Q5: Are tentative specifications for PPI-149, PPI-149-CMC, and PPI-149- acceptable for initiation of human studies?

A5: For a phase 1 study, it is acceptable. However, specific ID tests for PPI-149 and CMC, as well as dissolution tests should be developed during phase 2/3 studies.

Q6: Is it acceptable to submit this and future information as an IND amendment to IND 51,710?

A6: Yes

Unresolved Issues: None

Action Items:

Item:	Responsible Person:	Due Date:
♦ submission of 3-month pre-clinical and human safety data	Praecis Pharmaceuticals, Inc.	?
♦ schedule teleconference with PPI to discuss chemistry issues	Alvis Dunson	June 26, 1997
♦ send subpart H-21 CFR 314.500 - 560 to sponsor	Alvis Dunson	June 26, 1997

/S/ /S/

Signature, minutes preparer Concurrence, Chair

drafted: ADunson/6.19.97/i51710im
cc:
NDA Arch:
HFD-580
HFD-580/JMercier/Attendees
HFD-580/ADunson/6.19.97

Concurrences:
LPauls, KSrinivasachar, HJolson6.19.97/GBarnette, KRaheja6.20.97/KMeaker6.23.97/ JFourcroy, MRhee6.24.97

Concurrence Not Recieved:
PStinavage

DRAFT

MEETING MINUTES

Date: April 17, 1996 Time: 3:15 - 4:30 PM Location: C/R 14-56; Parklawn

NDA: none Drug Name: PPI-149

External Participant: Pharmaceutical Peptides, Inc. (PPI)

Type of Meeting: pre-IND

Meeting Chair: Lana Pauls, M.P.H. External Participant Lead: Marc Garnick, M.D.

Meeting Recorder: Lana Pauls, M.P.H.

FDA Attendees:

Lisa Rarick, M.D. - Acting Deputy Director II, Division of Metabolism and Endocrine Drug Products (DMEDP; HFD-510)
Jean Fourcroy, M.D., Ph.D. - Medical Officer, DMEDP (HFD-510)
Alexander Jordan, Ph.D. - Pharmacology Team Leader, DMEDP (HFD-510)
Jeri El-Hage, Ph.D. - Pharmacologist, DMEDP (HFD-510)
Moo-Jhong Rhee, Ph.D. - Chemist, DMEDP (HFD-510)
Lana L. Pauls, M.P.H. - Project Manager, DMEDP (HFD-510)
Angelica Dorantes, Ph.D. - Team Leader, Division of Pharmaceutical Evaluation II (DPE II; HFD-870)
K. Gary Barnette, Ph.D. - Pharmacokinetics Reviewer, DPE II (HFD-870)

External Constituents:

PPI
Marc Garnick, M.D. - Executive Vice President, Chief Medical Officer
Malcolm Gefter, Ph.D. - Chairman
Lauren Linton, Ph.D. - Program Manager
Christopher Molineaux, Ph.D. - Director, Pharmacology
Gary Musso, Ph.D. - Director, Chemistry

Outside Consultant

Meeting Objectives:

To discuss the preclinical safety and the registration strategy for a new LHRH antagonist for the treatment of prostate cancer

Discussion Points:

- PPI discussed the following points regarding their product and prostate cancer
  - 318,000 reported cases of prostate cancer in 1996 (3x that of 1990)
  - hormonal therapy is more frequently used at earlier stages (e.g., A, B, C, D1 and D2)
  - LHRH superagonists have significant disadvantages, including an initial stimulation of serum testosterone levels (flare)
  - LHRH antagonists have significant advantages, and are a more potent gonadotropin suppressant

- Preclinical Pharmacology
  - In rats, PPI-149
    - induces castrate levels of testosterone
    - blocks the superagonist flare response at a dose of 50 μg/kg/day
    - causes medical castration levels at a dose of 30 μg/kg/day
    - causes complete testosterone (T) suppression within 6 hours
    - is completely reversible

- Phase I Clinical Development
  - based on T suppression as well as flare suppression
  - is designed to treat previously untreated stage D1 or D2 patients
  - to determine safety and appropriate dose (dose escalation)

- Preclinical Safety
  - completed/ongoing GLP studies include
    - 30 day rat @ 1000μg/kg/day with no overt toxicity
    - 30 day non-human Primate (NHP) @ at 30, 100, and 300 μg/kg/day
  - planned GLP toxicology study - 4 week + recovery in rat, NHP @ 10, 100, and 1000μg/kg/day
  - planned bioavailability studies in rat
  - planned toxicology study - 3 month + recovery in rat, NHP @ dose TBD

- Chemistry/Manufacturing Controls
  - PPI-149 has ——
  - initial batch of drug substance has ——
  - accelerated stability studies suggest that a formulation at —— will provide stability

——

Decisions reached:

- If the duration of treatment is greater than 12 weeks, a carcinogenicity study will be required
- A comparison to the 3-month formulations of leuprolide and/or gosserelin should be made
- Toxicity studies should be performed using a high dose level which produces frank toxicity. If PPI-149 is non-toxic, the highest dose tested should be 50-100 times the highest therapeutic dose (e.g., doses of 100, 1000, 5000, and 1000μg/kg/day
- The number of animals/per sex/group should be increased

- rat - 10/sex/group (15/sex/group with recovery)
- NHP - 8 total (5 + 3 recovery)

- The proposed preclinical safety (with suggestions above) is sufficient
- Two clinical trials (per indication) are required for approval
- Sequence analysis data of PPI-149 should be submitted

DRAFT

Unresolved Issues: none

Action Items: none

/S/

Signature, minutes preparer

/S/

Concurrence, Chair

cc:
NDA Arch:
HFD-510
HFD-510/DJenkins/Attendees
HFD-870/KGBarnette/ADorantes
HFD-510/LPauls/04.09.96

Concurrences:
JFourcroy 04.18.96/GBarnette, ADorantes 04.23.96/LRarick, JEl-Hage, AJordan, MRhee 04.24.96

Please note final signed-off minutes were unable to be located. GRumble 12/24/96

NDA 21-320
Plenaxis (abarelix for injectable suspension)
Praecis Pharmaceuticals, Inc.

There was no Advisory Committee Meeting held during the 2nd review cycle.

/S/

11/25/03

NDA 21-320
Plenaxis™ (abarelix for injectable suspension)
Praecis Pharmaceuticals, Inc.

There was no Advisory Committee Meeting held for this application.

5/7/01

NDA 21-320
Plenaxis : (abarelix for injectable suspension)
Praecis Pharmaceuticals, Inc.

There was no Federal Register Notices for this application on this review cycle.

11/25/03

NDA 21-320
Plenaxis™ (abarelix for injectable suspension)
Praecis Pharmaceuticals, Inc.

There was no Federal register Notice for this application.

/S/

5/7/04

NDA 21-320
Plenaxis™ (abarelix for injectable suspension)
Praecis Pharmaceuticals, Inc.

There were no Labeling discussions for this review cycle.

NDA 21-320
Plenaxis (abarelix for injectable suspension)
Praecis Pharmaceuticals, Inc.

The Chemist reviewed Praecis' proposed labeling dated June 3, 2003 and relayed suggestions to modify the container labels via Information Request letter dated October 17, 2003.

APPEARS THIS WAY
ON ORIGINAL

NDA 21-320
Plenaxis™ (abarelix for injectable suspension)
Praecis Pharmaceuticals, Inc.

The review of Carton Labeling was deferred until the next review cycle.

/S/

5/15/01

NDA 21-320
Plenaxis™ (abarelix for injectable suspension)
Praecis Pharmaceuticals, Inc.

Sponsor Revised Carton Labels, April 13, 2001.

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

NDA 21-320
Plenaxis™ (abarelix for injectable suspension)
Praecis Pharmaceuticals, Inc.

Sponsor Original Carton Labels, December 11, 2000.

[S] - 10mg 5/15/01

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

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

DATE RECEIVED: 1/03/01	**DUE DATE:** 05/01/01	**OPDRA CONSULT #:** 00-0270

TO:
Susan Allen, MD.
Director, Division of Reproductive and Urologic Drug Products
HFD-580

THROUGH:
Eufrencia Deguia
Project Manager
HFD-580

PRODUCT NAME: Plenaxis (abarelix) **NDA 21-320**	**MANUFACTURER:** Praecis Pharmaceuticals, Inc.,

SAFETY EVALUATOR: David Diwa, Pharm.D.

OPDRA RECOMMENDATION:
OPDRA has no objections to the use of the proprietary name, Plenaxis.

☐ FOR NDA/ANDA WITH ACTION DATE BEYOND 90 DAYS OF THIS REVIEW
This name must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDA's from the signature date of this document. A re-review request of the name should be submitted via e-mail to "OPDRAREQUEST" with the NDA number, the proprietary name, and the goal date. OPDRA will respond back via e-mail with the final recommendation.

☐ FOR NDA/ANDA WITH ACTION DATE WITHIN 90 DAYS OF THIS REVIEW
OPDRA considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDA's from this date forward.

☐ FOR PRIORITY 6 MONTH REVIEWS
OPDRA will monitor this name until approximately 30 days before the approval of the NDA. The reviewing division need not submit a second consult for name review. OPDRA will notify the reviewing division of any changes in our recommendation of the name based upon the approvals of other proprietary names/NDA's from this date forward.

/S/

Jerry Phillips, RPh
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3242
Fax: (301) 480-8173

/S/

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

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

PROPRIETARY NAME REVIEW

DATE OF REVIEW: 12/12/00

NDA, 21-320

NAME OF DRUG: Plenaxis (abarelix)

IND, HOLDER: Praecis Pharmaceuticals Inc.,

I. INTRODUCTION:

The consult is written in response to a request from the Division of Reproductive and Urologic Drug Products, (HFD-580) first received on 9/20/00 as an IND to review the proposed proprietary name, The sponsor submitted an NDA for review on 12/12/00.

The sponsor initially submitted two proposed names, and for review. was submitted for the proposed indication of prostate cancer . The Division objected to names for abarelix. The sponsor subsequently resubmitted a new name Plenaxis for review.

PRODUCT INFORMATION

Plenaxis (abarelix) is a synthetic decapeptide gonadotropin-releasing hormone (GnRH) antagonist proposed for the treatment of local, regional or advance prostate cacinoma. The product will be available in sustained release formulation. The usual dose of Plenaxis for prostate cancer treatment will be 100 mg IM (abarelix injection monthly. Product administration is recommended initially on days 1, 15, and 29 of the first month and every 28 days thereafter under the supervision of a clinician. Plenaxis will be available in single use vials of 100 mg preservative free sterile dry powder. The product package will also contain a vial of 10ml 0.9% sodium chloride injection USP diluent, a 3cc syringe, an 18 gauge 1.5 inch injection needle and a 22 gauge 1.5 inch injection needle.

II. RISK ASSESSMENT:

The medication error staff of OPDRA conducted a search of several standard published drug product reference texts[1,2,3] as well as several FDA databases[4] for existing drug names which sound-alike or

[1] MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc, 2000).

look-alike to Plenaxis to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted[5]. An expert panel discussion was conducted to review all findings from the searches. In addition, OPDRA conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the proposed name.

A. EXPERT PANEL DISCUSSION

The expert panel consists of members of OPDRA's medication error safety evaluation team and a representative from the Division of Drug Marketing, Advertising and Communications (DDMAC).

1. The panel expressed concern with sound-alike/look-alike quality between Plenaxis and Plenax.

2. DDMAC

   DDMAC had no objection to the proposed name.

3. In addition, the panel discussed the following sound-alike/look-alike drug names to Plenaxis summarized below.

Product Name	Dosage form(s), Generic name	Usual Dose	Observation
Plenaxis	Injectable IM/SC, abarelix	100mg IM for Prostate Cancer 30-60 SC for Endometriosis pain management	
Prolixin	Injectable: 2.5mg/ml 10 vial, 25mg/m^2 5ml vials, Tablet 25mg.	Table: 4-16mg bid to qid. Injection: 5mg IM q 6 hrs	*SA
Plenax	Cefixime (Marketed in Mexico)		*SA/LA
Plendil	Tablets, 2.5, 5, 10 mg , felodipine	5mg daily	*SA/LA
Plavix	Tablets, 75mg, clopidogrel	75 mg daily	*LA
Pyrinex	Shampoo, 2% Pyrethrin, 2% piperonyl butoxide, 0.8% kerosine	Apply as directed	*SA/LA
Peroxin	Gel 5 & 10% Benxoyl peroxide	Apply as directed	*LA
Pernox	Scrub, shampoo, lotion Ployethylene 20%, 2% sulfur, 1.5-2% salicylic acid	Apply as directed	*SA
Peroxyl	OTC Gel & rinse, hydrogen peroxide 1.5%, alcohol 6%	Use as directed	*SA
Phenadex	OTC cough syrup dextromethophen 10mg, guaifenesin 200mg/5ml	5-10 ml q4-6 hrs prn	*SA/LA

*SA = Sound-alike *LA = Look-alike

The panel concluded that the above listed drugs will unlikely cause significant confusion with the proposed product name therefore, we do not object to the use of the proprietary name Plenaxis.

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[2] American Drug Index, 42nd Edition, online version, Facts and Comparisons, St. Louis, MO.
[3] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.
[4] The Established Evaluation System [EES], the Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, New Drug Approvals 98-00, and the electronic online version of the FDA Orange Book.
[5] WWW location http://www.uspto.gov/tmdb/index.html.

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three studies were conducted by OPDRA involving 88 health professionals comprised of pharmacists, physicians, and nurses within the FDA. The objective was to test the degree of confusion between Plenaxis and other drug names due to similarity in handwriting and verbal pronunciation. Inpatient and outpatient prescription orders were written, each consisting of (known/unknown) drug products including a prescription for Plenaxis (see below). These prescriptions were scanned into a computer and subsequently delivered to a random sample of participating healthcare professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

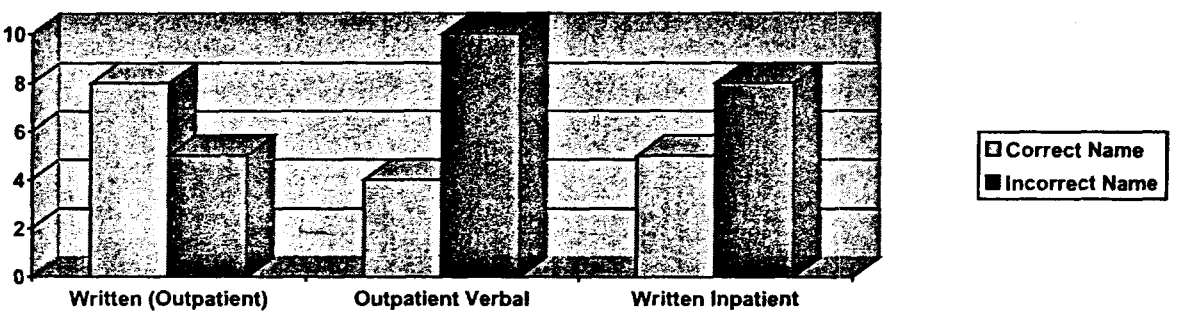
HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Outpatient RX: Plenaxis use 100mg IM monthly	Outpatient Verbal RX: Plenaxis use 100mg IM monthly
Inpatient RX: Pt to be transferred to m/s Plenaxis 100mg IM mon	

2. Results:

The results are summarized in Table I.

Table I

Study	# of Participants	# of Responses (%)	Correctly Interpreted	Incorrectly Interpreted
Written Inpatient	29	13 (45%)	8	5
Written Outpatient	29	14 (48%)	4	10
Verbal	29	13 (45%)	5	8
Total	87	40 (46%)	17(43%)	23 (57%)



Fifty-seven percent of all study participants responded incorrectly. The incorrect written and verbal scores are summarized below in Table II.

Table II

Incorrectly Interpreted	
Written Outpatient	Phanaxis
	Phenarais
	Phegixis
	Phelbixis
	Phenexis
Verbal Outpatient	Pinexus (2)
	Pinexis (2)
	Ponexis (3)
	Planix
	Planexus
	Planexy
Written Inpatient	Phenacis (3)
	Plenacio
	Phenacia (4)

C. SAFETY EVALUATOR RISK ASSESSMENT

The result of the written outpatient prescription study showed that 10 out of 14 respondents interpreted the proposed proprietary name Plenaxis incorrectly. In the written inpatient study, 5 out of 13 respondents interpreted Plenaxis incorrectly, and in the verbal study 8 out of 13 respondents interpreted Plenaxis incorrectly. Most of the incorrect responses were misspelled/phonetic variations of the proposed drug name. Result of the studies did not show an overlap of incorrect interpretation between Plenaxis and currently marketed drug products.

The expert panel identified names of nine proprietary drug products with sound-alike/look-alike qualtieis to Plenaxis. Eight of these products, Prolixin, Plendil, Plavix, Pyrinex, Peroxin, Pernox, Peroxyl and Phenadex are marketed in the US. One product, Plenax (cefixime) is a cephalosporin antibiotic marketed in Mexico therefore the potential for name confusion in the US is unlikely. Five products, Pyrinex, Peroxin, Pernox, Peroxyl and Phenadex are OTC products. Plendil and Plavix are available in tablet formulation. Plendil is indicated for the treatment of hypertension and congestive heart failure. Plavix is an antiplatelet agent. Prolixin is an antipsychotic available in both tablet and injectable formulations. Although the injectable form of Prolixin does have overlapping formulation and sound-alike qualities with Plenaxis, the two products have different indication, pharmacological class and dosing interval.

Plenaxis is proposed for use in the treatment of hormonally responsive prostate carcinoma. Missing a monthly dose of testosterone suppression therapy due to name confusion with any of the identified products will have significant impact on drug therapy outcome. However, the potential risk of such an occurrence appears unlikely.

D. STUDY SUBMITTED BY APPLICANT – **Confidential and proprietary and should be noted for FOI purposes**

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OBSERVATIONS

[redacted]

[redacted]

The sponsor recommends that this product should be administered under the supervision of a clinician. It is most likely that nurses will administer Plenaxis IM injections. The [redacted] failed to include this group of healthcare providers in their study.

IV. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In the review of the container labels, carton and insert labeling of Plenaxis, OPDRA has attempted to focus on safety issues relating to possible medication errors. OPDRA has reviewed the current container labels and carton and insert labeling and has identified several areas of possible improvement, which might minimize potential user error.

A. CONTAINER LABEL

100mg Sterile Powder; 10ml diluent; 3cc syringe with 18 gauge 1.5 inch and 22 gauge 1.5 inch injection needles.

The Principal Display Panel

We recommend the following:

a. The statement "abarelix for suspension" should appear at least half as prominent as the proprietary name in accordance with 21 CFR 201.10(g)

b. The words "abarelix for suspension" should be changed to read abarelix for injectable suspension in line with USP naming convention.

c. The display 100 mg in a black circle is detached thus rendering it to various interpretations. For clarity, we recommend that it should be replaced with 100mg sterile powder. in bold could replace the 100mg in black circle and provide more space for increased prominence of the established name and strength of the product.

d. The statement "A Synthetic Gonadotropin Releasing-Hormone (GnRH) Antagonist" should be removed.

Side Panel

e. On the side panel, the words each power filled vial contains 113mg abarelix carboxymethly cellulose as anhydrous free base peptide should be relocated to package insert and replaced with Each powder filled vial contains an equivalent of 100mg abarelix when reconstituted. The prominence of this statement should be increased. should be moved further left to make more room for the statement of identity and strength.

f. Under the statement "....the sterile powder for suspension is to be reconstituted in accordance with the following directions:" Box #8 of the reconstitution cartoon should specify that the drug be delivered intramuscularly.

B. CARTON LABELING

a. The words "abarelix for suspension" should be changed to read abarelix for injectable suspension. See comment above (b) above.

b. The "100 mg" display in a black circle placed prominently on the left should be replaced with 100 mg sterile powder and placed under the established name. The concentration of the reconstituted injectable suspension should follow the strength identity of the sterile powder.

APPEARS THIS WAY
ON ORIGINAL

III. RECOMMENDATIONS:

A. OPDRA has no objections to the use of the proprietary name, Plenaxis.

B. OPDRA recommends the above labeling revisions that might lead to safer use of this product.

OPDRA would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact David Diwa, Pharm.D. at 301-827-0892

/S/

David Diwa, Pharm.D.
Safety Evaluator
Office of Post-Marketing Drug Risk Assessment

Concur: /S/

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

/s/

David Diwa
/29/01 02:58:07 PM
HARMACIST

Jerry Phillips
1/29/01 03:48:57 PM
DIRECTOR

Martin Himmel
2/2/01 12:53:57 PM
MEDICAL OFFICER

NDA 21-320
Plenaxis — (abarelix for injectable suspension)
Praecis Pharmaceuticals, Inc.

Praecis' Post-Marketing Commitments are incorporated in the Risk Management Program, under the Evaluation of Risks section, page 4, of the November 7, 2003 submission.

C. Adverse Event Reporting

PRAECIS commits to implement a reporting and collection system for serious adverse events associated with the use of Plenaxis™ that complies with the reporting requirements for an approved NDA (21 CFR§314.80 and 314.81). The following spontaneous events will be reported by PRAECIS to FDA under 15-day alert reporting procedures, and a summary and discussion of the clinical significance of these events will be provided in periodic reports.

Anaphylaxis	Syncope	Hospitalizations or
Anaphylactic reaction	Near-syncope	Emergency room visits for:
Anaphylactoid (or reaction)	Loss of consciousness	Angioedema
Anaphylactic shock	Shock	Urticaria
Angioedema of throat	Hypotension	
Angioedema of tongue		Death, regardless of causality
Laryngeal obstruction	Treatment with:	
Laryngeal angioederma	Epinephrine	
Upper respiratory tract obstruction	Parenteral antihistamine	
Systemic allergic reaction	Inhaled bronchodilator	
Immediate hypersensitivity reaction	Parenteral corticosteroids	
Acute bronchospasm	Intubation	
Wheezing	Tracheostomy	
	Cricothyroidotomy	

D. Risk Management Evaluation Program

PRAECIS will implement a program to evaluate the effectiveness of the **PLUS** Program in assuring that Plenaxis™ is used safely and in the appropriate patient population. This information will allow the Agency to assess, on an ongoing basis, whether Plenaxis™ continues to be safe for use under the conditions of use for which Plenaxis™ is approved, whether additional conditions are needed or conditions may be reassessed. The program will include the following elements:

Evaluation of the Risk

1. Conduct a phase 4 study to estimate the incidence of immediate-onset systemic allergic reactions (anaphylaxis, hypotension and/or syncope) in the indicated population.
   Protocol submission: January 2004 (See protocol concept, Attachment 6)
   Study start: 2nd Q 2004

Final report submission: 3rd Q 2008; Current data will be provided in Annual Reports

2. Conduct a phase 4 study to characterize Plenaxis™-induced immediate-onset systemic allergic reactions by evaluating skin test reactivity to abarelix and determination of anti-abarelix IgG and IgE antibody levels in patients experiencing an immediate-onset systemic allergic reaction.
   Protocol submission: January 2004 (See protocol concept, Attachment 7)
   Study start: 2nd Q 2004
   Final report submission: 3rd Q 2008; Current data will be provided in Annual Reports

3. Conduct a phase 4 study to assess the effectiveness of pre-treatment with oral antihistamine plus/minus oral steroids in patients who experienced Plenaxis™-induced urticaria and/or pruritis within 2 hours of injection and continued Plenaxis™ therapy.
   Protocol submission: January 2004 (See protocol concept, Attachment 8)
   Study start: 2nd Q 2004
   Final report submission: 3rd Q 2008; Current data will be provided in Annual Reports

Compliance

1. Quarterly, the integrity of the Prescribers' Registry will be verified. The following audits will be conducted:
   - Enrollment forms (physician and pharmacy) will be reviewed for completion
   - Enrollment forms will be reviewed against the Registry database.

   On an annual basis the Registry database will be audited for system compliance with 21 CFR§11, 211 and 314, for physical and logical security and for maintenance of a complete electronic audit trail. Corrective action will be implemented for all observations. The enrollment system will be re-evaluated if compliance is <95%.

2. Quarterly, the restricted distribution control mechanism will be verified. The distribution system will be re-evaluated if compliance is <95%. The following items will be included in the audits:
   - Distributor's physician sales data against Registry enrollment and Registry sales confirmation numbers
   - Distributor's pharmacy sales data against Registry enrollment and Registry (pharmacy) confirmation numbers
   - Distributor's shipment dates against Registry enrollment dates
   - Distributor's shipping address against enrolled physician's address.

   Contractual non-compliance will result in termination of a distribution agreement.

   Note that physicians may substitute a licensed retail pharmacy as the shipping point for a specific patient that must purchase drug through a pharmacy due to insurance considerations. A quarterly record of distribution to retail pharmacies will be created.

NDA 21-320
Plenaxis™ —— (abarelix for injectable suspension)
Praecis Pharmaceuticals, Inc.

There are no Phase 4 Commitments for this application at this time.

/S/ 5/7/05

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PRODUCT

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Risk management

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

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

FACSIMILE TRANSMITTAL SHEET

DATE: November 18, 2003

To: J.D. Bernardy	**From:** Nenita Crisostomo
Company: Praecis Pharmaceuticals, Inc.	Division of Division of Reproductive and Urologic Drug Products
Fax number: 781-890-7015	**Fax number:** 301-827-4267
Phone number: 781-795-4100 x4282	**Phone number:** 301-827-4260

Subject: Risk Management Program: Evaluation of Risk--Phase 4 Studies

Total no. of pages including cover: 3

Comments:

Dear Mr. Bernardy,

The Division is seeking your agreement to the following Phase 4 studies as enclosed. Please send your written response with the Phase 4 studies attached.

Thank you,

Nita Crisostomo

Document to be mailed: ☐YES ☑NO

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

2. Conduct studies 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

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

4. 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

5. Conduct a clinical study to characterize Plenaxis™-induced immediate-onset system allergic reactions by evaluating skin test reactivity to Plenaxis™ 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

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

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

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

FACSIMILE TRANSMITTAL SHEET

DATE: November 18, 2003

To: J.D. Bernardy	**From:** Nenita Crisostomo
Company: Praecis Pharmaceuticals, Inc.	Division of Division of Reproductive and Urologic Drug Products
Fax number: 781-890-7015	**Fax number:** 301-827-7260
Phone number: 781-795-4100 x4282	**Phone number:** 301-827-4260

Subject: Information Request: RMP: Adverse Event Reporting

Total no. of pages including cover: 2

Comments:

Document to be mailed: ☐YES ☑NO

Attachment

COMMENTS AND INFORMATION REQUEST

Please refer to your submission dated November 15, 2003 containing your revised Risk Management Program and we have the following comments and information requests.

Provide clarification of your Adverse Event reporting:

It appears as if Sentrx will be doing all the processing of the Adverse Drug Event (ADE) data and producing the complete hardcopy MedWatch reports and then sending them to Praecis for a final determination of reportability, and submission to the FDA.

1. How will Praecis be ensuring that the reporting activities by Sentrx are compliant with regulations?
2. How will Praecis access the ADE data in the . — system to support the — ?
3. Where will source documents such as complaint letters, documentation of efforts to obtain follow-up, and the database be archived?
4. How will Praecis access the source documents and the ADE data in the — system to perform any follow-up or clarification activities requested by Office of Drug Safety?

APPEARS THIS WAY
ON ORIGINAL

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

FACSIMILE TRANSMITTAL SHEET

DATE: November 17, 2003

To: J.D. Bernardy	**From:** Nenita Crisostomo
Company: Praecis Pharmaceuticals, Inc.	Division of Division of Reproductive and Urologic Drug Products
Fax number: 781-890-7015	**Fax number:** 301-827-4267
Phone number: 781-795-4100 x4282	**Phone number:** 301-827-4260

Subject: Information Request: Clinical, Race—Subgroups, November 17, 2003.

Total no. of pages including cover: 2

Comments:

Document to be mailed: ☐YES ☑NO

Attachment

1. Provide information about the relative effectiveness of abarelix, in terms of reduction of serum testosterone to ≤ 50 ng/dL, in African American men with prostate cancer compared to non-African American men. Provide, at a minimum, the following additional analyses.

   a. Provide the numbers and percentages separately for the non-African American patients and the African American patients who had serum testosterone ≤ 50 ng/dL at each study visit for controlled Studies 149-98-02, 149-98-03, and 149-99-03 and uncontrolled study 149-98-04. Provide the data separately for (1) each treatment arm in each study and (2) each of the 4 studies. Use the general format previously used to present similar data (i.e., Table 12.4.4, pg 84 of Vol 1.52 in the December 2000 submission and in your recent response of 30 October 2003 [Table 12.4.4b]).

   b. Provide the numbers and percentages separately for the non-African American patients and the African American patients who had a serum testosterone of ≤ 50 ng/dL on each of Study Days 2, 8, 15, and 29 in Studies 149-98-02 and 149-98-03. Provide the data separately for (1) each treatment arm in each study and (2) each of the studies. Use the general format previously used in the Final Study Reports for each of these studies.

   c. Provide the numbers and percentages separately for the non-African American patients and the African American patients who achieved and maintained medical castration from Day 29 through Day 85 by Definition 2 (no two consecutive testosterone values > 50 ng/dL) that was used in the primary efficacy analyses for the 3 controlled trials (Studies 149-98-02, 149-98-03, and 149-99-03) in the December 2000 submission.

   d. Provide the numbers and percentages separately for the non-African American patients and the African American patients who achieved and maintained medical castration from Day 29 through Day 169 by Definition 5 (no two consecutive testosterone values > 50 ng/dL) that was used in the primary efficacy analyses for the 2 controlled trials (Studies 149-98-02 and 149-98-03) in the December 2000 submission. Provide a similar analysis for Study 149-99-03. If Study 149-99-03 cannot be calculated by Definition 5, use an alternate definition (i.e., Definition 4 or 6).

2. Provide any other analyses that you believe would be helpful to assess the relative effectiveness of abarelix in African American men with prostate cancer compared to that in non-African American men.

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

FACSIMILE TRANSMITTAL SHEET

DATE: November 14, 2003

To: J.D. Bernardy	**From:** Nenita Crisostomo
Company: Praecis Pharmaceuticals, Inc.	Division of Division of Reproductive and Urologic Drug Products
Fax number: 781-890-7015	**Fax number:** 301-827-4267
Phone number: 781-795-4100 x4282	**Phone number:** 301-827-4260

Subject: Information Request: PI, PPI, Physician Attestation Form, Hospital Pharmacie's Acceptance of Responsibilities Form--November 14, 2003

Total no. of pages including cover: 4

Comments:

Hello JD,

ClinPharm has one additional request: Please verify origin (Study #) for PK parameters reported in Table 1, page 3 of the Physician Insert as enclosed. Thanks somuch! Have a nice weekend!

Regards,

nita

Document to be mailed: ☑ YES ☐ NO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

FACSIMILE TRANSMITTAL SHEET

DATE: November 14, 2003

To: J.D. Bernardy	**From:** Nenita Crisostomo
Company: Praecis Pharmaceuticals, Inc.	Division of Division of Reproductive and Urologic Drug Products
Fax number: 781-890-7015	**Fax number:** 301-827-4267
Phone number: 781-795-4100 x4282	**Phone number:** 301-827-4260

Subject: Information Request: "Comments on the November 7, 2003 Amendment 080"---November 14, 2003

Total no. of pages including cover: 4

Comments:

Document to be mailed: ☑ YES ☐ NO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

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 submission, Amendment 080 dated November 7, 2003 containing revisions to your Risk Management Program, following our teleconference dated November 4, 2003.

We are reviewing your submission and have the following comments and information requests 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 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

Enclosure

Comments on the November 7, 2003 Amendment 080

- We will send you labeling comments for the Package Insert, Patient Information, Physician Attestation, and Hospital Pharmacies form.
- FDA disagrees with your new proposed overarching objectives for the PLUS Program. We agreed with your August 8, 2003 goal "to ensure that Plenaxis is used in the population where the benefits outweigh the risk" and we sent you on October 10, 2003 our view of the goals of your risk management program. We stated "use of the drug in the indicated population where benefits exceed risk" and "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." You now drop reference to use in the indicated population where benefit exceeds risk as a goal. This makes your risk management program unacceptable. We do not believe that under these circumstances your restricted distribution program can achieve management of risk such that the drug would be considered safe. In fact, we remind you that your application was found neither safe nor effective in the remaining prostate cancer population not mentioned in the currently agreed upon indication. If this matter cannot be resolved, we anticipate this deficiency will be addressed next cycle.
- Prescribing Program
  Your processes and procedures must be written, verifiable, and open to inspection by FDA.
  1. What procedures will you follow for if a physician designates "other" and is not an oncologist, urologist, or internist (or with combined specialization)?
  2. What service is Sentrix actually providing Praecis: StudyTrak, CaseTrak, EventTrak, OnTrak, and SurveyTrak?
  3. How is Sentrix providing information regarding adverse events to Praecis?
  4. If Sentrix will be reporting adverse events directly to FDA, how will Praecis be monitoring Sentrix's performance?
  5. You will need to develop operating procedures and processes for handling all sources of adverse events: patient direct reports, your field representatives' reports, physicians, authorized buyers, distributors, etc. should they be received.
  6. Center for Medicare and Medicaid Services (CMS) requests that we collect UPIN numbers. This will be added to the Physician Attestation form.
  7. Praecis reports that [redacted] will not be part of the Prescribing Program. Revise this section to state this.
  8. FDA requests Praecis commit to monitoring quarterly the proposal you presented November 4, 2003 in which retail pharmacies would only be used in the case of patients needing to pick up drugs at a retail pharmacy address for reimbursement purposes and that you reported this to be needed in very few occasions. Tracking of this arrangement would be reported in quarterly updates to FDA. If this arrangement shows increased utilization, Praecis should propose how dispensing outside the risk management program would be addressed.

9. Revise your program so that physicians report serious adverse events to the company or directly to FDA MedWatch program using hardcopy or online MedWatch form, not the CIOMS form.

- Educational Program
  1. #B1- "...(including the Package Insert and the Patient Information form, *particularly the approved population of use and treatment recommendations.)*"
- Adverse Event Reporting
  1. See list of terms to be reported in 15 days sent to Praecis on November 7, 2003.
- Risk Management Evaluation

  As part of your risk management evaluation, processes and procedures should be written, verifiable, and open to inspection by FDA to confirm compliance.
  1. Add a proposal to evaluate whether physicians are complying with agreed upon responsibilities in the prescribing program. Included in this study would be an examination of the frequency at which the Patient Information is signed and placed in the patient's medical record, use of Plenaxis in the indicated population, and the frequency of monitoring of serum testosterone. Praecis Pharmaceuticals, Incorporated and FDA will review study findings and agree to educational and/or other activities that may be needed to address observations.
  2. Study 1-add "and determine whether the hazard rate changes over time."
  3. Compliance #3-Office of Drug Safety will provide comments. In general, we recommend participation be 20% of entire enrolled prescribers for this knowledge survey.
  4. Compliance #4- Office of Drug Safety will provide additional comments. This proposal appears to lack robustness to judge success of your risk management program. Also, we recommend at least 95% compliance with labeled population. We recommend you chose a percentage of total claims in a system or a percentage of all of Plenaxis in a time period for auditing. You will need to do a records review to validate your claims database results.
  5. Compliance #5- Office of Drug Safety will provide comments. In general, we recommend at least 95% compliance.
  6. Compliance #6-We do not understand why patients who complain cannot be asked permission for medical records release. We do not understand why you cannot investigate an allegation made by a third party. We do not understand why you cannot investigate your own field's allegation.
  7. Compliance #7-Define "Fraud" and provide examples of fraud that clarify your view of the critical elements of the risk management program. Also, define any non-compliance issues that would lead to deactivation. Provide a description of what procedures would be employed prior to deactivation to solve the problem and what would trigger deactivation. Also, include a description of what organizational unit oversees investigations for deactivation.
  8. Identify conditions and methods for withdrawing the authorization of authorized buyers and distributors and enrolled physicians to receive Plenaxis. Also include a description of what organizational unit oversees investigations for deactivation. Deactivations should be reported to FDA quarterly.
  9. Your discussions with CMS must happen prior to the application action date to be considered part of your risk management plan.

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

/s/

Margaret Kober
11/14/03 01:20:48 PM
Chief, Project Management Staff

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

FACSIMILE TRANSMITTAL SHEET

DATE: October 28, 2003

To: Carol Hurt	**From:** Nenita Crisostomo
Company: Praecis Pharmaceuticals, Inc.	Division of Division of Reproductive and Urologic Drug Products
Fax number: 781-890-7474	**Fax number:** 301-827-4267
Phone number: 781-795-4344	**Phone number:** 301-827-4260

Subject: Information Request: Risk Management Plan dated October 20, 2003

Total no. of pages including cover: 5

Comments:

Dear Carol,

Here is the copy now with the electronic appended signature.

Thank you so much,

Nita

Document to be mailed: ☑ YES ☐ NO

Attachment/nic

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

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 "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

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

/s/

Daniel A. Shames
10/28/03 04:13:43 PM

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

FACSIMILE TRANSMITTAL SHEET

DATE: October 28, 2003

To: J.D. Bernardy	**From:** Nenita Crisostomo
Company: Praecis Pharmaceuticals, Inc.	Division of Division of Reproductive and Urologic Drug Products
Fax number: 781-890-7015	**Fax number:** 301-827-4267
Phone number: 781-795-4100 x4282	**Phone number:** 301-827-4260

Subject: Information Request: Clinical, October 28, 2003

Total no. of pages including cover: 3

Comments:

Document to be mailed: • YES ☑ NO

Attachment

1. Provide the following additional analyses and information for Study 149-01-05 . For each of the requested analyses, perform the analysis for each of the efficacy subgroups described below. For each subgroup, include only patients who (a) received all 4 doses of abarelix and both doses of Lupron or Zoladex and (b) had serum testosterone measurements following each dose of LHRH agonist at the times listed below for the specific subgroup, or (c) failed to meet the criteria of adequate testosterone suppression during the LHRH treatment period (based on the criteria for success/failure for each of the requested analyses), regardless of the patient's having testosterone values at all required times. For each subgroup, consider an acceptable dosing regimen for LHRH to be instances in which (1) the first dose of LHRH was administered within 28 (±2) days of the fourth dose of abarelix and the second dose of LHRH was administered within 28 (±3) days of the first dose of LHRH.

   a. Efficacy Subgroups

      Efficacy Subgroup 1. Patients in Efficacy Subgroup 1 will have serum testosterone values at the following times relative to dosing with LHRH where dosing with LHRH is considered to be Day 1 for each of the 2 LHRH dosing cycles. To avoid excessive disqualification of patients, consider the following windows (ranges) to be acceptable blood collection times:

      - LHRH Treatment Cycle 1: Day 2 or 3, Day 4 (±1), Day 8 (±2), Day 15 (±3), Day 29 (±3).
      - LHRH Treatment Cycle 2: Day 2 or 3, Day 4 (±1), Day 8 (±2), Day 15 (±3), Day 29 (±3).

      Efficacy Subgroup 2. Patients in Efficacy Subgroup 2 will have serum testosterone values at the following times relative to dosing with LHRH.

      - LHRH Treatment Cycle 1: Day 2 or 3, Day 4 (±1), Day 8 (±2), Day 29 (±3).
      - LHRH Treatment Cycle 2: Day 2 or 3, Day 4 (±1), Day 8 (±2), Day 29 (±3).

   b. Analyses

      Perform the following analyses separately on each of the Efficacy Subgroups. In addition, for each Efficacy Subgroup, perform the requested analysis separately for (1) all patients in the subgroup, and (2) only those patients in the subgroup for whom their serum testosterone value was ≤ 50 ng/dL on the day of the first dose of LHRH (usually Study Day 85). Thus, each of the requested analyses will be performed on 4 populations.

      Each of the requested analyses will determine the proportion (and 95% confidence interval for the proportion) of patients in the respective subgroup or population for whom serum testosterone values were at or below a designated value (e.g., the proportion of treatment successes) throughout treatment with LHRH.

      Analysis No. 1. Patients for whom all serum testosterone values during the LHRH treatment period were ≤ 50 ng/dL.

      Analysis No. 2. Patients for whom all serum testosterone values during the LHRH treatment period were ≤ 75 ng/dL.

      Analysis No. 3. Patients for whom all serum testosterone values during the LHRH treatment period were ≤ 100 ng/dL.

      Analysis No. 4. Patients for whom all serum testosterone values during the LHRH treatment period were ≤ 150 ng/dL.

      In summary, the request will generate values for 16 proportions (i.e., 4 populations x 4 analyses). For each proportion provide, at a minimum, the number of patients in the population, the number of successes, the actual proportion, and the 95% CL for the proportion.

   c. Patient Listings.

      1. Provide a listing of the patients who qualify for each of Efficacy Subgroups 1 and 2 as well as a listing of those patients in each of the Efficacy Subgroups whose serum testosterone value at the time of first dosing with LHRH was ≤ 50 ng/dL (a total of 4 listings).

   2. For each of the 16 analyses requested in 1b above, provide a listing of the patients who were classified as treatment failures.

2. Combine the data for the percentage of patients in the abarelix treatment group with a serum testosterone ≤ 50 ng/dL at each assessment time for Study 149-98-02 (listed in Table 12.4.4, pg 84 of Vol 1.52 of the December 2000 submission) with that for Study 149-98-03 (listed in Table 12.4.4, pg 89 of Vol 1.76 of the December 2000 submission). Provide the combined data in the same format (e.g., study week, number of patients evaluated at the assessment, and number and percentage of patients at the assessment with a testosterone value ≤ 50 ng/dL).

3. Provide an analysis comparable to that represented in Item 2 above (Table 12.4.4, number and percentage of patients at each assessment with a serum testosterone ≤ 50 ng/dL) for the abarelix treatment group and the Zoladex plus Casodex treatment group in Study ABACAS 1.

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

/s/

Nenita Crisostomo
10/28/03 11:55:01 AM
CSO

Nenita Crisostomo
10/28/03 11:58:27 AM
CSO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

FACSIMILE TRANSMITTAL SHEET

DATE: October 27, 2003

To: Carol Hurt	**From:** Nenita Crisostomo
Company: Praecis Pharmaceuticals, Inc.	Division of Division of Reproductive and Urologic Drug Products
Fax number: 781-890-7015	**Fax number:** 301-827-4267
Phone number: 781-795-4344	**Phone number:** 301-827-4260

Subject: Information Request: Risk Management Plan dated October 20, 2003

Total no. of pages including cover: 5

Comments:

Dear Carol,

Copy of this faxed document will also be sent in the mail. Please note that due to electronic problems at this time, the attached documents are in draft form as it is unsigned. However, the same document will be faxed to you with electronic signature tomorrow (10/28/03).

Thank you so much,

Nita

Document to be mailed: ☑ YES ☐ NO

Attachment/nic

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

FACSIMILE TRANSMITTAL SHEET

DATE: October 20, 2003

To: Carol Hurt	**From:** Nenita Crisostomo
Company: Praecis Pharmaceuticals, Inc.	Division of Division of Reproductive and Urologic Drug Products
Fax number: 781-890-7015	**Fax number:** 301-827-4267
Phone number: 781-795-4100 x4282	**Phone number:** 301-827-4260

Subject: Information Request: CMC—Labeling 10/17/03

Total no. of pages including cover: 4

Comments:

Dear Carol,

Copy of this faxed document will also be sent in the mail.

Regards,

Nita

Document to be mailed: ☑ YES ☐ NO

Attachment/nic

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

FACSIMILE TRANSMITTAL SHEET

DATE: October 10, 2003

To: Carol Hurt	**From:** Nenita Crisostomo
Company: Praecis Pharmaceuticals, Inc.	Division of Division of Reproductive and Urologic Drug Products
Fax number: 781-890-7015	**Fax number:** 301-827-4267
Phone number: 781-795-4344	**Phone number:** 301-827-4260

Subject: Information Request: Risk Management Plan dated August 8, 2003

Total no. of pages including cover: 7

Comments:

Dear Carol,

Copy of this faxed document will also be sent in the mail.

Regards,

Nita

Document to be mailed: ☑ YES ☐ NO

Attachment/nic

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

FACSIMILE TRANSMITTAL SHEET

DATE: September 24, 2003

To: J.D. Bernardy	**From:** Nenita Crisostomo
Company: Praecis Pharmaceuticals, Inc.	Division of Division of Reproductive and Urologic Drug Products
Fax number: 781-890-7015	**Fax number:** 301-827-4267
Phone number: 781-795-4100 x4282	**Phone number:** 301-827-4260

Subject: Clinical Information Request

Total no. of pages including cover: 3

Comments:

Document to be mailed: ☑ YES ☐ NO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

FACSIMILE TRANSMITTAL SHEET

DATE: August 27, 2003

To: J.D. Bernardy, JD	**From:** Nenita Crisostomo, R.N.
Company: Praecis Pharmaceuticals, Inc.	Division of Division of Reproductive and Urologic Drug Products
Fax number: 781-890-7015	**Fax number:** 301-827-4267
Phone number: 781-795-4100 x4282	**Phone number:** 301-827-4260

Subject: Information Request: CMC.8/21/03

Total no. of pages including cover: 4

Comments:

Dear Mr. Bernardy,

Copy of this faxed document will also be sent in the mail.

Regards,

Nita

Document to be mailed: ☑ YES ☐ NO

Attachment/nic

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

FACSIMILE TRANSMITTAL SHEET

DATE: July 9, 2003

To: J.D. Bernardy	**From:** Nenita Crisostomo
Company: Praecis Pharmaceuticals, Inc.	Division of Division of Reproductive and Urologic Drug Products
Fax number: 781-890-7015	**Fax number:** 301-827-4267
Phone number: 781-795-4100 x4282	**Phone number:** 301-827-4260

Subject: INFORMATION REQUEST

Total no. of pages including cover: 5

Comments:

Document to be mailed: ☑ YES ☐ NO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

FACSIMILE TRANSMITTAL SHEET

DATE: June 10, 2003

To: J.D. Bernardy	**From:** Nenita Crisostomo
Company: Praecis Pharmaceuticals, Inc.	Division of Division of Reproductive and Urologic Drug Products
Fax number: 781-890-7015	**Fax number:** 301-827-4260
Phone number: 781-795-4100 x4282	**Phone number:** 301-827-4260

Subject: Teleconference Type B Meeting Granted

Total no. of pages including cover: 4

Comments:

Document to be mailed: ☑ YES ☐ NO

Attachment

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

FACSIMILE TRANSMITTAL SHEET

DATE: June 5, 2003

To: Carol Hurt Regulatory Affairs Associate	**From:** Nenita Crisostomo, R.N. Regulatory Health Project Manager
Company: Praecis Pharmaceuticals, Inc.	Division of Reproductive and Urologic Drug Products
Fax number: 781-890-7015	**Fax number:** 301-827-4267
Phone number: 781-795-4344	**Phone number:** 301-827-4260

Subject: Division of Biometrics II Information Sheet for Submission of Carcinogenicity Data; Guidance for Industry: Providing Regulatory Submissions in Electronic Format--NDAs

Total no. of pages including cover: 4

Comments:

Document to be mailed: ☐ YES ☑ NO

Hello Carol,

Hope you find the attached documents helpful. Also, the teleconference is tentatively scheduled for June 10, 2003 At 3:30 P.M., the soonest date that the following reviewers can attend:

Mark Hirsch, MD, Urology, Team Leader, Division of Reproductive and Urologic Drug Products
Scott Monroe, M.D., Medical Team Leader, DRUDP
Krishan Raheja, D.V.M., Ph.D. - Pharmacologist, DRUDP
Nita Crisostomo, RN, Regulatory Project Manager, DRUDP
Charles Lee, MD, Medical Officer, Division of Pulmonary and Allergy Products

Please confirm the date and time of the teleconference and to which contact number do we call in.

/S/

Attachment

Division of Biometrics II
Information Sheet for Submission of Carcinogenicity Data

The statistical reviewer responsible for this carcinogenicity-study review requests that the sponsor recreate the tumor data in conformance to the electronic format specified in the Agency's guidance document of January 1999.

To streamline the reviewing process and improve the review quality, the Agency published *Guidance for Industry, Providing Regulatory Submissions in Electronic Format-NDAs* in January 1999. In Appendix 1 of this document the Agency details the data-format specifications for the pharmacology and toxicology datasets. The sponsor needs to familiarize itself with the data-format requirements in detail. We are only requesting the tumor dataset at this time (see page 61 of the guidance).

The above guidance document can be found at http://www.fda.gov/cder/guidance/2353fnl.pdf (or, one can go to the Guidances index page (http://www.fda.gov/cder/guidance/index.htm) then find the Electronic Submissions section, then access Regulatory Submissions in Electronic Format: New Drug Application (Issued 1/1999, Posted 1/27/1999). To assist the sponsor to correctly construct the tumor data, the Agency provides a downloadable example. Please visit *Example of an Electronic New Drug Application Submission* (posted 2/17/1999) at http://www.fda.gov/cder/guidance/NDA_Example.htm. The data for submission should have exactly the same format as the data in the example (named tumor.xpt), including designated variable names.

Please contact the Agency to provide a time line regarding providing the tumor data. The sponsor needs to carefully meet the data-format specifications in order to comply with the above guidance. Any data without 100% conformity will have to be returned for resubmission.

Full cooperation in providing data sets in the required format will facilitate a prompt review of the submission. In addition to a copy for the statistical reviewer, NDA submissions require an archival copy of all data sets for the Electronic Document Room - see Guidance for Industry: Providing Regulatory Submission in Electronic Format - General Considerations at http://www.fda.gov/cder/guidance/2867fnl.pdf for instructions.

Note that the current draft guidance for the statistical analysis of chronic rodent carcinogenicity studies is available on the FDA web site at http://www.fda.gov/cder/guidance/815dft.pdf. Sponsors are urged to use the statistical methods recommended in the guidance to analyze the carcinogenicity study data in their IND or NDA submissions.

Guidance for Industry

Providing Regulatory Submissions in Electronic Format — NDAs

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
IT 3
January 1999

http://www.fda.gov/cder/guidance/2353fnl.pdf

Tumor Dataset For Statistical Analysis[1,2] (tumor.xpt)				
Variable	**Label**	**Type**	**Codes**	**Comments**
STUDYNUM	Study number	char		[3]
ANIMLNUM	Animal number	char		[1,3]
SPECIES	Animal species	char	M=mouse R= rat	
SEX	Sex	char	M=male F=female	
DOSEGP	Dose group	num	Use 0, 1, 2, 3, 4, . . . in ascending order from control. Provide the dosing for each group.	
DTHSACTM	Time in days to death or sacrifice	num		
DTHSACST	Death or sacrifice status	num	1 = Natural death or moribund sacrifice 2 = Terminal sacrifice 3 = Planned intermittent sacrifice 4 = Accidental death	
ANIMLEXM	Animal microscopic examination code	num	0 = No tissues were examined 1 = At least one tissue was examined	
TUMORCOD	Tumor type code	char		[3,4]
TUMORNAM	Tumor name	char		[3,4]
ORGANCOD	Organ/tissue code	char		[3,5]
ORGANNAM	Organ/tissue name	char		[3,5]
DETECTTM	Time in days of detection of tumor	num		
MALIGNST	Malignancy status	num	1 = Malignant 2 = Benign 3 = Undetermined	[4]
DEATHCAU	Cause of death	num	1 = Tumor caused death 2 = Tumor did not cause death 3 = Undetermined	[4]
ORGANEXM	Organ/Tissue microscopic examination code	num	1 = Organ/Tissue was examined and was usable 2 = Organ/Tissue was examined but was not usable (e.g., autolyzed tissue) 3 = Organ/Tissue was not examined	

[1] Each animal in the study should have at least one record even if it does not have a tumor.
[2] Additional variables, as appropriate, can be added to the bottom of this dataset.
[3] ANIMLNUM limit to no more than 12 characters; ORGANCOD and TUMORCOD limited to no more than 8 characters; ORGANNAM and TUMORNAM should be as concise as possible.
[4] A missing value should be given for the variable MALIGNST, DEATHCAU, TUMOR and TUMORCOD when the organ is unuseable or not examined.
[5] Do not include a record for an organ that was useable and no tumor was found on examination. A record should be included for organs with a tumor, organs found unusable, and organs not examined.

DATA REQUEST MEMORANDUM
Statistical Review

DATE: April 23, 2003

BETWEEN: Eufrecina DeGuia (HFD-580)

AND: Katherine B. Meaker, M.S. (HFD-715)

SUBJECT: **NDA 21-320 Amendment 42**; Data request to convey to sponsor

The data sets submitted to the electronic document room are not in a consistent format across all the clinical studies. Please request that PRAECIS Pharmaceuticals Inc. submit a SAS dataset with the following information:

Studies to include:	149-97-04 149-98-02 149-98-03 149-98-04 149-99-03 149-99-04 149-01-03 149-01-05 ABACUS 1 ABACUS 1 Extension
One record per subject	If a subject was enrolled in more than one study: combine the total length of drug treatment STUDY variable will be last study only list all studies in a descriptive variable
Variables to include:	Patient Number (unique identifier) Study Site Treatment code (include code list; specify dose level) Number of days on treatment Completer (Y/N)? If no, reason for stopping treatment (include code list) Multiple study indicator variable (Y/N) Multiple study description field (if in more than one study, list all studies for subject)

/S/

Katherine B. Meaker, M.S.
Mathematical Statistician

Concur: Dr. Welch

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

/s/

Katherine Meaker
4/23/03 09:33:59 AM
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