

Abarelix, in contrast to GnRH super agonist such as leuprolide, is a true GnRH antagonist that is devoid of any LH and FSH releasing activity. Consequently, administration of abarelix and other compounds in this class, rapidly reduce the secretion of LH, and secondarily testicular androgens, without initially producing a surge of testosterone. The sponsor believes that the use of a true GnRH antagonist for the medical treatment of men with advanced carcinoma of the prostate will not cause an increase in prostate cancer-related symptoms often observed following the onset of treatment with a GnRH superagonist. The sponsor believes that rapid castration without a testosterone surge will offer clinical advantage to all men in whom medical castration is appropriate. In men who are in imminent danger from complications of an expanding mass of prostate cancer, abarelix should be especially useful in preventing serious acute sequelae of advanced prostate cancer.

The sponsor submitted the results of three comparative trials in men (N approximately 1000) with prostate cancer in whom medical castration would be appropriate but in whom variations in time to castration and testosterone surge would not alter the clinical course of the patients in a clinically significant manner. Testosterone measurements including rapidity of castration, testosterone surge and maintenance of castration were used a surrogate of for clinical outcomes in patients with prostate cancer.

The sponsor also submitted data from an open label trial men with advanced prostate cancer (N=71) whom the sponsor believes were at risk for significant sequelae (ureteral obstruction, neurologic compromise etc.) of their metastatic prostate cancers. The sponsor believes that this population of patients would potentially benefit clinically from rapid medical castration the avoidance of a testosterone surge. and in whom a testosterone surge could theoretically result in tumor growth and subsequent adverse sequelae.

2.0 NDA DATA

2.1 CLINICAL

2.1.1 Primary Trials

The primary clinical studies conducted by the Sponsor to support the efficacy of abarelix were Study 149-98-02 (N=269, Lupron comparator) and Study 149-89-03 (N=251 Lupron +Casodex comparator). Both were controlled, randomized, open label, multicenter clinical trials in which patients with prostate cancer that might benefit from hormonal therapy (i.e., reduction in androgen levels) were enrolled in a 2:1 ratio to treatment with either abarelix or active comparator (Lupron or Lupron + oral Casodex [an antiandrogen]). All patients were to receive an injection of abarelix or Lupron once every 28 days through Study Day 141. Patients assigned to the abarelix group also received Study Drug on Day 15. Patients, who in the Investigator's opinion had benefited from their initial treatment, were offered the opportunity to continue treatment for an additional 28 weeks (through Study Day 337).

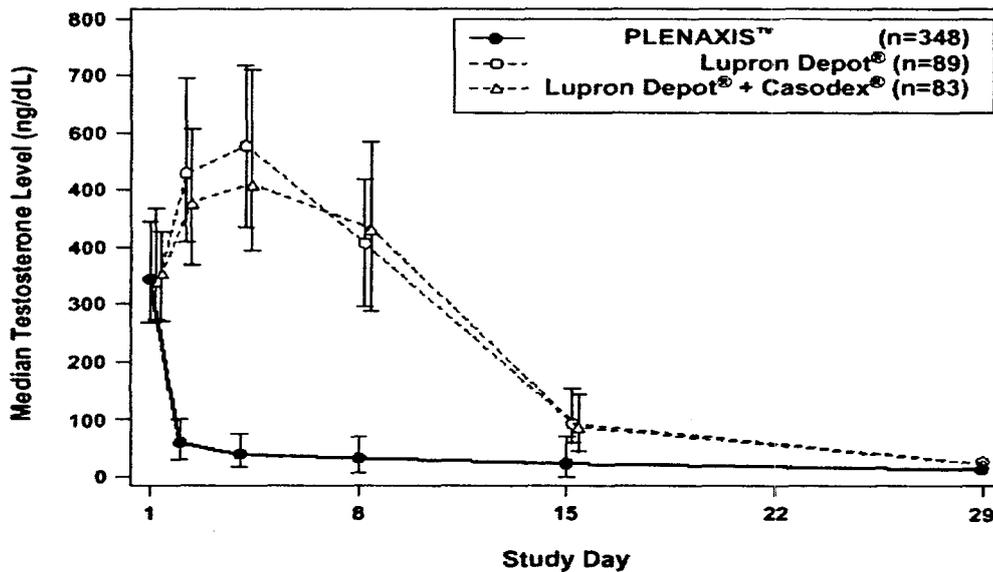
A third clinical trial (Study 149-99-03, N=735, Lupron comparator) was conducted primarily to increase the size of the safety database. The enrollment criteria and treatment regimen for this study were essentially identical to those of Study 149-98-02.

2.1.1.1 *Integrated Review of Efficacy*

The 3 primary efficacy endpoints are all dependent upon changes in serum concentrations of testosterone following administration of Study Drugs. They are achievement and maintenance of serum testosterone concentration of <50ng/dL. from day 29 to 85, avoidance of testosterone surge and time to castration.

Figure 1 represents data from trials 98-02 and 03 and is representative of the effect of abarelix (Plenaxis) and the comparators on serum testosterone levels during the first month of therapy

Figure 1. Serum Testosterone Concentrations During the First 4 Weeks of Treatment with Abarelix, Lupron Depot®, or Lupron Depot® Plus Casodex®



Bars represent the interquartile range.

Efficacy during first three months (See fig. 2 and 3)

Within 24 hrs of administration of abarelix, median serum testosterone levels had declined from baseline values of 350 and 340 ng/dL to 59 and 58 ng/dL and were less than 50 ng/dL by Day 4. In contrast, median testosterone levels in both the Lupron and Lupron plus Casodex groups increased by about 50% following initial dosing, with maximal levels observed on Day 4. Median testosterone levels in the active control

groups then gradually declined, reaching castrate values by Day 29. Abarelix is clearly superior to the comparators in rapidity of castration and avoidance of testosterone surge. Abarelix was not inferior to Lupron in maintaining castrate testosterone levels up to 3 months.

Efficacy from 3 month to 12 months (See fig 2 and 3)

The primary medical officer did an intensive analysis of testosterone levels over time for abarelix and the comparators. **The primary medical officer and Urology Team leader agree that from 6 to 12 months, abarelix treatment is inferior to Lupron in maintaining serum testosterone levels at or below 50 ng/dL.** While the primary medical officer believes that abarelix is inferior to Lupron in maintaining testosterone from three to six months, the urology team leader believes that abarelix is substantially equivalent to Lupron in terms of maintaining castration out to 6 months.

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Figure 2
Mean (\pm SD) Serum Testosterone in Representative Study comparing Abarelix and Lupron

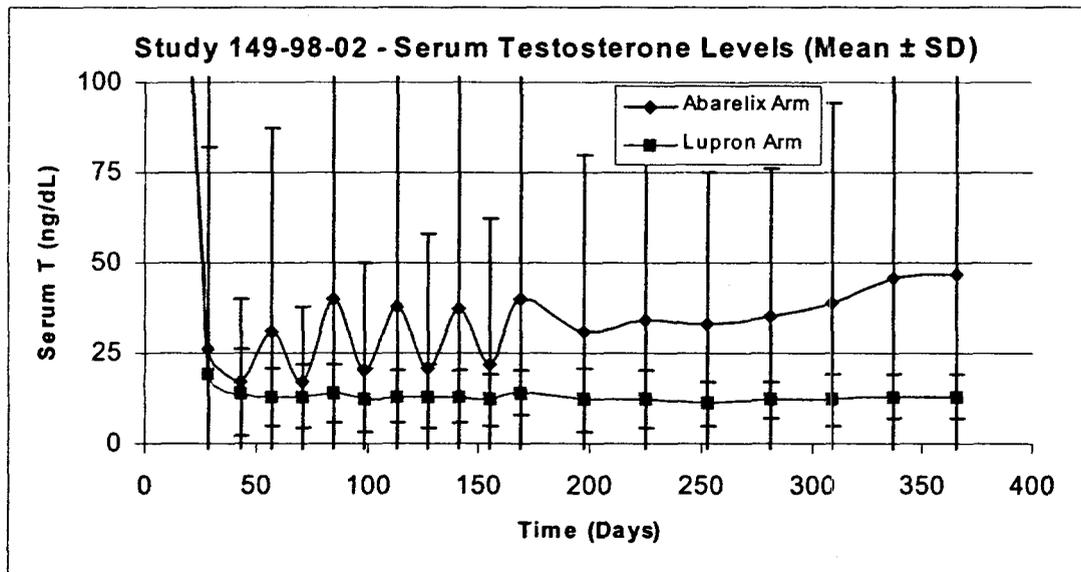
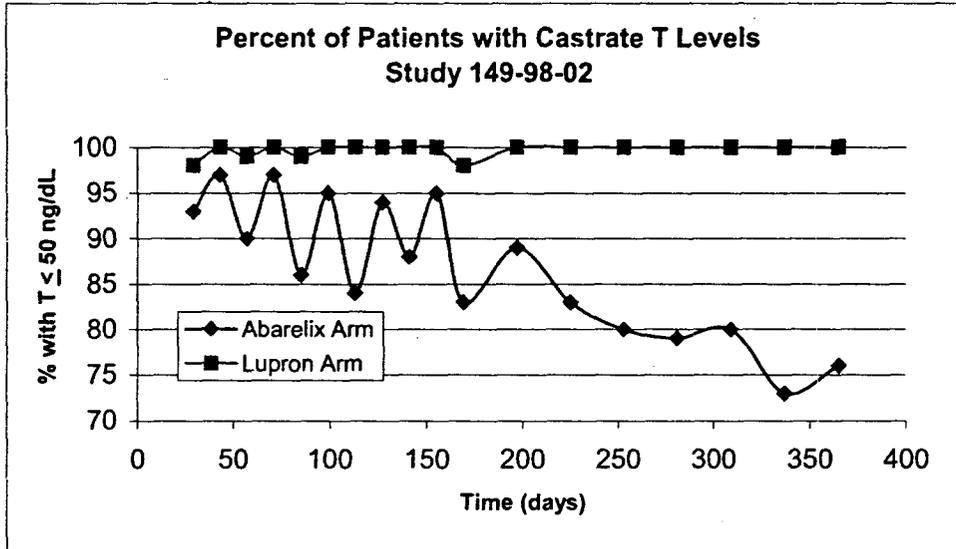


Figure 3

Representative study comparing Abarelix and Lupron in Percent of Patients with Serum Testosterone \leq 50 ng/dL



2.1.1.2 Safety

There are two specific areas of concern with abarelix that require particular attention. They are allergic reactions and liver toxicity.

Allergic Reactions (cutaneous):

Allergic-type skin disorders reported to have an unknown, possible, probable, or definite relationship to study drug are summarized in Table 1.

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Table 1 Treatment-Related Allergic-Type Skin Disorders (Studies 149-98-02, 149-98-03, and 149-99-03)

Preferred Term	Lupron N = 284 n (%)	Lupron Plus Casodex N = 83 n (%)	Abarelix N = 735 n (%)
Rash ¹	3 (1)	3 (4)	19 (3)
Pruritus	5 (2)	1 (1)	15 (2)
Urticaria ²	2 (1)	0	2 (< 1)
Dermatitis	0	0	2 (< 1)
Eczema	0	0	0
Overall ³	10 (4)	4 (5)	36 (5)

¹ Rash, erythematous rash, maculopapular rash

² Urticaria and acute urticaria

³ Total number (percentage) of patients with any allergic-type skin disorder. Patients with multiple events were counted once.

Source: Table 4.3.1. and Data Listing 15.24.1 in the 149-98-02, 149-98-03, and 149-99-03 clinical study reports

The primary medical officer notes that “the percentage of patients exhibiting these **“allergic” cutaneous disorders was similar in the 3 treatment groups. Allergic cutaneous disorders do not, in general, represent a serious safety concern if they** (a) are not accompanied by other systemic changes such as hypotension or syncope and (b) do not initially occur within 1-2 hours of dosing. Some of the patients in the abarelix group exhibited these latter symptoms of a more serious reaction and are reviewed in the following section.”

Allergic Reactions Causing Safety Concerns:

A total of 20 patients participating in the abarelix clinical development program were either withdrawn because of an allergic type of reaction ,experienced an immediate post-dosing hypotensive reaction, and or experienced an immediate post dosing allergic reaction. Seventeen of these 20 patients were treated with abarelix. Table 2 lists for each of these patients the following information: treatment assignment, time of onset of adverse reaction relative to dosing, and whether the reaction included hypotension and/or syncope.

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Table 2

Patients Withdrawn from Clinical Trial Due To an Allergic Reaction or With an Immediate Systemic Adverse Reaction Post Dosing ¹

Study Number	Patient Number	Treatment	Time of Reaction Onset After dosing	Syncope or Hypotension
<i>Onset of adverse reaction within 2 hours of dosing</i>				
149-97-04	02-4635	Abarelix	2 min	No
149-98-02	11-2218	Abarelix	5 min	No
149-98-03	16-3028 ¹	Abarelix	5 min	No
149-98-03	27-3200	Abarelix	2 hrs	No
149-98-03	76-3224	Abarelix	Immediate	No
149-98-03	09-3246	Abarelix	<15 min	No
149-98-04	401-4001	Abarelix	Immediate	Yes
149-98-04	409-4057	Abarelix	Immediate	No
149-99-04	416-4067	Abarelix	5 min	No
149-99-03	357-2226	Abarelix	45 min	No
149-99-03	313-3087	Abarelix	<10 min	Yes
149-99-03	333-3336	Abarelix	Immediate	Yes ²
149-99-04	01-2192	Abarelix	5 min	Yes
Abacus	THY-JP	Abarelix	Immediate	Yes
Abacus	DRO-JA	Abarelix	5 min	Yes
<i>Onset of adverse reaction more than 2 hours after dosing</i>				
149-97-04	38-4700	Abarelix	5 days	No
149-98-02	13-2144	Lupron	5 days	No
149-99-03	301-1295	Lupron	6 days	No
Abacus	21540077	Abarelix	1 day	No
Abacus	7450299	Lupron	10 days	No

¹ All patients were withdrawn except for Patient 16-3028.

² Investigator classified event as a severe vasovagal reaction with unknown association to study drug.

Fifteen (15) of the 20 reactions (all in the abarelix group) occurred within 2 hours of dosing. Thirteen (13) of these 15 reactions occurred within 15 minutes of dosing. Allergic signs or symptoms in 6 of the 20 patients included **loss of consciousness and or hypotension**. These latter 6 reactions all occurred in patients receiving abarelix and all occurred within 10 minutes of dosing.

The clinical presentations of the systemic allergic reactions in at least 15 of the 20 patients receiving abarelix are clearly different than those observed in patients receiving Lupron. These 15 reactions occurred within 2 hours of dosing while the 3

reactions in patients receiving Lupron occurred several days after dosing. The clinical presentation of several of the rapidly occurring reactions in the abarelix group suggests that patients experienced an acute release of histamine or other vasoactive substance (i.e., an anaphylactoid or anaphylactic type of reaction).

All patients recovered without sequelae. Management ranged from no treatment in 6 of the 15 patients with an early allergic reaction to aggressive therapy that included oxygen, IV fluid, epinephrine, Benadryl, Solumedrol and albuterol in 1 patient.

Hepatic toxicity

Liver function was monitored fairly frequently in all the important clinical trials submitted with the NDA. Comparative data was analyzed by the sponsor and medical reviewer's using multiple approaches such as "clinically notable" transaminase elevations ($>2.5 \times \text{ULN}$ or $>200 \text{U/L}$) and "shift analysis" (using WHO Toxicity Grading System).

Both the primary medical officer and Urology Team Leader believed there is a trend toward increased liver toxicity in the abarelix group versus Lupron.

The data of most concern relates to those patients that demonstrated markedly increased serum transaminases (at least $5.1 \times \text{ULN}$, or $>200 \text{U/L}$). Although the overall incidences are small in all three treatment groups, there appears to be a subtle difference between the Abarelix group and the Lupron alone, and Lupron + Casodex groups. There also appears to be some evidence that the percentage of withdrawals due to increased hepatic enzymes was somewhat greater in the Abarelix group compared with the Lupron-only group. None of the markedly increased transaminase concentrations was associated with a drug-related clinically important increase in serum bilirubin.

2.1.2 High Risk Population Trial (149-98-04)

Seventy-one patients in whom LHRH agonists were "contraindicated" were enrolled in this open-label, multi-center (18 US and 1 Mexico) trial. All patients had 1 of the 4 following conditions secondary to prostate cancer: 1) bone pain from skeletal metastases 2) bilateral retroperitoneal adenopathy causing ureteral obstruction 3) impending neurological compromise and/or 4) the presence of an enlarged prostate gland or pelvic mass causing bladder outlet obstruction. Patients received 7 doses of abarelix depot 100 mg on Days 1, 15, 29, 57, 85, 113, and 141. Table 3 indicates the proportion of patients in each category.

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Table 3

Proportion of Patients with Symptomatic Conditions for Study Entry

Impending neurological compromise	6 (8%)
Ureteral obstruction	9 (13%)
Enlarged prostate or pelvic mass	25 (35%)
Bone pain from skeletal metastases	31 (43%)
Other	1 (1%)

LHRH agonists are not “contraindicated” in the 4 conditions listed. Because of the testosterone “surge” seen with LHRH agonists, product labels describe clinical “flare” in the warnings section and state that patients with any of the 4 conditions listed should be “closely observed” during LHRH therapy.

2.1.2.1 Efficacy

Efficacy summary: The primary efficacy endpoint was the avoidance of orchiectomy at Days 29 and 85. These results are shown in Table 4.

Table 4. Percentage of patients who avoided orchiectomy through day 29 and through day 85 (N=72).

	Avoided orchiectomy N (%)	95% confidence interval
Through day 29	70 (97%)	(90.3, 99.7)
Through day 85	70 (97%)	(90.3, 99.7)

2.1.2.2 Safety

Allergic reactions: One patient experienced a severe systemic allergic reaction (loss of consciousness, generalized skin rash, hypotension (blood pressure of 80 mmHg measured by Doppler), and peri-orbital, facial, and peripheral edema) and 2 other patients withdrew from the study because of allergic symptoms (both had urticaria). No deaths from allergic reactions occurred. The incidence of study withdrawal because of an allergic adverse event was 4%. This patient was included in the general safety analysis.

Elevated transaminases: Three patients experienced elevated AST and ALT to >2.5 times the upper limit of normal. These patients were included in the general safety analysis.

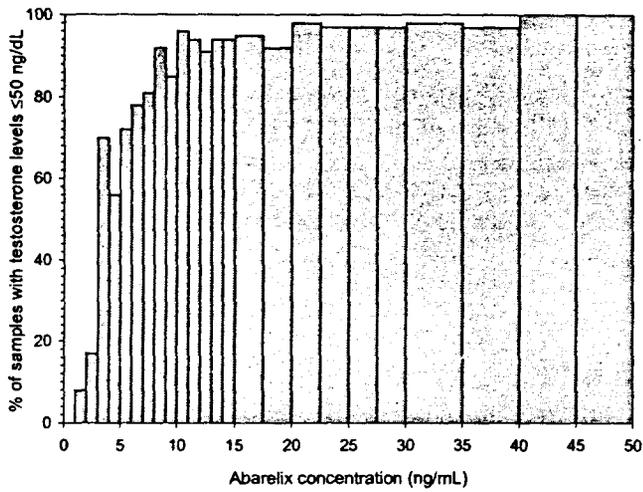
3.0 OTHER CLINICALLY RELEVANT INFORMATION

3.1 NDA Clinical Pharmacology Review

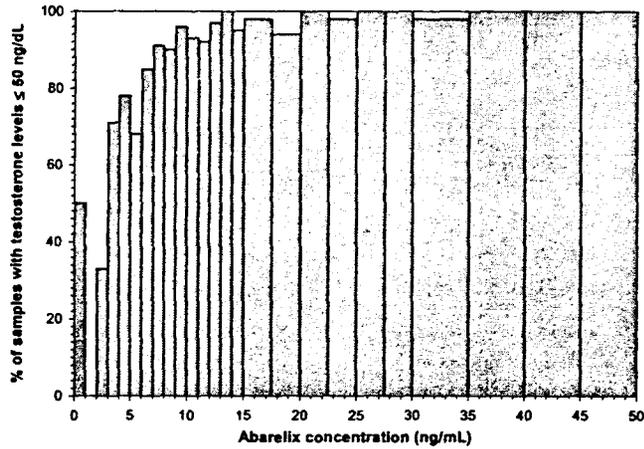
The pharmacology reviewer noted the diminished testosterone suppression over time with abarelix and performed an exposure (serum abarelix concentration) response (% patients achieving castration).analysis. The exposure-response relationship indicated that the serum levels of abarelix need to be >10ng/ml for more than 90% of the samples to be below castrate level (50ng./dL).(See Figure 4) Examination of the serum abarelix levels in individual patients, while a majority were around 10 ng/ml, some were as low as 1-5ng/ml. There was significant variability of serum abarelix and testosterone levels at later time points "which may have contributed to diminished overall efficacy". **The pharmacology reviewer concluded "abarelix doses higher than those studied in the NDA may provide higher sustained serum levels of drug for the longer term resulting in a higher degree of testosterone suppression and lower variability in serum testosterone levels".**

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Figure 4. Percentage of Reported Testosterone Levels \leq 50 ng/dL at Various Serum Abarelix Concentration Intervals in Clinical Study 149-98-02 (A) and 149-98-03 (B).



(A)



(B)

3.2 Consult From Allergy/Pulmonary:

The Division of Pulmonary and Allergy Drug Products (DPADP) was consulted regarding the issue of systemic allergic reactions that occurred almost immediately after dosing with abarelix in some patients. They **identified 6 cases of anaphylaxis with hypotension or syncope in 1166 patients who were treated with abarelix and no cases of anaphylaxis in 367 patients treated with Lupron.** The consultants felt that the allergic reactions were most likely IgE mediated (anaphylactic) but also could be a result of a direct action of abarelix on mast cells and basophils causing the release of histamine from these cells. These reactions could also be the result of an carboxymethylcellulose (CMC), an ingredient in the drug product know to cause allergic reactions or even abarelix-CMC complexes. In their opinion, **these reactions represented a significant safety concern and would need to be carefully considered in arriving at a final regulatory decision regarding the approvability of abarelix.** They recommended that the Sponsor conduct additional investigations, including appropriate intradermal testing and screening for the presence of IgE antibodies, to better understand the mechanism(s) responsible for these systemic allergic reactions.

3.3 OPDRA Review: A review of all post-marketing adverse event reports for Lupron revealed 23 cases (8 in men) of anaphylaxis reported in 15 years of marketed use. The current package insert for Lupron states that “symptoms consistent with an anaphylactoid or asthmatic process have been rarely reported with an incidence of 0.002%”. Although there was no data for the denominator, I believe hundreds of thousands perhaps millions of doses have been administered.

4.0 Integrated Assessment of Risk and Benefit:

In my opinion, abarelix offers no substantial benefit over presently available therapies for medical castration in most men with prostate cancer despite the lack of induction of testosterone surge and more rapid time to castration. In its present formulation and with the sponsor’s recommended dosing regimen, it appears to be somewhat less effective than once-monthly Lupron in reliably suppressing serum testosterone to levels ≤ 50 ng/dL during long term treatment. In addition, because of the incidence of serious systemic allergic reactions in 0.4% of patients, the risk benefit ratio for abarelix is too high to allow it’s for the treatment of prostate cancer in most men.

Abarelix, because of its rapid time to castration (3 or 4 days) and lack of testosterone surge may potentially offer a clinical benefit over Lupron and other GnRH super agonist for the hormonal treatment of some men with advanced prostate cancer. These men might include those categories of men that the sponsor included in their trial 149-98-04. Such men are those with metastatic lesions in “critical” locations (i.e., adjacent to the spinal cord or ureters) that theoretically could expand and produce serious clinical sequelae in response to the initial surge of testosterone. In addition, these men would potentially benefit from a more rapid time to castration.

The number of such patients, however, represents a decreasing percentage of men who are newly diagnosed with prostate cancer as diagnostic procedures for early detection continue to improve. In addition, even in the population of patients used by the sponsor in their "high risk" trial, other maneuvers, such as percutaneous nephrostomy tubes and urethral catheters could obviate the need for immediate medical castration. In men who truly require immediate castration (impending spinal cord) compression, the 3 or 4 days it takes for abarelix to induce castration may be too long and surgical castration may be necessary.

There are probably a tiny number of men who would benefit from abarelix but these men would then be exposed to a potentially fatal allergic reaction and the long term maintenance of castrate levels of testosterone may be problematic. I believe that a post marketing risk management program would be unable to confine the use of abarelix to the small potential appropriate population and that prescribers would have insufficient information regarding the severe allergic reactions and long term treatment efficacy.

5.0

I would recommend that abarelix not be approved.

I would recommend that the sponsor study the following issues if they seek approval in the future:

1. The sponsor should conduct investigations to better clarify the nature of the severe systemic allergic reactions that were reported in approximately 0.4% of the population. The ultimate objectives of these investigations should be to either lessen the actual incidence of severe systemic allergic reaction or to mitigate their consequences.
2. The sponsor should revisit the issue of dosing and address the reduced efficacy observed over time during the trials submitted with the NDA.
3. The sponsor should propose a post marketing risk management plan once further data regarding the allergic reactions and dosing are obtained. This plan could include proposed labeling, physician and /or patient education, distribution options, phase 4 studies or anything else that would decrease the risk benefit ratio

Daniel A. Shames MD
Deputy Director, DRUDP
CDER, FDA

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this page is the manifestation of the electronic signature.**

/s/

Daniel A. Shames
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MEDICAL OFFICER

NDA 21-320

Supervisory Medical Officer's Memorandum

FROM: Mark S. Hirsch, M.D.
Medical Team Leader, HFD-580

TO: Susan Allen, M.D.
Division Director, HFD-580

THROUGH: Dan Shames, M.D.
Deputy Division Director, HFD-580

DATE: May 18, 2001

REGARDING: Recommendations for regulatory action - NDA 21-320

SPONSOR: Praecis Pharmaceuticals Inc, Cambridge, MA

DATE SUBMITTED: December 11, 2000

CDER STAMP DATE: December 12, 2000

DIV DOC ROOM DATE: December 26, 2000

DRUG PRODUCT: *Trade name:* Plenaxis™
Established name: Abarelix for suspension (abarelix
carboxymethyl cellulose)

DOSAGE: 100 mg

ROUTE: intramuscular injection

DOSAGE REGIMEN: Single-dose administration on Days 1, 15, 29, then every 28 days
thereafter

DRUG CLASS: Gonadotropin releasing hormone (GnRH) antagonist

PROPOSED INDICATION:

RELATED INDs: IND #51,710 (Praecis Pharmaceuticals, prostate cancer)

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1. Materials used in conducting the review:

In arriving at my decision, I conducted a supervisory medical review of the following items:

From the original NDA:

1. Integrated Summaries of Efficacy and Safety
2. Narrative portions of final study reports for Studies 98-02, 98-03, 99-03 and 98-04
3. Clinical data summary (Volume 1)
4. Proposed annotated physician package insert
5. Minutes of all previous FDA/sponsor interactions
6. Narrative portion of the 3-month safety update
7. Amendments 011 and 012 to the NDA (Responses to FDA requests for information)

Draft reviews by the primary medical officers:

1. Dr. Benson’s review of Study 98-04 and related efficacy issues
2. Dr. Monroe’s review of all other relevant clinical trial data

Consultation reports:

1. Dr. Diwa’s (OPDRA) Proprietary Name Review
2. Dr. Toyer’s (OPDRA) Postmarketing Safety Review – dated March 10, 2001
3. Dr. Lee and Chowdhury’s (DPADP) Consultation – dated April 20, 2001

2. Executive summary:

2.1. Recommendation:

The purpose of this memorandum is to provide the Division Director with the supervisory medical officer's recommendation regarding this request for marketing approval.

In my opinion, abarelix should not be approved at this time. My reason for this decision is that under the conditions of use currently recommended by the sponsor in the proposed label, and given the current safety information in the submission, I believe that the drug is unsafe. The drug is considered unsafe because:

1. In the proposed patient population, the benefits do not outweigh the risks.
2. The proposed warnings are inadequate.
3. The proposed information for patients is inadequate.
4. The type of safety investigations that have been conducted to date are inadequate.

In order to obtain approval for this product, the sponsor should conduct additional investigations to better clarify the nature of the severe systemic allergic reactions that were reported in approximately 0.4% of the population. In their recommendation, The Division of Pulmonary and Allergy Drug Products (DPADP) proposed several additional avenues for investigation. These should be forwarded to the sponsor. The ultimate objectives of these investigations should be to either lessen the actual incidence of severe systemic allergic reaction or to mitigate their consequences.

In addition to conducting this additional research, drug approval would be conditional upon the sponsor proposing additional steps to manage and/or lessen the significant risks of anaphylaxis associated with abarelix (e.g. a risk management "proposal").

The sponsor's risk management proposal should include a discussion of whether the recommended additional research was fruitful in providing information towards safer use of the drug.

Additional risk management steps that may be considered in this proposal might include:

1. Limiting the use of abarelix to a particular patient subgroup in whom the benefits would outweigh the risks (e.g. those with impending neurological compromise).
2. Additional labeling emphasis on the risk of anaphylaxis immediately after dosing (e.g. a boxed warning).
3. Additional labeling emphasis on limiting post-dosing complications by keeping patients under observation for some period of time.
4. Additional labeling information to make patients sufficiently aware of risk (e.g. a MedGuide and/or patient informed consent).
5. Additional physician education about the risk and treatment of anaphylaxis using labeling, advertising, or mandated face-to-face seminars.

Other clinical deficiencies noted in the application which would require additional discussion between the Division and the sponsor, but would not preclude approval, include:

1. When is it advisable to measure serum testosterone and serum liver function tests during treatment with abarelix?
2. What is recommended for patients who fail therapy with abarelix, either due to adverse reaction or lack of efficacy (serum testosterone level above castrate limit)?

3. Are there specific recommendations for treatment or treatment monitoring based on patient weight?

Other parts of the proposed labeling are also likely to require clarification and negotiation.

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3. *Summary comments pertaining to efficacy:*

3.1. Primary efficacy analysis:

In my opinion, the results of all controlled clinical trials that have been conducted by the sponsor demonstrate that abarelix is effective in inducing medical castration in men with prostate cancer and maintaining that castrate level at least through 85 days.

For purposes of regulatory decision-making, I believe that abarelix therapy was demonstrated to be non-inferior to leuprolide monotherapy in the critical primary endpoint, percentage of patients who achieved and maintained castration from Days 29 through Day 85, in Study 149-98-02 and 149-99-03. I also believe that non-inferiority to combined androgen blockade (leuprolide + bicalutamide) was demonstrated in Study 149-98-03. These results are as follows (as derived from Medical Officer's Table 11):

1. In Study 98-02, **95.4%** for Lupron Depot (N=89) and **91.7%** for Abarelix Depot (N=180). The difference is 3.8% with 95% CI of (-9.7 to 2.1).
2. In Study 98-03, **95.2%** for Lupron Depot + Casodex (N=83) and **92.9%** for Abarelix Depot (N=168). In this case the difference is 2.3% with 95% CI of (-8.4 to 3.7).
3. In Study, 99-03, **97.4%** for Lupron Depot (N=195) and **89.6%** for Abarelix Depot (N=387). In this case, the difference is 7.7% with 95% CI of (-11.5 to -4.0).

It should be noted that the primary endpoint (biochemical castration) is obviously a surrogate marker for clinical efficacy. In this analysis, the cut-point for "castration" was serum testosterone ≤ 50 ng/dL. In order for an individual patient to "fail" on the therapy, it was required that TWO CONSECUTIVE serum testosterone concentration were >50 ng/dL. These definitions were proposed by the sponsor and agreed to by the Division prior to submission of the NDA.

As secondary analyses, the data was also analyzed using different definitions for success. For example, in one of the analyses, "failure" was defined as any SINGLE serum T concentration above 50 ng/dL.

When the data was analyzed using this more rigorous definition, the results are as follows (as derived from Medical Officer's Table 12):

1. In Study 98-02, **89.4%** for Lupron Depot (N=89) and **83.1%** for Abarelix Depot (N=180). The difference is -6.3% with 95% CI of (-14.9 to 2.3).
2. In Study 98-03, **90.0%** for Lupron Depot + Casodex, (N=83) and **88.9%** for Abarelix Depot (N=168). In this case, the difference is -1.2% with 95% CI of (-9.4 to 6.9).
3. In Study 99-03, **95.7%** for Lupron Depot (N=195) and **83.0%** for Abarelix Depot (N=387). In this case, the difference is -12.7% with 95% CI of (-17.6 to -7.9).

Based on these results, the medical officer believes that abarelix was "not non-inferior" to Lupron in Studies 98-02 and 99-03 from Day 21 to Day 85

Although the results of this secondary analysis reveals that the "success rate" was numerically lower with abarelix, I still believe that pivotal studies 98-02 and 98-03 demonstrated non-

inferiority of therapies out to Day 85, and Study 99-03 provides support for non-inferiority, albeit somewhat less compelling support.

3.2. Primary efficacy analysis – avoidance of surge/rapidity of castration

I believe that the sponsor adequately supported the contention that initial biochemical testosterone “surge” was not seen in patients administered abarelix (0% of patients both Studies 98-02 and 98-03) and was usually seen with leuprolide (82% and 86% of patients in Studies 98-02 and 98-03, respectively).

I also agree that the time to castration was generally more rapid with abarelix. In Study 98-02, the percentages of castrate patients at Days 8, 15 and 20 after dosing in the abarelix arm were 72%, 75% and 93%, respectively. In the same study, these same percentages in the leuprolide arm were 0%, 10%, and 98%, respectively. The results of Study 98-03 confirmed these results.

3.3. Benefit over available therapies:

The question of whether lack of surge and more rapid time to castration is ultimately a real clinical benefit (compared with an initial surge seen with LHRH agonist therapy) remains confusing. Substantial evidence to prove this hypothesis was not provided in this application. Review of the available scientific literature was not very helpful in this regard.

On its face (and without substantial evidence), the pharmacologic property of abarelix that allows it to avoid biochemical testosterone surge appears to offer clinical benefit over leuprolide in those patients at high risk for a clinically negative outcome from a “clinical flare” related to “testosterone surge”. In Study 149-98-04, such patients were defined as follows (verbatim):

1. Bone pain from prostate cancer skeletal metastases in whom the administration of a GnRH agonist (Lupron or Zoladex) would be expected to cause significant exacerbation of pain.
2. Impending neurological compromise from spinal, spinal cord, or epidural metastases in whom the administration of a GnRH agonist (Lupron or Zoladex) would be expected to cause worsening of neurological symptoms or spinal cord compression.
3. Presence of bilateral retroperitoneal adenopathy with ureteral obstruction (with or without azotemia) in whom the administration of a GnRH agonist (Lupron or Zoladex) would be expected to cause hydronephrosis, azotemia, or worsening obstruction.
4. Presence of an enlarged prostate gland or pelvic mass, resulting from prostate cancer, causing bladder outlet obstruction in whom the administration of a GnRH agonist (Lupron or Zoladex) would be expected to cause exacerbation of obstructive symptoms or urinary retention.

The data and evidence that was used to define these groups (especially the data used to determine that GnRH agonist “would be expected to” exacerbate symptoms) is not available to this reviewer.

In this study, 83 patients were enrolled. Eighty-one patients received at least one dose of open-label Abarelix Depot. Of 72 evaluable patients (nine patients excluded from one site due to non-compliance), no patient experienced biochemical testosterone surge, none reported symptoms consistent with clinical flare, and none required orchiectomy. The medical officer’s review reveals that some of these patients were “protected” from flare by other means (e.g urethral catheters in 10 patients) and some simply complained of bone pain without risk of fracture (19

patients as judged by the individual investigators). However, others were noted to harbor lesions more likely to be exacerbated by biochemical surge, including six patients with vertebral or spinal metastases and “impending neurological compromise” as assessed by the individual investigator.

The issue of whether abarelix therapy offers clinical benefit over other available therapies is particularly important in the regulatory decision for this NDA because 5 of 1166 abarelix-treated patients (approximate incidence of 0.4%) experienced severe, drug-related, systemic allergic reactions immediately after dosing (see Safety comments). Thus, in this case, the weight of “risk” must be carefully weighed against benefit. The term “benefit” for abarelix includes both:

1. the fundamental efficacy of the drug in attaining and maintaining castrate levels of testosterone, and
2. any superior clinical beneficial effect over the currently available treatments.

The argument for approving abarelix (as assessed by a risk/benefit ratio) would be far more compelling if abarelix therapy was intended only for a patient population that could not otherwise be treated by available medical therapy or that would derive substantial clinical benefit from abarelix over available products.

3.4. “Waning” of treatment effect

The medical officer’s review of the original NDA data raised a concern that the treatment effect observed with abarelix is less robust after the first three months of therapy and even less robust after the first six months of therapy. These issues were discussed with the sponsor during the review. For a detailed analysis of this entire issue, please see the primary medical officer’s review (pages 38-44). However, herein, I will attempt to provide a brief discussion.

3.4.1. Background/waning of treatment effect

First, it is important to understand that the evidence for efficacy is based on a surrogate marker, serum testosterone levels. The objective is to attain and maintain “castrate” levels of serum testosterone. This endpoint, itself, poses several problems. First, what serum level shall we define as the maximum allowable blood concentration for an “effective” castrate level? Second, if a person’s blood concentration is above that cut-point, is that prima facie evidence of treatment failure? Is there a clinically meaningful difference between a blood concentration slightly above the cut-point or markedly above the cut-point? How many times can a patient’s blood concentration rise above the cut-point before we conclude that treatment has failed? Are there any other markers that can be used to help in these decisions? Is there a correlation between the surrogate marker and long-term clinically meaningful effects?

For purposes of regulatory-decision making, the Division has set 50 ng/dL (serum total testosterone concentration) as the cut-point. The definition of success for the primary endpoint requires that an individual patient must reach serum testosterone levels at or below that cut-point by Day 29 post-dosing and must maintain such levels until Day 85 post-dosing. This sponsor requested and the Division agreed that a single serum T level above 50 ng/dL during that period of time would NOT constitute treatment failure for purposes of analyzing the primary endpoint. Failure would require TWO CONSECUTIVE concentrations above 50 ng/dL. It should be noted that serum testosterone was measured biweekly from Day 15 to Day 169 and then every 28 days thereafter.

Although not considered essential for purposes of approval, the sponsor submitted data on serum T levels drawn after Day 85 (secondary analyses). Studies 98-02 and 98-03 had treatment periods of one year and serum T concentrations were drawn biweekly in both trials from Day 15 to Day

169 and monthly thereafter until Day 365. Serum T values were available for almost all patients out to Day 169 and about one third to Day 365.

I believe that it was appropriate to perform a regulatory review this data even though such analysis is acknowledged not to constitute the primary analysis.

3.4.2. Out to Day 169

Using the primary definition for successful responder (achievement of T \leq 50 ng/dL by Day 29, and no two consecutive T levels >50 ng/dL in the treatment period), the results through Day 169 are reported by the sponsor as follows (as derived from Table 5-12, Integrated Summary of Efficacy):

1. In Study 98-02, **92.1%** for Lupron Depot (N=89) and **87.2%** for Abarelix Depot (N=180). The difference is **-4.9%** with 95% CI of (-12.3 to 2.5).
2. In Study 98-03, **84.3%** for Lupron Depot + Casodex, (N=83) and **90.5%** for Abarelix Depot (N=168). In this case the difference is **+6.1%** with 95% CI of (-2.9 to 15.1).

The sponsor believes that these data demonstrate that abarelix is not inferior to Lupron (or Lupron + Casodex) in achieving castration by Day 29 and maintaining it out to Day 169.

Again, it should be reiterated that this data was analyzed using several different definitions for "success". In one of these, for example, "failure" was defined as any SINGLE serum T concentration above 50 ng/dL.

When the data was analyzed using this more rigorous definition out to Day 169, the results (described as cumulative probability of achieving an maintaining medical castration where no serum T value was > 50 ng/dL) are as follows (as derived from Medical Officer's Table 12):

1. In Study 98-02, **85.6%** for Lupron Depot (N=89) and **74.7%** for Abarelix Depot (N=180). The difference is **-11.0%** with 95% CI of (-21.0 to -0.9).
2. In Study 98-03, **83.0%** for Lupron Depot + Casodex (N=83) and **82.8%** for Abarelix Depot (N=168). In this case the difference is **-0.3%** with 95% CI of (-10.6 to 10.0).
3. In Study 99-03, **90.9%** for Lupron Depot (N=195) and **75.7%** for Abarelix Depot (N=387). In this case the difference is **-15.2%** with 95% CI of (-21.4 to -9.0).

The medical officer believes that these data demonstrate that abarelix was "inferior" to Lupron Depot out to Day 169.

Data was also provided for mean serum T levels (\pm SD) from baseline through Day 169. The medical officer believes that these data reflect numerically higher means for abarelix at each timepoint. In addition, he comments that the numerically greater standard deviations reflect greater variability in serum T concentrations in men treated with abarelix.

In concluding this section, first, I would say that Study 98-03 demonstrates statistical non-inferiority of the two treatments out to Day 169.

However, I would agree with the medical officer that when the “stricter” endpoint is used, then the data from Studies 98-02 and 99-03 reveals abarelix to be statistically inferior to Lupron out to Day 169. I would also agree that the mean serum T concentrations are uniformly higher in the abarelix groups and the variability is greater.

Ultimately, it is not possible to assess the clinical implications of these differences. At most, the maximum absolute difference between abarelix and Lupron in percentage of castrate patients through Day 169 is -15.2%, with a maximum lower bound of the 95% confidence of -21.4%.

In summary, I believe the results of both the sponsor’s and the medical officer’s review of efficacy data out to Day 169 still support the approval of abarelix, albeit with more descriptive labeling.

3.4.3. Out to Day 365

Serum T concentrations out to Day 365 were available for some patients in Studies 98-02 and 98-03. Blood draws were conducted on Days 197, 225, 253, 282, 309, 337, and 365.

In these studies combined, 248 total patients continued treatment with abarelix after Day 169, while 110 continued treatment with Lupron. Only 182 total patients completed 365 days of abarelix treatment and 79 completed 365 days of Lupron treatment.

Serum testosterone data was available beginning at Day 197. Table 1 presents the percentage of patients with serum T ≤ 50 ng/dL at the time of each blood draw from Day 197 to day 365 (as derived from Tables 12.4.4 from Study Reports 98-02 and 98-03).

Table 1. Percentage of patients with serum T ≤ 50 ng/dL at each blood draw: Combined patients from Studies 98-02 and 98-03.

	Day 197	Day 225	Day 253	Day 281	Day 309	Day 337	Day 365
Abarelix	92.4%	87.9%	85.2%	83.5%	82.7%	79.0%	81.0%
N	238	223	209	200	197	186	179
Lupron	100%	100%	100%	100%	100%	100%	100%
N	102	98	92	94	90	86	75

When the data was analyzed using the mean serum testosterone concentrations (±SD) at each timepoint from Day 197 to Day 365, differences are again noted between abarelix and Lupron arms in Studies 98-02 and 98-03. The data is listed below in Tables 2 and 3 (as derived from Table 12.5.7 of Study Reports 98-02 and 98-03).

Table 2. Mean (±SD) serum T concentrations (ng/dL): Patients from Study 149-98-02

	Day 197	Day 225	Day 253	Day 281	Day 309	Day 337	Day 365
Abarelix							
Mean (±SD)	31 (49)	34 (52)	33 (42)	35 (41)	39 (55)	46 (65)	47 (63)
N	118	106	102	98	96	93	93
Lupron							
Mean (±SD)	12 (8)	12 (6)	11 (5)	12 (7)	12 (6)	13 (6)	13 (8)
N	60	56	52	54	53	51	44

Table 3. Mean (\pm SD) serum T concentrations (ng/dL): Patients in Study 149-98-03

	Day 197	Day 225	Day 253	Day 281	Day 309	Day 337	Day 365
Abarelix							
Mean (\pm SD)	18 (20)	21 (26)	24 (33)	27 (47)	31 (55)	30 (43)	31 (41)
N	120	117	107	102	101	93	86
Lupron							
Mean (\pm SD)	12 (8)	12 (7)	12 (7)	13 (8)	12 (5)	13 (7)	12 (6)
N	42	42	40	40	37	35	31

Based on these results, the mean serum T levels were numerically higher in the abarelix group compared with the Lupron groups at virtually all timepoints, but especially after Day 169. In addition, and of particular relevance, the standard error associated with each assessment time was greater in the abarelix group. The medical officer believes that this reflects “variability in serum testosterone values in the abarelix group.”

Ultimately, the medical officer concludes that:

1. The agreed-upon primary analyses demonstrates that abarelix is not inferior to Lupron in achieving and maintaining castration through 85 days.

However, when the data is analyzed using alternate definitions of success, all of which he believes “have more clinical relevance” (including, all serum T values at or below 50 ng/dL), then abarelix “was inferior to Lupron in maintaining testosterone suppression through Day 85.”(derived from Medical Officer’s Conclusions Regarding Efficacy)

2. Abarelix is inferior to Lupron in maintaining testosterone suppression from Day 21 to Day 169.
3. Monitoring serum T in men treated with abarelix is particularly important.

I conclude the following:

1. Based on the agreed-upon endpoint and analysis, I believe that abarelix has been shown to be not inferior to Lupron in achieving and maintaining castrate levels of serum T up to Day 85.
2. Overall, I believe that abarelix treatment out to Day 169 is adequate therapy, although it cannot be concluded that abarelix is non-inferior to Lupron. Revised labeling will be required to place this issue into proper context for prescribers and patients.
3. From Day 169 to Day 365, abarelix treatment is inferior to Lupron in maintaining serum T levels at or below 50 ng/dL. Nevertheless, if serum T is monitored during treatment, I believe that abarelix can still be used effectively in the treatment of advanced carcinoma of the prostate. Revised labeling will be required to place this issue into context for prescribers and patients.

The reason for this waning of effect (relative to the active comparator, and relative to the pre-defined castration cut-off point of 50 ng/dL) is unclear. Pharmacokinetic/pharmacodynamic analyses by the sponsor, by the primary clinical pharmacologist (Dr. Chatterjee), and by our Pharmacometrics consultant provided evidence that serum levels of abarelix need to be maintained over 10 ng/mL so that >90% of serum T levels will be “castrate”. While the actual

reason is still unclear, Dr. Chatterjee implied that low serum levels of abarelix (approximately 1 to 5 ng/mL) could lead to diminished T suppression. This is especially important in light of the variability of serum abarelix levels.

Both Drs Chatterjee and Monroe advise further research by the sponsor to reduce the variability and increase the clinical efficacy by investigating alternate dosages, dose regimens, and perhaps, the formulation itself.

Ultimately, the clinical impact of these findings in terms of survival and disease progression cannot be discerned with clarity. Although T levels were noted to increase in some patients, measurements of serum PSA, a biochemical marker often used clinically to monitor the progress of patients with prostate cancer, and visual analogue pain scores did not reveal obvious increases over time in most patients. In those patients who did show rising PSAs or increased pain, the sponsor proposed alternative (and reasonable) etiologies.

Despite the “waning” of treatment effect relative to Lupron and relative to the absolute castration limits, I do not believe that this issue would preclude approval, if other safety concerns could be mitigated and the label was revised to inform prescribers and patients more adequately.

**APPEARS THIS WAY
ON ORIGINAL**

**APPEARS THIS WAY
ON ORIGINAL**

4. Summary comments pertaining to safety:

4.1. Severe systemic allergic reactions

In terms of the safety results, the critical issue is that of drug-related severe systemic allergic reaction (anaphylaxis).

The sponsor's first proposed PLENAXIS label clearly stated (in the WARNINGS section),

[

In addition, the PRECAUTION section stated,

]

The safety database of approximately 1166 patients who were administered abarelix reveals that 6 patients experienced severe systemic allergic reactions resulting in syncope or hypotension within 10 minutes of drug administration, an incidence of approximately 0.5%. In one of these cases, the sponsor believes that clinical signs and symptoms were not characteristic of an allergic reaction, but rather a "vasovagal syncope" (Subject #333-3336). In this one case, I believe the sponsor's argument is reasonable.

In the other five cases (Subjects # 401-4001, 313-3087, 01-2192, 14070281, and 29410085), reactions were characterized by sudden bodily warmth, facial, truncal and arm redness, itching, generalized rash, angioedema, abrupt drop in the blood pressure, mental obtundation, and in two cases, abnormal respirations. These events resolved promptly with emergent administration of antihistamine, epinephrine, and in one case, steroid. The events were noted after the first dose in one case, but in the other four cases after multiple doses (including the fourth, seventh, fifteenth and Day 617).

In actuality, there were fifteen cases of systemic allergic reaction resulting in treatment discontinuation and subject withdrawal, one case occurring immediately post-dosing but not leading to withdrawal, and one case disputed as a "vasovagal reaction" reported for the abarelix group (see Medical Officer's Review, Table Number 32). These reactions included symptoms consistent with acute allergic response including pruritis, urticaria, rash, and flushing. In these patients, however, signs of shock were not reported.

When analyzed as the percentage of patients withdrawn from study due to a drug-related, allergic-type reaction, the incidence for abarelix was 15/1166 or approximately 1.29%.

The sponsor does not deny that these events were related to abarelix. In addition, the sponsor acknowledges that there is a definite temporal relationship to drug dosing with abarelix (within minutes) which was clearly different from that seen with the active comparator (days after dosing). However, the sponsor believes:

1. that the incidence of such events leading to study discontinuation in the abarelix arm was not significantly different from that seen in the active comparator arm (3/457, or 0.7%), and
2. that those incidences are even less pronounced when corrected for patient-years of exposure.

In response to these arguments, the clinical review team notes that no leupolide-treated patient had a severe systemic reaction resulting in hemodynamic compromise (anaphylactic shock) and none had a systemic allergic reaction immediately after dosing. Two leuprolide-treated patients (2/457, 0.5%), however, did have systemic allergic reactions that necessitated withdrawal. These

occurred four days after the first dose (Subject 13-2144) and six days after the third dose (Subject 301-1295), respectively. The former patient experienced moderate urticaria, insomnia due to the urticaria, and lack of energy. He was given Benadryl and the event resolved in 4 days. The latter patient complained of swelling and numbness of his bottom lip, red patches on his palms, severe urticaria, and "itchy, red hives" over his entire body. He was seen in an emergency room and was treated with subcutaneous epinephrine, intramuscular Benadryl, and antihistamine. After emergency treatment he felt better, but his rash remained. He was treated with Benadryl and his rash resolved nine days after the emergency room visit.

A review of all post-marketing adverse event reports for Lupron revealed only 23 cases (only 8 in men) of anaphylaxis reported in 15 years of marketed use. The current package insert for Lupron states that "symptoms consistent with an anaphylactoid or asthmatic process have been rarely reported with an incidence of 0.002%".

Unfortunately, the mechanism for these reactions with abarelix has not been explained. The sponsor neglected to check for the presence of IgE antibodies in those patients who had an immediate reaction. Analysis for IgG antibodies did not reveal their presence. It remains unknown whether this phenomenon is an IgE-mediated Type 1 hypersensitivity reaction (anaphylactic) in response to abarelix or perhaps to the drug product excipient, carboxymethylcellulose, or whether it is a direct drug-induced "anaphylactoid" reaction. It appears very unlikely that this problem is solely "anaphylactoid" since only one case was reported after the first dose and all others were reported after repeated doses. Anaphylactoid reactions are generally expected to occur after the first dose.

No further information was provided to explain the mechanism for this adverse event.

Regardless of the mechanism for the reaction, however, the most critical issue, in my opinion, is that sponsor has not provided adequate guidance to prescribers on mitigating the risk or the consequences of these reactions. The label is silent on any means of reducing this risk (e.g. pre-medication with antihistamines or steroids, skin testing for sensitivity, etc.) or means of predicting an event (e.g. identifying susceptible patients, avoiding risk-enhancing concomitant medications, etc). One must assume, therefore, that the sponsor is currently unaware of any additional means to mitigate risk other than simply describing the events in the WARNINGS and PRECAUTIONS sections.

What additional risk management steps could be taken to mitigate or lessen the overall risk of this particular adverse reaction and yet still allow access to abarelix? Some measures could include:

- a. A mandated in-clinic, post-dosing observation period
- b. Limiting abarelix therapy to those patients at greatest risk of a detrimental clinical effect from "clinical flare" with agonist therapy (as described above). This may be accomplished through labeling or through some form of restricted distribution.
- c. An aggressive educational program for physicians geared towards the recognition and management of acute anaphylaxis.
- d. An informed consent for patients such that the risk of anaphylaxis is described clearly prior to initiating abarelix therapy.

In addition, additional research to characterize the mechanism for these allergic reactions could lead to other more focused means of reducing risk. These efforts might include checking for IgE antibodies to abarelix or to carboxymethylcellulose (CMC), or skin testing for abarelix drug substance alone, CMC alone, and abarelix drug product. The sponsor must commit to conducting

such research, must inform the Agency of the results of the research, and must discuss these results in context of risk management.

Until additional research is conducted, this reviewer believes that the additional risk of acute severe systemic allergic reaction with hemodynamic compromise (anaphylactic shock) is not acceptable in the overall prostate cancer population. In that population, the risks of abarelix would greatly outweigh its benefits, given the currently available agents for medical castration.

However, the risks of treatment with abarelix would become more acceptable in a population who could not tolerate or who were not appropriate candidates for alternative medical treatment. I believe that this group consists only of those patients at high risk for significant morbidity from “clinical flare” related to initial testosterone surge with agonist therapy. These patients were described in detail in the efficacy section.

Therefore, in order to meet the requirements for approval, the sponsor would have to commit to the following in regard to this particular issue:

1. Limiting abarelix therapy to those patients at greatest risk of a detrimental clinical effect from “clinical flare” with agonist therapy (as described above).
2. A mandated in-clinic, post-dosing observation period
3. An aggressive educational program for physicians geared towards the recognition and management of acute anaphylaxis.
4. An informed consent for patients such that the risk of anaphylaxis is described clearly prior to initiating abarelix therapy.
5. Conducting additional research to characterize the mechanism for these allergic reactions, as guided by the Division of Pulmonary and Allergy Drug Products.

4.2. Hepatic toxicity

In the pivotal safety studies 98-02 and 99-03, liver function tests (LFTs) were performed at baseline, Day 15, Day 28, Day 43 and at monthly planned visits for up to 1 year. In the third pivotal safety study, 98-03, serum LFTs were obtained every two weeks.

In all three studies combined, through Day 169, the sponsor believes that shifts above the upper limit of normal in ALT and AST were noted in some patients in all treatment groups.

The incidence of “clinically notable” transaminase elevations ($>2.5x$ ULN or >200 U/L) were compared between between Lupron Depot and Abarelix Depot. As derived from the Table 7-B of the 3-Month Safety Update, the sponsor presented the following data:

$>2.5x$ ULN

For serum ALT, these incidences were 7% (21/283) for Lupron Depot, 8% (56/733) for Abarelix Depot, and 2% (2/83) for Lupron + Casodex.

For serum AST, these incidences were 3% (9/283) for Lupron Depot, 3% (20/734) for Abarelix Depot, and 2% (2/83) for Lupron + Casodex.

>200 U/L

For serum ALT, these incidences were 1% (3/283) for Lupron Depot, 2% (12/733) for Abarelix Depot, and 1% (1/83) for Lupron + Casodex.

For serum AST, these incidences were 1% (2/283) for Lupron Depot, 0.7% (5/734) for Abarelix Depot, and 0% (0/83) for Lupron + Casodex.

The sponsor also analyzed these data using a “shift analysis”; that is, analyzing shifts in serum transaminase values using the WHO Toxicity Grading System (e.g. No shift, shift to Grades 1, 2, 3 or 4). Although there was no meaningful differences between Lupron and Abarelix in shifts to Grade 1 or 2, there did appear to be more patients in the abarelix group who demonstrated maximal elevations to Grades 3 (2.51 – 5.0 x ULN) and 4 (5.1 – 10X ULN) from normal baselines. For example, through Day 169:

For serum ALT, 10 patients who were normal at baseline (10/735, 1.36%), and 1 patient who was normal at baseline (1/735, 0.014%) shifted to Grade 3 and Grade 4, respectively in the Abarelix group. Two patients who were normal at baseline shifted to Grade 3 (2/284, 0.7%) in the Lupron group, none to Grade 4, and there were no such patient shifts in the Lupron + Casodex group.

For serum AST, 3 patients who were normal at baseline (3/735, 0.4%), and 2 patients who were normal at baseline (2/735, 0.3%) shifted to Grade 3 and Grade 4, respectively in the Abarelix group. One patient who was normal at baseline shifted to Grade 4 (1/284, 0.35%) in the Lupron group, and there were no such patient shifts in the Lupron + Casodex group.

Overall, I believe that the notable data here revolves around those patients who demonstrated markedly increased serum transaminases (at least 5.1 X ULN, or >200 U/L). Although the overall incidences are small in all three treatment groups, there appears to be a subtle difference between the Abarelix group and the Lupron alone, and Lupron + Casodex groups. There also appears to be some evidence that the percentage of withdrawals due to increased hepatic enzymes was somewhat greater in the Abarelix group compared with the Lupron-only group.

Of note, none of the markedly increased transaminase concentrations was associated with a drug-related clinically important increase in serum bilirubin.

In concluding this section, I would again note the differences between abarelix and Lupron in the percentages of markedly increased transaminases and withdrawals due to increased hepatic enzymes. I believe that this issue would not preclude approval (if other risks were managed), however, labeling should be revised:

1. To present these results to health care professionals, and
2. To provide guidance to prescribers in monitoring serum transaminases in patients administered abarelix.

4.3. Other safety issues, including overall adverse events

4.3.1 Overall adverse events

Overall, approximately 1166 patients were exposed to abarelix depot in all studies submitted in the NDA. A total of 752 were exposed to the proposed to-be-marketed dose for at least 6 months and 190 were exposed for at least 1 year. Thus, the extent of exposure is considered adequate by ICH guidelines for assessing the safety profile of a new molecular entity.

This section focuses on the overall adverse reactions reported during these investigations, other than the previously discussed allergy and hepatic toxicity issues.

In general, most of the adverse reactions reported were associated with the well-recognized sequelae of castration itself, co-morbid conditions, and signs and symptoms of prostate cancer.

For example, when Studies 98-02, 98-03 and 99-03 were pooled for purposes of safety analyses, the most commonly reported treatment-related adverse events up to Day 169 were reported in the 3-Month Safety Update as follows:

1. For Abarelix (N=735) – fatigue (14%), headache (8%), testes disorder (5%), pain (4%), impotence (4%), frequency of micturition (4%), diarrhea (3%), decreased libido (3%), dizziness (3%), rash (3%), weight increase (2%), flatulence (2%), muscle weakness (2%), pruritis (2%), insomnia (2%), nausea (2%), nocturia (2%) and myalgia (2%).
2. For Lupron (N =284) – fatigue (12%), headache (7%), libido decreased (7%), impotence (6%), testes disorder (4%), pain (4%), diarrhea (4%), nausea (4%), myalgia (4%), insomnia (4%), frequency of micturition (3%), dizziness (3%), flatulence (2%), pruritis (2%), weight increase (1%), flatulence (1%) and rash (1%).
3. For Lupron + Casodex (N =83) – fatigue (14%), headache (8%), diarrhea (4%), flatulence (4%), testes disorder, impotence, nocturia, libido decreased, pain, dizziness, muscle weakness, myalgia, insomnia (all 2%), frequency of micturition, nausea, pruritis (all 1%).

In general, I believe that these low incidences reflect the fairly healthy overall patient population that was enrolled in these trials. By agreement with the Division, the sponsor was permitted to enroll patients of virtually any cancer stage as long as the investigator felt that medical castration was indicated. This decision was based on the understanding that the primary endpoint is a surrogate (biochemical castration) and that the ultimate labeled indication would be the same as all other previously approved products intended for medical castration in the treatment of advanced prostate cancer.

Nevertheless, I conclude that the overall adverse events (other than those previously discussed in the preceding two sections) were not significantly different between Lupron, Lupron + Casodex, and Abarelix.

However, it is surprising that treatment-related hot flashes and breast discomfort/enlargement were not reported as treatment-related adverse events in greater than or equal to 2% of the population.

4.3.2. Deaths and other non-fatal serious adverse events

4.3.2.1. Deaths

In the pooled, pivotal safety trials (98-02, 98-03 and 99-03), no patients died in the Lupron + Casodex group (0/83), one died in the Lupron group (myocardial infarction, 1/284), and 11 died in the abarelix group (11/735). In the abarelix group, two died from metastatic prostate cancer, two died from cardiac disease, three died from co-existing cancers, three died from pulmonary disease (COPD, pneumonia, and empyema), and one died from an intracranial hemorrhage. None of these deaths were attributed by the investigator to study medication.

In other supporting studies (97-04, 98-04, and 99-04), an additional 16 patients who received abarelix died. In eight of these, death was attributed to progression of prostate cancer. In the other eight, death was either due to myocardial infarction, stroke, pneumonia, or pulmonary embolism. No death was attributed to study drug.

4.3.2.2. Non-fatal serious adverse events (SAEs)

In all patients from the pooled, pivotal safety trials (Studies 98-02, 98-03 and 99-03), the following constitute the reports of treatment-related serious adverse events:

For Lupron + Casodex (2/83, 2%)

1. moderate increase in hepatic enzymes
2. moderate increase in hepatic enzymes

For Lupron (2/284, 1%)

1. severe diabetic ketoacidosis
2. severe urticaria

For Abarelix (10/735, 1%)

1. severe syncope (“vasovagal reaction”)
2. moderate migraine headache
3. severe increase in hepatic enzymes
4. moderate increase in hepatic enzymes
5. moderate increase in hepatic enzymes
6. severe allergic reaction (Patient #11-2218)
7. severe allergic reaction (Patient #09-3246)
8. life-threatening allergic reaction
9. moderate rash (Patient # 357-2226)
10. mild allergic reaction (Patient # 76-3224)

Patient numbers are listed beside those four patients who have not been described previously in this memo. Of those four, three experienced flushing, generalized bodily warmth, and rash within 5 minutes of dosing and one within 45 minutes of dosing. One patient required a dose of Medrol and one a dose of Benadryl. In all four patients, the event resolved with 1 day.

In Study 97-04, there were only two (2) reported treatment-related SAEs, one deep venous thrombosis and one allergic reaction of moderate severity (Patient 02-4635). The allergic reaction was not actually serious by strict criteria, but was reported expeditiously as a “patient of special concern”.

In Study 98-04, there were six (6) reported treatment-related SAEs. Of these, five were related to progression of cancer or co-morbidity and one was an allergic-type reaction, previously described. Two other patients in this trial reported “severe” treatment-related allergic-type events (urticaria in Patient 416-4067 and skin rash in Patient 473-4003) and one withdrew due to “moderate” urticaria (409-4057).

In Study 99-04, there was one (1) reported treatment-related SAE (related to allergy), and this case has been previously described in this memo.

In summary, there were no treatment-related deaths, and only several treatment-related serious adverse events and these were related either to post-dosing allergic-type reaction or increase in hepatic enzymes. These issues have been discussed in previous sections of this memo.

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/s/

Mark S. Hirsch
6/11/01 06:03:16 PM
MEDICAL OFFICER

Daniel A. Shames
6/12/01 05:18:05 PM
MEDICAL OFFICER

18. User Fee

In accordance with Item 736 d (1)(E) of the Food, Drug & Cosmetic Act, a waiver of the application fee for this NDA was granted just after the NDA's original submission (FDA and SBA correspondence attached). Since that determination, both partnership collaborations (potential business affiliates with respect to granting our exemption to the fee) with _____ Sanofi-Synthelabo, Paris, France have been terminated _____ Sanofi-Synthelabo notices attached). PRAECIS itself has continued to grow and at the time of this resubmission (Amendment 042 to NDA 21-320) has _____ employees, still well under the 500 employee threshold to be considered a small business. A list of current PRAECIS directors and executive officers is also attached.

APPEARS THIS WAY
ON ORIGINAL

- ◆ Status of advertising (if AP action) Reviewed (for Subpart H – attach review) Materials requested in AP letter
- NA
- ◆ Post-marketing Commitments NA _____
- Agency request for Phase 4 Commitments..... NA _____
- Copy of Applicant's commitments NA _____
- ◆ Was Press Office notified of action (for approval action only)?..... NA Yes No
- Copy of Press Release or Talk Paper..... NA _____
- ◆ Patent
- Information [505(b)(1)] X _____
- Patent Certification [505(b)(2)]..... X _____
- Copy of notification to patent holder [21 CFR 314.50 (i)(4)]..... X _____
- ◆ Exclusivity Summary NA _____
- ◆ Debarment Statement X _____
- ◆ Financial Disclosure
- No disclosable information X _____
- Disclosable information – indicate where review is located NA _____
- ◆ Correspondence/Memoranda/Faxes X _____
- ◆ Minutes of Meetings X _____
- Date of EOP2 Meeting 8/4/98
- Date of pre NDA Meeting 8/4/98, 2/10/99, 7/20/00
- Date of pre-AP Safety Conference NA
- ◆ Advisory Committee Meeting NA _____
- Date of Meeting NA _____
- Questions considered by the committee NA _____
- Minutes or 48-hour alert or pertinent section of transcript NA _____
- ◆ Federal Register Notices, DESI documents NA _____

CLINICAL INFORMATION:

Indicate N/A (not applicable), X (completed), or add a comment.

- ◆ Summary memoranda (e.g., Office Director's memo, Division Director's memo, Group Leader's memo) X _____
- ◆ Clinical review(s) and memoranda X _____

- ◆ Safety Update review(s) X_____
- ◆ Pediatric Information
 - Waiver/partial waiver (Indicate location of rationale for waiver) Deferred Pediatric Page..... NA_____
 - Pediatric Exclusivity requested? Denied Granted ■ Not Applicable
- ◆ Statistical review(s) and memoranda X_____
- ◆ Biopharmaceutical review(s) and memoranda..... X_____
- ◆ Abuse Liability review(s) NA_____
 - Recommendation for scheduling NA_____
- ◆ Microbiology (efficacy) review(s) and memoranda NA_____
- ◆ DSI Audits X_____
 - Clinical studies bioequivalence studies _____

CMC INFORMATION:

Indicate N/A (not applicable), X (completed), or add a comment.

- ◆ CMC review(s) and memoranda X_____
- ◆ Statistics review(s) and memoranda regarding dissolution and/or stability X_____
- ◆ DMF review(s) X_____
- ◆ Environmental Assessment review/FONSI/Categorical exemption NA_____
- ◆ Micro (validation of sterilization) review(s) and memoranda X_____
- ◆ Facilities Inspection (include EES report)
 - Date completed _____ Acceptable ■ Not Acceptable
- ◆ Methods Validation Completed ■ Not Completed

PRECLINICAL PHARM/TOX INFORMATION:

Indicate N/A (not applicable), X (completed), or add a comment.

- ◆ Pharm/Tox review(s) and memoranda X_____
- ◆ Memo from DSI regarding GLP inspection (if any) NA_____

- ◆ Statistical review(s) of carcinogenicity studies Under review
- ◆ CAC/ECAC report Carci studies under review, will be sent to CAC when review complete

**APPEARS THIS WAY
ON ORIGINAL**

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Applicant Information		
NDA 21-320	Efficacy Supplement Type SE-	Supplement Number
Drug: Plenaxis (abarelix suspension for injection) 100 mg		Applicant: Praecis Pgharmaceuticals, Incorporated
RPM: Nenita I. Crisostomo, RN Eufrecina DeGuia		HFD-580 Phone # 301-827-7260
Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)		Reference Listed Drug (NDA #, Drug name): N/A
❖ Application Classifications:		
• Review priority		<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority
• Chem class (NDAs only)		1/P, NME
• Other (e.g., orphan, OTC)		N/A
❖ User Fee Goal Dates		November 27, 2003
❖ Special programs (indicate all that apply)		<input type="checkbox"/> None <input type="checkbox"/> Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input checked="" type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2
❖ User Fee Information		
• User Fee		<input type="checkbox"/> Paid
• User Fee waiver		<input checked="" type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other
• User Fee exception		<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) <input type="checkbox"/> Other
❖ Application Integrity Policy (AIP)		
• Applicant is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• This application is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Exception for review (Center Director's memo)		N/A
• OC clearance for approval		N/A
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.		<input checked="" type="checkbox"/> Verified
❖ Patent		
• Information: Verify that form FDA-3542a was submitted.		<input checked="" type="checkbox"/> Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted.		21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> I <input type="checkbox"/> II <input checked="" type="checkbox"/> III <input type="checkbox"/> IV 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).		<input type="checkbox"/> Verified N/A

❖ Exclusivity (approvals only)	
• Exclusivity summary	X
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!	() Yes, Application # _____ (X) No
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	November 23, 2003
General Information	
❖ Actions	
• Proposed action	(X) AP () TA () AE () NA
• Previous actions (specify type and date for each action taken)	Not Approvable—June 12, 2003
• Status of advertising (approvals only)	() Materials requested in AP letter (X) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	(X) Yes () Not applicable
• Indicate what types (if any) of information dissemination are anticipated	() None (X) Press Release () Talk Paper () Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	none
• Physician Insert	
• Most recent applicant-proposed	November 24, 2003
• Original applicant-proposed	February 25, 2003
• Patient Package Insert	
• Most recent applicant-proposed	November 24, 2003
• Original applicant-proposed	February 25, 2003
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings (indicate dates of reviews and meetings)	See also CMC review, pg. 46-49
• Labeling Meetings Minutes—See Minutes of Meetings	Nov. 4, 2003 Nov. 18, 2003 Nov. 20, 2003
• DSRCS	May 29, 2003 October 8, 2003 October 27, 2003
• DMETS	June 3 & October 7, 2003
• DDMAC	May 27, 2003
Other relevant labeling (e.g., most recent 3 in class, class labeling)	
• Physician Attestation	November 24, 2003
• Hospital Pharmacy Agreement	November 24, 2004
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	See CMC Info Request ltr: 10/17/03
• Most recent Applicant-proposed labels	October 30, 2003 November 24, 2004—carton only
• Original Applicant proposed labels-	June 3, 2003
• Reviews	

• Chemistry Review, pg. 46-49	November 5, 2003
• Division of Medication Errors and Technical Support	October 7, 2003
• Division of Medication Errors and Technical Support	June 3, 2003
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	
• Documentation of discussions and/or agreements relating to post-marketing commitments	November 21, 2003—Amend 091
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	x
❖ Memoranda and Telecons	x
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	August 4, 1998
• Pre-NDA meeting (indicate date)	July 20, 2000
• Pre-Approval Safety Conference (indicate date; approvals only)	July 25, 2003
• Regulatory Briefing	July 28, 2003
• Other	
❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	
Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	(See below)
• Office Director	November, 25, 2003
• Division Director	see Medical Team Leader Memo
• Medical Team Leader	November 25, 2003
Clinical Information	
❖ Clinical review(s) (indicate date for each review)	November 25, 2003
❖ Clinical Review: Div. Of Pulmonary and Allergy Drug Products—Allergic Reactions	July 2, 2003
❖ Clinical Review: Div of Cardio-Renal Drug Products—QT Prolongation	July 3, 2003
❖ Microbiology (efficacy) review(s) (indicate date for each review)	N/A
❖ Safety Update review(s) (indicate date or location if incorporated in another review)	Clinical review
❖ Risk Management Plan review(s) (indicate date/location if incorporated in another rev)	
• DDRE review of original RMP dated February 25, 2003	June 13, 2003
• Incorporated in review of Div. Of Pulmonary and Allergy	July 2, 2003, Section 7.6, pg. 22
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	waived
❖ Demographic Worksheet (NME approvals only)	
❖ Statistical review(s) (indicate date for each review)	July 25, 2003
❖ Biopharmaceutical review(s) (indicate date for each review)	November 20, 2003
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	N/A
• Clinical Inspection Review Summary (DSI)	
• Clinical studies	July 16, 2003

• Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) (indicate date for each review)	November 5, 2003
❖ Environmental Assessment	
• Categorical Exclusion (indicate review date)	See CMC review, 11/5/03
• Review & FONSI (indicate date of review)	See CMC review, 11/5/03
• Review & Environmental Impact Statement (indicate date of each review)	See CMC review, 11/5/03
❖ Microbiology (validation of sterilization & product sterility) review(s) (indicate date for each review)	July 3, 2003
❖ Facilities inspection (provide EER report)	Date completed: June 3, 2003 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ Methods validation—will be requested by CMC upon approval of the NDA	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input checked="" type="checkbox"/> Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	March 11, 2003
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	August 6, 2003
❖ CAC/ECAC report	July 22, 2003

**APPEARS THIS WAY
ON ORIGINAL**

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

/s/

Nenita Crisostomo
11/25/03 06:16:35 PM

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: <http://www.fda.gov/cder/pdufa/default.htm>

1. APPLICANT'S NAME AND ADDRESS

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

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

021-320

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

YES NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:

THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

(APPLICATION NO. CONTAINING THE DATA.)

2. TELEPHONE NUMBER (Include Area Code)

(781) 795-4100 ext 4282

3. PRODUCT NAME

abarelix for injectable suspension
Plenaxis™

6. USER FEE I.D. NUMBER

4068

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)

A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE (See item 7, reverse side before checking box.)

THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)

THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)

THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory)

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

YES NO

(See Item 8, reverse side if answered YES)

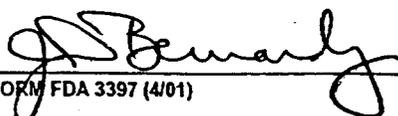
Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER, HFD-94
and
12420 Parklawn Drive, Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE



TITLE

Vice President, Regulatory Affairs &
Quality Assurance

DATE

20 February 2003

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

1. APPLICANT'S NAME AND ADDRESS PRAECIS PHARMACEUTICALS INC. One Hampshire Street Cambridge, MA 02139	3. PRODUCT NAME PLENAXIST™ abarelix for suspension
2. TELEPHONE NUMBER (include Area Code) (617) -494-8400 ext 2282	4. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW: <input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION. <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO _____ (APPLICATION NO. CONTAINING THE DATA).
5. USER FEE I.D. NUMBER 4068	6. LICENSE NUMBER / NDA NUMBER 021-320

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

<input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)	<input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE (See item 7, reverse side before checking box.)
<input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)	<input type="checkbox"/> THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)
<input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory)	

FOR BIOLOGICAL PRODUCTS ONLY

<input type="checkbox"/> WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION	<input type="checkbox"/> A CRUDE ALLERGENIC EXTRACT PRODUCT
<input type="checkbox"/> AN APPLICATION FOR A BIOLOGICAL PRODUCT FOR FURTHER MANUFACTURING USE ONLY	<input type="checkbox"/> AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT LICENSED UNDER SECTION 351 OF THE PHS ACT
<input type="checkbox"/> BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92	

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? YES NO
(See reverse side if answered YES)

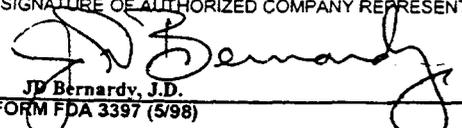
A completed form must be signed and accompany each new drug or biologic product application and each new supplement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment.

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0297)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Please **DO NOT RETURN** this form to this address.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE  JD Bernardy, J.D. FORM FDA 3397 (5/98)	TITLE Vice President, Regulatory Affairs	DATE 11 December 2000
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pages of trade

secret and/or

confidential

commercial

information

NDA 21-320

Plenaxis (abarelix for injectable suspension)

Praecis Pharmaceuticals, Inc.

This application is not in the Application Integrity Policy list.

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

There was no Advertising Information submitted for this application.

ISI

5/7/01

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

There was no Press Office Information for this application.

— ' | S | —

← 5/7/4

NDA 21-320

Plenaxis (abarelix for injectable suspension)

Praecis Pharmaceuticals, Inc.

This application is requested to be approved under Subpart H, as indicated in the letter from Praecis dated November 4, 2003.

**APPEARS THIS WAY
ON ORIGINAL**

**APPEARS THIS WAY
ON ORIGINAL**

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

This Application is not on the Application Integrity Policy (AIP).

— [S] —

3/7/01

APPEARS THIS WAY
ON ORIGINAL

NDA FILEABILITY CHECKLIST

NDA Number: 21-320
Stamp Date: 12/12/00
Drug Name: Plenaxis™

Applicant: Praecis Pharmaceuticals Inc.

IS THE CMC SECTION OF THE APPLICATION FILEABLE? (Yes_X_ No_)

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	X		
2	Is the section indexed and paginated adequately?	X		
3	On its face, is the section legible?	X		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	X		
5	Is a statement provided that all facilities are ready for GMP inspection?	X		
6	Has an environmental assessment report or categorical exclusion been provided?	X		
7	Does the section contain controls for the drug substance?	X		
8	Does the section contain controls for the drug product?	X		
9	Has stability data and analysis been provided to support the requested expiration date?		X	Review issue
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		
11	Have draft container labels been provided?	X		
12	Has the draft package insert been provided?	X		
13	Has an investigational formulations section been provided?	X		
14	Is there a Methods Validation package?	X		
15	Is a separate microbiological section included?	X		

If the NDA is not fileable from a manufacturing and controls perspective state why it is not.

Review Chemist: Swapan K. De, Ph. D.

Date: 1/23/01

Team Leader: Moo-Jhong Rhee, Ph. D.

Date: 1/23/01

cc:

Original NDA 21-320
HFD-580/Division File
HFD-580/Chem/De/Rhee
HFD-580/PM/EDeguia
HFD-580/DivDir/SAllen

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information

NDA REGULATORY FILING REVIEW

NDA # 21-320
 Trade Name: Plenaxis
 Generic Name: abarelix for injectable suspension
 Strengths: 100 mg per dose
 Applicant: Praecis Pharmaceuticals, inc.

Date of Application: December 11, 2000
 Date of Receipt: December 12, 2000
 Date of Not Approvable Letter: June 11, 2001
 Complete Response Resubmitted: February 25, 2003
 Date of Acknowledgment to Class 2 Complete Response: March 18, 2003
 PDUFA Goal Date: August 27, 2003
 Date of Major Amendment: July 14, 2003
 PDUFA Goal Date—extension: November 25, 2003

Indication requested:

J

Type of Application: Original (b)(1) NDA X Original (b)(2) NDA _____
 (b)(1) Supplement _____ (b)(2) Supplement _____
 [If the Original NDA was a (b)(2), all supplements are (b)(2)s; if the Original NDA was a (b)(1), the supplement can be either a (b)(1) or a (b)(2).]

If the application is a 505(b)(2) application, complete the 505(b)(2) section at the end of this summary.

Therapeutic Classification: S _____ P X
 Resubmission after a withdrawal No or refuse to file No
 Chemical Classification: (1,2,3 etc.) 1P
 Other (orphan, OTC, etc.) _____

Has orphan drug exclusivity been granted to another drug for the same indication? YES NO

If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?
 N/A YES NO

Is the application affected by the application integrity policy (AIP)? YES NO
 If yes, explain.

If yes, has OC/DMPQ been notified of the submission? N/A YES NO

User Fee Status: Paid _____ Waived (e.g., small business, public health) X
 Exempt (orphan, government) _____

Form 3397 (User Fee Cover Sheet) submitted: YES NO

User Fee ID # 4068

Clinical data? YES X NO _____, Referenced to NDA # N/A

Date clock started after UN: N/A

User Fee Goal Date: November 26, 2003

Action Goal Date (optional): November 25, 2003

- Does the submission contain an accurate comprehensive index? YES NO
- Was form 356h included with an authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. agent must sign.
- Submission complete as required under 21 CFR 314.50? YES NO
 If no, explain:
- If an electronic NDA, does it follow the Guidance? N/A YES NO
If an electronic NDA, all certifications must be in paper and require a signature.

Which parts of the application were submitted in electronic format? Case Report Forms for deaths,
 Adverse Event withdrawals and Serious Adverse Events plus SAS transport files

Additional comments: N/A

- If in Common Technical Document format, does it follow the guidance? N/A YES NO
- Is it an electronic CTD? N/A YES NO
If an electronic CTD, all certifications must be in paper and require a signature.
 Which parts of the application were submitted in electronic format?

Additional comments:

- Patent information included with authorized signature? YES NO
- Exclusivity requested? YES, _____ years NO
 Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.
- Correctly worded Debarment Certification included with authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: Debarment Certification must have correct wording, e.g.: "I, the undersigned, hereby certify that _____ Co. 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 the studies listed in Appendix ____." Applicant may not use wording such as "To the best of my knowledge"

- Financial Disclosure information included with authorized signature? YES NO

(Forms 3454 and/or 3455 must be used and must be signed by the APPLICANT.)

- Has the applicant submitted request for waiver for pediatric use? YES NO
- If no, explain.
- Field Copy Certification (that it is a true copy of the CMC technical section)? YES NO

Refer to 21 CFR 314.101(d) for Filing Requirements

- PDUFA and Action Goal dates correct in COMIS? YES NO
 If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections. YES NO
- List referenced IND numbers: IND 51,710 ; _____
- End-of-Phase 2 Meeting? Date _____ NO
 If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s)? Date(s) July 20, 2000 NO
 If yes, distribute minutes before filing meeting.

Project Management

- Package insert consulted to DDMAC? YES NO
- Trade name (plus PI and all labels and labeling) consulted to ODS/Div. of Medication Errors and Technical Support? YES NO
- MedGuide and/or PPI (plus PI) consulted to ODS/Div. of Surveillance, Research and Communication Support? N/A YES NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted? N/A YES NO

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/ Div. of Surveillance, Research and Communication Support? N/A YES NO
- Has DOTCDP been notified of the OTC switch application? N/A YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?
N/A YES NO

Chemistry

- Did applicant request categorical exclusion for environmental assessment?
YES NO
- If no, did applicant submit a complete environmental assessment?
YES NO
- If EA submitted, consulted to Nancy Sager (HFD-357)?
YES NO
- Establishment Evaluation Request (EER) submitted to DMPQ?
YES NO
- If parenteral product, consulted to Microbiology Team (HFD-805)?
YES NO

If 505(b)(2) application, complete the following section:

- Name of listed drug(s) and NDA/ANDA #:
- Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").
- Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs.)
YES NO
- Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 314.101(d)(9).
YES NO
- Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD? (See 314.54(b)(2)). If yes, the application should be refused for filing under 314.101(d)(9).
YES NO
- Which of the following patent certifications does the application contain? Note that a patent certification must contain an authorized signature.

___ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA.

___ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired.

___ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire.

___ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted.

IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must submit a signed certification that the patent holder was notified the NDA was filed [21 CFR 314.52(b)]. Subsequently, the applicant must submit documentation that the patent holder(s) received the notification ([21 CFR 314.52(e)].

___ 21 CFR 314.50(i)(1)(ii): No relevant patents.

___ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications.

___ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above.)

___ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.

- Did the applicant:

- Identify which parts of the application rely on information the applicant does not own or to which the applicant does not have a right of reference?

YES NO

- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

YES NO

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

N/A YES NO

- Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?

N/A YES NO

- If the (b)(2) applicant is requesting exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

- Certification that each of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

YES NO

- A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

YES NO

- EITHER

The number of the applicant's IND under which the studies essential to approval were conducted.

YES, IND # _____ NO

OR

A certification that it provided substantial support of the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

N/A YES NO

- Has the Director, Div. of Regulatory Policy II, HFD-007, been notified of the existence of the (b)(2) application?

YES NO

*Note: There was no Filing Meeting for the 2nd review cycle. However, on March 18, 2003 FDA sent an acknowledgement of the sponsor's letter dated February 25, 2003 that constituted a complete response to the deficiencies cited in the Agency's Not Approvable letter dated June 11, 2001, thus a resubmission of NDA 21-320.

{see appended electronic signature}



Nenita Crisostomo, R.N.
Regulatory Project Manager, HFD-580

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/s/

Nenita Crisostomo
11/25/03 11:54:47 AM
CSO

MEETING MINUTES

Date: November 20, 2003 **Time:** 2:00 – 3:00 P.M. **Location:** Teleconference

NDA: 21-320

Drug Name: Plenaxis™ (abarelix for injectable suspension)

Sponsor: Praecis Pharmaceuticals Incorporated

Indication: advanced symptomatic prostate cancer

Type of Meeting: Labeling

External Lead Participant: J.D. Bernardy, JD

Meeting Chair: Mark Hirsch, M.D.

Meeting Recorder: Nenita Crisostomo, R.N.

FDA Attendees:

Florence Houn, M.D., M.P.H., Director, Office of Drug Evaluation III, Center for Drug Evaluation and Research, HFD-103

Mark S. Hirsch, M.D., Medical Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP), HFD-580

Scott Monroe, M.D., Medical Officer, DRUDP, HFD-580

Anthony Orenca M.D., Ph.D., Medical Officer, DRUDP (HFD-580)

Carol Krueger, R.N., Office of Compliance, HFD-332

Mary E. Willy, Ph.D., Epidemiologist, Team Leader, Division of Drug Risk Evaluation (DDRE), Office of Drug Safety (ODS), HFD-440

Paula Gish, R.Ph., Pharmacist, DDRE, ODS, HFD-430

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

Nenita Crisostomo, R.N., Project Manager, DRUDP, HFD-580

External Attendees:

Malcolm Gefter, Ph.D., Chief Executive Officer

William Heiden, President, Chief Operations Officer

Marc B. Garnick, M.D., Executive Vice President & Chief Medical Officer

James Shipley, M.D., Senior Vice President, Clinical Research

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

Marilyn Champion, M.S., Vice President, Clinical Operations & Biometrics

Mary Beth DeLina, J.D., Vice President, Legal

Kevin McLoughlin, Senior Vice President, Chief Financial Officer

Michael O'Meara, Director, Clinical Operations

Carol Hurt, Senior Regulatory Affairs Specialist

Background: On December 11, 2000, the original New Drug Application (NDA) was submitted for Plenaxis (abarelix for injectable suspension), a gonadotropin releasing hormone (GnRH) antagonist. On June 11, 2001, a Not Approvable action was taken due to chemistry and clinical deficiencies. On February 25, 2003, a Complete Response to the action letter was submitted. During the third month of the current review cycle, the following issues were conveyed to the sponsor:

- continued evaluation of anaphylactic/anaphylactoid reaction individual cases and incidence rates
- continued evaluation of the effect of the drug on the QT interval
- the risk/benefit ratio in the “bone pain” population
- adequacy of the risk management plan.

On July 14, 2003, a major amendment on QT data was submitted by the sponsor and triggered a 3-month extension of PDUFA goal date to November 26, 2003.

Purpose: The purpose of this teleconference is to continue the discussions regarding revisions to the Risk Management Plan (RMP), Patient Information and Physician Insert. In addition, Amendment 088 and 089, received November 20, 2003, containing the sponsor’s response to the Agency’s Information Requests dated November 18, 2003 regarding Phase 4 Studies and Adverse Event Reporting, will also be discussed.

Discussion:

Revisions to the RMP, Physician Attestation, Patient Information (PPI), Physician Insert (PI), and the Phase 4 Studies were discussed and sponsor will submit the revised versions for these documents on or before November 21, 2003.

Praecis will revise the six Phase 4 Studies to include the ancillary study of 2000 patients pertaining to risk management evaluation of physician prescribing, signed patient information signature pages in medical records, frequency of measuring serum testosterone, and other responsibilities of the prescribing program. In addition, the company will include the evaluation of claims data for appropriate use in an _____ database. There will be a total of seven Phase 4 studies. The sponsor agrees to obtain FDA review and comment prior to initiation of the Phase 4 studies. For risk management evaluation studies/audits, a priori goals will be discussed and set prior to initiation.

The sponsor clarified that the Adverse Drug Event Reports will be generated by SENTRX for Praecis’ review and submission to FDA.

Action Item:

Sponsor will revise and submit above documents as per above discussions, to include electronic Word format of the Phase 4 Studies.



Signature: Internal Lead Participant

{See Appended Electronic Signature}

Florence Houn, M.D., M.P.H.,

NDA 21-320 Plenaxis (abarelix for injectable suspension)

T-con Minutes—November 20, 2003

Page 3

Cc:

HFD-332/Krueger

HFD-410/Best

HFD-430/Gish

HFD-440/Willy

HFD-580/Division Files

HFD-580/Original NDA 21-320

HFD-580/Hirsch/Monroe/De/Rhee/Raheja/Thornton/Parekh/Welch/Chatterjee/Meaker/Orencia/
Crisostomo

Created by: Nenita Crisostomo 11/20/03

Concurrence: Fhoun11/21/03, Mhirsch11/21/03, Smonroe11/21/03, MWilly, PGish, Jbest11/20/03,
Ckrueger, AOrencia

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/s/

Florence Houn
11/24/03 08:49:16 AM

MEETING MINUTES

Date: November 13, 2003 **Time:** 2:10 – 3:00 P.M. **Location:** Teleconference

NDA: 21-320

Drug Name: Plenaxis™ (abarelix for injectable suspension)

Sponsor: Praecis Pharmaceuticals Incorporated

Indication: of advanced symptomatic prostate cancer

Type of Meeting: Status Meeting

External Lead Participant: J.D. Bernardy, JD

Internal Lead Participant: Florence Houn, M.D., M.P.H.,

Meeting Chair: Mark Hirsch, M.D.

Meeting Recorder: Nenita Crisostomo, R.N.

FDA Attendees:

Florence Houn, M.D., M.P.H., Director, Office of Drug Evaluation III, Center for Drug Evaluation and Research, HFD-103

Mark S. Hirsch, M.D., Medical Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP), HFD-580

Scott Monroe, M.D., Medical Officer, DRUDP, HFD-580

Nenita Crisostomo, R.N., Project Manager, DRUDP, HFD-580

External Attendees:

Malcolm Gefter, PhD, Chief Executive Officer

William Heiden, President, Chief Operations Officer

Marc B. Garnick, MD, Executive Vice President & Chief Medical Officer

James Shipley, MD, Senior Vice President, Clinical Research

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

Marilyn Campion, MS, Vice President, Clinical Operations & Biometrics

Mary Beth DeLina, JD, Vice President, Legal

Kevin McLoughlin, Senior Vice President, Chief Financial Officer

Michael O'Meara, Director, Clinical Operations

Carol Hurt, Senior Regulatory Affairs Specialist

Jennifer Brooks, Quality Assurance Manager

Background: On December 11, 2000, the original New Drug Application (NDA) was submitted for Plenaxis (abarelix for injectable suspension), a gonadotropin releasing hormone (GnRH) antagonist. On June 11, 2001, a Not Approvable action was taken due to chemistry and clinical deficiencies.

On February 25, 2003, a Complete Response to the action letter was submitted. During the third month of the current review cycle, the following issues were conveyed to the sponsor:

- continued evaluation of anaphylactic/anaphylactoid reaction individual cases and incidence rates
- continued evaluation of the effect of the drug on the QT interval
- the risk/benefit ratio in the “bone pain” population
- adequacy of the risk management plan.

On July 14, 2003, a major amendment on QT data was submitted by the sponsor and triggered a 3-month extension of PDUFA goal date to November 26, 2003.

Purpose: The purpose of this teleconference is to discuss the Agency’s comments on the sponsor’s submission dated November 7, 2003, Amendment 080 containing the revisions to the Risk Management Plan (RMP).

Discussion:

1. Action date: planned for before November 27, 2003.
2. All amendments to the application for review should be received in FDA by November 21, 2003.
3. Use of the drug by indicated population:
 - The sponsor states that there is no way to verify the number of urologists and oncologists who will prescribe the drug. All physicians, including internists, who are caring for patients with prostate cancer will be enrolled in the RMP. The sponsor stated other physicians such as gynecologists will not be enrolled.
 - The sponsor admitted that physicians had negative reactions to the Physician Attestation Form, and therefore, they will investigate further what steps would be needed to address the physicians’ concerns.
 - FDA states that the estimated number of patients by the sponsor who will use abarelix seems higher than expected (24,000 patients). The sponsor states that they can only estimate that number of patients per the indication, but that they remain focused on the robustness of the RMP which will strengthen appropriate use to the approved indicated population.
 - According to the sponsor’s submission dated October 20, 2003, Page 12, the sponsor estimates 12,000 to 24,000 newly diagnosed patients per year based upon a — data analysis, or 12% of the 200,000 new US diagnoses per year. Due to variety of reasons, the numbers may be under-reported, including lack of specific diagnostic codes for the indication.
 - ---

The sponsor reports that in Study # 98-02 and 98-04, 7-10% of patient population received initial hormonal therapy.
4. Inconsistency of RMP goals: FDA stated that the goal outlined by the sponsor in the RMP dated August 8, 2003 regarding ensuring use in the population where the benefits outweigh the risks (for the population identified on November 4, 2003) was later reiterated by the Agency’s October 10, 2003. However, the sponsor’s revised RMP dated November 7, 2003 did not reflect the August 8 submission or the FDA October 10, 2003 letter. In addition, on page 6 of the November 7 submission, the statement, “*PRAECIS is precluded by the practice and ethics of medicine, HIPAA and other confidentiality laws and regulations from assessing the*

appropriateness of use with respect to the indication” was noted. FDA reminded the sponsor that the appropriate use is the essence of the RMP and that it was unclear how HIPPA and other confidentiality laws prevented Praecis from following up on patient complaints or other complaints.

- The sponsor states that the issue is that information is obtained through studies. There are legal jurisdictions that prevent them from obtaining analysis on compliance rates. For example, if a patient complains of an adverse event, the sponsor states that they can call the physician but they can not get medical records or visit the clinic to obtain patient information.
- The Agency acknowledges that the sponsor would need to obtain patient permission for release of medical records and asked why this would not be done. The sponsor agreed that there will be processes to follow up and address the problem of when complaints are obtained from a variety of sources. The sponsor also committed to:
 - Educate physician regarding appropriate use of the drug.
 - Educate the distributors to ensure that the restricted distribution plan is implemented accordingly. Sponsor agreed to expand on proposed interventions when distributors fail to comply with the RMP.
 - Adverse event reporting will include a medial chart review correlation.
 - Incorporating a chart review to evaluate use of the drug in the indicated population that would include chart review criteria to ensure that the patients are with approved indication.
 - Checks to see if unenrolled physicians are obtaining the drug.
 - Evaluate the frequency that serum testosterone levels are drawn.

Agreement:

- The sponsor will revise the RMP goals to include:
 - Physicians prescribing the drug are qualified.
 - Drug use is for the indicated population where benefits exceed risks.
- The sponsor stated that they had decided distribution will not include _____ sponsor will revise distribution to hospital pharmacies and direct physician purchases only. The sponsor also had decided previously that no retail pharmacies would be in the system except for “drop off” purposes based on patient reimbursement needs.
- Evaluation Program—The program would evaluate:
- Signed Physician Attestation Form placed in patient’s medical record.
- The sponsor stated that their proposal to _____ is now superseded with a protocol proposal to audit the 2000 persons with prospective allergic reaction study for various program elements such as, testosterone level testing, presence of the signed patient information page, patient diagnosis, etc.

Action Items:

- Sponsor to submit revised RMP as per above agreement.
- Agency to send comments on November 7, 2003 submission on November 14, 2003.
- Agency will send labeling, Physician Attestation and Buyer Form on November 14, 2003.

Next Meeting: Teleconference on November 18, 2003 to discuss labeling and additional comments.

Signature: Internal Lead Participant

{See Appended Electronic Signature}

Florence Houn, M.D., M.P.H.

APPEARS THIS WAY
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HFD-400/Dempsey

HFD-410/Best

HFD-430/Farinas

HFD-440/Willy

HFD-580/Division Files

HFD-580/Original NDA 21-320

HFD-580/Hirsch/Monroe/De/Rhee/Raheja/Thornton/Parekh/Welch/Chatterjee/Meaker/Crisostomo

Created by: Nenita Crisostomo 11/12/03

Concurrence: Fhoun11/20/03, Mhirsch11/20/03, Smonroe11/20/03

Finalized: NIC/DFS/11/20/03

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/s/

Florence Houn
11/21/03 10:27:28 AM

MEETING MINUTES

Date: November 5, 2003 **Time:** 10:30 – 11: 00 A.M. **Location:** Teleconference

NDA: 21-320

Drug Name: Plenaxis™ (abarelix for injectable suspension)

Sponsor: Praecis Pharmaceuticals Incorporated

Indication: t of advanced symptomatic prostate cancer

Type of Meeting: Status Meeting

External Lead Participant: J.D. Bernardy, JD

Meeting Chair: Moo-Jhong Rhee, Ph.D.

Meeting Recorder: Nenita Crisostomo, R.N.

FDA Attendees:

Moo-Jhong Rhee, Ph.D., Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II)

@ Division of Reproductive and Urologic Drug Product (HFD-580)

Swapan De, Ph.D. - Chemist, DNDC II @ DRUDP (HFD-580)

Nenita Crisostomo, R.N., Project Manager, DRUDP, HFD-580

External Attendees:

JD Bernardy, JD, Vice President, Regulatory Affairs & Quality Assurance

Gary Musso, Ph.D., Vice President, Development

Pat McKenna, Associate Director, Packaging and Logistics

Carol Hurt, Senior Regulatory Affairs Specialist

Background: On December 11, 2000, the original New Drug Application (NDA) was submitted for Plenaxis (abarelix for injectable suspension), a gonadotropin releasing hormone (GnRH) antagonist. On June 11, 2001, a Not Approvable action was taken due to chemistry and clinical deficiencies. On February 25, 2003, a Complete Response to the action letter was submitted. On July 14, 2003, a major amendment on QT data was submitted by the sponsor and triggered a 3-month extension of PDUFA goal date to November 26, 2003.

Purpose: The purpose of this teleconference is to discuss labeling revisions.

Discussion:

1. Patent Information—Since the patent information is not required on the Physician Insert (PI), the sponsor is agreeable to deleting this information.
2. Method Validation Package—The sponsor will send one copy to the division in addition to those sent on September 10, 2003.

3. Container Label—The Division referred to the Information Request sent on October 17, 2003 suggesting a change to the vial label to read as follows:

Plenaxis
(abarelix for injectable suspension)
100 mg abarelix
(Actual content is 113 mg to deliver 100 mg abarelix)

This suggestion was not reflected in the response dated October 24, 2003. The sponsor agreed to change as requested by the Division and will submit a final vial label to reflect this change.


Signature: Meeting Chair
{See Appended Electronic Signature}

Moo-Jhong Rhee, Ph.D.

NDA 21-320 Plenaxis (abarelix for injectable suspension)

T-con Minutes—November 5, 2003

Page 3

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HFD-580/Division Files

HFD-580/Original NDA 21-320

HFD-580/Hirsch/Monroe/De/Rhee/Raheja/Thornton/Parekh/Welch/Chatterjee/Meaker/Crisostomo

Created by: Nenita Crisostomo 11/20/03

Concurrence: Rhee 11/21/03, De 11/21/03

Finalized: NIC/DFS/11/21/03

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Moo-Jhong Rhee
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MEETING MINUTES

Date: July 28, 2003 **Time:** 2:00 – 3:30 A.M. **Location:** CDER WOC2 6FL-G Conf Room

NDA: 21-320

Drug Name: Plenaxis (abarelix for injection suspension)

Sponsor: Praecis Pharmaceuticals, Inc.

Indication: Treatment of advanced prostate cancer

Type of Meeting: Regulatory Briefing

Meeting Chair: John Jenkins, M.D.

Meeting Recorder: Nenita Crisostomo, R.N.

Attendees:

Renata Albrecht HFD 590	Mark Avigan HFD 430	Jane Axelrad (by phone) HFD 005	Julie Beitz HFD 103
George Benson HFD 580	Allen Brinker HFD 430	Jonca Bull HFD 105	Dhruba J. Chatterjee HFD 870
Badrul Chowdhury HFD 570	Kim Colangelo HFD 020	Edward Cox HFD 104	Nenita Crisostomo HFD 580
Swapan De HFD 580	Evelyn Farinas HFD 430	Lydia Gilbert-McClain HFD 570	Mark Goldberger HFD 104
Donna Griebel HFD 580	Brian Harvey HFD 105	Maureen Hess HFD 006	Mark Hirsch HFD 580
Dena Hixon HFD 600, representing Gary Buehler (HFD 600)	Florence Houn HFD 103	Shiew-Mei Huang HFD 850	David Jacobson- Kram HFD 024
Venkat Jarugula HFD 580	John Jenkins HFD 020	Leslie Kenna HFD 870	Margaret Kober HFD 580
Sandy Kweder HFD 020	Katherine Meaker HFD 715	Robert Meyer HFD 102	Charles Lee HFD 570
Shirley Murphy HFD 960	Edward Nevius HFD 715	Bob O'Neill HFD 700	Scott Monroe HFD 580
Ameeta Parekh HFD 580	Richard Pazdur HFD 150	Krishan Raheja HFD 580	Lana Pauls HFD 001
Daniel Shames HFD 580	Sol Sobel HFD 003	Bob Temple HFD 040	Paul Seligman HFD 030
Anne Trontell HFD 400	Mary Willy HFD 430	Janet Woodcock HFD 001	Suzanne Thornton HFD 580

Background: On December 11, 2000, the original New Drug Application (NDA) was submitted for Plenaxis (abarelix for injectable suspension), a gonadotropin releasing hormone (GnRH) antagonist. On June 11, 2001, a Not Approvable action was taken due to chemistry and clinical deficiencies. On February 25, 2003, a Complete Response to the action letter was submitted. During the third month of the current review cycle, the following issues were conveyed to the sponsor:

- continued evaluation of anaphylactic/anaphylactoid reaction individual cases and incidence rates
- continued evaluation of the effect of the drug on the QT interval
- the risk/benefit ratio in the “bone pain” population
- adequacy of the risk management plan.

Meeting Objectives: To obtain advice from the attendees regarding the applicability of a mandatory restricted distribution program with respect to the questions as listed below.

Presentations: Overhead projection was utilized by the Division of Reproductive and Urologic Drug Products (DRUDP) abarelix review team members to present the following:

- Efficacy—Dr. Scott Monroe
- Safety Part I, Anaphylactic/anaphylactoid reaction events and Life Table—Dr. Charles Lee and Ms. Katherine Meaker
- Safety Part II, QT prolongation data—Dr. Dhruba Chatterjee
- Risk/Benefit Summary—Dr. Mark Hirsch

□

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DISCUSSIONS—based on the following questions posed by DRUDP:

DRUDP Question 1: Is a mandatory restricted distribution plan under Subpart H a reasonable approach to managing the risks of Plenaxis™ in the indicated population?

Response: Yes. The attendees expressed concern about the increased frequency of anaphylactic/anaphylactoid reactions with longer duration of exposure to Plenaxis™. Another concern expressed was the dosing schedule (monthly) or the dose may be inadequate, producing the “saw-toothed” pattern of testosterone levels. One way to minimize the risk and address the concern of waning efficacy over time □

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Results from such studies may be submitted as a future supplement to the current NDA, but it was noted that existing data — should be reviewed.

DRUDP Question 2: If your answer to #1 is yes, then, is a “physician attestation” a reasonable centerpiece to such a restricted distribution plan? Specifically, we envision a program whereby a physician who wished to prescribe Plenaxis™ would have to become a “registered Plenaxis™ prescriber” by signing an attestation to this effect:

- a. They are knowledgeable and experienced in the management of prostate cancer.
- b. That they are aware of the labeled indication and instructions for use of Plenaxis™.
- c. That they have the facilities available to manage anaphylactic/anaphylactoid reactions and are competent to manage such an event.
- d. They will report the adverse event of concern (anaphylactic/anaphylactoid reactions) in a timely manner.

Response: Yes. The criteria for “knowledgeable and experienced” physicians should be better defined.

DRUDP Question 3: Can you suggest any additional or alternative measures to be included in such a restricted distribution program?

Response:

- Yes, a centralized pharmacy would appear critical to the mandatory restricted distribution plan.
-  
- The sponsor should also be asked to evaluate the effects of pre-treatment with steroids and anti-inflammatories before dosing to minimize possibility of an anaphylactic/anaphylactoid reaction.



Signature: Meeting Chair

{See appended electronic signature page}

John Jenkins, M.D.