CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-320

Administrative Documents

13. Patent Information

As required under 21 CFR § 314.53(c), the following patent information for NDA 21-320, Amendment 042 is provided:

Trade Name:	PLENAXIS™ (proposed)
Active Ingredient:	abarelix (USAN)
Strength:	100 mg injectable suspension
Dosage form:	intramuscular injection
Approval Date:	pending

The patent number(s) listed below cover abarelix, pharmaceutical compositions containing abarelix, and/or use thereof in the treatment of prostate cancer. PPI-149 (compound 3827 in US 5,843,901) is the active pharmaceutical ingredient in the new drug for which approval is being sought and with respect to which claim of patent infringement of each patent listed below could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use or sale of the drug:

U.S. Patent Number	Expiration Date	Patent Type	Patent Owner
5,843,901	December 1, 2015	Composition of matter	Advanced Research and Technology Institute
5,968,895	December 11, 2016	Pharmaceutical compositions	PRAECIS
6,180,608 B1	December 11, 2016	Pharmaceutical compositions	PRAECIS
6,423,686 B1	December 1, 2015	Composition of matter	Advanced Research and Technology Institute
6,455,499 B1	December 1, 2015	Method of use	Advanced Research and Technology Institute

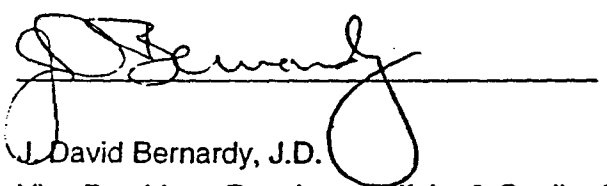
J. David Bernardy, J.D.
Vice President, Regulatory Affairs & Quality Assurance
PRAECIS PHARMACEUTICALS INCORPORATED

20 February 2003
Date

14. Patent Certification

As required under 21 CFR § 314.53(c), the following certification for NDA 21-320, Amendment 042 is provided:

The undersigned declares that United States Patent **Numbers: 5,843,901; 5,968,895; 6,180,608 B1; 6,423,686 B1 and 6,455,499 B1** are valid patents claiming abarelix, pharmaceutical compositions containing abarelix, and/or uses thereof in the treatment of prostate cancer, the subject of this New Drug Application.



20 February 2003

J. David Bernardy, J.D. Date
Vice President, Regulatory Affairs & Quality Assurance
PRAECIS PHARMACEUTICALS INCORPORATED

Item 13

PATENT INFORMATION

As required under 21 CFR 314.53(c), the following patent information for NDA # 21-320 is provided:

TRADE NAME: Plenaxis®
ACTIVE INGREDIENT: abarelix (USAN)
STRENGTH: 100 mg
DOSAGE FORM: intramuscular injection
APPROVAL DATE: pending

The patent number(s) listed below cover abarelix, pharmaceutical compositions containing abarelix, and/or uses thereof in the treatment of prostate cancer. PPI-149 (compound 3827 in US 5,843,901) is the active ingredient in the new drug for which approval is being sought and with respect to which claim of patent infringement of each patent listed below could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug:

U.S. Patent Number	Expiration Date	Patent Type	Patent Owner
5,780,435	December 15, 2015	Method of use	PRAECIS
5,843,901	December 1, 2015	Composition of matter	Advanced Research and Technology Institute
5,843,902	December 15, 2015	Method of use	PRAECIS
5,968,895	December 11, 2016	Pharmaceutical compositions	PRAECIS
6,153,586	December 15, 2015	Method of use	PRAECIS
6,180,608 B1	December 11, 2016	Pharmaceutical compositions	PRAECIS
6,180,609 B1	December 15, 2015	Method of use	PRAECIS
6,211,153 B1	December 15, 2015	Method of use	PRAECIS

23 Apr '01

Name JD Bernardy, J.D. *Date*
Title Vice President, Regulatory Affairs & Quality Assurance
Company PRAECIS PHARMACEUTICALS INCORPORATED

Item 14

PATENT CERTIFICATION

As required under 21 CFR 314.53(c), the following patent certification for NDA # 21-320 is provided:

The undersigned declares that United States Patent Number 6,211,153 B1 covers the composition and/or method of use of abarelix. This product is the subject of NDA 21-320, for which approval is being sought.

JD Bernardy 23 Apr '01

Name JD Bernardy, J.D. *Date*

Title Vice President, Regulatory Affairs & Quality Assurance

Company PRAECIS PHARMACEUTICALS INCORPORATED

Item 13

PATENT INFORMATION

As required under 21 CFR 314.53(c), the following patent information for NDA # 21-320 is provided:

TRADE NAME: Plenaxis®
ACTIVE INGREDIENT: abarelix (USAN)
STRENGTH: 100 mg
DOSAGE FORM: intramuscular injection
APPROVAL DATE: pending

The patent number(s) listed below cover abarelix, pharmaceutical compositions containing abarelix, and/or uses thereof in the treatment of prostate cancer. PPI-149 (compound 3827 in US 5,843,901) is the active ingredient in the new drug for which approval is being sought and with respect to which claim of patent infringement of each patent listed below could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug:

U.S. Patent Number	Expiration Date	Patent Type	Patent Owner
5,780,435	December 15, 2015	Method of use	PRAECIS
5,843,901	December 1, 2015	Composition of matter	Advanced Research and Technology Institute
5,843,902	December 15, 2015	Method of use	PRAECIS
5,968,895	December 11, 2016	Pharmaceutical compositions	PRAECIS
6,153,586	December 15, 2015	Method of use	PRAECIS
6,180,608 B1	December 11, 2016	Pharmaceutical compositions	PRAECIS
6,180,609 B1	December 15, 2015	Method of use	PRAECIS

9 Mar '01

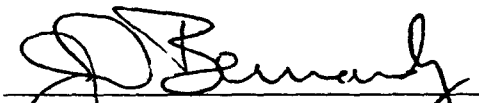
Name JD Bernardy, J.D. *Date*
Title Vice President, Regulatory Affairs & Quality Assurance
Company PRAECIS PHARMACEUTICALS INCORPORATED

Item 14

PATENT CERTIFICATION

As required under 21 CFR 314.53(c), the following patent certification for NDA # 21-320 is provided:

The undersigned declares that United States Patent Numbers 6,180,608 B1 and 6,180,609 B1 cover the composition and/or method of use of abarelix. This product is the subject of NDA 21-320, for which approval is being sought.



9 Mar '01

Name JD Bernardy, J.D *Date*

Title Vice President, Regulatory Affairs & Quality Assurance

Company PRAECIS PHARMACEUTICALS INCORPORATED

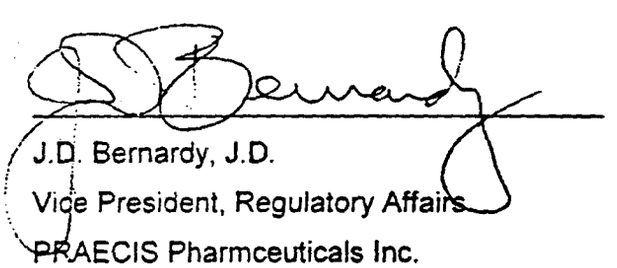
13. Patent Information

As required under 21 CRF 314.53(c), the following patent information for NDA # 21-320 is provided:

TRADE NAME: Plenaxis® (proposed)
ACTIVE INGREDIENT: abarelix (USAN)
STRENGTH: 100 mg
DOSAGE FORM: intramuscular injection
APPROVAL DATE: pending

The patent number(s) listed below cover abarelix, pharmaceutical compositions containing abarelix, and/or uses thereof in the treatment of prostate cancer. PPI-149 (compound 3827 in US 5,843,901) is the active pharmaceutical ingredient in the new drug for which approval is being sought and with respect to which claim of patent infringement of each patent listed below could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug:

US Patent Number	Expiration Date	Patent Type	Patent Owner
5,780,435	December 15, 2015	Method of use	PRAECIS
5,843,901	December 1, 2015	Composition of matter	Advanced Research and Technology Institute (licensed to PRAECIS)
5,843,902	December 15, 2015	Method of use	PRAECIS
5,968,895	December 11, 2016	Pharmaceutical compositions	PRAECIS



10 Dec '00

J.D. Bernardy, J.D.
Vice President, Regulatory Affairs
PRAECIS Pharmceuticals Inc.

Date

14. Patent Certification

As required under 21 CRF 314.53(c), the following certification for NDA # 21-320 is provided:

The undersigned declares that United States Patent **Numbers 5,780,435, 5843,901, 5,843,902, and 5,968,895** covers the composition, formulation and/or method of use of abarelix. This product is the subject of NDA # 21-320, for which approval is being sought.

J.D. Bernardy

10 Dec '02

J.D. Bernardy, J.D.
Vice President, Regulatory Affairs
PRAECIS Pharmceuticals Inc.

Date

EXCLUSIVITY SUMMARY

NDA #	**21-320**
Trade Name Requested	**Plenaxis**
Generic Name	**abarelix for injectable suspension**
Applicant Name	**Praecis Pharmaceuticals, Incorporated**
HFD-	**580**
Approval Date	**November 25, 2003**

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

   a) Is it an original NDA? YES/_X__/ NO /__/

   b) Is it an effectiveness supplement? YES /__ / NO /_X__/

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

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES /_X__/ NO /___/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data: _____

d) Did the applicant request exclusivity?

YES /_ _/ NO /_X__/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_X__/

* The indicated disease/condition (Treatment of the involuntary loss or leakage of urine in women during physical exertion or activities such as laughing, coughing, sneezing, lifting, exercising- stress urinary incontinence(SUI))does not exist in children.

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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

YES /___/ NO /__X_/

If yes, NDA # _____ Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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

YES /___/ NO /_X__/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /_X__/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

2. Combination product. N/A

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /_ _/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement

or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /__/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /__/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #_3_, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the

conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # __ YES /_ _/ ! NO /___/ Explain:

Investigation #2

IND # ____ YES /___/ ! NO /___/ Explain:

Investigation #3

IND # _____ YES /_ __/ ! NO /___/ Explain:

Investigation #4

IND # _____ YES /_ __/ ! NO /___/ Explain:

Investigation #5 IND # _____ YES /__/	NO /___/ Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 YES /___/ Explain _____ _____ _____	NO /___/ Explain _____ _____ _____
Investigation #2 YES /___/ Explain _____ _____ _____	NO /___/ Explain _____ _____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /__/

If yes, explain: _____

_____

_____

{See appended electronic signature page}

Nenita Crisostomo, R.n. — November 23, 2003
Signature of Preparer — Date

Title: Project Manager

{See appended electronic signature page} Date

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

cc:
Archival NDA 21-320
HFD-580/Division File
HFD-580/RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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
11/25/03 11:09:00 AM

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

The Exclusivity Summary is NA for this application for this review cycle.

5/7/03

20. Request for Waiver for Pediatric Use

PRAAECIS PHARMACEUTICALS INCORPORATED requests a waiver of the requirements of 21 CFR 314.55 Part (a0 (Pediatric use Information) because Plenaxis™ will not be used in pediatric patients for the indication described in this NDA amendment / resubmission.

APPEARS THIS WAY
ON ORIGINAL

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA # : 21-320

Supplement Type (e.g. SE5): N/A **Supplement Number: N/A**

Stamp Date: February 25, 2003 **Action Date: November 25, 2003**

HFD 580

Trade and generic names/dosage form: **Requested Tradename - Plenaxis™**
Generic: abarelix suspension for injection
dosage form: 100 mg intamuscular injection

Applicant: Praecis Pharmaceuticals Incorporated

Therapeutic Class: 1P

Indication(s) previously approved: N/A

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application: 1

Is there a full waiver for this indication (check one)?

☒ **Yes: Please proceed to Section A.**

☐ **No: Please check all that apply: ___Partial Waiver ___ Deferred ____Completed**
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver: not applicable to NDA

☐ **Products in this class for this indication have been studied/labeled for pediatric population**
☐ **Disease/condition does not exist in children**
☐ **Too few children with disease to study**
☐ **There are safety concerns**
☒ **Other: Plenaxis™ will not be used in pediatric patients for the indication described in this NDA submission.**

studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min_____ kg_____ mo._____ yr.____ Tanner Stage_____
Max_____ kg_____ mo._____ yr.____ Tanner Stage_____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**

- ☐ **X Too few children with disease to study**

The basis of this partial waiver request was that

(A copy of Section C of IND serial #142,

- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **X Adult studies ready for approval**
- ☐ **X Formulation needed**

Other:

Date studies are due (mm/dd/yy): The sponsor suggested

(See copy of Section B is included in the action packet as reference).

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min ____	**kg_____**	**mo._____**	**yr._____**	**Tanner Stage_____**
Max____	**kg_____**	**mo._____**	**yr._____**	**Tanner Stage_____**

Comments: [redacted]

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Nenita Crisostomo, R.N.
Regulatory Project Manager

cc: NDA 21320
HFD-950/ Terrie Crescenzi
HFD-960/ Grace Carmouze
(revised 9-24-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

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

/s/

Jennifer L. Mercier
11/25/03 11:11:13 AM

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

- Pediatric Page: Praecis Pharmaceuticals Inc. requested a full waiver.

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

A Pediatric Page is NA for this review cycle.

5/9/01

Request for Waiver for Pediatric Use

PRAECIS PHARMACEUTICALS INCORPORATED requests a waiver of the requirements of 21 CFR 314.55 Part (a) (Pediatric Use Information) because PLENAXIS™ [redacted] will not be used in pediatric patients for the indication described in this NDA.

APPEARS THIS WAY
ON ORIGINAL

16. Debarment Certification

PRAECIS PHARMACEUTICALS INCORPORATED hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application. (NDA 21-320, Amendment 042, abarelix for injectable suspension)

J. David Bernardy, J.D.
Vice President, Regulatory Affairs & Quality Assurance
PRAECIS PHARMACEUTICALS INCORPORATED

20 February 2003
Date

16. Debarment Certification

PRAECIS Pharmaceuticals Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

J.D. Bernardy, J.D.
Vice President, Regulatory Affairs
PRAECIS Pharmceuticals Inc.

9 Dec 10
Date

MEMORANDUM

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

DATE: November 25, 2003

FROM: Florence Houn MD MPH

SUBJECT: Office Director Memo

TO: NDA 21-320 Plenaxis (abarelix suspension) 100mg for injection by Praecis Pharmaceuticals, Inc.

This memo documents my decision to approve under provisions of 21 CFR Part 314 Subpart H for restricted marketing, Praecis Pharmaceuticals, Inc.'s (Praecis, the manufacturer) application for abarelix, a GnRH (gonadotropin releasing-hormone) antagonist to suppress testosterone in advanced symptomatic prostate cancer. This drug has risks but the risk management program with its restrictions on distribution and use is sufficient to ensure that in the specified population designated in the INDICATIONS section of the labeling, in which benefits of the drug outweigh risk, the drug can be safely used. Effectiveness is acceptable in this particular population and only in this population. Effectiveness is not acceptable in patients with longer life expectancy because alternative treatments exist with long term efficacy (as well as no risk of allergic reaction). Abarelix has increased risk of effectiveness failure over time. However, the indicated population has shortened life expectancy. This application would not be approved absent restrictions of distribution and use. The safety and effectiveness data are extensively documented by the Division of Reproductive and Urologic Drug Product's (the Division, DRUDP) reviews. This memo will document risk management decisions.

Brief Regulatory History

The February 25, 2003 submission constituted a complete response to our Not Approvable letter of June 11, 2001. This NDA was not approved because of the risk of serious allergic reactions, including anaphylaxis with hypotension and syncope, and because the risk of loss of efficacy over time. Neither the review division nor the office found data to support safety and effectiveness for the intended use population. For Praecis' then proposed target population of men with local, regional, or advanced carcinoma of the prostate where androgen suppression is appropriate, the Agency determined that risks of Plenaxis ™ exceeded its benefits.

In the entire safety database (mostly in men in the non-indicated population), the one year the risk is about 1.24% and at 676 days it is 2.9%). The risks consisted of increasing cumulative incidence of immediate-onset systemic allergic reactions (including hypotension, syncope, and life-threatening anaphylaxis). This risk is not associated with any of the currently approved hormonal therapy used as synthetic agonistic analogues called luteinizing hormone-releasing hormone (LHRH). The manufacturer argued that absence of a testosterone "surge" in month one of therapy, which accompanies LHRH agonist use, and the quicker suppression of testosterone in month one by 1-2 weeks were the benefits of the drug. One benefit claimed was [redacted] but no data were provided to support this. Moreover, the patients in this original submission did not benefit from lack of surge or from quicker suppression of serum testosterone in any clinical (non-biochemical) endpoint. These biochemical measures in and of themselves did not off-set life-threatening risk of immediate-onset systemic allergic reactions. Finally, the data showed that after 6 months, efficacy of testosterone suppression appeared to wane. A more detailed analysis of serum testosterone levels showed that the manufacturer's formulation or dose may not be providing sustained 30-day suppression and mid-monthly cycle measurements of testosterone were increased compared to measurements taken immediately after injection. This risk of loss of efficacy in the greater prostate cancer population was also not acceptable. This is because oftentimes prostate cancer is indolent and chronic. Inferior long term efficacy is not acceptable as currently men often die of other causes besides their cancer.

The application was the subject of a Center for Drug Evaluation and Research regulatory briefing in the spring of 2001 and the concurrence with the non-approval action was voiced.

Since the non-approval action, the Division and the Office have worked with Praecis to try to find a path forward. The manufacturer refused to reformulate or re-study new doses to address the waning efficacy. The manufacturer was not willing to conduct long-term mortality or morbidity studies, which could overcome the allergic risk issue if benefit was shown, to support their claims in the literature that lack of a testosterone flare has these benefits. The manufacturer did not pursue studies of allergy pre-medication. Consideration was given

but the risk of immediate-onset systemic allergic reactions would still exist even with a first dose. The division was reluctant to pursue

prostate cancer would be treated.

which complicates treatment with no clinical benefit to offer, but still there would be a risk of immediate-onset systemic allergic reactions that could be more life-threatening that the patient's prostate cancer.

Along with these discussions, FDA did discuss with the manufacturer the option of restricted distribution for a narrow population in whom benefits may exceed risk. Much internal effort between the Division director, team leader, primary medical officer and others went into discussions to identify exactly who these men are with the manufacturer. It was not until November 4, 2003 that final agreement over this population was achieved. This population is:

> Men with advanced symptomatic prostate cancer, in whom LHRH (luteinizing hormone-releasing hormone) agonist therapy is not appropriate and who refuse to undergo surgical castration, and have one or more of the following: 1) risk of neurological compromise due to metastases, 2) ureteral or bladder outlet obstruction due to local encroachment or metastatic disease, or 3) severe bone pain from skeletal metastases persisting on narcotic analgesia.

In the above indicated population of advanced, symptomatic prostate cancer patients, the risk of immediate-onset systemic allergic reactions is such that by Day 141, there were 3 cases of serious allergic reactions (two causing withdrawal and one with hypotension) out of the 81 patients in the clinical trial, giving a crude rate of 3.7%. It is not known if men with advanced disease may be at greater allergic reaction risk, but certainly the severity of allergic reaction will be tolerated more poorly with this sicker population. On November 24, 2003 the risk of immediate onset systemic allergic reaction that occurred in the indicated population was placed in the forefront of the WARNINGS section of labeling and the larger population data was moved as secondary. The company was told that and agreed to allergic rates should refer to the rate seen in the indicated population (which is now bolded and underlined in labeling).

Current Application Cycle Safety and Effectiveness Review

In the manufacturer's resubmission to the Not Approvable letter of June 11, 2001, there is no change in the data related to safety of the drug product. An allergy consult from the Division of Pulmonary and Allergy Drug Products was obtained and there is FDA agreement on the incidence of this reaction as well as our understanding that risk exists for serious allergic reaction even with the first dose of this drug. The allergy consult recommends observation of the patient for up to one hour, but most events occurred within 30 minutes.

This cycle's effectiveness review focused on a single open-label, multi-center, uncontrolled, single-arm study of 81 men with advanced symptomatic prostate cancer to demonstrate evidence of avoidance of bilateral orchiectomy through 12 weeks. Seventy-two patient's data were analyzed showing none needed orchiectomy at week 12. In addition, secondary endpoints of signs of neurologic compromise (n=8), urinary obstruction and hydronephrosis, and bone pain showed trends towards benefit.

Data from the non-symptomatic and non-advanced prostate cancer patients were reviewed for biochemical efficacy of testosterone suppression. It is believed this pharmacodynamic effect and mechanism of action is the same for the indicated population, but effects on prostate specific antigen may not be similar as the advance cancer population's PSAs may not be predictive of disease.

As stated above, in this non-symptomatic, non-advanced population, there is increase risk of loss of efficacy over 6 months. Furthermore, the data suggest this risk of loss of efficacy may be greater in men over 225 pounds.

21 CFR 314.520 Subpart H

The manufacturer and FDA discussed use of the provisions under this regulation to assure safe use. In July 2003 and again November 4, 2003, the manufacturer requested FDA review the NDA under 21 CFR 314.520 (Subpart H).

Advanced symptomatic prostate cancer, as described in the indication, is a serious and life-threatening condition. This stage of disease with the degree of complications from the disease usually predicts short life-span. Moreover, these specific patients may experience worsening of their symptomology (neurologic compression, urinary obstruction, or bone pain) with LHRH agonists (see the LHRH product labeling that cautions physicians about the use of these drugs in patients with the aforementioned symptomology). While surgical castration is the treatment of choice for immediate relief of these symptoms, in some men this choice is unacceptable. The indicated population is those men in whom LHRH agonists are not appropriate and who refuse surgical castration, and have neurologic, urologic obstructive, or severe pain symptoms. This drug provides this patient group an effective therapy where none exists.

This drug has increasing risk of loss of effectiveness over time. However, in symptomatic, advanced prostate cancer patients, who have no therapeutic alternative except without risk of increased morbidity (during the testosterone surge of 1-2 weeks from LHRH agonist therapy), and who have short life-expectancy, the loss of efficacy over time is moot. Also, for the acute situation of impending neurologic compression, progressive urologic obstruction, or severe pain despite narcotics, abarelix can effectively lower serum testosterone and address many men's symptoms. Moreover, testosterone monitoring is recommended to detect this loss of efficacy so other therapy, such as LHRH therapy or castration, can be re-discussed at that point with the patient, if testosterone increases.

The company has also agreed to provisions under Subpart H for review of promotional materials. This includes their educational materials that they will use for physicians, patients, distributors, and hospital pharmacists.

I agree with the Division that the drug is not safe unless there are marketing restrictions in distribution and use. These are discussed below.

Risk Management Program

Narrowing the Indication

The manufacturer on November 4, 2003 agreed that the use of Plenaxis ™ (abarelix for injectable suspension, 100mg) is limited to being a palliative treatment for men with advanced symptomatic prostate cancer, in whom LHRH agonist therapy is not appropriate and who refuse surgical castration, and have one or more of the following: (1) risk of neurological compromise due to metastases, (2) ureteral or bladder outlet obstruction due to local encroachment or metastatic disease, or (3) severe bone pain from skeletal metastases persisting on narcotic analgesia. This is a very small population consisting of 15,000 to 24,000 men by manufacturer estimates. On November 13, 2003, in a telecom to the company with the Division, I stated that if use and production exceeded this estimate, then the manufacturer would be viewed as unable to restrict use outside this approved population and this would not be acceptable. The company agreed that use in the non-indicated population was not acceptable and such a finding would not be their desire.

Because the drug was not and can not be approved for use in the general prostate cancer population because risks exceed benefits, the Division would not recommend nor would I approve this application unless the risk management program assured use is in this exact population. Moreover, years of anticipation in the urology community and desires by gynecologist to use a gonadotropin releasing hormone antagonist in female patients with endometriosis are forces that push for off-label use.

Assuring Appropriate Use in the Indicated Population

Risk management steps include physician attestation about understanding why because of safety concerns and risk of loss of long-term effectiveness that the drug is only indicated in the advanced, symptomatic prostate cancer population. There is also an educational program to ensure understanding of the indicated population and risks and benefits of the drug. This educational program will be for physicians, patients, hospital pharmacists, and distributors so that each will understand their role in managing risks of the drug. For example, physicians will be educated not only on the appropriate population of use, but also on how to report adverse events to FDA or Praecis. There will be evaluation of use in the indicated population through a phase 4 study of 2000 patients who are prescribed abarelix. In addition, a claims data base study to correlate claims with diagnostic codes to evaluate indicated use will be performed. Distributors will have on their re-ordering sites the approved indication to remind physicians who direct order the indication. Moreover, FDA has discussed with Centers for Medicare and Medicaid Services their role in supporting safe use, such as development of diagnostic codes to allow monitoring of claims databases for use in the indicated population.

Qualified Physicians to Manage Disease and Drug Risks and Acceptance of Responsibilities

Praecis Pharmaceuticals, Incorporated has agreed to enroll in a prescribing program physicians who meet all the following qualifications:

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

Physicians may self-attest to meeting these prescribing qualifications. Praceis Pharmaceuticals, Incorporated's receipt of the completed physician attestation from will precede distribution of Plenaxis™ by its agents to physicians or pharmacies.

The above 5 abilities are needed to ensure safe use because doctors who do not mange this patient population will not be able to: 1) possess the capacity to weigh risks and benefits of abarelix therapy with other options for the patient or to monitor effectiveness of therapy, and 2) treat a predictable adverse event of the drug, allergic reactions. The company is stating in it risk management program that oncologists, urologists, and internists will be targeted for enrollment "because they are the most likely to be qualified in accordance with the risk management program objectives." Praecis' Compliance Evaluation Board will review other specialties concerning enrollment.

Praecis Pharmaceuticals, Incorporated has also agreed to enroll in the prescribing program physicians who agree to do each of the following:

i. Educate patients about the risks and benefits of Plenaxis™ therapy and give to each patient the Patient Information.

Physicians who prescribe Plenaxis™ will be asked to agree to obtain the patient's signature on the Patient Information signature page, co-sign the form, place the original signed form in the patient's medical record and give a copy of the Patient Information leaflet with the signed page to the patient.

ii. Report serious adverse events to Praecis Pharmaceuticals, Incorporated or to the Food and Drug Administration's (FDA) MedWatch Program.

iii. Participate in a system that will identify for distributors of Plenaxis™ the physicians who are enrolled in Praeceis Pharmaceuticals, Incorporated's Plenaxis™ prescribing program (the Plenaxis User Safety Program (PLUS) program).

These responsibilities are needed to ensure patients understand the drug's risks and the need to stay 30 minutes under observation after each injection. A medication guide was discussed. A med guide is required distribution when pharmacists dispense the drug. The team felt that because only hospital pharmacists would be part of the distribution system, the medication guide, per se, was not a fit into this distribution system. Because most drug will be directly distributed to physicians, the sponsor will have contractual agreements to have distributors distribute the patient information leaflet. However, the tenets of the med guide still were applicable in that patients needed information on risks and benefits to decide on accepting or rejecting this therapy held, and, to ensure continued effectiveness, the patient needed information to understand monitoring of serum testosterone every 8 weeks. The patient information leaflet was developed. The manufacturer has agreed to having the patient sign receipt and understanding of the leaflet and the physicians providing the patient with a copy of the information, and putting the original signed sheet in the medical record in order to document provision of information. This is needed to ensure patients understand and accept risks and benefits. The signed sheet will serve as evidence that the physician and patient discussed risks and benefits. The signed sheet is auditable.

Adverse event reporting is important to monitor post-marketing safety. Physician acceptance of reporting helps ensure the spectrum of adverse events is received.

Without physician acceptance of participating in the Plenaxis PLUS program, there is no way to assure safe use. Verification of participation ensures the drug is being distributed to qualified physicians. The company also stated the PLUS program attestation would also have physicians attest to no further distribution of the drug (outside the system).

The company has proposed evaluation of this component of their risk management program. They will be ensuring that all attestations are complete, that a unit within Praecis can evaluate qualifications if issues arise, that educational programs will be available to help physicians understand the requirements and responsibilities, and a chart audit under a Phase 4 study will be conducted to check that patients are having their signed information leaflet inserted into the chart, the frequency of serum testosterone testing, and appropriate use in the indicated population. The company has planned an evaluation for AE reporting by physicians as well.

Distribution Controls

The company's plan is centered around the estimate that 93% of use will be through a direct physician-distributor system. The company believes 7% will be hospital use. The company believes roughly 24,000 patients fit the indication. They believe the incident number is 7% of those whom are starting hormonal therapy fit the indication. The company is targeting 15,000 urologists and 15,000 oncologists to enroll, knowing a small percentage will eventually complete enrollment. Distribution will be through 4 distributors who will have contractual agreements with Praecis to check all physician orders with physician enrollment status in PLUS. In addition, audits will be performed to ensure orders and tracking is occurring.

The company has decided no retail pharmacies will be used except in the rare circumstance that for patient reimbursement, a retail pharmacy is needed for drug to be dispensed to the patient. The company is stating that the retail pharmacy in this case is a "drop off point" and it has agreed to monitor the percentage of retail pharmacies used in this manner. Should this exceed 5% of total distribution, this risk management program would need to incorporate the retail pharmacy sector.

The company has decided to not pursue [redacted]

The distribution controls will be audited and reported on quarterly.

Hospital Pharmacies

Hospital pharmacies will be able to obtain drug with a signed agreement with Praecis to ensure physicians that order this drug in the hospital are enrolled in the Praecis PLUS program. The hospital pharmacies will ensure that their prescribing physicians are part of the PLUS program (qualified physicians). We acknowledge that hospital pharmacies may move drug to clinic pharmacies or other related facilities they service. Praecis is planning to conduct a study of pharmacy adherence to responsibilities through a random sample of pharmacies who agree to participate in such a study.

Patients Understanding of Drug Risks and Benefits

FDA accepts that the patient signing the Patient Information signature page means they have discussed and understand the risks and benefits of the drug. This signed signature page is placed in the medical record and is thus verifiable that physicians fulfilled this responsibility. Praecis is planning to conduct a study of such records.

Adverse Event Collection and Reporting System

Praecis has contracted with Sentrix to assist them in collection, follow up, and adverse event reporting to the FDA. Praecis has agreed to 15 day reporting for a number of MEDRA terms concerning immediate-onset systemic allergic reactions (see approval letter). This will help FDA monitor adverse events postmarketing.

Phase 4 Studies to Explore Safety Improvements and Evaluate Risk Management Program

Praecis has proposed studies to better understand the immediate-onset systemic allergic reaction phenomena and other allergic reactions. They proposed studies consist of following 2,000 patients to determine the incidence of development of reactions and to determine if the hazard rate changes over time, collecting IgG and IgE titres in those who develop allergic reactions, and assessing if use of oral anti-histamines and oral steroids lower risk for patients who experience allergic skin reactions and continue on the drug.

In addition to these studies, risk management evaluation studies are proposed (as mentioned previously) for physician knowledge assessment, use in the indicated population, compliance with placement of signed Patient Information signature page in the medical chart, frequency of serum testosterone testing, and adherence of hospital pharmacies to responsibilities. Protocols will be submitted to FDA prior to initiation for our review and comment. Quarterly reports will be provided on these studies.

Conclusion

This application contains an adequate risk management program that restricts distribution and use of the drug to assure safe use. The manufacturer has been told that they need to have policies and procedures in place that are written and verifiable and that typically FDA inspects restricted distribution systems within a year or so of marketing. FDA did review with Praecis on November 24, 2003 the provisions for withdrawal of approval, including if use after marketing demonstrates that postmarketing restrictions are inadequate to assure safe use of the drug, or, the applicant fails to adhere to the postmarketing restrictions agreed to. All issues have been satisfactorily resolved and this application is approved.

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/s/

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MEDICAL OFFICER

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

Division Director Summary Review: See Team Leader Review

/S/
11/25/03

MEDICAL TEAM LEADER'S MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
ODE 3
Division of Reproductive and Urologic Drug Products (DRUDP)

Date: November 25, 2003

From: Mark S. Hirsch, M.D., Medical Team Leader, DRUDP

To: Daniel A. Shames, M.D., Division Director, DRUDP

Subject: NDA 21-320; Praecis Pharmaceuticals Inc
Plenaxis™ (abarelix for injectable suspension) –
Indicated for the palliative treatment of men with advanced symptomatic prostate cancer, in whom LHRH agonist therapy is not appropriate and who refuse surgical castration, and have one or more of the following:
(1) risk of neurological compromise due to metastates,
(2) ureteral or bladder outlet obstruction due to local encroachment or metastatic diseasem, or
(3) severe bone pain from skeletal metastases persisting on narcotic analgesia.
Complete Response to Not Approvable Action

1. Executive summary:

The purpose of this memo is to provide the Division Director with my recommendation for action on this NDA. I recommend **approval** of NDA 21-320; Plenaxis™ (abarelix for injectable suspension) –indicated for the palliative treatment of men with advanced symptomatic prostate cancer, in whom LHRH agonist therapy is not appropriate and who refuse surgical castration, and have one or more of the following:

(1) risk of neurological compromise due to metastases,
(2) ureteral or bladder outlet obstruction due to local encroachment or metastatic disease, or
(3) severe bone pain from skeletal metastases persisting on narcotic analgesia.

Following substantial revision, it is my opinion that the sponsor's Complete Response to Not Approvable now adequately addresses the Not Approvable deficiencies. Adequate information has now been submitted to the Agency to allow for approval of the product in the indicated population.

Labeling negotiations have been successful in producing materials that adequately describe risks and benefits to patients and to prescribers and are appropriate to manage those risks. At this point in the review, the labeling requires only minor revision. Negotiations between Agency and sponsor have been successful in producing a substantive *risk management program (RMP)* under the Subpart H restricted distribution regulations. The RMP requires that sponsor may supply drug only to those physicians who enroll in the program and only through those pharmacies that also commit to certain specific procedures. In order to enroll, qualified personnel are required to formally commit to very specific responsibilities; all of which are intended to maximize the risk/benefit ratio for Plenaxis. Sponsor has agreed to 7 different *Phase 4 commitments*, four of

which are intended to assure successful functioning of the RMP, the remaining three are intended to investigate clinical efficacy and safety issues even further. Comments by Office of Drug Safety (ODS), Office of Compliance (OC), and Division of Pulmonary and Allergy Drug Products have been addressed satisfactorily. All chemistry, manufacturing and controls (CMC) deficiencies have been resolved to the satisfaction of Office of New Drug Chemistry (ONDC).

Therefore, in summary, based in large part on the specifics of the agreed-upon RMP under restricted distribution regulations, the agreed-upon labeling, and the agreed-upon post-marketing monitoring of this crucial risk management program, I can conclude that Plenaxis is safe and effective as labeled.

2. Brief summary of original deficiencies and the complete response:

2.1. Clinical Efficacy:

2.1.1. Clinical Efficacy: Issue of waning efficacy

In the original NDA, the Division noted that in at least one head-to-head controlled clinical trial, Plenaxis was marginally less effective than LHRH agonist therapy within 85 days of initiating therapy. In addition, the Division noted that there was insufficient long-term efficacy data to support chronic use. The sponsor was asked to address these issues in this Response.

In the review of this Complete Response, the efficacy issues were clarified. I conclude that Plenaxis is effective and is reasonably similar to LHRH therapy within the first 85 days following the first dose. In the two pivotal pharmacodynamic trials, 92% (N=164) and 93% (N=176) of patients attained medical castration (defined as attaining a serum testosterone ≤ 50 ng/dL) by Day 29 and maintained castrate levels until Day 85 (defined as no two consecutive values >50 ng/dL). When this data was analyzed using only one serum T > 50 ng/dL as the definition of failure, these success rates are somewhat lower (84% and 92%, respectively). To this reviewer, this data demonstrates that treatment with Plenaxis through Day 85 is efficacious. In fact, time to medical castration is shorter with Plenaxis than with LHRH therapy. The percentage of patients who reach medical castration by Days 2, 4, 8, 15 and 29 following Plenaxis injections on Days 1 and 15 are: 24%, 56%, 70%, 73% and 94%, respectively. In addition, I am also convinced that there is no testosterone surge with Plenaxis; 100% of Plenaxis patients avoided surge.

On the other hand, I am also convinced that the long-term effectiveness of Plenaxis is worse than LHRH therapy and this difference is likely to be clinically meaningful. The crucial finding is "waning" of effectiveness with continued dosing. When the data after Day 85 is assessed using the definition of <u>any one</u> serum testosterone above 50 ng/dL to define "failure", the effectiveness of Plenaxis in maintaining castration wanes. Specifically, at Days 85, 169 and 365, the results are as follows:

- in Study 1: 84% (N=176), 75% (N=166), and 62% (N=93), respectively.
- in Study 2: 92% (N=164), 87% (N=155), and 71% (N=86), respectively.

In my opinion, this level of effectiveness would not be appropriate in a prostate cancer population that could otherwise be treated with existing LHRH therapy. Therefore, in defining the role of Plenaxis therapy, I take the position that Plenaxis could only be considered "effective" in a group of patients who could not be treated by LHRH agonists and also refuse surgical castration. The sponsor agreed to this restriction of the population and provides data from one controlled clinical trial (98-04) in 81 patients to support clinical efficacy in this population. The reader is referred to Dr. Benson's original review of Study 98-04 and Dr. Monroe's subsequent review of that same study. Suffice to say that in 98-04, 81 patients were enrolled who were not believed to be

candidates for LHRH therapy as a consequence of the advanced stage of their prostate cancer and the risk of "flare". Of 72 evaluable patients, none required surgical orchiectomy. The expected benefits of medical castration were seen in this group, including prompt relief of severe bony pain and removal of bladder drainage catheters in those with outlet obstruction. In addition, none of 6 patients with risk of neurological compromise secondary to vertebral or epidural metastases developed neurological symptoms.

Based upon the pharmacodynamic data, the clinical efficacy data from Study 98-04, the sponsor's agreement to advocate monitoring of serum T in labeling (via blood draw on Day 29 and every two months thereafter), the sponsor's agreement to include all this information in the label, and the agreed-upon RMP that limits use to the indicated population, I can conclude that the efficacy of Plenaxis as labeled is supported. Therefore, in my view, the issue of waning efficacy has been successfully resolved.

2.1.2. Clinical Efficacy: Issue of dose and dosing frequency.

In their original NDA reviews, Drs. Chatterjee of Office of Clinical Pharmacology and Biopharmaceutics and Monroe of Clinical noted that the "breakthroughs" in medical castration (serum T above 50 ng/dL) with Plenaxis appears to be occur towards the end of each dosing cycle. In fact, group mean testosterone concentrations appear to vary in a predictable way, where lower levels occur right after the dose but higher levels occur at the end of each dosing cycle, just prior to the next dose. This allows some patients to "fail" as a consequence of serum T above 50 ng/dL towards the end of each dosing cycle. Dr. Chatterjee concluded that the reason for this "sawtooth" pattern might be that the dose of Plenaxis was slightly too small to maintain efficacy through the entire cycle for every patient with a high level of assurance. Alternatively, the selected dosing frequency might be slightly too long. Since the sponsor has conducted all their clinical trials using the 100mg dose and the same dosing intervals (Days 1, 15, 29 and every 28 days therafter), this team leader must make a regulatory decision based upon the available evidence. I conclude that minor elevations of the serum T above 50 ng/dL at the end of the dosing interval in some patients should not preclude approval in the indicated population because: this information is disclosed to patients, labeling advocates routine monitoring of serum T, there is currently no adequate medical treatment for these patients, and finally, the overall clinical impact of minor "breakthroughs" is not known.

2.1.3. Clinical Efficacy: Issue of patient weight

In his original NDA review, Dr. Chatterjee also noted that efficacy of Plenaxis in obese patients was reduced and this posed a concern for efficacy in the broad prostate cancer population. This reviewer agrees that there is reduced effectiveness in maintaining castrate serum T levels in patients who weigh >225 pounds (see the Clinical and Clinical Pharmacology primary reviews). The decrease in overall effectiveness of Plenaxis with increased duration of treatment is more obvious in this type of patient. I believe that this deficiency can be managed through labeling that advocates strict monitoring of serum T in those patients who weigh more than 225 pounds. Also, I believe that obesity it is not likely to be a frequent problem in the population of men with these subcategories of advanced symptomatic prostate cancer. Overall, I believe the issue is resolved.

2.2. Clinical Safety

2.2.1. Clinical safety: Issue of immediate-onset systemic allergic reactions

The major concern in the original NDA, as voiced in the Not Approvable letter, was the issue of severe, immediate-onset systemic allergic reactions. In the NA letter, the Division described the overall incidence of these types of reactions as 0.4%. We asked for further investigations into these reactions to attempt to characterize them better. For example, were these reactions mediated by IgE ("anaphlactic") or were they due to direct effect of drug on the mast cell ("anaphylactoid")? The intent of our request was to generate data that might help in reducing the incidence of these reactions or in mitigating their consequences.

In response, the sponsor has conducted all agreed-upon investigations and has attempted to better characterize the reactions. Our consultation with DPADP confirms that the investigations have been conducted properly. This scientific research has resulted in a better understanding of the nature of the reactions, but the information has not served to reduce their incidence nor mitigate their consequences. Therefore, this issue remains a major safety concern.

However, this reviewer no longer finds this particular concern to be a reason for not approving Plenaxis. I take this position because:

1) Even with this known risk, the risk/benefit ratio has been sufficiently improved through the modification of the indicated use (only for patients with symptomatic advanced prostate cancer patients who cannot be treated appropriately with available therapy and who refuse surgical treatment) and,
2) The agreed-upon risk management program should succeed in preventing use outside the indicated populations, and
3) The RMP mandates a 30 minute observation period following each and every dose of Plenaxis, and
4) The physician and patient labeling is extremely clear on the incidence, severity, and risks associated with these reactions, and
5) The sponsor has committed to conduct Phase 4 studies to further characterize the incidence, nature, and possible ways to prevent these reactions, and
6) The sponsor has committed to report all such reactions to the Agency (including ones that are not "serious" in strict regulatory terms) in a timely way and to seek out additional information about each such reaction. Mechanisms are in place to enforce this reporting.

It is important for the reader to understand the nature of these reactions and their incidence.

Incidence of allergic reactions: Allergic reactions with systemic manifestations were reported by 18 of 1397 patients treated in all Praecis-sponsored trials combined. (*Two Plenaxis-treated patients in studies not sponsored by Praecis also reported allergic reactions.*) The overall incidence of systemic allergic reactions with Plenaxis, *not* corrected for exposure, was estimated to be 1.3%. Of these 18 cases, most (N=15) occurred within the first hour after the injection and these were treated as clinically significant. Therefore, if we define these reactions as "immediate-onset" systemic allergic reactions, the overall incidence of these is **1.1%**. Of all systemic allergic reactions, 7 were accompanied by symptoms of hypotension or syncope. The overall incidence of allergic reactions accompanied by syncope or hypotension was **0.5%.**

The Agency held that the most appropriate way to describe the frequency of these events is to use a life table analysis. This allows for the correction of incidence rates for treatment exposure. Therefore, the Division calculated cumulative incidence rates for the 15 immediate-onset systemic allergic reactions. Cumulative incidence rates (95% CI) for these reactions at Days 56, 141, 365 and 676 were **0.51%** (0.13%, 0.88%), **0.80%** (0.30%, 1.29%), **1.24%** (0.43%, 2.04%), and **2.91%** (0.87%, 4.95%), respectively.

The life table analysis approach was also used to describe the frequency of immediate-onset systemic allergic reactions accompanied by hypotension or syncope (7 total cases). For allergic reactions with hypotension or syncope, the cumulative incidence rates (95% CI) at Days 56, 141, 365 and 617 were **0.22%** (0.00%, 0.46%), **0.32%** (0.00%, 0.64%), **0.61%** (0.00%, 1.24%), and **1.67%** (0.07%, 3.28%), respectively.

Of note, 3 of 81 patients in the pivotal trial 98-04 reported allergic reactions (urticaria, urticaria and pruritis, and allergic reaction accompanied by hypotension). All three were withdrawn from the trial. This reflects an incidence of 3.7%. The overall sample size in this trial was small. I believe that this information should be placed prominently in the label in juxtaposition to the overall (full NDA) incidences of allergic reaction. The difference may or may not be statistically or clinically meaningful. Still, prescribers should be aware of the greater incidence rate for these reactions that was noted in the target population in 98-04.

Nature of allergic reactions: The allergic reactions seen in the abarelix-treated patients were consistent with the spectrum of the signs and symptoms of systemic allergic reactions. Symptoms included flushing, itching, and urticaria and in some cases, angioedema, hypotension and syncope. One patient required treatment with bronchodilators which suggests associated bronchospasm in this patient. In one of the 18 total patients, the reaction occurred after the first dose. Of the 18 patients, 14 had the reaction within five minutes of dosing, and 15 were within 1 hour of doing. No patient treated with active comparitor developed an immediate-onset systemic allergic reaction.

The sponsor concluded that the reactions were "anaphylactoid" in nature, not IgE-mediated or "anaphylactic". This conclusion was based on the results of skin testing and in vitro data. There is some support for the sponsor's conclusions. First, the fact that even one patient had a reaction after first dose speaks against a pure IgE-mediated phenomenon. The skin tests revealed no IgE-mediated type reactions in normal volunteers and none in the one patient who was tested who had previously had an allergic reaction in the clinical trials. These results speak against IgE mediation. In vitro tests revealed no meaningful differences between abarelix- or comparitor-treated patients in abarelix-specific IgE, carboxymethylcellulose-specific IgE or IgG, or total IgE or IgG. This also speaks against an IgE-mediated phenomenon. Our consultant from DPADP concludes that the data suggests that the reactions do not reflect IgE-mediated allergy. Finally, incidence rates do not appear to increase over time by a factor greater than the expected cumulative increase as a consequence of additional dosing, and not greater than that sort of an increase, as might be expected with an IgE-mediated phenomenon.

Therefore, taking all this into account, this reviewer concludes that such risks, coupled with the previously described efficacy results would still not support approval in a broad prostate cancer population. However, given the efficacy results previously described and the safety risks described herein, I believe the benefits of abarelix outweigh the risks in the population of advanced symptomatic prostate cancer patients as proposed by sponsor now. This is supported even further by a substantive RMP that includes the following:

1. Intent to prevent use outside the indication, and
2. Assurance that all prescribers are capable of treating advanced prostate cancer, and
3. Assurance that all prescribers can treat systemic allergic reaction, and
4. All patients will be monitored for at least 30 minutes after each injection.
5. All such reactions will be reported expeditiously.
6. Patients will be made aware of the risks by signing a Patient Information leaflet.

Finally, there are Phase 4 commitments for further investigation of the allergic reactions, as well as studies to perhaps pre-medicate patients in an attempt to lessen the occurrence of allergic

reactions. Based upon all these measures, I can support approval in the indicated population and I find the allergic reaction issue to be adequately managed at this time.

2.2.2. Clinical safety: Issue of QT prolongation

As part of the Complete Response (actually, during the course of review of this Complete response), Praecis submitted information concerning the effect of Plenaxis on the QT interval. This new information was considered to be a major clinical amendment. The new QT information was reviewed by Dr. Chatterjee and OCPB, by Dr. Monroe, and by Dr.Norman Stockbridge of Cardio-Renal Division. In at least one large, open-label comparitor trial (ABACAS 1), there were significant increases from baseline in both the Plenaxis group and the comparitor group. The mean Fridericia-corrected QT interval in the abarelix arm was approximately 11 msec, and in the LHRH + non-steroidal antiandrogen arm, the increase was 20msec. The number of outliers was lower in the abarelix arm. While the results may have appeared to be of lesser significance for abarelix compared to approved comparitor, Dr. Chatterjee points out that the ECGs and blood draws were collected at abarelix trough concentrations and such could have lessened the impact of abarelix on the QT interval. Further, there was no active nor placebo control. Finally, the study was conducted in fairly advanced prostate cancer patients with varied co-morbid conditions. To investigate this issue further, Dr. Chatterjee requested ECG data from 2 large open-label abarelix pharmacodynamic trials. The results confirmed those from ABACAS 1, indicating that abarelix was associated with mean increase from baseline of approximately 10-15 msec. Again, these studies were neither positive- nor placebo-controlled.

Dr. Stockbridge of the Cardio-Renal Division was asked to comment on the ABACAS1 results. He opined that "both treatments [abarelix and comparitor] clearly prolong repolarization". He concurred with Dr. Chatterjee's assessment that the effect on QT may actually be worse, since the only data comes from timepoints around the trough concentrations. He concluded that:

"At the end of the day, if a case can be made that abarelix confers a substantial clinical benefit in its target population, some proarrythmic risk should be acceptable." His note continues that if the benefit is less than mortality, he would advise further characterization of the affect of abarelix on the QT interval prior to approval. He also advises characterization of the affect of the already approved comparitors.

Ultimately, this reviewer holds that this QT issue should not prevent approval. First, the benefit to patients with symptomatic advanced prostate cancer patients who refuse orchiectomy is substantial. Second, the results with abarelix were actually less concerning than with approved products. This reviewer acknowledges the issue of peak versus trough testing. In my opinion, the Agency will need to formally discuss the QT issue in regard to all androgen deprivation treatments. Such a discussion is likely to require our consultation with special experts in cardiac arrythmia in order to obtain their advice. This process may be lengthy and in my opinion, it should not prevent abarelix from reaching those in whom its benefits may be substantial. This is especially true when one considers that the comparitor agents, which were also positive in the controlled abarelix trials, have been marketed for at least a decade. Regardless, the QT information has been placed in the PI and PPI prominently (as Warnings). The label advises against use in conjunction with drugs known to be associated with torsades and in patients with congenital QT prolongation. Pending further discussion of this entire issue for all such products, I am of the opinion that at this time, nothing is further required for NDA 21-320 regarding QT.

2.2.3. Clinical safety: Issue of hepatotoxicity

The review of this Complete Response included an assessment of the effect of Plenaxis on liver function. Data was available from two active-controlled clinical trials. There were clinically meaningful increases in serum transaminases in a small percentage of patients in both treatment groups in both active-controlled studies. In the pivotal pharmacodynamic studies combined, the percentage of Plenaxis patients reporting serum ALT >2.5 times upper limit of normal or >200 U./L was 8.2% and 1.8%, respectively. The percentage reporting serum AST >2.5 times upper limit of normal or >200 U/L was 3.1% and 0.8%, respectively. Similar results were reported for active comparators in both studies. In regard to these findings, this reviewer believes that the appropriate regulatory action is to advise prescribers in the label and to advocate the measurement of serum transmainases before starting treatment and then periodically thereafter. Considering the serious clinical situation of the indicated population, the modest increase in LFTs, the similarity with already approved comparitors, and appropriate labeling, in my view, this issue is resolved.

2.2. Chemistry, manufacturing and controls (including microbiology)

There were some chemistry deficiencies that precluded approval of the Original NDA. In his final draft review dated 12-November-2003, Dr. De states:

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

The NDA received an "acceptable" recommendation from Compliance based upon their inspection of the manufacturing facilities. In their final memo dated 22-July-2003, Drs. Languille and Cooney of Microbiology stated: "NDA 21-320 is recommended for approval from the standpoint of microbial product quality." There were no outstanding microbiology deficiencies.

Therefore, to my knowledge, there are no remaining chemistry deficiencies.

3. Relevant issues from other disciplines and consultants

3.1. Division of Pulmonary and Allergy Drug Products (DPADP)

The Division of Pulmonary and Allergy Drug Products (DPADP) was asked to review the original NDA and the Complete Response with special emphasis on the allergic reactions and the studies done to characterize these. Dr. Charles Lee did the primary consult review. In his finalized review, dated 3-July-2003, Dr. Lee concludes:

> "The sponsor has narrowed the proposed indication to patients with advanced symptomatic carcinoma of the prostate who have impending neurologica compromise, urinary tract obstruction, and/or bone pain from prostate cancer skeletal metastatses requiring narcotic analgesia. The new narrowed proposed indication focus on a population in which the risk of immediate allergic reactions may be acceptable."

In summating, Dr. Lee points out the following:

1. The sponsor's risk management plan appears to be acceptable from the clinical standpoint.
2. The sponsor's plan to communicate appropriate risk and benefit information to healthcare providers and patients is comprehensive.

3. The sponsor's plan to monitor the success of the risk management plan is appropriate from the clinical standpoint.
4. In order to further characterize the etiology of these immediate-onset allergic reactions, and as part of the risk management plan, consideration should be given to requesting the sponsor make a Phase 4 commitment to perform skin testing and in vitro testing of a defined number of patients who have such reactions to abarelix in the post-approval period.

In regulatory response to this recommendation, such a Phase 4 commitment has been obtained.

Dr. Lee contributed to our understanding of the nature of the adverse reactions. Some of his findings have already been described in the Clinical Safety section above. In sum, after reviewing the sponsor's in-vitro testing study, and the skin testing study, and the ISS, Dr. Lee concluded:

1. The sponsor's skin testing and in vitro data suggest an anaphylactoid (not IgE-mediated) mechanism, but this isn't conclusively demonstrated.
2. The life table analysis expresses the frequency data in a more appropriate way then a simple incidence.
3. A Boxed Warning is appropriate.
4. A post-dosing observation period should be mandatory.
5. One hundred percent (100%) of physicians who administer this drug should have the facilities and the ability to treat allergic reaction.
6. Immediate-onset systemic allergic reactions were not seen in the comparitor arms in any trial.
7. The per-injection frequency of immediate-onset systemic allergic reactions associated with hypotension or syncope with abarelix was 0.04% which is similar to penicillin and low osmolar radiocontrast material, but lower than for high osmolar radiocontrast material. However, these other drugs are not for chronic and regular use like abarelix.

3.2. Biometrics

In their finalized memo dated 29-July-2003, Drs. Meaker and Welch state that for the original NDA: "A life table analysis was presented to quantify the risk [of immediate onset allergic reactions]." In this review:

> "The statistical review analyzes the updated safety data for this particular risk of concern. Also, the descriptive statistics for the single arm trial [Study 98-04] are confirmed."

The results from the life table analysis have already been presented in this review in the Clinical safety section. To highlight:

1. The estimated event rate for immediate onset systemic allergic reaction is 1.2% at one year, with a 95% confidence interval of (0.4%, 2.0%).
2. At two years, this event rate increases to 2.9% (0.9%, 5.0%) – on Day 676.
3. The overall event rate is 1.1%.
4. For those reactions accompanied by hypotension or syncope, the event rate is 0.6% at one year with 95% CI of (0.0%, 1.2%). This increase at Year 2 to 1.7% (0.1%, 3.3%).

Finally, Dr. Meaker's brief review of Study 98-04 ("the pivotal trial") confirms the descriptive results of this open-label, non-comparitor trial.

3.3. Pharmacology and toxicology

In their final memo for this Complete Response, dated 17-March-2003, Drs. Raheja and Jordan stated: "This is a resubmission of NDA 21-320" and "Under the present submission, sponsor has included minor additions to the P/T data." They conclude:

"The toxicity data confirm the safety of abarelix for clinical use."

Dr. Raheja discusses four minor issues, including two pharmacodynamic studies, one 6-month toxicity study and a supplement to the carcinogenicity results. The pharmacodynamic demonstrates the ability of abarelix to reduce tumor burden in the TRAMP mouse model. The 6-month SC toxicity study was no different than previous. Finally, the updated carcinogenicitiy results actually increase the multiples between concentrations attained in the animal studies and the human exposure.

3.4. Clinical Pharmacology and Biopharmaceutics (OCPB)

Dr. Chatterjee wrote an "addendum" to his original NDA review. In this document, OCPB does not change its previous recommendation of "acceptable" for this NDA.

In the Complete Response,

However, during the Complete Response review, *new QT information* was submitted by sponsor. This information came from the ABACAS1 study and was further supplemented by data requested from the Studies 149-98-02 and 149-98-03.

The QT data collected in *ABACAS1* were scrutinized by Dr. Chatterjee. It reveals a prolonging effect of abarelix and of the comparitor (LHRH + nonsteroidal antiandrogen). The mean individual prolongation from baseline, measured as Fridericia-corrected QT was 11 msec for abarelix and 20msec for the comparitor group. The percentages of patients who sustained either an increase in QTc of >30 msec or a final QT above 450 msec for abarelix was 25% and 25%, respectively. For comparitor, these results were 43% and 26%, respectively. This information has been placed in the label as a Warning, with emphasis on carefully assessing risk/benefit in those patients with baseline QT prolonging syndromes or in those taking medication that might also prolong the QT. Of interest, in ABACAS1, Dr. Chatterjee notes that ECGs were done at times of trough concentrations for Plenaxis. Therefore, these QT results may not reflect the worst possible prolongation of the QT by abarelix, if QT effect is related to drug concentration. In addition, he notes that comparisons between groups are not valid based upon the pK/pD issue, as well as the lack of a placebo or active control group. Further, the results may have been confounded by the use of prostate cancer patients and not normal volunteers.

Dr. Chatterjee further reviewed the available QT data from *Studies 149-98-02 and 149-98-03.* The Fridericia-corrected results in these studies were similar to those in ABACAS1. The mean individual Fridericia-corrected for abarelix versus comparitor (LHRH alone) were 13 msec and 17 msec, respectively. The percentages of patients who sustained either an increase in QTc of >30 msec or a final QT above 450 msec for abarelix was 25% and 19%, respectively. For comparitor, these results were 41% and 30%, respectively. In my opinion, the labeling is sufficient regulatory action for this issue at the moment and for this approval. Ultimately, a major

effort should be undertaken to better understand the effect of androgen deprivation products on the QT interval. This, I believe, should not preclude approval at this time.

Finally, Dr. Chatterjee's original NDA referred to issues of dose selection, patient weight and waning efficacy. In my opinion, the current labeling reflects his concerns clearly. Taking these concerns into account, I still believe the drug may be approved as labeled.

3.5. Division of Cardio-Renal Drug Products (DCRDP)

The Division of Cardio-Renal Drug Products provided a final consult to DRUDP on 17-June-2003 in regard to the QT data from ABACAS1. Drs. Stockbridge and Throckmorton provided their analysis and opinions on the data as described in the Clinical Pharmacology Section 3.4 above. The analysis of the data by Cardio-Renal was not different than that by Dr. Chatterjee of OCPB. In sum, Dr. Stcokbridge drew the following conclusions:

1. Both abarelix and active comparitor prolong repolarization at 3 months after dosing and at 12 months.
2. The sponsor's report of +12 milliseconds for abarelix and +18 msec for comparator appears correct.
3. Available clinical data does not reveal "overt or likely latent proarrythmic risk", although the database is fairly small.
4. Standard pre-clinical evaluations should be performed.
5. Comparisons between drugs cannot be made based upon the design of the trial.
6. The potential arrythmogenic risk could be acceptable if abarelix "confers a substantial clinical benefit in the target population". Otherwise, if the benefit is less than mortality, "it would appear that a more complete characterization should be obtained and iven the difficulty with enforcing phase IV commitments, such information should be obtained and reviewed prior to approval."
7. Additional information should be obtained on QT effects of "standard therapy".

In response to Dr. Stockbridge's comments, this reviewer has posed an argument (see Clinical Safety section above) that the drug IS of substantial benefit to a sub-population of men with symptomatic advanced prostate cancer in whom LHRH therapy is not appropriate and who refuse surgical castration. Further, the approved comparitors in each trial also prolonged QT (acknowledging the deficiencies in trial design and lack of placebo and active control preclude comparison). The labeling contains an appropriate Warning. Additional research on QT effects across all these products will be encouraged by DRUDP.

3.6. Office of Drug Safety: Division of Drug Risk Evaluation (ODS/DDRE) and Division of Surveillance, Research and Communication (ODS/DSRCS)

ODS/DDRE was consulted to review the sponsor's Risk Management Plan (RMP). ODS/DSRCS was consulted to review the sponsor's proposed Patient Information materials.

Throughout the review of the Complete Response, Drs. Wiley, Avigan and Trontell of DDRE have provided their detailed comments and recommendations in regard to the sponsor's RMP. Minutes of our meetings with sponsor document their input. With DDRE and DSRCS input, the sponsor and Agency have come to agreement on a comprehensive RMP. The critical components of the RMP are restricted distribution to certain physicians who meet the qualifications and

commit to meet all responsibilities of the program. There is also limited distribution to those pharmacies that similarly commit to RMP responsibilities and obligations. The sponsor has committed to a system of adverse event collection, monitoring and periodic reporting. The RMP has appropriate educational objectives. The RMP is designed so that the success of the program is monitored and action is taken if the program isn't functioning as expected. The reader is referred to Dr. Houn's memo for a detailed explanation of the RMP, as constructed under the relevant Subpart H regulation.
Also throughout the process, Ms. Best has provided her input on the Patient Information materials. After a great deal of consideration of the options, the Division agreed with sponsor that a PPI would be appropriate, but only if it was in MedGuide format and only if it required a patient's signature. Labeling negotiations were successful in producing an agreed-upon PPI. This part of the RMP is considered an important component of optimizing the risk/benefit ratio for abarelix.

3.7. Division of Scientific Investigations (DSI)

In their final consult to the Division dated 21-July-2003, Drs. Blay and Kin Maung U conclude that:

> "The data submitted in support of this NDA by Drs. Centeno, Gange, and Friedel appear acceptable."

3.8. Division of Drug Marketing and Advertising (DDMAC)

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The Division and Office acknowledge all DDMAC's important concerns and have acted upon these to craft an accurate label. The sponsor has cooperated in this effort.

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/s/

Mark S. Hirsch
11/25/03 06:28:44 AM
MEDICAL OFFICER

Daniel A. Shames
11/25/03 10:14:36 AM
MEDICAL OFFICER

MEMORANDUM

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

DATE: October 27, 2003

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

VIA: Nita Crisostomo, Regulatory Health Project Manager
Division of Reproductive and Urologic Drug Products
HFD-580

FROM: Jeanine Best, M.S.N., R.N., P.N.P.
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support
HFD-410

THROUGH: Toni Piazza-Hepp, Pharm. D., Acting Director
Division of Surveillance, Research, and Communication Support
HFD-410

SUBJECT: ODS/DSRCS Memo to File for Summary of Patient Information for Plenaxis (abarelix for injectable suspension), NDA 21-320

Summary of Patient Information
Appropriate patient information and education can inform patients about possible adverse events, signs and symptoms to watch for, and actions to take. This memo outlines three options to enable receipt of patient information for abarelix. We have summarized the three options under consideration.

1. **Patient Package Insert (PPI)**
   A PPI is FDA-approved patient labeling that is not mandated by regulation to be dispensed with the product. If the PPI is appended to the professional labeling (package insert or PI) it is likely to be packaged with the medication since abarelix will be dispensed as a single unit-of-use dose. The PI is typically printed in small font, such as 4 to 6 point. Font less than 10 point are difficult to read for an older population, the usual age of the indicated population for abarelix, thus if this option is used, we would recommend the larger font size for the PPI portion of the labeling. Further, there would need to be a mechanism by which the physician would make sure that the PPI is provided to the patient and the patient has an opportunity to read and understand the information in the PPI prior to receiving the dose.

2. **Medication Guides**
   Medication Guides are mandatory patient information and are required to be dispensed to the patient when they receive the prescription drug product as per 21CFR 208. Medication Guides have a required format and content with a required font size of at least 10 point. If

this option is used, there would technically be a requirement to dispense this patient information, however, as with the PPI option, there is currently not a clear mechanism as to how the patient would receive the Medication Guide prior to injection. The Medication Guide regulation also specifies that if a prescriber determines that "it is not in a particular patient's best interest to receive a Medication Guide because of significant concerns about the effect of the Medication Guide on a patient", then the Medication Guide would not have to be dispensed. However, a patient, filling his/her own prescription can request a Medication Guide from a dispensing pharmacy, even if a physician has requested that one not be provided. A patient would not have this choice with abarelix, if the physician chose not to provide the Medication Guide.

The Patient Information Subcommittee met on October 9, 2003 and determined that a Medication Guide was appropriate for abarelix, but left the final decision with the review division as to which form of patient information would better achieve the objectives for abarelix.

Additional Comment on Options 1 and 2: Specification in the Prescriber's Agreement (fourth bullet) that the PPI or Medication Guide be *reviewed with the patient* prior to the injection should be considered. The current wording specifies that the information is merely provided to the patient.

3. **Patient Information / Acknowledgement Form**
A form requiring signature from the patient that the PPI or Medication Guide for abarelix has been received and reviewed with them could increase the likelihood that the patient's understanding of the appropriate risk information. The patient could receive and sign this form prior to each dose. This form would not be consent for treatment, but rather serve as an acknowledgement / documentation that information was received. This method could also be used to track use of abarelix if needed. If such a form is developed, it should be written in consumer friendly language at the 6th to 8th grade reading comprehension level.

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/s/

Jeanine Best
10/27/03 04:16:39 PM
DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp
10/27/03 04:20:26 PM
DRUG SAFETY OFFICE REVIEWER

MEMORANDUM

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

DATE: October 8, 2003

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

VIA: Nita Crisostomo, Regulatory Health Project Manager
Division of Reproductive and Urologic Drug Products
HFD-580

FROM: Jeanine Best, M.S.N., R.N., P.N.P.
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support
HFD-410

THROUGH: Toni Piazza-Hepp, Pharm. D., Acting Director
Division of Surveillance, Research, and Communication Support
HFD-410

SUBJECT: ODS/DSRCS Review #2 of Patient Labeling for Plenaxis (abarelix for injectable suspension), NDA 21-320

The patient labeling which follows represents the revised risk communication materials of the Patient Labeling for Plenaxis (abarelix for injectable suspension), NDA 21-320. It has been reviewed by our Office and by DDMAC. We have simplified the wording, made it consistent with the PI, removed promotional language and other unnecessary information (the purpose of patient information leaflets is to enhance appropriate use and provide important risk information about medications, not to provide detailed information about the condition), and put it in the format that we are recommending for all patient information. Our proposed changes are known through research and experience to improve risk communication to a broad audience of varying educational backgrounds. These revisions are based on draft labeling submitted September 17, 2003 (PI) and September 24, 2003 (PPI).

Comments to the review Division are bolded, italicized, and underlined. We can provide marked-up and clean copies of the revised document in Word if requested by the review division.

We also have the following comments:

1. We have revised the patient information, following the Medication Guide Regulations (21 CFR 208) for content and format since this product is being considered by the Patient Information Subcommittee for a Medication Guide. If the product is approved with a Medication Guide, then the term "Medication Guide' is substituted wherever the terms

'Patient Information', 'patient leaflet', or 'leaflet' appear. The term "Medication Guide' may not be used if the product is not recommended for and approved with a Medication Guide.

2. Ideally, patients should receive and read the important risk information prior to receiving a Plenaxis injection. The sponsor has not provided information on how the patient will receive the Plenaxis Patient Information/Medication Guide. Usually, Medication Guides are dispensed in outpatient pharmacies along with the prescription. This medication will only be administered in certain medical offices and facilities. We recommend that a patient consent form or other mechanism be developed to ensure that the patient is informed of the important risk information and receives a copy of the Patient Information/Medication Guide prior to injection.

3. The Medication Guide Regulations [21 CFR 208.20(a)(4)] mandate font size of at least 10 point for all sections of the Medication Guide except for the manufacturers name and address and revision date. An even larger font size, at least 12 point, should be considered, as this medication will be used mainly in older males.

Please let us know if you have any questions.

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/s/

Jeanine Best
10/8/03 04:39:55 PM
DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp
10/8/03 04:46:38 PM
DRUG SAFETY OFFICE REVIEWER

MEMORANDUM

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

DATE: May 29, 2003

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

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

FROM: Jeanine Best, M.S.N., R.N., P.N.P.
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support
HFD-410

THROUGH: Toni Piazza-Hepp, Pharm. D., Acting Director
Division of Surveillance, Research, and Communication Support
HFD-410

SUBJECT: ODS/DSRCS Review of Patient Labeling for Plenaxis (abarelix for injectable suspension), NDA 21-320

The patient labeling which follows represents the revised risk communication materials of the Patient Labeling for Plenaxis (abarelix for injectable suspension), NDA 21-320. It has been reviewed by our Office and by DDMAC. We have simplified the wording, made it consistent with the PI, removed promotional language and other unnecessary information (the purpose of patient information leaflets is to enhance appropriate use and provide important risk information about medications, not to provide detailed information about the condition), and put it in the format that we are recommending for all patient information. Our proposed changes are known through research and experience to improve risk communication to a broad audience of varying educational backgrounds.

Please let us know if you have any questions. Comments to the review Division are bolded, italicized, and underlined. We can provide marked-up and clean copies of the revised document in Word if requested by the review division.

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/s/

Jeanine Best
5/29/03 02:53:58 PM
CSO

Toni Piazza Hepp
5/30/03 09:13:25 AM
DRUG SAFETY OFFICE REVIEWER

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Mail: ODS (Room 15B-08, PKLN Bldg.)
Attention: Leslie Stephens, Project Manager, DSRCS

FROM: Freshnie DeGuia, Regulatory Health Project Manager
Division of Reproductive and Urologic Drug Products; HFD-580
(301) 827-4252

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
May 5, 2003		21-320	N	February 25, 2003

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Plenaxis (abarelix for inj. Suspension)	RUSH	GnRH Antagonist	June 5, 2003

NAME OF FIRM: Praecis Pharmaceuticals

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILITY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: This is a consult request from Dr. Mark Hirsch, Urology Team Leader. Please review attached PPI.
The User Fee Goal Date is August 27, 2003. This is an NME (New Molecular Entity) and will need an office sign off. Please call me if you have any questions.

Thanks.
Freshnie

Cc: Hirsch, Monroe, Best

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Eufrecina deGuia
5/5/03 12:46:59 PM

Office of Drug Safety

Memo

To: Daniel Shames, M.D.
Director, Division of Reproductive and Urologic Drug Products
HFD-580

From: Tia Harper-Velazquez, Pharm.D.
Safety Evaluator, Division of Medication Errors and Technical Support
HFD-420

Through: Alina Mahmud, R.Ph.
Team Leader, Division of Medication Errors and Technical Support
HFD-420

Carol Holquist, R.Ph.
Deputy Director, Division of Medication Errors and Technical Support
HFD-420

CC: Nenita Crisostomo
Project Manager, Division of Reproductive and Urologic Drug Products
HFD-580

Date: October 7, 2003

Re: ODS Consult 00-0270-2; Plenaxis (Abarelix for Injection) 113 mg/vial; NDA 21-320.

This memorandum is in response to an September 29, 2003, request from your Division for a re-review of the proprietary name, Plenaxis and its package insert. In our last review, dated June 3, 2003, (ODS Consult # 00-0270-1), DMETS did not have any objections to the use of the proprietary name Plenaxis. Label and labeling recommendations were included in ODS Consult # 00-0270-1.

Since that review, the DMETS Expert Panel identified one additional proprietary name as having the potential to cause name confusion with Plenaxis. The Panel identified Plexion to have look-alike to Plenaxis. Plexion is an over-the-counter drug product which contains 10% sodium sulfacetamide and 5% sulfur. It is indicated for the treatment of acne. Plexion is applied to clean, wet skin, avoiding the eyes and inside of the nose and mouth. It is rinsed off with water after ten minutes, or when the medicine is dry. Plexion is available as a cleanser in stock sizes of

170 grams and 340 grams; and as a cream (Plexion SCT), in a stock size of 120 grams. The names share look-alike similarity in that both names contain the same prefix ("Ple"). Although the suffixes ("xion" vs. "naxis") contain the same letter combination of "xi", is located at different positions in each name, which helps to distinguish the names from each other when scripted. The products are each available as a single strength. Therefore, a prescription written for either medication does not have to indicate a strength. However, if a strength is indicated, the products do not overlap in this regard (10% / 5% vs. 113 mg). Plexion and Plenaxis also differ in route of administration (topical vs. intramuscular or subcutaneous), dosage form (cream or cleanser vs. powder for injection), and indication for use. Also, Plenaxis must be administered under the supervision of a physician, since it is known to cause immediate on-set allergic reactions. Lastly, the availability of Plenaxis will be restricted to physicians or health care personnel familiar with its use. Given these differences, DMETS believes that the potential for confusion between Plexion and Plenaxis is minimal.

Plexion **Plenaxis**

Plexion Plenaxis

In review of the revised package insert, it does not appear that our recommendations in ODS Consult # 00-0270-1 were addressed. Please advise us as to whether or not these recommendations were taken into consideration.

DMETS considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary/established names from this date forward.

If you have any questions or need clarification, please contact the medication errors project manager, Sammie Beam at 301-827-3242.

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/s/

Tia Harper-Velazquez
10/14/03 07:35:16 AM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
10/16/03 02:58:11 PM
DRUG SAFETY OFFICE REVIEWER

Office of Drug Safety

Memo

To: Daniel Shames M.D.
Director, Division of Reproductive and Urological Drug Products
HFD-580

From: Alina R. Mahmud, R.Ph.
Team Leader, Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-420

Through: Carol Holquist, R.Ph.
Deputy Director, Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-420

CC: Freshnie DeGuia
Project Manager
HFD-580

Date: June 3, 2003

Re: ODS Consult 00-0270-1; Plenaxis (Abarelix for Injection) 133 mg/vial; NDA 21-320.

*****NOTE: This review contains proprietary and confidential information that should not be released to the public.*****

This memorandum is in response to an April 25, 2003, request from your Division for a re-review of the proprietary name Plenaxis. Container labels, carton and insert labeling for Plenaxis were also provided for review.

Plenaxis was reviewed and found acceptable by DMETS on March 19, 2003 (see ODS consult 00-0270). Since our initial consult, DMETS has identified one additional — name, — that may cause a potential for confusion with Plenaxis.

Additionally, please consult Dan Boring, Chair of CDER's Labeling and Nomenclature Committee for guidance on the proper designation of the established name.

In review of the container labels, carton and insert labeling of Plenaxis, DMETS has identified the following areas of possible improvement, which might minimize potential user error.

A. CONTAINER LABEL

1. The strength is currently presented on the labels and labeling as "Provides a 100 mg dose." However, according to the package insert, each vial actually contains 113 mg of abarelix sterile powder. The labels and labeling should be revised to include the actual amount (total drug content) of abarelix per vial. See example at the top of page 3.

***
NOTE: This review contains proprietary and confidential information that should not be released to the public.***

Plenaxis
(abarelix for Injection)
113 mg per vial
(delivers 100 mg)

2. Relocate the expression of strength so that it appears immediately following the established and proprietary name as shown above.

3. We question the necessity of the numbers "01-01" appearing at the upper right corner of the label. If not necessary, please delete as it may cause confusion with the strength, dose or other quantifiable information on the label.

4. If space permits, include directions for reconstitution and resultant concentration (mg/mL). For example, once reconstituted with 2.2 mL of Sodium Chloride Injection, the resultant solution contains XX mg/mL.

B. CARTON LABELING

1. See General Comments A1 and A2 above.

2. Relocate the "Contents:..." statement from the side panel to the front panel.

3. Relocate the "Dosage and Administration:..." statement to the side panel.

4. Number each step and the corresponding pictorial under the Reconstitution and Administration of Plenaxis section.

5. Include the resultant concentration (mg/mL) once reconstituted with 2.2 mL of Sodium Chloride Injection.

6. The statement "...withdraw the entire contents (at least 2 mL) following the schematic for needle position" is ambiguous and confusing. Revise the statement to read "...withdraw 2 mL by positioning the needle at a 45degree angle as shown in the pictorial." Additionally, Numbering the steps along with the pictorials will assist health care practitioners in properly reconstituting the drug.

7. The instructions "Exchange the 18G x 1½" needle with the enclosed 22 G x 1½" Safety Glide injection needle" could potentially cause needle sticks as the 18G x 1½" needle is exposed during the exchange of needles. Please provide a needle shield for the 18G x 1½" needle to prevent needle sticks.

8. The color of the print for the statement "Observe the patient after injection for any sign of an allergic-type response" should appear in red rather than black to alert the healthcare professional of its importance.

C. INSERT LABELING

1. See comments B5 through B8.

2. Revise the statement "Plenaxis 100 mg Must be Administered Under the Supervision of a Physician" to read "Plenaxis Must be Administered Under the Supervision of a Physician". The current presentation is misleading because it presents the proprietary name as Plenaxis 100 mg rather than Plenaxis. This revision should be applied to the two subsequent sentences as well.

3. Please include a recommended dose statement. For example, the statement

   should be revised to read, "The recommended dose of Plenaxis is 100 mg on day 1, 15, 29 (week 4), and every 4 weeks thereafter."

If you have any questions or need clarification, please contact the Division Project Manager, Sammie Beam, at 301-827-3242.

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/s/

Alina Mahmud
6/10/03 03:34:46 PM
PHARMACIST

Carol Holquist
6/10/03 03:38:26 PM
PHARMACIST

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information

Deputy Division Director's Memorandum

From:	**Daniel A. Shames MD** **Deputy Director, DRUDP**
To:	**Victor Raczkowski MD** **Deputy Director ODE III**

NDA	21-320
Sponsor	Praecis Pharmaceuticals Inc One Hampshire Street Cambridge, MA 02139
Submission Type	Original NDA
Drug	
Established name	Abarelix for suspension (abarelix carboxymethylcellulose)
Trade name	Plenaxis™
Chemical class	Synthetic decapeptide
Drug Class	Gonadotropin releasing hormone (GnRH) antagonist
Proposed Indication	
Route of Administration	Intramuscular injection
Dosage Form	Suspension
Dosing Regimen	Administered on Day 1, Day 15, and Day 29 and once every 28 days thereafter
Dose	100 mg per dosing
Dates	
Submitted	December 11, 2000
CDER stamp date	December 12, 2000
PDUFA date	June 12, 2001
Related NDAs	None
Related INDs	IND 51-710 (Prostate cancer)
Memo complete	May 23, 2001

1.0 BACKGROUND

Surgical castration or treatment with high doses of estrogenic compounds (generally diethylstilbestrol [DES]) to suppress testicular androgen production were the mainstay of treatment for advanced prostate cancer for decades. However, the reluctance of many men to accept surgical castration for therapy and the adverse effects of estrogen therapy (particularly cardiovascular adverse events) lead investigators to develop alternative methods of medical castration. Today, GnRH super agonists such as leuprolide (approved by the FDA for the treatment of prostate cancer in 1985) and goserelin, have essentially replaced estrogenic compounds as a medical treatment choice.

The therapeutic activity of GnRH superagonists in the management of prostate cancer is via a reduction in circulating levels of testicular androgens. GnRH agonists down-regulate their own receptors resulting in an almost complete suppression of LH secretion, and secondarily, a suppression of testicular androgen production. Achievement of castration levels of serum testosterone is generally obtained by 1 month after the start of therapy. Orchiectomy results in a decrease in serum testosterone levels to castrate levels in approximately 4 to 8 hours. LHRH agonists cause an initial testosterone "surge" in >80% of patients because of initial stimulation of LH release. Testosterone levels are increased 50 to 100% for approximately 2 weeks. Testosterone levels then fall and castrate levels of T are achieved by approximately 95% of patients by 28 days. This testosterone "surge" has been associated with clinical "flare" in 5 to 10% of patients treated with LHRH agonists. A potential advantage of abarelix (a GnRH antagonist) is the lack of testosterone "surge" and, therefore, absence of clinical "flare."

Most commonly, the immediate consequence of this initial increase in circulating androgen levels is an increase in bone pain. Less frequently, more serious adverse events can occur, including ureteral obstruction, bladder neck outlet obstruction, spinal cord compression and paralysis. For these reasons, it is believed that a GnRH superagonist should be used with caution in patients at potential risk for complication secondary to testosterone surge. In these situations, GnRH super agonists are generally administered concurrently with antiandrogens to prevent clinical "flares".

Dr. George Benson did an extensive review of the literature regarding the clinical importance or testosterone surge and clinical flare (see Benson review p4-6). He concludes that there is "general agreement that patients at risk for clinical flare should be treated for flare prevention. Because of drug availability, most US studies have utilized non-steroidal anti-androgens (flutamide, bicalutamide, and nilutamide). Although these anti-androgens do have significant side effects (diarrhea, abdominal pain, and hepatic and pulmonary toxicity), they are generally prescribed for only 2 to 3 weeks. Literature concerning the efficacy of various drugs used for flare prevention is controversial. No data exist which compare the efficacy and safety of GnRH antagonists with GnRH superagonists with or without anti-androgens in patients at risk for the development of clinical flare"