

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER**

**21-320**

**Chemistry Review(s)**

NDA 21-320  
Plenaxis (abarelix suspension for injection)  
1P

Praecis Pharmaceuticals, Inc.

HFD-580  
Nita Crisostomo  
7-4260

Original application date: December 11, 2000  
NA Action: June 11, 2001  
Resubmission Date: February 25, 2003  
Goal Date Extension: November 25, 2003

Volume 4  
**CHEMISTRY**

**NDA 21-320**

**Plenaxis™ (abarelix suspension for injection) 100 mg**

**CHEMISTRY DIVISION DIRECTOR REVIEW**

**Applicant:** Praecis Pharmaceuticals Inc.

**Indication:** /

**Presentations:** Single-dose vials containing 113 mg abarelix-CMC (carboxymethylcellulose) to be reconstituted with 0.9% sodium chloride injection for intramuscular delivery of 100 mg abarelix-CMC in 2mL.

**EER Status:** Acceptable, 5/12/2003

**Consults:** OPDRA, acceptable 7/10/2003; EA, not applicable (categorical exclusion); Microbiology, Adequate, 7/21/2003

**Plenaxis™ (abarelix suspension for injection)** is a product of abarelix acetate for treatment of advanced symptomatic carcinoma of the prostate where immediate androgen suppression is appropriate. Abarelix acetate which acts as an antagonist of gonadotropin releasing hormone and rapidly suppresses testosterone, dihydrotestosterone (DHT), follicle stimulating hormone (FSH), Leuteotropic hormone (LH), and prostate specific antigen (PSA) levels. The formulation is given to the patients on Day 1, 15, 29 and every 4 weeks thereafter.

Chemically, abarelix acetate is a decapeptide (described as acetyl-D-β-naphthylalanyl-D-4-chlorophenylalanyl-D-3-pyridylalanyl-L-seryl-L-N-methyl-tyrosyl-D-asparagyl-L-leucyl-L-N(ε)-isopropyl-lysyl-L-prolyl-D-alanyl-amide) synthesized by

It is an amorphous, hygroscopic powder that contains associated water and acetate, which is soluble in water. The solubility of abarelix acetate has been shown to decrease proportionally with higher pH at room temperature. The specific rotation of abarelix acetate:

For subsequent formulation, Abarelix acetate is converted to the drug product intermediate, a complex of abarelix and carboxymethylcellulose (abarelix CMC). Abarelix CMC is a tight, stable, water-insoluble complex and allows for the loading of a high concentration of the peptide into the formulation. **In the abarelix CMC complex, CMC acts as a carrier molecule which upon patient administration aids in**

**continuous delivery of abarelix for a prolonged period of time (in this case for one month).**

Abarelix for injectable suspension is supplied as a white to off-white sterile dry powder which, when mixed with the diluent, 0.9% Sodium Chloride Injection, USP, becomes a depot suspension intended for intramuscular (IM) injection. The single-dose vial contains 113 mg of anhydrous free base abarelix peptide (net) supplied in an abarelix CMC complex. This complex also contains 19.1 to 31 mg of CMC. After the vial is reconstituted with 2.2 mL of 0.9% sodium chloride injection, 2 mL is administered to deliver a dose of 100 mg of abarelix (net) as the abarelix CMC complex at a pH of  $5 \pm 1$ . To manufacture the final drug product, abarelix CMC complex is filled in a vial which is then stoppered, sealed, and sterilized by \_\_\_\_\_ The vials are then labeled and packaged into kits including 1) 3 cc \_\_\_\_\_ syringe with a 18 gauge 1-1/2" needle, 2) 22 gauge 1-1/2" safety glide needle, 3) 10 ml vial of 0.9% sodium chloride injection, USP. The drug product is delivered following reconstitution with 2.2 ml of 0.9% sodium chloride.

Abarelix acetate drug substance is manufactured by \_\_\_\_\_  
\_\_\_\_\_. Abarelix CMC is manufactured by \_\_\_\_\_  
\_\_\_\_\_. All facilities have been found acceptable the Office of Compliance.

CMC information was previously reviewed in 2001 (see Chem Review dated 6/11/01) and was found deficient concerning lack of sterility assurance, inadequate specifications and stability data. Among the issues, there was a question whether \_\_\_\_\_ acceptance criteria should be established for a controlled release product like this. The deficiencies have since been addressed by the applicant (see Chem Review #2). There are no remaining CMC issues.

**Based on the stability data, the proposed expiration dating period of 24 months for Plenaxis is acceptable. The recommended storage condition of Plenaxis is 25°C (77°F), excursions permitted to 15-30°C (59-86°F) [USP Controlled Room Temperature].**

**Overall Conclusion:**

From a CMC perspective the application can now be approved.

Duu-Gong Wu, PhD  
Deputy Director, DNDC II/ONDC

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pages of trade

secret and/or

confidential

commercial

information

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

# Memo

To: NDA 21-320  
From: Swapan K. De, Ph.D.  
Through Moo-Jhong Rhee, Ph.D., Chemistry Team Leader  
Date: 11/25/2003  
Re: Amendment #092 dated November 24, 2003

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In response to a t-con dated 24-Nov-2003, the sponsor submitted (Amendment #092 dated 24-Nov-2003) a final revisions for the PI, PPI, Hospital Pharmacy Agreement, Physician Attestation and Carton label. The response are satisfactory due to following reasons.

- The sponsor has added a statement "Plenaxis vials are not to be resold or redistributed" in the How Supplied section. The statement "Not for resale or redistribution" is also added in the carton label as suggested during the t-con (24-Nov-2003) as part of risk management plan for Plenaxis. The response is deemed satisfactory.

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/s/

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Swapn De  
11/25/03 10:14:04 AM  
CHEMIST

Moo-Jhong Rhee  
11/25/03 10:18:41 AM  
CHEMIST  
I concur



**NDA 21-320**

**Plenaxis<sup>TM</sup>**  
**(Abarelix for Injectable suspension)**

**Praecis Pharmaceuticals Inc.**

**SWAPAN K. DE**

**DIVISION OF REPRODUCTIVE & UROLOGIC DRUG  
PRODUCTS (HFD-580)**



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# Chemistry Review Data Sheet

1. NDA 21-320
2. REVIEW #: 2
3. REVIEW DATE: November 12, 2003 (Revised)
4. REVIEWER: Swapan K. De, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original	11-Dec-2000
See Chemistry Review #1 for previous amendments	29-Apr-2001

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Resubmission (Amendment #042)	25-Feb-2003
Amendment #043	19-Mar-2003
Amendment #044 additional tests for CMC sodium	20-Mar-2003
Amendment #048 updated stability data	16-May-2003
Amendment #050 updated carton labeling copy	03-Jun-2003
Amendment #064 Response to CMC deficiencies	29-Jul-2003
Amendment #067 Response to CMC deficiencies	10-Sept-2003
Amendment #073 updated stability data	14-Oct-2003
Amendment #075 CMC labeling revisions	24-Oct-2003
Amendment #082 CMC labeling revisions	11-Nov-2003

7. NAME & ADDRESS OF APPLICANT:

Name: PRAECIS PHARMACEUTICALS INCORPORATED  
Address: 830 Winter Street  
Waltham, MA 02451-1420



## Chemistry Review Data Sheet

Representative: J. D. Bernardy  
Vice President, Regulatory Affairs and Quality  
Assurance

Telephone: 781-795-4100 ext. 4282

## 8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: PLENAXIS™
- b) Non-Proprietary Name (USAN): Abarelix for injectable suspension
- c) Code Name/# (ONDC only): PPI-149
- d) Chem. Type/Submission Priority (ONDC only):
  - Chem. Type: 1
  - Submission Priority: S

## 9. LEGAL BASIS FOR SUBMISSION: N/A

## 10. PHARMACOL. CATEGORY: /

11. DOSAGE FORM: Injection, Powder, for Suspension

12. STRENGTH/POTENCY: 100 mg abarelix acetate

13. ROUTE OF ADMINISTRATION: Intramuscular

14. Rx/OTC DISPENSED:  Rx  OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

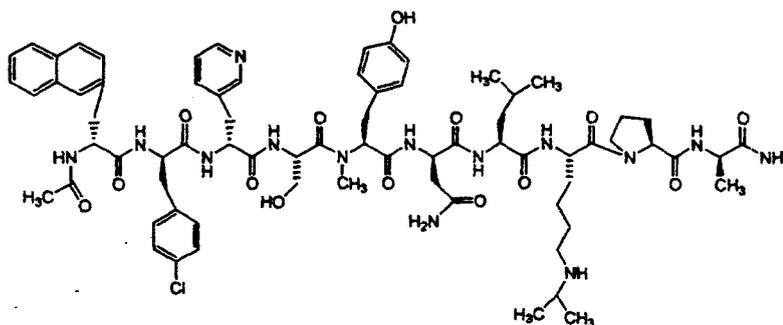
## 16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

## Chemistry Review Data Sheet

Chemical name: Acetyl-D- $\beta$  naphthylalanyl-D-4-chlorophenylalanyl-D-3-pyridylalanyl-L-seryl-L-N-methyl-tyrosyl-D-asparagyl-L-leucyl-L-N(•)-isopropyl-lysyl-L-prolyl-D-alanyl-amide

CAS number: 183552-38-7

Structural Formula:



Molecular Formula:  $C_{72}H_{95}N_{14}O_{14}Cl$ , anhydrous free base

Abarelix acetate refers to the powder form with associated water and acetate

Relative molecular mass: 1414.68, anhydrous free base

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Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
	III			3	Adequate	26-Oct-00	Reviewed by A. Raw, Ph.D.
	III			3	Adequate	29-Sept-01	Reviewed by S. E. Langille, Ph.D.
	III			3	Adequate	31-Jan-03	Reviewed by R. K. Kasliwal, Ph.D.
	V			1	Adequate	09-Oct-03	Reviewed by Swapan K. De, Ph.D.

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

**CHEMISTRY REVIEW**

## Chemistry Review Data Sheet

**B. Other Documents:**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND Application	IND 51,710	18-Oct-1996; Phase 3 IND

## 18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	12-May-2003	S. Ferguson (HFD-322)
Pharm/Tox	Adequate	11-Jun-2001	Krishan L. Raheja, Ph.D., D.V.M.
Biopharm	Adequate	05-Nov-2003	D. J. Chatterjee, Ph.D.
LNC	N/A		
Methods Validation	Will be initiated		Swapn K. De, Ph.D.
OPDRA	Adequate	10-Jun-2003	Alina Mahmud, Pharmacist
EA	Categorical exclusion granted	14-Aug-2003	Swapn K. De, Ph.D.
Microbiology	Adequate	21-Jul-2003	Stephen Langille, Ph.D.

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# The Chemistry Review for NDA 21-320

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

From chemistry, manufacturing, and controls point of view, this NDA may be approved.

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

### II. Summary of Chemistry Assessments:

#### A. Description of the Drug Product(s) and Drug Substance(s):

**Dosage form:** Injection, Powder, for Suspension

**Strength:** 100 mg Abarelix acetate

**Route of Administration:** Intramuscular

Abarelix acetate is a new molecular entity decapeptide, which acts as an antagonist of gonadotropin releasing hormone and rapidly suppresses testosterone, dihydrotestosterone (DHT), follicle stimulating hormone (FSH), Leuteotropic hormone (LH), and prostate specific antigen (PSA) levels. Within 24 hours serum testosterone levels falls to castrate levels. The effect is different from a GnRH agonist that initially increases the testosterone levels (called 'flare') and then reduces the testosterone to castrate levels.

Abarelix acetate is unique because

The peptide synthetic organic chemistry, with a based protection strategy is used to synthesize abarelix acetate. The starting materials used in the synthesis have been qualified by tests that include

The drug substance is manufactured Bulk abarelix acetate is packaged bags and are placed in a foil laminate pouch and pouch is then heat sealed. The drug substance is stored at 2-8°C and adequate data have been provided to support a month retest period.

Abarelix acetate is first converted to a drug product intermediate (abarelix CMC), which is a complex of abarelix and carboxymethylcellulose. Abarelix CMC is a tight, stable, water-insoluble complex and allows for the loading of a high concentration of the peptide into the formulation. In the abarelix CMC complex, CMC acts as a carrier molecule which upon patient-administration aids in continuous delivery of abarelix for a prolonged period of time (in this case for one month).

The abarelix CMC complex is filled in a vial with a targeted quantity of abarelix CMC to obtain a dosage strength of 100 mg abarelix. Filled vials are stoppered, sealed, and sterilized by

## Executive Summary Section

The vials are then labeled and packaged into kits. The proprietary name of the drug product "Plenaxis" was re-reviewed and found to be acceptable by DMETS on 10-June-2003. The other components of the kit include the following items: 1) 3 cc syringe with a 18 gauge 1-1/2" needle, 2) 22 gauge 1-1/2" safety glide needle, 3) 10 ml vial of 0.9% sodium chloride injection, USP, 4) frequently asked questions insert, 5) package insert, 6) 2 alcohol pads, and 7) a bandage. The drug product is delivered following reconstitution with 2.2 ml of 0.9% sodium chloride. The drug product is manufactured under aseptic conditions with sterility assurance and from Microbiologist's point of view, the whole process as well as the container/closure integrity is deemed satisfactory. The drug product is manufactured

retest period for this intermediate is when stored at 2-8°C and is supported by stability data up to from 9 batches. filled in vials to obtain deliverable dose. The vials are stoppered, sealed and packaged

The sterilized product is then shipped back to

The drug product stability data includes 6 primary stability batches manufactured supportive stability batches manufactured Up to 12 month stability data from the primary stability batches and up to stability data from the supportive batches were provided. Based on the stability data, 24-month expiry date is granted. Adequate chemistry information is presented in the labeling and labels of the primary as well as the secondary packaging.

## B. Description of How the Drug Product is Intended to be Used

This product is indicated for A risk management plan limits the use of Plenaxis to a narrow range of patients with advanced prostate cancer, who are not candidates for luteinizing hormone releasing hormone (LHRH) agonist therapy because of risks associated with testosterone surge.

The drug product is delivered following reconstitution with 2.2 ml of 0.9% sodium chloride and administered using aseptic technique. Direction for reconstitution and administration of the drug product is included in the physician insert. The recommended dose of Plenaxis™ is 100 mg on day 1, day 15, day 29 (week 4) and every 4 weeks thereafter.

The expiration dating period for Plenaxis is 24 months. The recommended storage condition of Plenaxis is 25°C (77°F), excursions permitted to 15-30°C (59-86°F) [USP Controlled Room Temperature)

## C. Basis for Approvability or Not-Approval Recommendation

The sponsor has provided adequate data to demonstrate product quality. Therefore, from a CMC point of view, the data support approval of the NDA.

## Executive Summary Section

The sponsor resubmitted the NDA with responses to the outstanding deficiencies for the original NDA (Not approvable letter dated 11-June-2002). During review of the resubmission, the sponsor changed the drug product manufacturing site from [redacted]. No significant changes are noticed due to the manufacturing site change. Primary stability data were provided from the batches manufactured [redacted] in the resubmission (Amendment #042 dated 25-February-2003), and was further updated (to provide more stability data) in Amendment #048 (dated 16-May-2003) and in Amendment #073 (dated 14-October-2003). Information request letters were sent to the sponsor with various issues on 14-July-2003, 27-Aug-2003 and 26-Sept-2003. The sponsor's submission of amendment #064 (29-Jul-2003) and amendment #067 (10-Sept-2003) includes the response to the deficiencies and was found to be adequate. Amendment 075 dated 24 October, 2003 and amendment 082 dated 11 November, 2003 include response on labeling comments sent to the sponsor on 26-Sept-2003 and response to a t-con dated 5 November, 2003. Some of the major issues and their resolution for this NDA include the following:

- Update on the in-process control and tests during manufacture of the drug products.
- Submission of additional stability data to support the 24-month drug product expiration dating period.
- Addition of [redacted] in the release specifications for the drug product. The acceptance criterion for [redacted] content was tightened to NMT [redacted] from the proposed acceptance criterion NMT [redacted].
- Dose delivery level acceptance criterion is revised from [redacted] to keep the value consistent with the [redacted] (assay) acceptance criterion.
- The drug product dissolution acceptance criterion is tightened to Q [redacted] % at 45 minutes from the proposed Q [redacted] % at 45 minutes.
- The sponsor provided satisfactory information to justify the [redacted] study for the drug product.

Thus, considering the provided information and their resolution, this NDA is deemed satisfactory regarding CMC and may be approved.

### III. Administrative

#### A. Reviewer's Signature

#### B. Endorsement Block

ChemistName/Date: Same date as draft review  
ChemistryTeamLeaderName/Date  
ProjectManagerName/Date

#### C. CC Block

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/s/

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Swapn De  
11/18/03 02:08:19 PM  
CHEMIST

David T. Lin  
11/18/03 02:11:05 PM  
CHEMIST  
I concur.

# Electronic Mail Message

**Date:** 6/13/01 9:20:52 AM  
**From:** Charles Hoiberg ( HOIBERG )  
**To:** Moo-Jhong Rhee ( RHEEM )  
**Cc:** Jeanine Best ( BESTJ )  
**Cc:** Bronwyn Collier ( COLLIERB )  
**Cc:** Patricia O'Connor ( OCONNORP )  
**Subject:** NDA 21-320 (Abarelix Suspension)

Moo-Jhong,

I received today the DMPQ(HFD-324) evaluation report for NDA 21-320/Praecis (Abarelix Suspension). They concur with the District's Withhold recommendation regrading           . In addition, it appears KAN-DO is completing a Warning Letter for GMP deviations observed during the April 2001 PAI inspection at           . You can pick up the document from Pat at your convenience.

Chuck

# Electronic Mail Message

**Date:** 6/11/01 12:42:42 PM  
**From:** Charles Hoiberg ( HOIBERG )  
**To:** Bronwyn Collier ( COLLIERB )  
**To:** Jeanine Best ( BESTJ )  
**Cc:** Moo-Jhong Rhee ( RHEEM )  
**Subject:** NDA 21-320 (abarelix)

I reviewed the action package for NDA 21-320 with Moo-Jung. Based on the updates of the draft reviews he showed me, my concerns have been addressed. I left the action package with Moo-Jung.

Chuck

**APPEARS THIS WAY  
ON ORIGINAL**

## Summary of Chemistry Review of NDA 21-320

### A. Drug Substances:

Abarelix is a synthetic decapeptide acting as an antagonist of gonadotropin releasing hormone, thereby suppressing testosterone, DHT, FSH, LH, and PSA. It is a new molecular entity and synthesized via a conventional organic chemistry.

is the manufacturer, and

and their inspection reports are pending.

The drug substance is manufactured as abarelix acetate, however, acetate is removed during manufacture of drug product.

Peptide drug is a relatively complex molecule

In this regard, the sponsor should establish an acceptance criteria of specific optical rotation of one of the starting materials,

The quality of abarelix acetate is controlled by series of specifications such as

One concern is that,

without explanation. It should be part of analysis to assure that the composition of the peptide is correct. Otherwise, all the methods and acceptance criteria of those specifications are considered to be adequate.

Stability of abarelix acetate is established with 8 batches and the proposed retest period of month, when stored at 5°C +/- 3°C, is acceptable.

### B. Drug Product:

The drug product is in a form of dry powder, which is a complex of abarelix with carboxymethylcellulose (CMC) and is to be reconstituted with 0.9% saline solution. The diluent is supplied by (DMF) From sterility assurance point of view, the DMF is not considered adequate.

The abarelix CMC complex is manufactured

is in compliance to cGMP, but is not (Withhold recommendation was made by the Office of Compliance).

The quality of the abarelix CMC is controlled by

One issue is that the proposed acceptance criteria for the content of CMC in the abarelix CMC complex is too wide. According to the batch analysis it is within. The proposed range is unnecessarily wide, which implicates that the amount of abarelix could also vary widely. This should be justified.

Once abarelix CMC is released and sterilized it is then filled into vials by  
One issue to be clarified is the added during  
process. It should be justified.

The quality of the final drug product in vial is controlled by specifications

**Sterility assurance is in question due to uncertainty of container/closure integrity.**

The drug product is packaged in vial (3.5ml) (DMF) with a stopper (DMF) and DMF and a aluminum flip-off seal. From Microbiologist's point of view, **container/ closure integrity is not deemed established.**

The proposed of expiry date is not acceptable. Based on available primary and supporting stability data, of expiry date can be granted.

The tradename, **Plenaxis**, was accepted by OPDRA, but there are labeling issues to be clarified including container and carton labels.

**C. Conclusion and Recommendation:**

From chemistry, manufacturing, and controls point of view, as the primary reviewer recommends, this NDA is **approvable** pending resolution of the following issues:

1. Quality of starting materials
2. Unnecessarily wide range of CMC in abarelix CMC complex
3. Unjustified overage of abarelix CMC in vials
4. Sterility assurance
5. Expiration date of the drug product
6. Revision of labeling (Description and How Supplied sections) as well as labels of container and carton

/S/

---

Moo-Jhong Rhee, Ph.D.  
Chemistry Team Leader  
For the Division of reproductive and Urologic Drug Products  
DNDC II, Office of New Drug Chemistry

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/s/

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Moo-Jhong Rhee  
6/11/01 10:30:14 AM  
CHEMIST

**DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS**  
Review of Chemistry, Manufacturing, and Controls

**NDA #: 21-320**

**DATE REVIEWED: 4-29-01**

**REVIEW #: 1**

**REVIEWER: Swapan K. De**

<b><u>SUBMISSION TYPE</u></b>	<b><u>DOCUMENT DATE</u></b>	<b><u>CDER DATE</u></b>	<b><u>ASSIGNED DATE</u></b>
ORIGINAL	12-11-00	12-12-00	12-20-00
AMENDMENT	01-05-01	01-09-01	01-16 -01
AMENDMENT	04-13-01	04-16-01	04-20 -01
AMENDMENT	04-23-01	04-24-01	04-28 -01
AMENDMENT	03-30-01	04-02-01	04-06 -01

**NAME & ADDRESS OF APPLICANT:**

Praecis Pharmaceuticals Inc.  
11 Hampshire Street  
Cambridge, MA 02139

**DRUG PRODUCT NAME**

Proprietary:

Plenaxis™

Established:

Abarelix for injectable suspension

Code Name/#:

PPI-149

Chem.Type/Ther.Class:

1/P

**PHARMACOL. CATEGORY/INDICATION:**

GnRH antagonist for treatment of Prostate cancer without testosterone surge

**DOSAGE FORM:**

Injectable

**STRENGTHS:**

100 mg

**ROUTE OF ADMINISTRATION:**

Intramuscular

**Rx/OTC:**

X Rx    OTC

**SPECIAL PRODUCTS:**

   Yes X No

(If yes, fill out the form for special products and deliver to TIA through team leader for data entry)

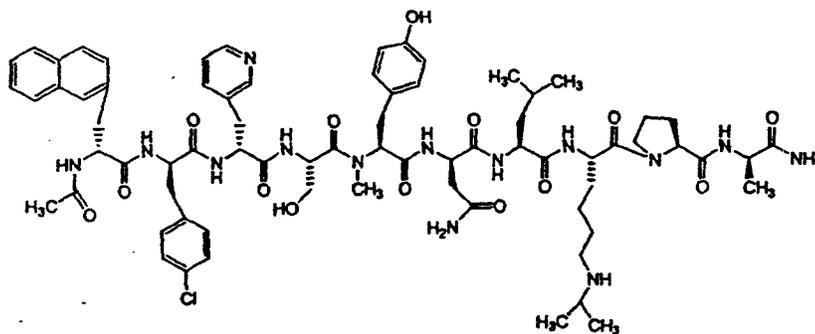
**CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA,**

**MOLECULAR WEIGHT:**

Chemical names: Acetyl-D-β naphthylalanyl-D-4-chlorophenylalanyl-D-3-pyridylalanyl-L-seryl-L-N- methyl-tyrosyl-D-asparagyl-L-leucyl-L-N(e)-isopropyl-lysyl-L-prolyl-D-alanyl-amide

CAS number: 183552-38-7

Structural Formula:



Molecular Formula: C<sub>72</sub>H<sub>95</sub>N<sub>14</sub>O<sub>14</sub>Cl, anhydrous free base

Abarelix acetate refers to the powder form with associated water and acetate

Relative molecular mass: 1414.68, anhydrous free base

**SUPPORTING DOCUMENTS:**

Type/Number	Subject	Holder	Status	Review date	Letter date
/	/		Reviewed Satisfactory	10/26/00 by A. Raw	N/A
/	/		Reviewed Not Satisfactory	S. Langille	June 7, 2001
/	/		Reviewed Satisfactory	5/25/99 by S. De	N/A
/	/		Reviewed Not Satisfactory	S. Langille	June 8, 2001

**RELATED DOCUMENTS (if applicable): None**

**CONSULTS:**

Sterility assurance section of the NDA has been consulted to a microbiology staff and the microbiology review indicates that sterility assurance has not been established. EER has been submitted to office of compliance and no overall recommendation has been made as of June 8, 2001. The Office of Post-Marketing Drug Risk Assessment (OPDRA) was consulted for the tradename, Plenaxis™ and on February 2, 2001, OPDRA recommended approval of the use of "Plenaxis™" as proprietary name.

**REMARKS/COMMENTS:**

Abarelix acetate is a new molecular entity, a decapeptide, and acts as an antagonist of gonadotropin releasing hormone and rapidly suppresses testosterone, DHT, FSH, LH, and prostate specific antigen (PSA) levels and within 24 hours serum testosterone levels falls to castrate levels. The effect is unique since the GnRH agonist initially increases the testosterone levels (called 'flare') and then reduces the testosterone to a castrate levels.

Abarelix acetate is unique

peptide synthetic organic chemistry, with based protection strategy is used to synthesize abarelix acetate. The starting materials, used in the synthesis have been qualified by test results. However, there are a couple of issues, which are to be clarified. Specifications limit and example of COA has been provided. Throughout the NDA, sponsor uses an alternative term for the drug substance abarelix acetate as 'Abarelix API'.

Abarelix acetate is converted to the drug product intermediate, a complex of abarelix and carboxymethylcellulose (abarelix CMC). Abarelix CMC is manufactured

The proposed proprietary name of abarelix for injectable suspension (drug product) is Plenaxis™. The drug product consists of a filled vial with a targeted quantity of abarelix CMC to obtain a dosage of 100 mg abarelix. Filled vials are stoppered, sealed, and sterilized

The vials are then labeled and packaged into kits. The other components of the kits include 3 cc syringe with 18 gauge 1-1/2" needle, 22 gauge 1-1/2" safety glide needle, 0.9% sodium chloride injection, USP, 10 ml vial, frequently asked questions insert, package insert, alcohol pads (2) and a bandage. The drug product is delivered following reconstitution with 2.1 ml of 0.9% sodium chloride. The drug product is manufactured under aseptic conditions with sterility assurance. The drug product has limited primary stability data from 3 batches manufactured. As indicated, the drug product will be stored at 25°C (USP controlled room temperature).

The sponsor initially submitted the application with primary stability data, which was updated, to primary stability data through an amendment on 3/30/01.

Amendment on "Draft Labeling" was submitted on 4/13/01.

On January 5, 2001, sponsor provided a letter of authorization for a DMF from —

Other submissions listed in the front sections are related to Patent Information and Patent Certification.

**CONCLUSIONS & RECOMMENDATIONS:**

This NDA is approvable from the standpoint of chemistry and manufacturing controls, pending resolution of issues, which are delineated in the draft letter.

**/S/**

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Swapan K. De, Ph.D.  
Review Chemist

cc:

Org. NDA 21-320  
HFD-580/Division File  
HFD-580/SDe/2/12/01  
HFD-580/Edeguia, JBest  
HFD-580/MRhee  
HFD-8XX/CHOiberg (NMEs only)  
R/D Init by: Moo-Jhong Rhee, Ph. D.

filename: N21320chem1F.doc

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information

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

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Swapn De  
6/8/01 04:56:49 PM  
CHEMIST

Moo-Jhong Rhee  
6/11/01 09:25:40 AM  
CHEMIST  
I concur

**NDA 21-320**

**Plenaxis (abarelix for injectable suspension)**

**Praecis Pharmaceuticals, Inc.**

The Environmental Assessment is acceptable as found in the Chemistry review, page 45,  
November 18, 2003.

*S*  
*11/25/03*

## Chemistry Assessment Section

**Question:** Please submit three copies of method validation packages, including a list of samples that will be provided for the analysis of the methods.

**Response:**

**Satisfactory**

An updated method validation package is provided.

**III. INVESTIGATIONAL FORMULATIONS**

**Satisfactory**

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⌋

**IV. ENVIRONMENTAL ASSESSMENT**

**Satisfactory**

A categorical exclusion is claimed for this NDA in accordance with 21 CFR part 25.31 (b) during the original submission. The EIC (Expected Introduction Concentration) is calculated and EIC value is — ppb. The calculated value is less than the 1 ppb upper limit described in 21 CFR section. Thus, the level is deemed acceptable and categorical exclusion may be granted.

**V. METHODS VALIDATION**

**Satisfactory**

All the methods need to be compiled together for the evaluation of the methods and should be provided to the agency, which will then be sent out to the district laboratories for validation.

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⌋

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

**There was no Environmental Assessment done for this application. The sponsor requested a Categorical Exemption (see attached).**

5/9/21

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

**The Methods Validation is pending for this application.**

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5/7/01