/s/

Eufrecina deGuia
4/12/01 03:34:22 PM
CSO

MEMORANDUM OF TELECON

DATE: March 26, 2001

APPLICATION NUMBER: NDA 21-320 Plenaxis (abarelix for injectable suspension)

BETWEEN:

Name: JD Bernardy, Vice President, Regulatory Affairs and Quality Assurance
Paul Damiani, Ph.D., Senior Director of Regulatory Affairs
Phone: (617) 494-8400 ext. 2282
Representing: Praecis Pharmaceuticals, Inc.

AND

Name: Eufrecina DeGuia, Regulatory Project Manager
Division of Reproductive and Urologic Drug Products, HFD-580

SUBJECT: Additional Information Requested for Medical Review of Abarelix (NDA 21-320)

1. Please provide a copy of the initial Serious Adverse Event (SAE) Report that was completed by the Investigator as well as any follow up information provided by the Investigator for the following 15 SAEs/AEs. We realize that MedWatch reports for several of these adverse events previously were submitted.

Subject No.	Study	Treatment	SAE/AE
13-2144	149-98-02	Lupron	Systemic pruritus/urticaria
11-2218	149-98-02	Abarelix	Drug Reaction
27-3200	149-98-03	Abarelix	Urticaria
09-3246	149-98-03	Abarelix	Allergic reaction
76-3224	149-98-03	Abarelix	Allergic reaction
16-3028	149-98-03	Abarelix	Flushing/erythematous rash
357-2226	149-99-03	Abarelix	Rash
313-3087	149-99-03	Abarelix	Allergic reaction
333-3336	149-99-03	Abarelix	Syncope (vasovagal reaction)
401-4001	149-98-04	Abarelix	Allergic reaction with mild anaphylactic symptoms
416-4067	149-98-04	Abarelix	Urticaria
409-4057	149-98-04	Abarelix	Allergic Reaction
02-4635	149-97-04	Abarelix	Allergic reaction with vascular flushing
38-4700	149-97-04	Abarelix	Pruritus/rash
01-2192	149-99-04	Abarelix	Allergic reaction

2. Please provide clarification for the following:

   a) Subject 13-2144: The AE CRF states that the patient was withdrawn because of the Sponsor's request. Why was this request made?

b) Subject 27-3200: The intensity of the SAE is reported as "mild." If this is correct, why was the event considered to be a SAE and treatment terminated?

c) Subject 76-3224: The intensity of the SAE is reported as "mild." If this is correct, why was the event considered to be a SAE and treatment terminated?

d) Subject 313-3087: The intensity of the SAE is reported as "life threatening." Is this compatible with your assessment of the event as a "vasovagal type reaction"?

/S/

Eufrecina DeGuia
Regulatory Project Manager

/s/

Eufrecina deGuia
4/12/01 03:28:36 PM
CSO

MEMORANDUM OF TELECON

DATE: March 22, 2001

APPLICATION NUMBER: NDA 21-320 Plenaxis (abarelix for injectable suspension)

BETWEEN:

Name: JD Bernardy, Vice President, Regulatory Affairs and Quality Assurance
Phone: (617) 494-8400 ext. 2282
Representing: Praecis Pharmaceuticals, Inc.

AND

Name: Eufrecina DeGuia, Regulatory Project Manager
Division of Reproductive and Urologic Drug Products, HFD-580

SUBJECT: Information Request for data

Please send us data from the two Phase 3 studies on:

1) Abarelix concentration (individual levels for each patient in each of the 2 studies) stratified by responders (efficacy criteria met) and non-responders (efficacy criteria failed).

2) T level for each patient for each group (responsders and non-responders) for each study.

3) % inhibition of T from baseline for each patient for each group for each study.

4) Clinical efficacy conclusions for each patient for each group for each study.

All the data should be for throughout the entire duration of study (i.e all time points).

The data may be submitted in 2 files (one for each study) in excel. Each file may have subsections for responders and non-responders.

Please send data in, preferably, EXCEL format on a CD.

/S/

Eufrecina DeGuia
Regulatory Project Manager

/s/

Eufrecina deGuia
4/12/01 01:33:02 PM
CSO

NDA 21-320

Meeting Minutes

Date: March 13, 2001 **Time:** 2:00 – 3:00 PM **Location:** PKLN; Room 13B-45

NDA 21-320 **Drug Name:** Plenaxis (abarelix for suspension)

Indication: Palliative treatment of advanced prostate cancer

Sponsor: Praecis Pharmaceuticals, Inc.

Type of Meeting: Status Meeting

Meeting Chair: Dr. Susan Allen

Meeting Recorder: Ms. Eufrecina DeGuia

FDA Attendees:
Susan Allen, M.D., M.P.H. – Director, Division of Reproductive and Urologic Drug Products DRUDP (HFD-580)
Mark Hirsch, M.D. - Team Leader DRUDP (HFD-580)
Scott Monroe, M.D. – Medical Officer, DRUDP (HFD-580)
George Benson, M.D. – Medical Officer, DRUDP (HFD-580)
Eufrecina De Guia - Regulatory Project Manager, DRUDP (HFD-580)
Moo-Jhong Rhee, Ph.D. - Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Ameeta Parekh, Ph.D. – Team Leader, OCPB @ DRUDP (HFD-580)
Dhruba Chatterjee, Ph.D. – Biopharmaceutics Reviewer, OCPB @ DRUDP (HFD-580)
Swapan De, Ph.D. - Chemistry Reviewer, DRUDP (HFD-580)
Kim Colangelo, B.S. – Senior Regulatory Associate, DRUDP (HFD-580)
Krishan Raheja, D.V.M., Ph.D. - Pharmacologist, DRUDP (HFD-580)
Barbara Chong, Ph.D. - Regulatory Reviewer, Division of Drug Marketing and Communication (DDMAC; HFD-40)

Meeting Objectives: To discuss the status of the on-going review of this NDA.

Background: This NDA was submitted on December 11, 2000. Plenaxis (abarelix for suspension) is a gonadotropin-releasing hormone (GnRH) antagonist for the palliative management of prostate cancer when androgen suppression is indicated. Abarelix is a new molecular entity and is the first antagonist to be reviewed for long-term therapeutic use. It may offer some clinical advantage over other GnRH analogs like Lupron and Zoladex because it does not initially stimulate the secretion of testosterone and suppresses testosterone to castrate levels more rapidly. Accordingly, the Division has determined this NDA will be designated a priority review.

The User Fee goal date is June 12, 2001.

Decisions Reached:

Clinical

- The following issues have been noted based on review of the three studies: Studies 149-98-02, 149-98-03 and 149-99-03:
    - adequacy (maintenance) of testosterone suppression, especially after six months of treatment compared to that of Lupron
    - likely increased frequency of clinically significant allergic type events
    - potential liver toxicity (manifested primarily as elevations in liver enzymes)
    - the risk/benefit ratio for abarelix in terms of its clinical benefits over a GnRH agonist either alone or with an anti-androgen for two to four weeks (Study 149-98-04)
    - labeling appears to be very promotional; significant editions/changes will have to be made

Chemistry

- still waiting for the stability data to be submitted
- sponsor will submit an amendment for the established name "abarelix for injectable suspension"

Pharmacology and Toxicology

- Carcinogenicity Study will be submitted by end of March 2001
- there is no consistent cross-species toxicity
- the *in-vitro* histamine release data seems to be missing; a possible GLP issue

Clinical Pharmacology and Biopharmaceutics

- there are no major issues at this time

Action Items:

- the Division will have a teleconference with the sponsor for additional clarification concerning:
    - the patient population that are not really contraindicated with GnRH agonist for the 149-98-04 study
    - the allergic reactions
    - the waning of efficacy with time

/S/ /S/

Signature, minutes preparer Concurrence, Chair

cc:
NDA Arch:
HFD-580/Division File
HFD-580/ SAllen/MRhee/AParekh/SDe/DChatterjee/MHirsch/Gbenson/Monroe
KRaheja/KColangelo
HFD-42/BChong
Concurrences:
Benson,Monroe,Raheja04.12.01/Rhee04.16.01/Chatterjee,Parekh04.18.01/De04.19.01/Hirsch04.20.01/
Shames,05.10.01

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
5/10/01 05:17:04 PM
For Susan Allen MD

NDA 21-320

Teleconference Minutes

Date: March 13, 2001 **Time**: 3:00 – 4:20 PM **Location:** PKLN; Room 17B-45

NDA 21-320 **Drug Name:** Plenaxis (abarelix for suspension)

Indication: Palliative treatment of advanced prostate cancer

Sponsor: Praecis Pharmaceuticals, Inc.

Type of Meeting: Guidance Meeting

Meeting Chair: Dr. Mark Hirsch **External Participant Lead**: Dr. Marc Garnick

Meeting Recorder: Ms. Eufrecina DeGuia

FDA Attendees:
Mark Hirsch, M.D. - Team Leader Division of Reproductive and Urologic Drug Products; DRUDP (HFD-580)
Scott Monroe, M.D. – Medical Officer, DRUDP (HFD-580)
George Benson, M.D. – Medical Officer, DRUDP (HFD-580)
Eufrecina DeGuia - Regulatory Project Manager, DRUDP (HFD-580)

External Participants:
Marc Garnick, M.D. – Executive Vice President, Chief Medical and Regulatory Affairs, PRAECIS
JD Bernardy, JD – Vice President, Regulatory Affairs/Quality Assurance, PRAECIS
Marilyn Campion, MS – Vice President, Clinical Operations and Biostatistics, PRAECIS
Paul Damiani, Ph.D. – Senior Director, Regulatory Affairs, PRAECIS

Meeting Objectives: To convey concerns related to safety and efficacy during the review and to obtain clarification and justification for the patient populations that were studied under Study 98-04.

Background: This NDA was submitted on December 11, 2000. Abarelix is a new molecular entity and is the first GnRH antagonist to be reviewed for long-term therapeutic use. It may offer clinical advantage over GnRH agonists because it does not initially stimulate the secretion of testosterone and suppresses testosterone to castrate levels more rapidly. Accordingly, the Division has determined this NDA be designated a priority review.

Discussion Points:
The following issues were discussed:
1. Concerns relating to efficacy (suppression of testosterone)

- there is some concern about the overall percentage of patients who continue to have castrate levels of testosterone (< 50ng/dL) after Day 85 through Day 365
- sponsor will provide information on clinical significance of non-castrate values and additional analyses of serum testosterone levels if warranted

2. Allergic Reactions as compared to Lupron and Lupron + Casodex
   - incidence and/or severity of allergic reaction appears to be higher with Abarelix
   - sponsor should submit support in writing why safety concerns relevant to severe systemic allergic reactions with Abarelix are unwarranted
   - justification for the conclusion in ISS that the incidence and severity of allergic reactions is similar between Abarelix and Lupron should be provided
   - In Table 6-J, it is difficult to compare the patients qualitatively; description of total exposures in both groups including incidences should be provided
   - the Division has focused upon those allergic – type events which led to subject withdrawal

3. With regard to the 98-04 study:
   - LHRH agonists are not "contraindicated"; rather, patients should be "closely observed"
   - the sponsor's rationale for including patients with impending neurological compromise, retroperitoneal adenopathy causing ureteral obstruction, bone pain from skeletal metastases, and presence of an enlarged prostate gland or pelvic mass causing bladder outlet obstruction was discussed
   - the sponsor indicated that those patients with impending neurological compromise had epidural metastases
   - although patients with urethral catheters and an "enlarged prostate" could be treated with LHRH agonists, the sponsor believes that the catheters could be removed more rapidly after therapy with abarelix

Decisions Reached:

- the sponsor agreed to submit the following:
  - analysis of the long-term efficacy data (maintenance of testosterone suppression) for Studies 149-98-02 and 149-98-03
  - analysis of the allergic-type reaction rates evident with abarelix compared to leuprolide and leuprolide plus biculatamide
  - additional individual patient information (including patient individual patient numbers) for Table 6-I of the Integrated Sumary of Safety (ISS)

Action Items:

- the sponsor will submit the requested information

(See appended electronic signature page)

/S/

Signature, minutes preparer

/S/

Concurrence, Chair

MEMORANDUM OF TELECON

DATE: March 5, 2001

APPLICATION NUMBER: NDA 21-320 Plenaxis (abarelix for injectable suspension)

BETWEEN:

Name: JD Bernardy, Vice President, Regulatory Affairs and Quality Assurance
Phone: (617) 494-8400 ext. 2282
Representing: Praecis Pharmaceuticals, Inc.

AND

Name: Eufrecina DeGuia, Regulatory Project Manager
Scott Monroe, M.D., Medical Officer
Division of Reproductive and Urologic Drug Products, HFD-580

SUBJECT: Additional Information Request for Medical Review of Abarelix (NDA 21-320)

Please provide the following additional hematology and chemistry analyses and listings.

1. For Tables 5.1.1, 5.2.1, 5.3.1, 5.4.1, 5.5.1, and 5.6.1 in the ISS (Vol. 110), please add for each post baseline assessment time the appropriate values for the (1) mean (SD) change from baseline, (2) median change from baseline, and (3) number of patients included in this descriptive statistic. If the baseline value is not available, the screening value should be used. Please regenerate the respective tables with the additional information included for each post baseline assessment time.
2. Please also provide the same analyses requested above in Item No. 1 for each of the 3 primary safety studies. These analyses (which are subsets of the analyses requested in Item No. 1) do not need to be incorporated into the existing Tables for the respective studies. The analyses can be presented as separate tables if this is easier for you to prepare. For Studies 149-98-02 and 149-98-03 please base the analyses on the data presented in the One-Year Safety Supplements.
3. For Tables 5.1.2, 5.2.2, 5.3.2, 5.4.2, 5.5.2, and 5.6.2 in the ISS (Vol. 110), please add under the category "Overall" the shift to low and the shift to high for the interval baseline through Day 365. This information can be provided either as an additional line on each of the existing tables (preferred) or as separate tables if this is easier to prepare.
4. For each of Tables 5.4.3.1, 5.4.3.2, 5.4.3.3, 5.4.3.4, and 5.4.3.5, please add information about the number (%) of patients who shifted to low or to high for each test for the interval baseline through Day 365. This information can be provided either as an additional line on the existing tables or as separate tables.
5. For each chemistry measurement represented in Table 5.4.3, please prepare an additional analysis for the interval baseline to Day 365.
6. Please provide the information represented in Table 5.4.3 (including the additional request in Item No. 5 above) separately for each of the 3 primary safety studies.
7. For Tables 5.7.1 and 5.7.2, please provide a listing of patient numbers by laboratory test and degree of abnormality for all patients represented in these tables.

Eufrecina DeGuia
Regulatory Project Manager

/s/

Eufrecina deGuia
4/12/01 10:27:46 AM
CSO

MEMORANDUM

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

PID#: D010038

DATE: March 10, 2001

FROM: Denise P. Toyer, Pharm.D.
Safety Evaluator
Division of Drug Risk Evaluation II, HFD-440

THROUGH: Kathleen Uhl, M.D., Acting Director
Division of Drug Risk Evaluation II, HFD-440

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

SUBJECT: OPDRA POSTMARKETING SAFETY REVIEW
Consult:
Drugs: Gonadotropin-releasing hormone (GnRH) antagonists
Cetrorelix (Cetrotide), Goserelin (Zoladex),
Leuprolide (Lupron) and Nafarelin (Synarel)
Reaction: Anaphylaxis

EXECUTIVE SUMMARY

The Division of Reproductive and Urologic Drug Products forwarded a consult to the Division of Drug Risk Evaluation II on January 25, 2001 requesting a review of all Adverse Event Reporting System cases of anaphylaxis associated with cetrorelix, goserelin, leuprolide, and nafarelin. DRUDP is currently conducting a priority review of the new drug application (NDA) for abarelix, a gonadotropin-releasing hormone (GnRH) antagonist for the palliative management of prostate cancer when androgen suppression is indicated. Clinical trials have identified several cases of "severe anaphylactic-like reactions" associated with repeat intramuscular dosing of abarelix. DDREII conducted a review in women of the hypersensitivity/anaphylactic-type/immune system reactions associated with leuprolide. The fourteen cases/patients identified had possible predisposing factors (e.g., food or medication allergies, asthma, or systemic lupus erythematosus). No changes were made in the leuprolide labeling at that time. A search was conducted, using the Adverse Event Reporting System (AERS), for all cases of anaphylaxis associated with cetrorelix, goserelin, leuprolide, and nafarelin. Thirty-one unduplicated cases were identified [cetrorelix (0), goserelin (4), leuprolide (23), and nafarelin (4)]. Fifty-one percent of the anaphylaxis episodes occurred after the initial dose of medication, whereas 32% of the cases occurred after a subsequent dose. The

timing of occurrence of anaphylaxis could not be determined in the remaining cases. The most frequently reported symptoms were shortness of breath, chest tightening, and pruritus. However, other events such as rash, urticaria, hypotension, and edema (e.g., throat and face) were also reported. The cetrorelix, goserelin, and leuprolide labeling contain references to anaphylaxis as a potential adverse event. The nafarelin labeling does not mention anaphylaxis, but notes that drug sensitivity occurred in approximately 2.6% of the clinical trial patients. Similarly, the proposed labeling for abarelix describes similar adverse events as transient adverse events. Clinical trial or postmarketing cases of anaphylaxis has been reported for cetrorelix, goserelin, leuprolide, and nafarelin. Using spontaneous reporting data, OPDRA cannot determine the incidence of anaphylaxis with the GnRH antagonists. Therefore, OPDRA cannot compare the incidence of anaphylaxis of the GnRH antagonists to the proposed 1% incidence for abarelix. The labeling for all of the GnRH antagonists should describe the possible occurrence of anaphylaxis. These statements should be consistent, in that; identical symptoms with similar severity should be labeled the same, and not be called three different terms (i.e., anaphylaxis, drug sensitivity, or transient allergic reactions).

INTRODUCTION

The Division of Reproductive and Urologic Drug Products (DRUDP) forwarded a consult to the Division of Drug Risk Evaluation II (DDREII) on January 25, 2001 requesting a review of all Adverse Event Reporting System cases of anaphylaxis associated with cetrorelix, goserelin, leuprolide, and nafarelin. DRUDP is currently conducting a priority review of the new drug application (NDA) for abarelix, a gonadotropin-releasing hormone (GnRH) antagonist for the palliative management of prostate cancer when androgen suppression is indicated. Clinical trials have identified several cases of "severe anaphylactic-like reactions" associated with repeat intramuscular dosing of abarelix. Cetrorelix, goserelin, leuprolide, and nafarelin are GnRH antagonists. However, only goserelin and leuprolide have indications that are comparable to the pending NDA. DRUDP plans to compare the post-marketing data (i.e., anaphylaxis cases) for these products to the clinical trial data for abarelix.

The Office of Postmarketing Drug Risk Assessment completed a safety review of leuprolide in March 1999. Based on the large number of reports in women for dermatitis, pruritus, urticaria, dyspnea, and arthralgia found during the safety review, a subsequent review was conducted that evaluated hypersensitivity/anaphylactic-type/immune system reactions. This review used the terms identified in the safety review to search for any anaphylaxis cases. Fourteen cases in women and three pediatric cases were identified during this review. This report concluded that eight of the fourteen women had possible predisposing factors (e.g., food or medication allergies, asthma, or systemic lupus erythematosus). No changes were made in the leuprolide labeling at that time.

Indication and Labeling

Cetrorelix acetate

- Approved August 11, 2000.
- Indicated for the inhibition of premature LH surges in women undergoing controlled ovarian stimulation.
- The labeling indicates that a severe anaphylactic reaction associated with cough, rash and hypotension was observed in one patient after seven months of treatment in a study for an indication unrelated to infertility.

Goserelin

- The first product was approved December 29, 1989.
- Approved for use in prostatic carcinoma, advanced breast cancer, endometriosis, and endometrial thinning.
- The labeling notes that a report of an anaphylactic reaction to synthetic GnRH has been reported in the medical literature. Additionally, the labeling states that hypersensitivity, antibody formation and acute anaphylactic reactions have been reported with LHRH agonist analogues.

Leuprolide

- The first product was approved April 9, 1985.
- Indicated for endometriosis, uterine leiomyomata, advanced prostatic cancer, and central precocious puberty.
- In addition to a statement similar to the goserelin labeling (pertaining to an anaphylactic reaction associated with synthetic GnRH), this labeling states that symptoms consistent with an anaphylactoid or asthmatic process have been rarely reported.

Nafarelin

- Approved February 13, 1990.
- Approved for the treatment of endometriosis and central precocious puberty.
- The labeling does not specifically list references to anaphylactic reactions, however in clinical trials, 2.6% of the patients reported symptoms suggestive of drug sensitivity (e.g., shortness of breath, chest pain, urticaria, rash, and pruritus).

Proposed labeling for Abarelix

- [redacted]

Literature Review

As of February 23, 2001, a MEDLINE search of the published English-language literature, using the names of the products and the terms: GNRH, anaphylaxis and hypersensitivity produced several case reports of anaphylaxis. These case reports were found in the cases identified in AERS.

SELECTION OF CASES

A search was conducted on February 12, 2001 using the Adverse Event Reporting System (AERS) for cetrorelix, goserelin, leuprolide, and nafarelin. AERS was searched using the MedDRA High Level Term "Anaphylaxis (All Forms)." Thirty-one unduplicated cases were identified.

Drug	# of Cases
Cetrorelix	0 cases
Goserelin	4 cases
Leuprolide Acetate	23 cases
Nafarelin Acetate	4 cases

Goserelin (n = 4)

Demographics

Age (n = 4)	23, 34, 71, 80 years
Gender	Female = 2; Male = 2
Date of Event	1995 = 1; 1998 = 1; 1999 = 2
Report Location	Domestic = 3; Foreign = 1

Two representative cases are listed below.

ISR# 3391747-7-00-01, MFG# 1999UW03935, Domestic

An 80-year old male patient received 10.8 mg of goserelin on October 15. Four days later the patient was seen in the ER with difficulty swallowing, systemic rash, itching, lip swelling, and hot flashes. The patient was released after treatment with intravenous Solu-Medrol 60 mg and oral Benadryl. The next day the patient was admitted to the hospital due to urticaria and angioedema. Solu-Medrol and intravenous Benadryl treatment were continued and ranitidine treatment started. Four days later (10/24) an attempt to switch the patient to oral prednisone was unsuccessful due to mouth swelling. The goserelin pellet was removed (10/27). Approximately eight days after the initial hospitalization, Solu-Medrol treatment was discontinued and oral prednisone was started. The plan was to taper the corticosteroids, however the outcome was not listed.

ISR# 3233872-7-00-01, MFG# 1999AP01434, Foreign

A 23-year old female patient was treated with goserelin every 4 weeks for endometriosis. Approximately three or four days after the treatment was initiated, the patient complained of breathlessness, urticarial rash, facial swelling, and swollen lips. She was treated with prednisolone and her symptoms resolved. The goserelin treatment was not continued.

Leuprolide (n = 23)

Demographics

Age (n = 17)	Range 8 to 75; Median = 37; Mean = 40.5 years
Gender	Female = 18; Male = 5
Date of Event	1987 = 1; 1988 = 1; 1990 = 1; 1991 = 1; 1993 = 6; 1994 = 2; 1995 = 2; 1996 = 1; 1997 = 1; 1998 = 1; 1999 = 1; 2000 = 1
Report Location	Domestic = 20; Foreign = 3

Four representative domestic cases are listed below.

ISR# 3210108-4-00-01, MFG# 28789, Domestic

A 64-year old male with no known allergies experienced a scratchy, sore throat and difficulty swallowing approximately 1-2 hours after receiving his first Lupron Depot 3-Month injection. His throat began to "close-up." The patient was admitted to the ICU, for three days, and treated with intravenous fluids and corticosteroids. Six weeks after the incident the patient had recovered.

ISR# 2017611, MFG# 24510, Domestic

A 66-year old male, with a history of diabetes, experienced periorbital edema, red-total-body rash, and hypotension after an injection of leuprolide. The patient may have also experienced oral, facial, and lingual edema (varying reports from two physicians). The patient was treated with intravenous fluids, corticosteroids, and diphenhydramine. This patient had experienced a similar response to leuprolide injection at an earlier time. However, the patient did not report the original episode when it occurred.

ISR# 1880507, MFG# 18008, Foreign

A 43-year old female had previously taken one dose of leuprolide for endometriosis and developed urticaria approximately 2 weeks after administration. However, after her second monthly injection she developed urticaria, dyspnea, tongue and palm edema, red/blue discoloration of palms and soles, joint ache, and generalized pruritus. She was hospitalized for two days and treated with corticosteroids and antihistamines. The patient's condition slowly improved during the next several weeks. Approximately 5 weeks after her second injection the urticaria resolved. The patient underwent extensive allergy testing which was negative. A skin "scratch test with leuprolide" was positive and the reaction lasted more than one hour (reddened area, surrounded by small, severely itching papules).

ISR# 1897648, MFG #PE007689/93, Domestic

A 12-year old female who had used leuprolide monthly for approximately one year experienced an adverse event 30 minutes after her last leuprolide injection. This patient experienced itching, hives "coalescing", choking, and turning blue/cyanotic. She was treated in the emergency room with epinephrine injections and oral diphenhydramine. Approximately, one month after the adverse event the patient was given a test dose of short-acting leuprolide (i.e., 0.1 ml subcutaneously). Within 10 minutes the patient experienced total body flushing, coalescent hives and itching, coughing, cyanosis, and tightness of the throat. She was treated again with epinephrine and diphenhydramine. The itching did not resolve and diphenhydramine was administered for 48 hours. After the diphenhydramine treatment the patient did not have any other problems.

Nafarelin (n = 4)

Demographics

Age (n = 2)	37 and 38 years
Gender	Female = 3; Male = 1
Date of Event	1992 = 2; 1998 = 1;
Report Location	Domestic = 4

One representative case is listed below.

ISR# 919622-5, MFG# 00021908, Domestic

A female patient of unknown age received nafarelin 800 mcg and Pergonal for an unknown indication. She experienced an anaphylactic reaction. The reaction was characterized by shortness of breath, chest tightness, and a cold and clammy feeling. No information on treatment or the outcome of the event was available.

DISCUSSION

Thirty-one cases were identified when AERS was searched using the term "Anaphylaxis (All Forms)." Seventeen cases were identified in the April 1999 DDREII review. Only two of the latter cases were duplicated in the "anaphylaxis" results. The April 1999 search encompassed a broader scope, including hypersensitivity reactions, anaphylactic-type reactions, and immune system reactions. For example, dyspnea, rash, and angioedema are a few of the search terms associated with anaphylaxis, which were used in the 1999 search. These cases did not have to include the term "anaphylaxis" to be a part of the case series. However, the results of the most recent search involved only cases that specifically used the term anaphylaxis.

Seventy-four percent of the anaphylaxis cases were associated with leuprolide. Even though leuprolide was the first GnRH approved, the distribution of cases is fairly equal

throughout the years. During 1993-1995 ten cases were received for leuprolide, however, during the remaining years only one case per year was received.

Fifty-one percent of the thirty-one anaphylaxis cases occurred after the initial dose of medication. Thirty-two percent of the cases occurred after subsequent doses of the suspect drugs. The timing of occurrence of anaphylaxis could not be determined in the remaining cases. In one case, the patient had taken 12 monthly injections before anaphylaxis occurred. It should be noted that the onset of symptoms was immediate in some cases but occurred as late as two weeks post dose in other cases.

The list of symptoms experienced in these anaphylaxis cases varied. The most frequently reported symptoms were shortness of breath, chest tightening, and pruritus. However, other events such as rash, urticaria, hypotension, and edema (e.g., throat and face) were also reported. The April 1999 review searched specifically on these terms and identified cases very similar to those identified in this review. The only difference was that the terms were not collectively listed under the anaphylaxis term.

An evaluation of the approved product labeling shows that the cetrorelix, goserelin, and leuprolide labeling contain varied statements pertaining to the possible occurrence of anaphylactic reactions. However, statements in both the goserelin and leuprolide labeling pertain to class affects (i.e., synthetic GNRH), whereas the cetrorelix labeling pertains to a case specifically associated with cetrorelix. The nafarelin labeling does not mention *anaphylactic reactions*, but notes that *drug sensitivity* occurred in approximately 2.6% of the clinical trial patients. It should be noted that the symptoms experienced in these drug-sensitivity cases were the same symptoms noted in some of the anaphylaxis cases reviewed (i.e., shortness of breath, chest pain, urticaria, rash, and pruritus).

The proposed abarelix labeling refers to similar adverse events (i.e., generalized rash, urticaria, pruritus, tingling, and flushing) as transient allergic events. This labeling notes that these events resolved spontaneously or with oral corticosteroids and/or diphenhydramine. The abarelix labeling also notes that epinephrine and intravenous corticosteroids were only *rarely* used for the patients who experienced a more severe adverse event--drop in blood pressure and temporary loss of consciousness. The majority of anaphylaxis cases reviewed for goserelin, leuprolide, and nafarelin were also treated with oral or intravenous corticosteroids and/or antihistamines.

Some of the limitations identified while reviewing these cases include the following:

1. Individual symptoms (e.g., pruritus, urticaria, hypotension, etc.) may be reported and not collectively called anaphylaxis.
2. The recognized level of underreporting experienced when using a spontaneous reporting system.
3. The unavailability of the actual number of prescriptions dispensed or units used in practitioners offices.

These limitations hamper OPDRA's ability to accurately estimate the reporting rate of anaphylaxis for the GnRH antagonists.

OPDRA CONCLUSION

Clinical trial or postmarketing cases of anaphylaxis has been reported for cetrorelix, goserelin, leuprolide, and nafarelin. Cases that include adverse event terms that collectively could be called anaphylaxis have also been reported. Using spontaneous reporting data, OPDRA cannot determine the incidence of anaphylaxis with the GnRH antagonists. Therefore, OPDRA cannot compare the incidence of anaphylaxis of the GnRH antagonists to the proposed 1% incidence for abarelix.

However, the labeling for all of the GnRH antagonists should describe the possible occurrence of anaphylaxis. These statements should be consistent, in that; identical symptoms with similar severity should be labeled the same, and not be called three different terms (i.e., anaphylaxis, drug sensitivity, or transient allergic reactions).

/S/ Denise P. Toyer
Denise P. Toyer, Pharm.D.
Safety Evaluator

Concur:

/S/ Debra E. Boxwell
Debra E. Boxwell, Pharm.D.
Team Leader

/S/ Kathleen Uhl 3/10/2001
Kathleen Uhl, M.D.
Acting Division Director

PID# D010038

cc:

Orig. NDA(s): 19-010, 19-726, 19-732, 19-886, 19-943,
20-011, 20-109, 20-515, 20-517, 20-578,
20-708, 21-197, 21-320
HFD-580/DIVISION FILE
HFD-580/DeGuia/Best/Monroe/Hirsch/Allen
HFD-440/Uhl/Boxwell/Toyer/Green

/s/

Denise Toyer
3/28/01 03:00:37 PM
PHARMACIST

Kathleen Uhl
3/30/01 01:05:36 PM
MEDICAL OFFICER

TO: MARY DEMPSEY, Regulatory Health Project Manager
OPDRA Safety Evaluation; HFD-440; PKLN; Room 15B18

FR: SCOTT MONROE MD
Division of Reproductive and Urologic Drug Products; HFD 580

RE: Serious drug reactions in patients treated with Lupron

DATE: January 25, 2001

CC: D. Shames MD, M. Hirsch MD

The Division of Reproductive and Urologic Drug Products is reviewing NDA 21-320 for use of abarelix, a gonadotropin-releasing hormone (GnRH) antagonist, for the palliative management of prostate cancer when androgen suppression is indicated. Abarelix is a new molecular entity and is the first GnRH antagonist to be reviewed for long-term therapeutic use. Abarelix may offer some significant clinical benefits compared to Lupron and other GnRH agonistic analogs (e.g., Zoladex) because it does not initially stimulate the secretion of testosterone and more rapidly suppresses testosterone to castrate levels. Because of this, NDA 21-320 has been given priority review status.

During our preliminary review of this NDA, we have noted that a few patients treated with abarelix experienced severe, anaphylactic-like allergic reactions very shortly after repeat IM dosing. To assist us in our assessment of the overall risk/benefit ratio for abarelix, we are requesting your assistance. In particular, we are requesting that you review for us the reported post marketing occurrence of significant drug-associated allergic reactions in (1) men receiving Lupron for the management of prostate cancer and (2) women receiving Lupron for the treatment of endometriosis or uterine fibroids. If possible, we also request that you review the reported occurrence of similar allergic drug-associated reactions in IND clinical trials with Lupron.

It is my understanding that Freshnie De-Guia has already provided you with a copy of the proposed drug label for abarelix. I can be contacted by telephone at 827-3203 or by e-mail (MONROES) should you wish to discuss this request with me.

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

Controlled Substance Review is not applicable on this review cycle.

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NDA 21-320

Meeting Minutes

Date: January 24, 2001 **Time:** 10:00 – 11:00 AM **Location:** PKLN; Room 13B-45

NDA 21-320 **Drug Name:** Plenaxis (abarelix for suspension)

Indication: Palliative treatment of advanced prostate cancer

Sponsor: Praecis Pharmaceuticals, Inc.

Type of Meeting: Filing Meeting

Meeting Chair: Dr. Susan Allen

Meeting Recorder: Ms. Eufrecina DeGuia

FDA Attendees:
Susan Allen, M.D., M.P.H. – Director, Division of Reproductive and Urologic Drug Products DRUDP (HFD-580)
Daniel Shames, M.D. – Deputy Director, DRUDP (HFD-580)
Mark Hirsch, M.D. - Team Leader DRUDP (HFD-580)
Scott Monroe, M.D. – Medical Officer, DRUDP (HFD-580)
George Benson, M.D. – Medical Officer, DRUDP (HFD-580)
Ashok Batra, M.D. – Medical Officer, DRUDP (HFD-580)
Eufrecina De Guia - Regulatory Project Manager, DRUDP (HFD-580)
Terri Rumble - Chief, Project Management Staff, DRUDP (HFD-580)
Moo-Jhong Rhee, Ph.D. - Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Ameeta Parekh, Ph.D. – Team Leader, OCPB @ DRUDP (HFD-580)
Dhruba Chatterjee, Ph.D. – Biopharmaceutics Reviewer, OCPB @ DRUDP (HFD-580)
Swapan De, Ph.D. - Chemistry Reviewer, DRUDP (HFD-580)
Kim Colangelo, B.S. – Senior Regulatory Associate, DRUDP (HFD-580)
Krishan Raheja, D.V.M., Ph.D. - Pharmacologist, DRUDP (HFD-580)
Kate Meaker, M.S. - Statistician, Division of Biometrics II (DBII) @ DRUDP (HFD-580)
Barbara Chong, Ph.D. - Regulatory Reviewer, Division of Drug Marketing and Communication (DDMAC; HFD-40)
Elena Ibarra-Pratt, R.N., M.P.H. – Consumer Safety Officer, Division of Scientific Investigations, Good Clinical Practice Branch 1 (HFD-46)
Susan Molchan, M.D. – Senior Regulatory Review Officer, Division of Scientific Investigations, Good Clinical Practice Branch; GCPB (HFD-46)

Meeting Objectives: To determine the fileability of this application.

Background: This NDA was submitted on December 11, 2000. Plenaxis (abarelix for suspension) is a gonadotropin-releasing hormone (GnRH) antagonist for the palliative management of prostate cancer when androgen suppression is indicated. Abarelix is a new molecular entity and is the first antagonist to be reviewed for long-term therapeutic use. It may offer some clinical advantage over other GnRH analogs like Lupron and Zoladex because it does not initially stimulate the secretion of testosterone and suppresses

testosterone to castrate levels more rapidly. Accordingly, the Division has determined this NDA will be designated a priority review.

The related INDs are IND 51,710 ——— The User Fee goal date is June 12, 2001.

Decisions Reached:

Clinical

- the clinical section of this NDA includes nine studies, eight studies conducted in men with prostate cancer and one study conducted in healthy males:
    - there were four controlled clinical studies in men with prostate cancer using abarelix depot
        - two phase 3 pivotal studies; 149-98-02 and 149-98-03, both conducted in US
        - one supportive phase 3 study; 149-99-03, conducted in US and Canada
        - one phase 2 study
    - one uncontrolled study in men with prostate cancer in whom treatment with GnRH agonist might be considered inappropriate by some clinicians (Study 98-04)
    - two phase 1/2 uncontrolled studies with abarelix in solution administered by continuous infusion
    - one PK study in healthy men (both depot and solution formulations)
    - one supportive safety study sponsored by Sanofi-Synthelabo (86 men treated with abarelix depot)
- total number of men treated with registration doses of abarelix depot for safety:
    - for any exposure – 810 men
    - for six months – 720 men
    - for one year – 188 men
- the two phase 3 studies and the supportive Phase 3 study are randomized, open-label, comparative (with Lupron Depot alone and Lupron Depot + Casodex) in men with prostate cancer
- in all studies, both Lupron and Abarelix were administered every 28 days for 24-week period; abarelix was administered on Day 15 and 28 and every 28 days thereafter; investigators had the option to continue treatment for an additional 24 weeks
- the primary efficacy endpoints are:
    - achievement and maintenance of medical castration from Day 29 through Day 85 (with medical castration defined as serum testosterone $\leq$ 50 ng/dL on Day 29 with no two consecutive T values > 50 ng/dL two weeks apart between Days 29 and 85, inclusive)
    - avoidance of testosterone surge
    - rapidity of medical castration
- safety may be a significant issue; the safety profile appears to be similar with Lupron with two possible exceptions, liver toxicity and systemic allergic reactions; the application will be consulted to OPDRA for a Safety Assessment and Evaluation; in addition, the proposed labeling, mentions the use of Plenaxis ——— being associated with transient and reversible transaminase elevations
- sponsor will be asked to also screen for IgE class of antibodies, not just for IgG class antibodies in patients who experienced systemic allergic reactions
- for Protocol 149-98-04, abarelix does appear to be effective in this group of patients at risk for GnRH agonists administration; all high risk patients with metastatic prostate cancer did avoid an orchiectomy through Days 29 and 85 and all but one did achieve castrate testosterone levels at Day 29; Abarelix monotherapy would not be appropriate for patients with acute neurologic disorders from spinal cord compression

- certain narratives for patients who experienced severe AEs and/or SAEs will be requested from the sponsor
- additional safety and efficacy issues will be addressed during the review; the Division does not intend to take this application to an Advisory Committee but would opt for a Pre-decisional Meeting if necessary
- this NDA is fileable from a clinical perspective; overall clinical program particularly phase III studies appear to be well-designed and adequate; the submission is well organized and appear to include all required components

Chemistry
- the application is fileable from a chemistry perspective; there are manufacturing sites that have been requested for inspection; whether the stability data and analysis provided support the requested expiration date is a review issue

Pharmacology and Toxicology
- the application is fileable; all the required studies were submitted

Clinical Pharmacology and Biopharmaceutics
- the application is fileable; it appears to be adequately organized; complete pharmacokinetic (PK) and pharmacodynamics (PD) studies were submitted

Biometrics
- the application is fileable; SAS datasets and documentation were submitted to the Electronic Document Room

Microbiology
- the application is fileable

DSI
- four sites have been identified and requested for inspection

Action Items:
- the Division will call sponsor for additional safety data, particularly for the 149-98-04 study

Signature, minutes preparer

Concurrence, Chair

cc:
NDA Arch:
HFD-580/Division File
HFD-580/ SAllen/MRhee/AParekh/DShames,TRumble/SDe/DChatterjee/MHirsch/GBenson/ABatra
KRaheja/Kcolangelo
HFD-400/Smolchan/EPratt
HFD-42/BChong

Concurrences:
TRumble02.21.01/DShames,MRhee,KRaheja,Epratt,GBenson02.22.01/KColangelo,KMeaker/ABbatra02
.26.01/SMonroe,SDe03.06.01/MHirsch03.13.01/Dchatterjee03.14.01
No Concurrence: BChong,SMolchan

/s/

Susan Allen
3/20/01 09:49:16 AM

MEMORANDUM
SERVICES

DEPARTMENT OF HEALTH AND HUMAN

PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND

RESEARCH

Date: January 8, 2001

To: Susan Molchan, GCPB Reviewer/HFD-46

From: Eufrecina DeGuia, Regulatory Project Manager, HFD-580

Subject: **Request for Clinical Inspections**
NDA 21-320 (PRIORITY REVIEW; SIX-MONTH CLOCK)
Praecis Pharmaceuticals Incorporated
Plenaxis (abarelix for suspension)

Protocol/Site Identification:

As discussed with you, the following protocols/sites essential for approval have been identified for inspection. These sites are listed in order of priority.

Indication	Protocol #	Site (Name and Address)
Palliative treatment of advanced prostate cancer	149-98-02	Norman Zinner, M.D. Western Clinical Research, Inc. 23451 Madison St. Suite 240 Torrance, CA. 90505
- same as above-	149-98-02	Donald Gleason, M.D. Advanced Clinical Therapeutics 5300 E. Erickson Drive, Suite 106 Tucson, AZ 85712
-same as above-	149-98-03	William Friedel, M.D. 8851 Center Drive, Suite 501 La Mesa, CA 91942
-same as above-	149-98-03	Winston Barzell, M.D. Urology Treatment Center 1921 Waldemere St. Suite 310 Sarasota, FL 34239

Note: International inspection requests or requests for five or more inspections require sign-off by the ORM Division Director and forwarding through the Director, DSI.

Goal Date for Completion:

We request that the inspections be performed and the Inspection Summary Results be provided by (inspection summary goal date) **May 12, 2001**. We intend to issue an action letter on this application by (action goal date) **June 12, 2001**.

Should you require any additional information, please contact Eufrecina DeGuia.

Concurrence: (if necessary)
Mark Hirsch, M.D., Medical Team Leader
Scott Monroe, M.D., Medical Reviewer

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/s/

Eufrecina deGuia

4/19/01 02:26:11 PM

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

There was no DSI GLP Inspection for this application.

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/s/

Khin U
7/24/03 09:22:52 AM

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PATIENT INFORMATION SUBCOMMITTEE (PISC) Meeting

October 9, 2003

Attendees: Piazza Hepp, Toni D; Trontell, Anne E; Stifano, Toni; Lechter, Karen J; Wheelock, Leslie D; Burke, Laurie B; Houn, Florence; Dempsey, Mary; Hirsch, Mark S; Shames, Daniel A; Batra, Ashok; Best, Jeanine A; Winestock, Karen; Crisostomo, Nenita; Monroe, Scott; Kober, Margaret

Meeting Recorder: Leslie Stephens

1. *Discussion of the need for a Medication Guide for Abarelix (NDA 21-320)*

Background: Scott Monroe

- Primary risk: anaphylactic-type reactions
- Drug will be administered in an doctor's office
- Mandatory post injection waiting period for patients
- Issues with distribution of patient package insert (PPI) or Medication Guide (MG) prior to each dose in the office setting
  - possibly include a patient attestation signature or some type of Informed Consent)
- The Division believes that restricted distribution of abarelix, preferably under Subpart H, is necessary to ensure that abarelix will be used only for therapy of advanced symptomatic prostate cancer, which is a patient subgroup for whom the risk benefit ratio is favorable. The division has proposed that the risk-management program (RMP) for abarelix should possibly include a Medication Guide. This reasoning appears to be consistent with two of the three criteria specified in the regulations for the Medication Guide (21 CFR § 208.1 (c)(1)(2), which states:
  - The drug product is one for which patient labeling could help prevent serious adverse effects.
  - The drug product is one that has serious risk(s) (relative to benefits), of which patients should be made aware because information concerning the risk(s) could affect patients' decision to use, or to continue to use, the product.

Decision:

- The PISC supports a Medication Guide for abarelix pending concurrence from Office of Medical Policy (who did not have representation at the meeting).

Actions:

- The review division will discuss the potential need for a Medication Guide as part of the Risk Management strategy with the sponsor.
- The division will follow-up with the PISC regarding final decision on requesting a Medication Guide from the sponsor

2. [ ]

Background:

- [ ]

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Teleconference Minutes

Date: October 26, 2000 Time: 1:30 – 2:00 PM Location: PKLN; RM 17B-45

IND 51,710 Drug Name: Abarelix Indication: Treatment for Prostate Cancer

Sponsor: Praecis Pharmaceuticals

Type of Meeting: Guidance (Chemistry)

Meeting Chair: Dr. Moo Jhong Rhee External Participant Lead: JD Bernardy

Meeting Recorder: Ms. Eufrecina DeGuia

FDA Attendees:
Moo Jhong Rhee, Ph.D. – Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ Division of Reproductive and Urologic Drug Products; DRUDP (HFD-580)
Eufrecina DeGuia - Regulatory Project Manager

External Constituents:
Praecis
JD Bernardy, J.D. – Vice President, Regulatory Affairs
Nick Barker, Ph.D. – Vice President, Development
Carol Hurt – Regulatory Affairs Associate
Mark Staples, Ph.D. – Director, Pharmaceutical Sciences

Meeting Objective: To discuss further the naming convention issues for Abarelix raised in a September 27, 2000 submission and to come in agreement an established name for the drug product.

Background: Praecis is currently preparing an NDA for abarelix 100 mg. It is anticipated to be submitted by December 2000. The naming convention was initially discussed at a pre-NDA meeting on July 27, 2000 wherein the Division recommended "abarelix for suspension" for the established name since acetate form of the drug substance is utilized for the manufacture of the final formulation of the drug product. Praecis submitted a request to remove from the established name and provided a rationale in a September 27, 2000 correspondence. In response to this request, the Division consulted with Labeling and Nomeclature Committee (LNC) and Office of New Drug Chemistry (ONDC) management for guidance.

Decision Points:
- "abarelix for suspension" is acceptable as the established name since is not in the final dosage form
- the Formulation Table in the Drug Product Section of the NDA should indicate form with an explanation that is removed during the manufacturing process, that it does not exist in the final formulation

- [redacted]
- in the **DESCRIPTION** section of the label, the sponsor needs to include an explanation that [redacted] form is used, but the final form is a complex with carboxymethylcellulose for slow release
- the sponsor was advised to apply for a USAN established name for abarelix [redacted]

/S/ 11/14/00
[redacted]
Signature, minutes preparer

/S/ 11/14/00
Concurrence, Chair

NOTE: These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you have regarding the meeting outcome.

Meeting Minutes

Date: July 20, 2000 Time: 10:00 – 11:30 AM Location: Chesapeake Room

IND 51,710 Drug Name: Abarelix Indication: Palliative Treatment for Prostate Cancer

Sponsor: Praecis Pharmaceuticals

Type of Meeting: Pre-NDA Meeting

Meeting Chair: Dr. Susan Allen External Participant Lead: JD Bernardy

Meeting Recorder: Ms. Eufrecina DeGuia

FDA Attendees:
Susan Allen, M.D., M.P.H. - Director, DRUDP (HFD-580)
Daniel Shames, M.D. - Acting Deputy Director, DRUDP (HFD-580)
Mark Hirsch, M.D. - Acting Team Leader, DRUDP (HFD-580)
George Benson, M.D. - Medical Officer, DRUDP (HFD-580)
Eufrecina DeGuia, Regulatory Project Manager - DRUDP (HFD-580)
Moo-Jhong Rhee, Ph.D. - Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Swapan De, Ph.D. - Chemist, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Ameeta Parekh, Ph.D. - Pharmacokinetic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Venkat Jarugula, Ph.D. - Pharmacokinetics Reviewer, OCPB @ DRUDP (HFD-580)
Kate Meaker, M.S. - Statistician, Division of Biometrics II (DBII) @ DRUDP (HFD-580)
Scott Monroe, M.D. - Medical Officer, DRUDP (HFD-580)

External Participants:
Marc Garnick, M.D. – Executive Vice President, Chief Medical and Regulatory Affairs, PRAECIS
JD Bernardy, JD – Vice President, Regulatory Affairs, PRAECIS
Marilyn Campion, MS – Senior Director, Biostatistics, PRAECIS
Nick Barker, Ph.D. – Vice President, Development, PRAECIS

Richard Gural – Vice President, Regulatory Affairs, SANOFI-SYNTHELABO

Meeting Objective: To discuss key issues impacting the sponsor's NDA preparation.

Background: Praecis is currently preparing an NDA for abarelix , 100 mg. It is anticipated to be submitted by the third or fourth week of December 2000. Draft questions were submitted on May 17, 2000 and subsequently updated and revised on the submissions dated June 20, July 5, 12 and 17, 2000.

Decision Points:

1:1: Does the agency concur with the proposed drug product names;

-
-

- **the sponsor was advised to apply for a USAN established name for abarelix —— before the NDA is approved**

1:2: Praecis intends to include a batch record abstract for the API in accordance with the agreements reached at the 10 Feb 1999 CMC Guidance meeting (Question 6 of FDA minutes of 10 Feb 1999). Praecis intends to submit complete blank batch records for the drug product intermediate and the drug product in the NDA. Praecis is not planning to provide completed sample batch records with the NDA Batch Documentation. Does the Agency concur with this approach?

- **one executed batch record from a stability or clinical lot would be required**

2:1 It is planned that items 11 and 12, Case Report Tabulations (CRT) and Case Report Forms (CRF), will be prepared in electronic form (no paper submitted). No other portions of the NDA are planned for electronic submission.

A demostration set of CRTs on CD-ROM was provided for review. Please advise on CD-ROM improvements that could be made, in writing, at the time of the meeting.

- **the Division cannot recommend any improvements pending receipt of the official submission; the CD-ROM of demonstration CRT was acceptable**
- **final database has to be in a usable format**

It is anticipated that Quality of Life (QOL) and pharmacoeconomic (PE) data will be presented in the electronic form only. Does the Agency concur with this approach?

- **yes, the approach is acceptable; only clinical data, not the QOL and Medical Resource Utilization (MRU) will be submitted electronically**

Electronic CRFs for patients who died or discontinued due to adverse events will be supplied for Studies 149-98-02, 149-98-03 and 149-99-03 only. A demonstration CD-ROM was provided for review. Does the Agency concur with this approach and presentation of this electronic component of the NDA?

- **Division may want full SAE data to be submitted, including narratives and Case Report Forms (CRF); elevated LFTs, histamine release, skin irritation are concerning; deaths and discontinuations due to AEs should also be included; the Division will determine whether the SAEs are drug related or not**
- **the sponsor confirmed that SAEs will be submitted in electronic format**

2.2 To further characterize a composite endocrine efficacy profile of the product, Praecis proposes to add an estimate of the overall "achieve and maintain" castration rate from day 29 through day 85 for all patients who were scheduled to receive abarelix 100 mg IM, on days 1, 15, 29 and 57. (This included 784 patients accrued in the Studies 149-98-02, 149-98-03, 149-98-04 and 149-99-03, but does not include approximately 75 patients in the on-going ABACAS-1 Study, being conducted in Europe by Sanofi- Synthelabo.) Does the Agency concur with this approach?

- proposal to add an estimate to "achieve and maintain" castration rate for the patients described is acceptable
- the data from this estimate will need to be reviewed by the Division
- report should be made separately for each study

2.3: Praecis intends to submit data from Phase 3 studies 149-98-02, 149-98-03 and 149-99-03 as the principal safety data. These studies involve approximately 1100 patients (>730 abarelix treated for 24 weeks, >250 abarelix treated for 52 weeks.) Does the Agency concur with this plan for the NDA safety data?

- Yes; and for Safety Update (SU), complete six-months follow-up data should be provided

2.4: On Abarelix usage

- this will be a review issue; the Division will have to review the proposed label

2.5: Does the Agency agree with the proposed data cut-off points for the NDA?

- yes, the Division agrees on the proposed data cut-off points

2.6: On Safety Update

- sponsor was advised that SU is required within 120 days after the initial submission

Additional comments:

- the abarelix NDA application may qualify for a priority review; however, final determination of priority review status will still be made at submission
- from a CMC perspective, if priority review status is granted, sufficient stability data for the product should be included for review at the time of submission
- the sponsor confirmed that the clinical formulation is identical to the to-be-marketed formulation
- for Section 6, Human Pharmacology and Bioavailability/Bioequivalence, of the NDA, the sponsor was advised to provide the following:
  - results of dose finding studies
  - *in-vitro/in-vivo* metabolism studies
  - ADME profile and mass balance data
  - single and multiple dose PK
  - information on Drug-drug interaction potential or rationale on why they were not studied/applicable
  - information in special populations (age, race, weight, renal/hepatic impairment) or rationale why they were not studied/applicable
  - *in-vitro* dissolution information
  - Microsoft WORD text files of Section 6, if available

Action Items:

- Minutes will be sent to sponsor within 30 days

/S/ 8/8/00
Signature, minutes preparer

/S/ 8/8/00
Concurrence, Chair

NOTE: These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you have regarding the meeting outcome.

Teleconference Minutes

Date: June 27, 2000 Time: 3:00 – 3:30 PM Location: PKLN; RM 17B-45

IND 51,710 Drug Name: — Indication: Treatment for Prostate Cancer
IND — Drug name: — Indication:

Sponsor: Praecis Pharmaceuticals

Type of Meeting: Guidance (Chemistry)

Meeting Chair: Dr. Swapan De External Participant Lead: JD Bernardy

Meeting Recorder: Ms. Eufrecina DeGuia

FDA Attendees:
Swapan De, Ph.D. – Chemistry Reviewer, Division of Reproductive and Urologic Drug Products DRUDP (HFD-580)
Eufrecina DeGuia - Regulatory Project Manager

External Constituents:
JD Bernardy, J.D. – Vice President, Regulatory Affairs
Nick Barker, Ph.D. – Vice President, Development
Jim Majewski – Director, Quality Assurance
Mark Staples, Ph.D. – Director, Pharmaceutical Sciences

Meeting Objective: To discuss key issues impacting the sponsor's NDA preparation regarding the change in the site for final drug manufacturing for abarelix — necessitated by the closure of the current drug product filling site, —

Background: Praecis is currently preparing an NDA for abarelix — 100 mgs. It is anticipated to be submitted by Fourth Quarter 2000. With the imminent closure of — the drug product — being transitioned to — Praecis proposes to provide 12-month stability data on — manufactured drug product as the primary NDA drug product stability.

Decision Points:
Question 1: Does the Agency concur with the naming conventions?
Answer:

- Sponsor may use the code name and other names for intermediate products and maintain it consistently throughout the submission. A proposal for trade name and established name should be submitted for review (sponsor is aware of the current Center policy and the upcoming guidance document soon to be released that a single proprietary name should be submitted for — indication — prostate cancer).

- The Division will re-confirm established name of the drug product at the upcoming pre-NDA meeting.

Question 2: Does the Agency concur with an NDA submission containing:

a) **three — lots with up to 12-month real-time stability data as primary drug product stability data?**
b) **one — drug product lot with 3-month real-time and accelerated data?**
c) **a shelf-life assignment of at least — at the time of approval?**
d) **updates during the NDA review for additional — (18-month) and — (6-9 month) stability data?**

Answer:

The detailed information of drug product manufacturing in the — sites should be submitted. All aspects of each step and how it is different from that used in — should be described in parallel to each other for review and should also include details of the process and equipment changes and batch analysis from both sites.

The following comments were conveyed to the sponsor in response to the above questions:

a) Three — lots up to 12 months are acceptable for the initial submission; sponsor will update with — stability data for all three lots.
b) Since the marketed drug will be manufactured from — site, it is important to submit as much stability data as possible from — sites. Usually, stability data from three lots manufactured from — sites would be required in this case. Sponsor proposed to submit one lot with three-months stability data and two release lots during submission of NDA. Furthermore, sponsor will submit an update of nine months stability data for the first lot and six months stability data for the later two lots.
c) Shelf-life of the drug product will be a review issue; proposal should be submitted
d) The sponsor requested to submit stability update two and a half months prior to goal date instead of the three months requirement from the Division; granting such request will be confirmed at the upcoming pre-NDA meeting.

Additional comment:

- Data from — lots will be considered as supportive data, not primary data.

Question 3: Does the Agency concur that the date of — should be delineated the "date of manufacture" of the drug product?

Answer:

Manufacturing date of the abarelix-CMC at — should be the date of manufacturing of the drug product; since — increases the impurities in the drug product it might be necessary to have in-process specifications for the initial manufacturing steps (up to filling in the vials) and release steps specifications following — However, date of — could be considered as "date of manufacture" of the drug product provided that:

a) sponsor's proposal of a reasonable time limit of the use of abarelix-CMC to it's filling in vial as well as time limit in between the steps of the filling and — of the filled vials
b) sponsor's specified proposal of storage condition for the drug product intermediate until — (this comment was conveyed to the sponsor via telephone after the teleconference meeting ended)

7.13.00
Signature, minutes preparer

7/13/00
Concurrence, Chair

Teleconference Meeting Minutes

Date: March 30, 2000 **Time:** 2:25-2:30 pm **Location:** Parklawn; 17-B45

IND 51,710 **Drug:** Abarelix

Indication: Palliative treatment of advanced prostate cancer

Sponsor: Praecis Pharmaceuticals, Inc.

Type of Meeting: Teleconference

Meeting Chair: Dr. Dan Shames

External Lead: J. D. Bernardy, J.D.

Meeting Recorder: Ms. Jeanine Best

FDA Attendees:
Dan Shames, M.D., Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP, HFD-580)
Jeanine Best, M.S.N., R.N., Regulatory Project Manager, DRUDP (HFD-580)

External Participants:
Praecis Pharmaceuticals, Inc.:
J. D. Bernardy, J.D., Vice President, Regulatory Affairs

Meeting Objective: To respond to March 27, 2000, serial number, 108, submission and relay Divison decision regarding the acceptable statistical analysis plan for their studies.

Background:
The sponsor has had ongoing concerns with the statistical analysis plans for their data and has submitted additional information to support their position.

Decisions:
Definition 2 will be the acceptable primary method of analysis. Definition 1 will be utilized for secondary analysis.

Definition 1	Requires patients to achieve and maintain castration on all days that testosterone was measured between Days 29 and 85, inclusive.
Definition 2	Requires that patients not have 2 consecutive non-castrate testosterone values 2 weeks apart between Days 29 and 85, inclusive.

Action Items:

- Sponsor to request pre-NDA meeting when ready with relevant pre-NDA issues

/S/

Minutes Preparer

/S/

Concurrence, Chair

Note to Sponsor:

These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes.

Teleconference Meeting Minutes

Date: March 8, 2000 **Time:** 11:30 am-12:00 pm **Location:** Parklawn; 17-B45

IND 51,710 **Drug:** Abarelix

Indication: Palliative treatment of advanced prostate cancer

Sponsor: Praecis Pharmaceuticals, Inc.

Type of Meeting: Teleconference

Meeting Chair: Dr. Dan Shames

External Lead: Dr. Marc B. Garnick

Meeting Recorder: Ms. Jeanine Best

FDA Attendees:
Dan Shames, M.D., Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP, HFD-580)
Jeanine Best, M.S.N., R.N., Regulatory Project Manager, DRUDP (HFD-580)

External Participants:
Praecis Pharmaceuticals, Inc.:
Marc B. Garnick, M.D., Executive Vice President and Chief Medical Officer
J. D. Bernardy, J.D., Vice President, Regulatory Affairs

Meeting Objective: To discuss pre-NDA meeting package received 3/7/00, and necessity for pre-NDA meeting at this time.

Background:
The sponsor requested and had a pre-NDA meeting scheduled with the Division for March 29, 2000. The meeting package received on March 7, 2000 contains clinical and statistical information only, and it essentially revisits the statistical analysis plans that were discussed previously with the sponsor in 1999.

Discussion:
- Fileability and approvability of an NDA cannot be determined until the NDA is received and reviewed by the Division
- Division generally grants only one Pre-NDA meeting; it is usually discipline inclusive, and plans for NDA submission are discussed
- Sponsor has continuing concerns with the statistical analysis plans for their data and feel that the Division is holding them to stricter standards; sponsor is proposing a superiority claim for their drug product so more rigorous statistics are required
- Sponsor feels that the Division is too conservative with their definition of failures, pooling, and confidence intervals

- Sponsor is requesting reconsideration of the recommendations regarding the statistical analysis plan and clinical judgement with failures in the achievement and maintenance of castration

Decisions:

- Pre-NDA meeting scheduled for March 29, 2000 will be cancelled
- Sponsor to submit more information on the regulatory history of criteria for approval of GnRH agonists, individual testosterone values for failures in the clinical trials, and copies of overheads intended for the pre-NDA meeting for review by the clinicians and statisticians
- Division will schedule a T-con with the sponsor (after above materials have been reviewed) in order to discuss the statistical rationale regarding the data analysis plans
- Pre-NDA meeting will be rescheduled when the sponsor is prepared to discuss the usual items in a pre-NDA meeting; sponsor will submit a new meeting request and meeting package at that time

Action Items:

- Sponsor to submit the regulatory history of criteria for approval of GnRH agonists for this IND
- Sponsor to submit individual testosterene values of "failures" in their clinical trials
- Sponsor to submit copies of the overheads that were intended for use in the pre-NDA meeting
- Division to schedule T-con with sponsor after the above materials have been reviewed

Minutes Preparer **Concurrence, Chair**

Note to Sponsor:
These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes.

Meeting Minutes

Date: September 21, 1999 **Time:** 3:00 – 3:25 PM **Location:** Parklawn; 17-B43

IND 51,710 **Drug:** Abarelix

Indication: Prostate Cancer

Sponsor: Praecis Pharmaceuticals, Inc.

Type of Meeting: Teleconference

Meeting Chair: Dr. Dan Shames

External Lead: Dr. Marc B. Garnick

Meeting Recorder: Ms. Jeanine Best

FDA Attendees:
Dan Shames, M.D. – Team Leader, Division Of Reproductive and Urologic Drug Products, (DRUDP, HFD-580)
Norman Marks, M.D. – Medical Officer, DRUDP, (HFD-580)
Kate Meaker, M.S. – Statistician, DB II @ DRUDP, (HFD-580)
Jeanine Best, M.S.N., R.N. – Regulatory Project Manager, DRUDP, (HFD-580)

External Attendees:
Praecis Pharmaceuticals, Inc.:
Marc B. Garnick, M.D., Executive Vice President and Chief Medical and Regulatory Officer
Marilyn Campion, M.S., Senior Director of Biostatistics

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Meeting Objective: To discuss clarification of statistical analysis plans for achieving and maintaining castration.

Background: The sponsor intends to pursue ——— and has had previous discussions with the Division on appropriate endpoints and statistical analysis plans for these endpoints.

Discussion and Decision:
Question 1:
The sponsor proposes to apply the agency's guidance on equivalence testing for anti-infectives (DAIDP – Points to Consider 1998) to the comparative analysis of the appropriate endpoint. Is this acceptable to the agency?

- The primary endpoints must first establish comparable efficacy before the — / claims are considered; the data must demonstrate castration at day 29 and maintenance of castration through day 85; rapidity of onset and demonstration of decrease surge — cannot be primary endpoints without first establishing efficacy
- Lupron is expected to be around 90% effective in achieving castration, therefore, for Abarelix we would accept a 95%, 2-sided confidence interval of +/- 10%; we would not accept a value of 15% if the absolute efficacy of Lupron is less than 90%; a review issue on trial design and controls would ensue, and an explanation would be needed in the submission as to why Lupron (the active comparitor) performed less than anticipated

Question 2:
Is ——— acceptable for each of the three endpoints, if a successful outcome for all three endpoints is required for approval?

- Yes, but all three endpoints must be met; if one is missed, how the sponsor will handle the data must be defined; alternatively, the sponsor could go back to the original proposal, which is to first test for equivalence ——— and then follow with two analyses for — claims ———
- Praecis Pharmaceuticals, Inc., as a corporate marketing decision, [redacted]

Other Discussion:
Open ended discussion on Statitistical Analysis Plan for Protocols 149-98-02 and 149-98-03, Serial No. 080, September 7, 1999:

- the three primary endpoints listed are acceptable
- regarding the endpoint of achieving and maintenance of castration through planned visit day 85, the intent-to-treat population must be used for the primary analysis.
- the Cochran-Mantel-Haenszel (CMH) test for analysis is acceptable
- the Kaplan-Meier (KM) analysis is not necessary; it is a more conservative estimate than straight forward proportion; provide proportions (incidence rates) along with KM analysis; address withdrawals if they affect the efficacy results
- the sponsor will be unblinding and beginning the analysis of Protocols 149-98-02 and 149-98-03 in 10/99-11/99; results should be available in Spring 2000 and will be provided to the division
- sponsor will request a pre-NDA meeting in 1st quarter 2000 to be scheduled 2nd quarter 2000
- sponsor plans to submit their NDA in December 2000

Unresolved decisions:

- regulatory concerns regarding public release of [redacted] prior to NDA review, i.e., cannot make definitive conclusions prior to NDA approval

Action Items:

- Kate Meaker to provide a written review of the Statistical Analysis Plan for Protocols 149-98-02 and 149-98-03

/S/ MSN RN
Minutes Preparer

/S/ MD
Concurrence, Chair

Meeting Minutes

Date: June 18, 1999 **Time:** 11:00-12:30 PM **Location:** Parklawn; 13B-45

IND 51,710 **Drug:** Abarelix(PPI-149) **Indication:** Treatment of palliative advanced prostate cancer

Sponsor: Praecis Pharmaceuticals Incorporated

Type of Meeting: Guidance

Meeting Chair: Daniel Shames, M.D.

External Lead: Marc B. Garnick, M.D.

Meeting Recorder: Jennifer Mercier, B.S.

FDA Attendees:
Daniel Shames, M.D. – Team Leader, Division of Reproductive and Urologic Drug Products; (DRUDP; HFD-580)
Norman Marks, M.D. – Medical Officer, DRUDP (HFD-580)
Kate Meaker, Ph.D. – Statistician, Division of Biometrics II(DBII) @ DRUDP (HFD-580)
Jennifer Mercier, B.S. – Regulatory Project Manager, DRUDP (HFD-580)

External Attendees:
Praecis
Marc Garnick, M.D. – Executive Vice President, Chief Medical and Regulatory Officer
Marilyn Campion – Senior Director of Biostatistics
Bernice Kuca – Director of Clinical Research
Janice Swirski – Vice President of Operations

Sanofi-Synthelabo
Alan Kerr – Registration Manager, Internal Medicine, Corporate Regulatory Affairs

Meeting Objective: To discuss the May 28, 1999 submission and the ongoing drug development for this product.

Background: In a teleconference dated April 28, 1999, it was communicated that interim analysis of endocrine efficacy is not required to determine NDA fileability. This meeting is to discuss additional efficacy bulleted points reflected in those meeting minutes.

Discussion:

Decisions made:
Questions

5. Definition of Achievement and maintenance of castration from study day 29 through study day 85. Does the Agency concur with these definitions?

   - testosterone levels must be below 50 ng/dL
   - one breakthrough is considered a failure
   - all timepoints should be measured after Day 29; this also applies to the comparator arm

2. "Primary endpoint of achievement and maintenance of castration" Does the Agency concur that this is an acceptable approach?

   - the protocol does not need to be revised
   - achievement and maintenance will be the first item that the reviewers will evaluate

4. Pooling of data

   - the primary efficacy analysis data should be provided individually for each study
   - pooling of data may be used in the ISE
   - the protocols were designed as two studies; therefore, the results should be presented as two studies

3. [redacted] Claim

   -
   -

1. Rapidity of Action

   - [redacted]
   - testing of both claims with an "or" test would result in α being split again
   - this endpoint is totally independent of the maintenance and castration endpoints; although no other claims can be made unless the maintenance and castration endpoint is deemed adequate for approval

6. Liver Toxicity information/guidance

- there is no guidance available from the FDA liver toxicity meeting

Unresolved decisions: None

Action Items:

- fax meeting minutes to sponsor within 30 days

/S/

Minutes Preparer

/S/

Concurrence, Chair

Meeting Minutes

Date: May 5, 1999 **Time:** 3:00 – 3:30 PM **Location:** Parklawn; 17B-45

IND 51,710 **Drug:** PPI-149 **Indication:** Treatment of Prostate Cancer

Sponsor: PRAECIS

Type of Meeting: Guidance

Meeting Chair: Marianne Mann, M.D.

External Lead: Dr. Paul Martha

Meeting Recorder: Jennifer Mercier

FDA Attendees:
Marianne Mann, M.D. – Deputy Director, Division of Reproductive and Urologic Drug Products; (DRUDP; HFD-580)
Daniel Shames, M.D. – Team Leader, DRUDP (HFD-580)
Norman Marks, M.D. – Medical Officer, DRUDP (HFD-580)
Jennifer Mercier – Regulatory Project Manager, DRUDP (HFD-580)

External Attendees:
Dr. Paul Martha, PRAECIS

Meeting Objective: To discuss the purpose of the study.

Discussion:
- the purpose of the study is to determine a bioequivalent link to the injectable drug product and drug product

Decisions made:
- informed consent should let the patient know of the theoretical possibility that erectile dysfunction, if it occurs, may persist after treatment is discontinued

Unresolved decisions: None

Action Items:
- fax meeting minutes to Dr. Paul Martha within 30 days

Minutes Preparer

M.D.
Concurrence, Chair

Meeting Minutes

Date: April 28, 1999 **Time:** 9:00 – 10:00 AM **Location:** Parklawn; 17B-43

IND 51,710 – **Drug:** Abarelix **Indication:** Advanced Prostate Cancer

Sponsor: PRAECIS

Type of Meeting: Guidance

Meeting Chair: Marianne Mann, M.D.

Meeting Recorder: Jennifer Mercier

External Lead: Marc Garnick, M.D.

FDA Attendees:
Marianne Mann, M.D. – Deputy Director, Division of Reproductive and Urologic Drug Products (DRUDP); HFD-580
Daniel Shames, M.D. – Team Leader, DRUDP (HFD-580)
Norman Marks, M.D. – Medical Officer, DRUDP (HFD-580)
Kate Meaker, Ph.D. – Statistician, Division of Biometrics II (DBII) @ DRUDP (HFD-580)
Jennifer Mercier – Project Manager, DRUDP (HFD-580)

External Participant:
Marilyn Campion, Senior Director of Biostatitics, PRAECIS
Marc Garnick, Executive Vice President, Chief Medical and Regulatory Officer, PRAECIS
Bernice Kuca, Director of Clinical Research, PRAECIS
Janice Swirski, Vice President of Operations, PRAECIS

Alan Kerr, Registration Manager, Internal Medicine, Corporate Regulatory Affairs, Synthelabo

Meeting Objective: To discuss the accrual into Phase 3 studies.

Decisions made: (Questions)
1. In addition to patient exposure to Abarelix listed in Tables A1, A2, and A3, does the FDA require a review of endocrine efficacy data on all patients treated for at least 12 weeks on Protocol 98-02 to render an opinion regarding the filability of the proposed application?

- No, the FDA does not require a review of endocrine efficacy data on all patients treated for at least 12 weeks. Fileability decisions are based on the type and amount of data provided, while review of efficacy data is part of the NDA review process.

Clinical/Statistical

Safety

- a recent FDA liver toxicity seminar has raised the awareness regarding concerns with the liver function tests (LFT) rises with the use of any drug product
- abarelix may cause rises in LFTs, and this is concerning
- the lower limit of patients numbers recommended in the ICH guidelines (300-600 patients with 6-months of data and 100 patients with 1 year data) for NMEs is not adequate for a product with safety concerns that are significant
- the recent proposal is very minimal for an NME, the data needs support a very safe profile
- because of the elevated liver function tests, this application could go to an Advisory Committee for review
- data for this product are similar to that of products that have been removed from the market due to post-marketing findings of serious hepatotoxicity
- the histamine release is also of concern, a single report of skin reaction has been reported in this regard

Efficacy

- maintenance of testosterone suppression should be a primary endpoint
- line listings, as previously stated, should be provided for the medical review
- a statistical analysis should be done with a P-value of .025 and 97.5% two-sided confidence intervals for statistical adjustment for the primary endpoints of castration and maintanence
- —
- an equivalence limit should be proposed by the sponsor

Unresolved decisions: None

Action Items:

- fax meeting minutes to sponsor within 30 days

/s/

Minutes Preparer

/s/ N.D.

Concurrence, Chair

MEETING MINUTES

Date: February 10, 1999 **Time:** 9:30 - 10:30 AM **Location:** Parklawn; Conference Rm. "K"

IND: 51,710 **Drug Name:** Abarelix

Indication: GnRH antagonist for treatment of prostate cancer without testosterone surge

External Participant: Praecis Pharmaceuticals Incorporated

Type of Meeting: Guidance (Chemistry)

Meeting Chair: Dr. Marianne Mann **External Participant Lead:** Dr. Marc Garnick

Meeting Recorder: Ms. Diane Moore

FDA Attendees:
Marianne Mann, M.D. - Deputy Director, Division of Reproductive and Urologic Drug Product (DRUDP; HFD-580)
Norman Marks, M.D. - Medical Officer, DRUDP (HFD-580)
Diane Moore - Project Manager, DRUDP (HFD-580)
Randy Olmstead – Project Manager DRUDP (HFD-580)
Eufrecina Deguia – Project Manager, DRUDP (HFD-580)
Dornette Spell-LeSane – Project Manager, DRUDP (HFD-580)
Moo-Jhong Rhee, Ph.D. - Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Ameeta Parekh, Ph.D. - Pharmacokinetic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Venkateswar R. Jarugula, Ph.D. - Pharmacokinetic Reviewer, OCPB @ DRUDP (HFD-580)
Paul Stinavage, Ph.D. – Microbiologist, Office of New Drug Chemistry (ONDC; HFD-160)

External Constituents:
Dr. Marc Garnick – Executive Vice President and Chief Medical and Regulatory Officer (Praecis Pharmaceuticals, Inc.
Dr. Nick Barker – Vice President, Development (Praecis Pharmaceuticals, Inc.)
Mr. Jim Majewski – Director, Quality Assurance (Praecis Pharmaceuticals, Inc.)
Dr. Gary Musso – Director, Chemical Development (Praecis Pharmaceuticals, Inc.)
Dr. Malcolm Gefter – Chief Scientific Officer (Praecis Pharmaceuticals, Inc.)

Dr. Alain Cuine – Director, Analytical Chemistry and Pharmaceutical (Synthelabo Groupe)
Dr. Alan Kerr – Regulatory Affairs Manager (Synthelabo Group)
Ms. Helen Ribbans – Regulatory Consultant (for United States to Praecis)
Ms. Janice Swirski – Project Manager (Praecis Pharmaceuticals, Inc.)

Meeting Objective:
To discuss Chemistry and Biopharmaceutical issues for the filing of an NDA for Abarelix- for the reduction of serum testosterone devoid of testosterone surge.

Discussion Points:

- Clinical Pharmacology and Biopharmaceutics dissolution method trials
  - in certain media, greater than — % of the product is released in all lots in — minutes, this does not satisfy quality control standards; the sponsor has tried multiple combinations of dissolution times, buffers and speeds with unsatisfactory results
  - the product has a variable dissolution rate and is almost insoluble ——
  - carbon methyl cellulose is soluble in water, but it is not controlled; the product has a one-month release as a — product (the precipitate slowly dissolves over time)
  - a dissolution measurement has been proposed; while other products target — for dissolution time points, this product is dissolved in — minutes
  - although the *in vitro* dissolution for this product is not physiologically relevant, the Quality Control issue should be resolved; the sponsor has unsuccessfully attempted many solutions to this problem using the 50 mg dose
  - because the 50 mg dose does not suppress testosterone levels for one month, the sponsor is proposing to use the 100 mg dose for the minimum effective dose
- Chemistry and Manufacturing and Quality Control
  - this product contains —— amino acids in the peptide that have not been quantitatively analyzed; all should have the same degree of accuracy
  - two reference standards were made, one at — ; other at — differences between the two reference standards were seen in ——

Decisions reached:

- many of the questions submitted for this meeting cannot be addressed without review of the data; therefore, the questions will be answered according to fileability issues
- Chemistry and Manufacturing and Quality Control
  - a justification for the absence of the batch with the — impurity content from the toxicity study should be provided
- this NDA could qualify as a priority drug because of the characteristic of not having the testosterone flare at initial dosing

Drug Substance Concurrence Items:

- **Does the FDA concur?**

  Question 1. The test criteria proposed for —— materials used in the synthesis of the active pharmaceutical ingredient are adequate for the NDA.
  Answer: The —— amino acids should be established.

  Question 2. The in-process tests for the production of drug substance are adequate.
  Answer: Monitoring the completion of the reaction will be a review issue.

  Question 3. The lots intended to support stability —— were made by equivalent processes.
  Answer: An HPLC assay should be included in the protocol ——

  Question 4. The analytical tests in place adequately monitor the purity and stability of the API.
  Answer: a) Quantitative analysis of — amino acids should be performed
  b) specific optical rotation should be included in the NDA
  c) — should be controlled under ICH guidelines
  d) — tests should be included in the NDA with specification limits
  e) peptide content should be based on validated HPLC

Question 5. The plan for identification, qualification and control of related substances is adequate.
Answer: the proposed plan is acceptable

Question 6. A comprehensive batch record abstract is planned for inclusion within the NDA.
Answer: the proposed plan is acceptable, as long as crucial information is included

Question 7. The drug substance reference standard characterization and retest programs are acceptable for the NDA.
Answer: a) comparative structural data of reference standards from ——— should be provided
b) specific optical rotation should be tested during retest

Drug Product Concurrence Items

- **Does the FDA concur?**

Question 1. The tests proposed for Carboxymethylcellulose Sodium USP used in the manufacture of the drug product intermediate are adequate.
Answer: ——— of CMC should be demonstrated to be consistent
——— specifications should be included in the NDA for CMC Sodium

Question 2. During development and scale-up, the overall process has remained essentially equivalent.
Answer: overall, the process appears to be appropriate

Question 3. The in-process analytical tests proposed for drug product manufacture are adequate for the NDA.
Answer: Wide variation in ——— are noted

Question 4. The stability program (protocols and test methods) are adequate to support the expiration dating period of the drug product.
Answer: a) effect of ——— on sterility and stability will be a review issue
b) uniformity of viral content should be in accordance with USP
c) dissolution tests should be incorporated into the stability tests

Question 5. The proposed dissolution method and tentative specification are adequate.
Answer: a) the proposed method for the Clinical Pharmacology and Biopharmaceutics *in-vitro* dissolution method trials uses ——— sponsor should consider evaluating a ——— on the reconstituted product or the powder
b) the proposed *in vitro* dissolution section appears to be adequate for filing for the proposed NDA

Question 6. The analytical tests are sufficient to ensure the purity and stability of the drug product.
Answer: content uniformity test should follow USP procedure

Question 7. The plan for ——— of related substances in the drug product is adequate.
Answer: the proposed strategy is acceptable

Question 8. A 100 mg vial strength of abarelix —— is planned for development. It is anticipated that 6-month stability data will be available at the time of NDA filing to support a ——
Is this acceptable?
Answer: six months room temperature and six months accelerated data can be submitted at the time of NDA submission for ——

Action Items:

• Item:	Responsible Person	Due Date:
• incorporate appropriate information from meeting discussions into NDA	Praecis	with NDA submission

/S/ 3/25/99
Signature, minutes preparer

/S/
Concurrence, Chair
3/25/99

MINUTES of TELECON

Date: December 21, 1998 Time: 10:30 - 11:30 AM Location: Parklawn; Rm. 17B-43

IND: 51,710 Drug Name: Abarelix Indication: Prostate Cancer

External Participant: Praecis Pharmaceuticals Incorporated

Type of Meeting: Clinical Guidance

Meeting Chair: Dr. Dan Shames External Participant Lead: Dr. Marc Garnick

Meeting Recorder: Ms. Diane Moore

FDA Attendees:
Daniel Shames, M.D. – Urology Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Norman Marks, M.D. - Medical Officer, DRUDP (HFD-580)
Diane Moore - Project Manager, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

External Constituents:
Marc B. Garnick, M.D. – Executive Vice President and Chief Medical and Regulatory Officer, Praecis
Marilyn Campion, M.S. – Senior Director, Biostatistics, Praecis
Janice Swinski, R.Ph. - Project Management, Praecis

Meeting Objectives:
To discuss the liver function tests to be used in the clinical trials and to clarify the testosterone end-points of the Phase 3 studies (Protocols 149-98-02 and 149-98-03).

Background:
On October 28, 1998, a Teleconference was held between the Agency and representatives of Praecis to discuss the clinical development plan and maintenance dose of Abarelix to be used in protocols 149-98-02 and 149-98-03. The sponsor submitted a protocol change on November 6, 1998. The Agency requested this Telecon to discuss outstanding issues regarding the Phase 3 protocols.

Discussion Points:
- Protocol 02 defines the successful endpoint as achievement of castration at study Days 29 and 57 and maintenance of androgen ablation through study Day 85
- patients who never achieve castration levels of testosterone and are not able to maintain castration are unsuccessful
- the second annual report (to be submitted) will contain detailed information relating to the percentage of the patient population who developed elevated liver enzymes
- in the Phase 2 study, 37% of the patients had at least one elevated laboratory evaluation, including glucose and creatinine kinase, ALT, AST and alkaline phosphatase
- all liver enzyme elevations were transient; the abnormal LFT levels returned to normal after two weeks and no further elevations were developed upon continued dosing

- the patients who had elevations 3 X the normal range were using concomitant medicines; there were eight to ten concomitant drugs studied
- patients on Casodex who develop liver values 2 X normal limits and maintain elevated levels after 2 weeks are discontinued from the study
- the sponsor plans to complete patient enrollment for Protocol 02 and Protocol 03 by late March 1999; the first patients are slated to be treated on December 1, 1999 (87)
- the 50 mg dose of Aberlix is too low for maintenance of castration; maintenance falls off between 4 and 6 months
- for patients using therapy longer than six months, if patients are not castrated at 26 weeks, the sponsor proposes to have a safety monitoring board decide on the patients to be reinduced and treated two weeks after Day 169 and then every 28 days

Decisions reached:

- the protocol should specify how patients who do not achieve castration by Day 29 but do so at later days are counted in the study.
- evaluable patients should show castration levels of testosterone at study Days 29 and 57; the subgroup population of patients who do not achieve castration by Day 29 but achieve castration by Day 57 should be followed and included in the analysis to see if they maintain castration through Day 85
- the definition for patient withdrawal should be provided
- patients with elevated liver function tests should be monitored at Day 2, 7 and 24; they should be discontinued from the drug if results do not return to normal after two weeks
- patients in the Casodex arm of the study who develop elevated liver enzymes at 2X normal levels should be discontinued from Study 03
- patients being studied for long-term use should be reinduced if castration is not maintained at 6 months; an appropriate proposal for re-inducing patients should be submitted; this parameter would not be related to the primary efficacy parameter
- safety data should not be used for comparator claims, labeling comments are deferred to review of data submitted in NDA submission
- a Teleconference should be requested in February 1999, for March 1999 to discuss further questions regarding NDA submission

Action Items:

Item	Responsible Person:	Due:
• send revised protocols	Praecis	next several days
• fax proposal for additional monitoring for comparator arms	Praecis	next several days
• request Telecon with Division for March 1999	Praecis	February 1999

/S/ 1/21/99
Signature, minutes preparer

/S/ 1/21/99
Concurrence, Chair

MINUTES of TELECON

Date: October 28, 1998 **Time:** 1:30 PM - 2:30 PM **Location:** Parklawn; Rm. 17B-43

IND: 51,710/S-040 **Drug Name:** Abarelix **Indication:** Prostate Cancer

External Participant: Praecis Pharmaceuticals Incorporated

Type of Meeting: Clinical Guidance

Meeting Chair: Dr. Dan Shames **External Participant Lead:** Dr. Marc Garnick

Meeting Recorder: Ms. Diane Moore

FDA Attendees:
Daniel Shames, M.D. - Medical Officer, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Norman Marks, M.D. - Medical Officer, DRUDP (HFD-580)
Diane Moore - Project Manager, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Kate Meaker, M.S. - Statistician, Division of Biometrics II (DBII) @ DRUDP (HFD-580)

External Constituents:
Marc B. Garnick, M.D. – Executive Vice President and Chief Medical and Regulatory Officer, Praecis
Marilyn Campion, M.S. – Senior Director, Biostatistics, Praecis
Bernice Kuca, M.S. – Director, Clinical Operations, Praecis
Janice Swirski, R.Ph. - Project Management, Praecis
Cristina DeMin, M.D., Ph.D. – Clinical Science Leader

Meeting Objectives:
To discuss the clinical development plan and maintenance dose of Abarelix to be used in protocols 149-98-02 and 149-98-03.

Background:
On October 13, 1998, Praecis sent a telefacsimile which included data generated since the meeting between the Agency and Praecis on August 4, 1998, and the Teleconference on August 24, 1998 (See attached telefacsimile from October 13, 1998, submission 038).

Discussion Points:
Study 149-98-02
- the Gn-rH agonists class of drugs are approved based upon patients reaching and maintaining castration levels of testosterone for three months
- testosterone levels of 50-54 ng/dl must be demonstrated in patients for maintenance of castration

- the sponsor plans to use the 100 mg dose of Albarelix for the maintenance dose for castration in studies 149-98-02 and 149-98-03; the 50 mg dose was found to be suboptimal for maintenance of castration
- a one-sided 95% Confidence Interval was proposed in a study comparing Albarelix to Lupron
- descriptive, proportional statistical data are needed; the Confidence Interval cannot be wide and should be a two-sided, 95% Confidence Interval
- the literature defines failure as two consecutive testosterone values greater than 50 ng; the protocol defines failure as one level of testosterone greater than 50 ng/dl
- the criteria to discontinue a patient who has liver function tests at five times the upper limit of normal appears to be too high
- patients with metastatic disease can have a looser discontinuation criteria than patients with localized disease
- if a patient on Abarelix has a liver function test two to five times the upper limit, the patient is tested at two weeks; if the level persists, the patient is dropped from the study; this side effect is reversible within two weeks of the initial observation; this side effect can also be observed in patients on concomitant medications

Decisions reached:

- an important endpoint is achieving and maintaining castration; historically, 90% of patients achieve and maintain castration.
- the NDA should include patient-by-patient listing of testosterone values at individual time-points
- the definition of failure in the protocol (a testosterone level greater than 50 ng/dL at any one time) should not be revised
- although the primary study period is 12 weeks or 3 months, the drug can be studied longer for safety purposes
- testosterone levels should be monitored up to one year, although the levels in the later months do not need to be tested as frequently as the first 3 months of treatment
- all claims should be supported by a statistical analysis, not an exploratory analysis; the primary analysis should include adjustments for multiple analyses
- the allergic reactions as an exclusion criteria can be eliminated, except for allergy to Gn-rH agonists, because no localized or systemic reactions have been seen in patients or animals
- the protocol should be revised to clarify if liver function tests are high with the initial dose of Abarelix and also high upon rechecking after two weeks, the patient will be taken off of the drug
- the entry criteria must include normal limits for liver function tests
- patients using Casodex who have liver function tests at two-times normal limits should be discontinued from the study drug
- a statistical analysis plan, including the intended claims, should be submitted for review prior to unblinding the study
- the most appropriate approach appears to be to use the 100 mg dose as the maintenance dose
- all patients should be treated for three months before an interim analysis is performed
- the sponsor should request a Pre-NDA meeting with the Agency for the second quarter of 1999 to discuss their plans to submit the NDA in the third quarter of 1999

Action Items:

Item	Responsible Person:	Due:
• submit final protocols	Praecis Pharms., Inc.	24 to 36 hours

• submit protocol amendment for dropouts with high liver function tests	Praecis Pharms. Inc	with final clarify protocols
• submit Quality of Life claims for review	Praecis Pharms. Inc.	when completed
• submit study information and status of for Study I49-98-03 and request pre NDA meeting	Praecis Pharms. Inc.	February 1999

[redacted]
Signature, minutes preparer 12/28/98

[redacted]
Concurrence, Chair 1/4/99

MEETING MINUTES

Date: August 4, 1998 Time: 1:30-3:00 PM Location: C/R "B"

IND: 51,710 Drug Name: Abarelix

Type of Meeting: End-of Phase 2/Pre-NDA

External Participant: Praecis Pharmaceuticals Incorporated (PPI)

Meeting Chair: Lisa Rarick, M.D. External Participant Lead: Marc B. Garnick, M.D.

Meeting Recorder: Alvis Dunson

FDA Attendees:

James Bilstad, M.D. - Director, Office of Drug Evaluation II (ODE-II; HFD-102)
Florence Houn, M.D., M.P.H. - Deputy Director, ODE-II (HFD-102)
Lisa Rarick, M.D. - Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Marianne Mann, M.D. - Deputy Director, DRUDP (HFD-580)
Daniel Shames, M.D., - Medical Officer, DRUDP (HFD-580)
Mark Hirsch, M.D., - Medical Officer, DRUDP (HFD-580)
Kate Meaker, M.S. - Statistician, Division of Biometrics II (DBII) @ DRUDP (HFD-580)
Venkateswar Jarugula, Ph.D. - Pharmacokineticist, Division of Pharmaceutical Evaluation II (DPEII; HFD-870)
Krishan Raheja, D.V.M., Ph.D. - Pharmacologist, DRUDP (HFD-580)
Lana L. Pauls, M.P.H. - Chief, Project Management Staff, DRUDP (HFD-580)
Alvis Dunson - Project Manager, DRUDP (HFD-580)

External Constituents:

PPI
Malcolm Gefter, M.D. - Founder and Chief Scientific Officer
Marc B. Garnick, M.D. - Executive Vice President and Chief Medical and Regulatory Officer
Christopher Molineaux, Ph.D. - Director of Pharmacology and PPI-149 Project Director
Bernice Kuca - Associate Director, Clinical Operations
Marilyn Campion - Senior Director of Biostatics

Advisors
Patrick Grippon, M.D. - Director of Internal Medicine, Development Strategy Department, Synthelabo

Alan Kerr - Internal Medicine Product Registration, Synthelabo Pharmaceuticals, Inc., Paris

Meeting Objectives:

To address sponsor questions related to the clinical program and registration of Abarelix

Discussion Points:

The sponsored proposed the following issues for Division comment:

Q1: Does the Division agree with the proposed indication for Abarelix for the treatment of prostate cancer?

A1: The indication should be similar to the currently approved labeling for the gnRH agonsists for the palliative treatment of advanced prostate cancer. More rigorous clinical trials than the trials proposed are needed to support additional labeling claims. These should be well-controlled studies designed for the intended patient population with such endpoints as time-to-progression and survival.

Q2: Does the Division agree that PRAECIS can submit a filable NDA based on phase 1 and 2 studies 149-96-01, 149-97-03, and 149-97-04?

A2: No, the three trials alone would not support filing an NDA because the number of patients exposed to the drug product is insufficient to demonstrate safety. However, completion of the two proposed Phase 3 studies, 149-98-02 and 149-98-03, along with the Phase 1 and 2 studies, appear to support the filing of an NDA based on the anticipated number of patients projected in the June 1999 NDA submission strategy.

Q3: Does the Division agree with the primary study endpoints?

A3: The Division agrees with the percentage of patients castrate on Day 8 and Day 85 as acceptable endpoints. However, it is not known if the AUC comparison through Day 13 endpoint will demonstrate a clinically meaningful difference. A binary variable was discussed as an alternative endpoint.

Q4: Does the Division agree with the proposed clinical pharmacology and biopharmaceutics program?

A4: Ideally for a new molecular entity, an *in vivo* mass balance study is recommended but not required for approval of an NDA. The proposal to compare *in vitro* metabolism in animal species with that in humans and determine metabolites in plasma and urine appears acceptable. The proposal to link the *in vitro* metabolism and the radiolabelled animal study data to *in vivo* metabolism appears acceptable.

Q5: Does the Division agree with the proposed filing of carcinogenicity studies?

A5: The Division agrees with the ICH document "Guideline on the Need for Carcinogenicity Studies of Pharmaceuticals" that indicates for pharmaceuticals developed to treat certain serious diseases, carcinogenicity testing, if needed, may be conducted post-approval.

Unresolved Issues: None

Action Items: Item:	Responsible Person:	Due Date:
Schedule a CMC teleconference with OCPB the sponsor and include Venkat Jarugula and microbiology (Paul Stinavage)	Christina Kish	?

/S/

Signature, minutes preparer 9/20/98

/S/ 9/31/98

Concurrence, Chair

MEETING MINUTES

Date: June 18, 1997 Time: 10:00 - 11:30 AM Location: Parklawn; Maryland Room

IND: 51,710 Drug Name: PPI-149

Type of Meeting: Industry meeting (face-to-face)

External Participant: Praecis Pharmaceuticals Incorporated (PPI)

Meeting Chair: Heidi Jolson, M.D., M.P.H. External Participant Lead: Marc B. Garnick, M.D.

Meeting Recorder: Alvis Dunson, B.S.

FDA Attendees:

Heidi Jolson, M.D., M.P.H. - Deputy Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Jean Fourcroy, M.D., Ph.D. - Medical Officer, DRUDP (HFD-580)
Moo-Jhong Rhee, Ph.D. - Chemistry Team Leader, Division of New Drug Chemistry II (DNDC) @ DRUDP (HFD-580)
Kasturi Srinivasachar, Ph.D. - Chemist, DNDCII @ DRUDP (HFD-580)
Kate Meaker, M.S. - Statistician, Division of Biometrics II (DBII) @ DRUDP (HFD-580)
K. Gary Barnette, Ph.D. - Pharmacokineticist, Division of Pharmaceutical Evaluation II (DPEII; HFD-870)
Krishan Raheja, D.V.M., Ph.D. - Pharmacologist, DRUDP (HFD-580)
Alvis Dunson, B.S. - Consumer Safety Officer, DRUDP (HFD-580)
Paul Stinavage, Ph.D. - Microbiologist, Office of New Drug Chemistry (HFD-850)

External Constituents:

PPI
Malcolm Gefter, M.D. - Founder and Chief Scientific Officer
Marc B. Garnick, M.D. - Executive Vice President and Chief Medical Officer
Christopher Molineaux, Ph.D. - Director of Pharmacology and PPI-149 Project Director
Nicholas Barker, Ph.D. - Vice President, Pharmaceutical Development
Bernice Kuca - Associate Director, Clinical Operations

Advisors

Patrick Grippon, M.D. - Director of Internal Medicine, Development Strategy Department, Synthelabo Pharmaceuticals, Paris (Synthelabo is PPI's collaborator for European Development of PPI-149-

Alan Kerr - Internal Medicine Product Registration, Synthelabo Pharmaceuticals, Inc., Paris

Meeting Objectives:

Phase I/II meeting to discuss a planned submission of an NDA for June/July1998.

Discussion Points:

Clinical

- definition of a rise in prostate specific antigen (PSA) needs to be clarified and standardized
- primary endpoint should be reduction of testosterone to castrate levels within 1 week of dosing and continued suppression throughout treatment

Biopharmaceutics

- the human pharmacokinetic (PK) data presented was [redacted] the sponsor agreed that all pharmacokinetic priorities must be generated with the to-be-marketed formulation
- OCPB regulations require an absolute or relative bioavailability assessment; the sponsor indicated that such a study was planned
- testosterone assay methodology should be validated with quality control (QC) samples from each analytical run
- the sponsor should submit a prospectus of the planned clinical pharmacology and biopharmaceutics studies for PPI-149 to the Division; this will allow the Division to make comments and recommendations on the overall drug development program

Pharmacology

- pre-clinical studies are required to be completed in two species (one rodent; one non-rodent) for 3-months; the results of these Non-GLP studies must be submitted to the Division for review before 12-week clinical trials begin
- 6-month rodent and 12-month non-rodent toxicology studies must be completed to meet pharmacology/toxicity requirements for an NDA
- carcinogenicity studies using the rat and mouse should be completed and submitted with the NDA; studies should be conducted in accordance with GLP regulations

- studies conducted in accordance with GLP regulation should be completed and submitted for the NDA

- Reprotoxicity/Return to fertility studies should be completed and submitted with the NDA

Chemistry

- proposed definition of the drug substance is unacceptable; sponsor should apply for USAN name for "PPI-149" only and not for the —— —— " as a drug substance

- tentative specifications are acceptable for a phase 1 IND study

- —— test need to be specific for both PPI-149 and CMC; if necessary, two test methods that evaluate both components may be used

- stability of the reconstituted solution need to be evaluated

- dissolution testing should be developed to demonstrate batch-to-batch consistency

- impurities and degradation products should be identified and qualified

Statistics

- type of protocol (i.e. open-label) should be specified

- time points to be used to determine efficacy should be identified; P-values may have to be adjusted if multiple time points are used

- active controls that will be used in the study may be combined in the analysis but should also be shown separately in a secondary analysis

- specification of whether equivalence or superiority will be claimed should be provided

Microbiology

- —— specifications for pharmacology ingredients and drug substance should be monitored closely using current FDA guidelines

Decisions reached:

The sponsor proposed the following six questions to be addressed:

Q1: May we extend the dosing duration from four weeks (as now conducted in our current Protocol 149-96-01) to twelve weeks, as indicated in Protocol 149-97-03?

A1: No, pre-clinical data plus human safety data should be submitted to the Division for review before extending the dosing duration to twelve weeks.

Q2: Is it acceptable for PPI-149 — (LHRH pure antagonist) to be registered as a means for achieving rapid medical castration (androgen ablation) in ——— patients with prostate cancer in whom endocrine (hormonal) therapy is indicated?

A2: The development appears to be generally appropriate to support this indication. Indications for Use will be determined once the application has been filed as an NDA with information to support any claim. Additionally,

Q3: Is it acceptable for PPI-149- ——— to be registered as ——— prostate cancer?

A3: The Division has initiated labeling changes that reword the indication as follows: "for the palliative treatment of advanced prostate cancer."

Q4. Are our preclinical safety and clinical/regulatory plans acceptable to support an approvable NDA for patients with prostate cancer?

A4: A determination of approvability cannot be made until the NDA has been deemed acceptable for filing by the FDA and reviewed; the recommendations made today, June 18, 1997, concern the filability of the application. The application is required to contain reports of all investigations of the drug product sponsored by the applicant, and all other information about the drug pertinent to an evaluation of the application. FDA will maintain guidelines on the format and content of applications to assist applicants in their preparation. It should be noted that PPI-149 may be eligible for an accelerated approval under guidelines set forth under "Subpart H - Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses," 21 CFR 314.500 - 560, April 1, 1996 edition.