affiliates. Consequently, your request for a small business waiver of the application fee for abarelix for [redacted] suspension, NDA 21-320, is granted.

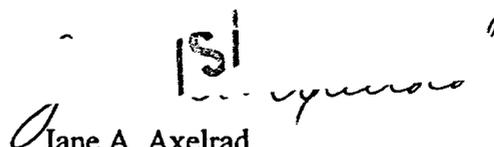
FDA records show that NDA 21-320 was submitted on December 12, 2000, and that FDA was notified of the payment of \$285,740 on December 8, 2000. If FDA refuses to file the application or Praecis withdraws the application before it is filed by FDA, a reevaluation of the waiver may be required should the company resubmit its marketing application. If this situation occurs, Praecis should contact this office approximately 90 days before it expects to resubmit its marketing application to determine whether Praecis continues to qualify for a waiver.

We have asked the FDA Office of Financial Management to refund the \$285,740 application fee paid by Praecis for NDA 21-320. If the refund is not received within 30 days of the date of this letter, please contact Donna Simms, Office of Financial Management, 301-827-5042.

FDA plans to disclose to the public information about its actions granting or denying waivers and reductions. This disclosure will be consistent with the laws and regulations governing the disclosure of confidential commercial or financial information.

If any billing questions arise concerning the marketing application or if you have any questions about this small business waiver, please contact Beverly Friedman or Michael Jones at 301-594-2041.

Sincerely,


Jane A. Axelrad
Associate Director for Policy
Center for Drug Evaluation and Research



NDA 21-320

Praecis Pharmaceuticals
Attention: JD Bernardy, J.D.
Vice President, Regulatory Affairs
One Hampshire Street
Cambridge, MA 02139

Dear Mr. Bernardy:

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

Name of Drug Product:	Plenaxis™	(abarelix for	suspension)
Review Priority Classification:	Priority (P)		
Date of Application:	December 11, 2000		
Date of Receipt:	December 12, 2000		
Our Reference Number:	NDA 21-320		

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on February 10, 2001 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be June 12, 2001.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 FR 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will make a determination whether to grant or deny a request for a waiver of pediatric studies during the review of the application. In no case, however, will the determination be made later than the date action is taken on the application. If a waiver is not granted, we will ask you to submit your pediatric drug development plans

within 120 days from the date of denial of the waiver.

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

Under 21 CFR 314.102(c) of the new drug regulations, you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the application's ultimate approvability. Alternatively, you may choose to receive such a report by telephone.

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

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call Eufrecina DeGuia, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

/s/

Terri Rumble
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

/s/

Terri F. Rumble
1/8/01 04:17:36 PM