Cc:
HFD-580/Division Files
HFD-580/Original NDA 21-320
HFD-580/Monroe/Hirsch/De/Lin/Chatterjee/Parekh/Meaker/Lee/Welch/Crisostomo/Kober

Created by: Nenita Crisostomo, 8.11.03
Concurrence: DS, DG, MH9/2/03, SM, AP, DC8/19, VJ, SD, MK8/19, KM8/22, ST, KR8/20, CL8/20, FH 9/8, RT 9/8
Finalized: NIC
Filename: C:Data/My Documents/NDAs/N21320/mtg.min.reg.brief.7.28.03.doc

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/s/

John Jenkins
9/24/03 08:28:58 AM

MEMORANDUM OF TELECON

DATE: July 25, 2003

APPLICATION: NDA 21-320, Plenaxis (abarelix suspension)

BETWEEN:

Name: JD Bernardy, JD, Vice President, Regulatory Affairs & Quality Assurance
Carol Hurt, Regulatory Affairs Associate
Marilyn Campion, Statistician
Bruce Belanger, Statistician

Phone: 781-795-4100

Representing: Praecis Pharmaceuticals, Inc.

AND

Name: Nenita Crisostomo, R.N., Regulatory Project Manager
Mark Hirsh, M.D., Medical Team Leader, Urology
Kate Meaker, M.S., Statistician
Charles Lee, M.D., Medical Officer, Pulmonology and Allergy

SUBJECT: Discussion of Datasets Regarding the Results in Life Table

Praecis Pharmaceuticals, Inc. requested clarification of data sets used by Food and Drug Administration (FDA) to generate the Life Table Analysis of Allergic Reactions.

Question 1: Please identify the 15 patients/events.

FDA Response: 11-2218, 76-3224, 09-3246, 16-3028, 357-2226, 313-3087, 333-3336, 401-4001, 409-4057, 416-4067, 02-4635, 01-2192, 29410085 (DRO-JA), 14070281 (THY-JP), 26860310

Question 2: Which groups of patients were included in the survival analysis? What was the total n for the analysis?

FDA Response: All Abarelix patients—(treatment codes 1-8). N=1397

Question 3: How was the censor day determined for patients who did not experience an allergic reaction?

FDA response: dyseyptt = total days exposed variable in SAS dataset.

Question 4: How was the event day determined for patients who experienced an allergic reaction?

FDA Response: Day reported in ISS.

Question 5:	Was a Kaplan-Meier or a life-table analysis performed?
FDA Response:	Kaplan-Meier
Question 6:	If life-table, how were the intervals constructed for the analysis?
FDA Response:	Not applicable.
Question 7:	Do the percentages you quoted (0.69% at 3 months, 1.24% at 1 year, and 2.91% at 2 years) represent the cumulative distribution for "failure", the conditional probability of "failure", or other?
FDA Response:	Probability of failure up to and through specified time.

{See appended electronic signature}

Mark Hirsh, M.D.
Medical Team Leader

Cc:
HFD-580/Division Files
HFD-580/Original NDA 21-230
HFD-580/hirsch/monroe/de/lin/rhee/raheja/thornton/chatterjee/parekh/welch/crisostomo/kober

Created by: Nenita Crisostomo, 7.25.03
Concurrence: mh8/4/03, km, cl
Finalized: NIC
Filename: C:Data/My Documents/NDAs/N21320/Memo.t-con.doc

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/s/

Nenita Crisostomo
8/5/03 02:35:29 PM
CSO

Mark S. Hirsch
8/5/03 05:31:36 PM
MEDICAL OFFICER
Concur.

M E M O R A N D U M DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: June 13, 2003

TO: Daniel Shames, M.D., Director
Division of Reproductive and Urologic Drugs (DRUDP), HFD-580

THROUGH: Mark Avigan, M.D. Acting Director
Division of Drug Risk Evaluation, HFD-430

FROM: Mary E. Willy, Ph.D., M.P.H., Epidemiologist Team Leader
Evelyn Farinas, R.Ph., Safety Evaluator
Debbie Boxwell, Pharm.D. Safety Evaluator Team Leader
Division of Drug Risk Evaluation, HFD-440

SUBJECT: **Drug: Abarelix (NDA-21-320)**
Topic: Risk Management Plan
PID#: D030251

EXECUTIVE SUMMARY

The Sponsor has submitted a risk management plan (RMP) for abarelix to address DRUDP's request for a plan that accomplishes the following three objectives: 1) ensures that abarelix be used only in the indicated treatment population, 2) ensures that healthcare professionals be made aware of the safety profile and be instructed on the treatment of any events that emerge following abarelix therapy (including hypersensitivity reactions), and 3) alerts healthcare professionals to the potential for fluctuating testosterone levels with a suggestion to perform periodic laboratory tests. These laboratory tests would monitor testosterone and PSA levels beyond six months of treatment to assess efficacy. The RMP primarily focuses on risk communication with special sales detailing, product labeling, product packaging, an open-access website, toll-free telephone numbers, and educational materials.

The following information is lacking from the RMP: a clear definition of what is the "clinically appropriate" time period for monitoring after treatment adminstration (referred to in sections 1.2 and 1.3.); sufficient data to support the sponsor's conclusions that the majority of practicing urologists are equipped to treat immediate-onset allergic reactions and that most patients will be receiving their treatment in a hospital or academic setting where equipment will be available for emergency response to life threatening hypersensitivity reactions; a definition of the planned sample size and the kind of information that will be collected in the survey of prescribing oncologists and urologists; a description of how practitioners will be made aware of the toll-free telephone number that is to be used for reporting adverse events; a description of how urologists

and oncologists who see the "highest number of symptomatic patients" will be identified; and whether the sponsor intends to assess physician prescribing patterns on a national level and if so, the intended methodology. Finally, there is no information provided as to how healthcare workers will be evaluated to determine whether they are periodically monitoring for fluctuating testosterone levels. The sponsor should be asked to provide additional information regarding the intervention plan and how it will be evaluated. A timeline that extends beyond the first 6-months of marketing should be provided. Although the proposed RMP includes a number of activities that may diminish the risk associated with abarelix treatment, sufficient details are missing from this proposal to draw any definitive conclusions.

BACKGROUND

Abarelix suspension for injection (Plenaxis) is a new molecular entity that has been developed by Praecis Pharmaceuticals for use in patients with metastatic prostate cancer for whom castration would be effective as a treatment but who are not candidates for luteinizing hormone-releasing hormone agonist therapy. The product rapidly suppresses testosterone, dihydrotestosterone, follicle-stimulating hormone, luteinizing hormone, and prostate-specific antigen. An immediate-onset, anaphylactoid-type allergic reaction was observed in clinical trials (and reported by the sponsor) in 0.03% of injections and 0.36% of patients. These reactions occurred anywhere between the first and 24th administered dose. An April 20, 2001 review of the clinical trial data by Dr. Charles Lee in the Division of Pulmonary and Allergy Drug Products concluded that the rate of these adverse events was higher (1.5%) and generally occurred within 24 hours, as is typical for an anaphylactoid reaction (two patients had reactions more than a day after dosing). The rate associated with Abarelix was higher than those associated with administration of many other drugs.

The sponsor was asked by the Division to develop a RMP that will: 1) ensure that abarelix is used only in the indicated treatment population, 2) ensure that healthcare professionals (HCPs) are aware of the safety profile and are adequately prepared to treat any life threatening events, and 3) alert HCPs to the potential for fluctuating testosterone levels and the need for periodic laboratory testing.

DESCRIPTION OF RISK MANAGEMENT PLAN

The RMP primarily focuses on risk communication with special sales detailing, product labeling, product packaging, an open-access website, toll-free telephone numbers, and educational materials.

Survey of Current Urological Practices: In section 1.2 the sponsor has described a survey of 33 HCPs identified through the American Urological Association (11 physicians and 22 nurses) who were questioned about their current knowledge regarding the treatment of immediate-onset systemic allergic reactions. The survey should have included a representative distribution of the practitioners that the sponsor anticipates would be the main prescribers (both urologists and oncologists). There was no description of the number of non-responders in this survey, so it is possible that the small sample overrepresents the preparedness of office practices (i.e. only

practices that are well prepared answered the survey questions). A number of the surveyed practitioners said they would be willing to hold patients for a "clinically-appropriate" observation period, but that time period was not defined. The sponsor concludes that the survey results suggest that the majority of practicing urologists are equipped to treat immediate-onset allergic reactions and that most patients will be receiving their treatment in a hospital or academic setting where equipment will be available for emergency response. The sponsor did not provide enough data to support either of these two concluding remarks.

Communications to Healthcare Professionals and Patients: In section 1.4.3 a toll-free number for healthcare professionals was described to provide guidance in the proper use of the product. Later in the document a toll-free number was provided for reporting adverse events. Will the same number serve both purposes and what type of training would the telephone workers have?

In section 1.4.6 the sales force outreach is described. The training described includes "the principal concepts of the risk management strategy" – Does the sponsor plan to include training about the risk for anaphylaxis and the preparation for and management of this event?

Evaluation of Risk Management Plan: In section 1.5 the sponsor briefly described plans to survey a random sample of prescribing oncologists and urologists (sample size not included) to determine physician prescribing patterns and knowledge of the risk/benefit profile. There is no further detail about the kind of information that will be collected, such as whether the physician will be queried about patient diagnoses, the number of adverse events, and whether they will be made aware of the risk of anaphylaxis and its management. Provision of a copy of the proposed survey would help clarify these questions. A contingency plan for evaluation of the RMP in the event that at six months post launch the number of prescribers is too small to be representative of prescribers is needed. The sponsor did not provide a timetable to the Agency for the submission of the evaluation results.

Spontaneous reporting of adverse events will be encouraged and a toll-free telephone number will be made available. It is not clear how practitioners and patients will be made aware of the phone number, and if a healthcare professional will be manning the toll-free number.

Distribution: In section 1.6 the sponsor discussed the pros and cons of different options for distribution plans, including a formalized restricted distribution plan. The sponsor listed several reasons not to employ a limited distribution plan. These were:

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A description of the use of a small sales force focusing on urologists and oncologists who see the "highest number of symptomatic patients" is put forth, although there is no explanation of how these practitioners would be identified.

An important component of any unrestricted risk management plan is the need to follow national prescribing patterns to determine if off-label prescribing occurs. Although physician prescribing patterns are listed as an item that will be assessed in section 1.5.1, it is not clear if that assessment will be on a national level and the methods that will be used.

Finally, there is no information provided as to how healthcare workers will be evaluated to determine whether they are periodically monitoring for fluctuating testosterone levels.

DISCUSSION

The sponsor has provided a summary of a proposed risk management plan that includes several different elements. The following information should be provided:

1. Define a "clinically appropriate" time period for monitoring post treatment (referred to in sections 1.2 and 1.3.
2. The sponsor has not provided sufficient data to support that the majority of practicing urologists are equipped to treat immediate-onset allergic reactions and that most patients will be receiving treatment in a hospital or academic setting where equipment will be available for emergency response to life threatening drug-related events. More information to support those conclusions should be provided. The survey should also have included all practitioners that the sponsor anticipates would be prescribing the product, that is, both urologists and oncologists.
3. The same toll-free number that provides guidance in the proper use of the product should be used to collect adverse event information. The type of training provided to the telephone workers should be specified.
4. A plan to include training for the sales force on the risk for anaphylaxis and the preparation for and management of this event should be provided.
5. The proposed survey of prescribing oncologists and urologists (section 1.5.1) does not include the planned sample size, detail about the kind of information that will be collected in the survey, such as whether the physician will be queried about the a) patient diagnoses of those treated with abarelix, b) the number of observed abarelix-related adverse events, and c) whether the surveyed practitioner was aware of and prepared to deal with anaphylaxis; the provision of a copy of the proposed survey would help clarify these questions. A contingency plan for evaluation of the RMP in the event that at six months post launch the number of prescribers is too small to be a true representation of prescribers is needed. The sponsor did not provide a timetable to the Agency for the submission of the evaluation results.
6. It is not clear how practitioners will be made aware of the toll-free telephone number that is to be used for reporting adverse events.
7. There is no explanation of how practitioners will be identified for focused detailing; a plan to identify urologists and oncologists who see the "highest number of symptomatic patients" should be provided.

8. Although physician prescribing patterns are listed as an item that will be assessed in section 1.5.1, it is not clear if that assessment will be on a national level and the methods that will be used.
9. A plan to determine whether healthcare workers are periodically monitoring for fluctuating testosterone levels should be provided.

CONCLUSION

Although the proposed RMP includes a number of activities that may help diminish the risk associated with abarelix treatment, sufficient details are missing from this proposal to make any definitive conclusions. The sponsor needs to provide additional information regarding the intervention plan and how it will be evaluating that plan, including a timeline that goes beyond the first 6-months of marketing.

/S/

Mary E. Willy, Ph.D. M.P.H., Epidemiology Team Leader

/S/

Evelyn Farinas, R.Ph., Safety Evaluator

/S/

Debbie Boxwell, Pharm.D., Safety Evaluator Team Leader

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/s/

Sandra Birdsong
6/13/03 01:05:25 PM
CSO
Entered in DFS for the Review Team

Mary Willy
6/13/03 01:45:03 PM
MEDICAL OFFICER

Mark Avigan
6/13/03 02:33:55 PM
MEDICAL OFFICER

Teleconference Minutes

Date: November 30, 2001 **Time:** 10:00-11:00 AM **Location:** Parklawn; 17B-43

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

Indication: Palliative treatment of advanced prostate cancer

Sponsor: Praecis Pharmaceuticals, Inc.

Type of Meeting: Guidance

Meeting Chair: Dan Shames, M.D..

Meeting Recorder: Jeanine Best, M.S.N., R.N.

External Lead: JD Bernardy, J.D.

FDA Attendees:
Dan Shames, M.D., Acting Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Mark Hirsch, M.D., Urology Team Leader, DRUDP (HFD-580)
Scott Monroe, M.D., Medical Officer, DRUDP (HFD-580)
George Benson, M.D., Medical Officer, DRUDP (HFD-580)
Badrul Chowdhury, M.D., Medical Team Leader, Division of Pulmonary Drug Products, (DPDP; HFD-570)
Charles Lee, M.D., Medical Officer, DPDP (HFD-570)
Jeanine Best, M.S.N, R.N., Senior Regulatory Associate, DRUDP (HFD-580)

External Participants (Praecis Pharmaceuticals and Guests):
Marc Garnick, M.D., Executive V.P. & Chief Medical Officer
JD Bernardy, J.D., V.P., Regulatory Affairs & Quality Assurance
Marilyn Campion, V.P., Clinical Operations & Biometrics
Bruce Belanger, Manager, Biostatistics
Michael O'Meara, Associate Director, Clinical Operations
Paul Damiani, Director, Regulatory Affairs
Carol Hurt, Regulatory Affairs Specialist

Non-Participating Guests:
Malcolm Gefter, Ph.D., Chief Executive Officer

[ ]

Meeting Objective: To discuss and provide comments on the October 25, 2001, sponsor response to the issues raised in the Not Approvable Letter, dated June 11, 2001, and in the End of Review Conference held on September 10, 2001.

Background: Plenaxis™ —— (abarelix for injectable suspension) is a new molecular entity and is the first GnRH antagonist to be reviewed for long-term therapeutic use (palliative treatment of advanced prostate cancer). It was submitted to the Agency on December 11, 2000, and received a Not Approvable Action on June 11, 2001 for insufficient clinical information to support the safe and effective use of the product in the intended population. The NDA submission also contained deficiencies in chemistry, microbiology and facilities. An End Of review Meeting was held on September 10, 2001, in which the Agency presented the sponsor with suggestions of additional studies for safety and efficacy that may generate data that supports the possibility of an approvable drug product. The sponsor submitted proposals on October 25, 2001, to address the safety and efficacy concerns raised by the Agency and is requesting Agency concurrence with regard to these proposals.

Discussion:

- the sponsor reported that they believe they have a thorough understanding of the Agency's concerns with regard to the safety and efficacy of abarelix and believe that they have arrived at appropriate approaches for handling these concerns in order to go forward with seeking approval of abarelix
- the Agency agrees with the sponsor's proposal to use abarelix as initial therapy for one to three months in patients with advanced prostate cancer, if the to-be-generated data demonstrates that conversion to treatment with a GnRH agonist can be achieved safely, without an increase in serum testosterone

Screening for antibodies and skin testing

- the sponsor's proposed assay methods and procedures to screen archived serum samples for IgG and IgE antibodies to abarelix and carboxymethylcellulose (CMC) from subjects who had allergic reactions that necessitated their withdrawal, as well as case-controlled patients who did not have reactions, are acceptable
- the sponsor's proposed plan to skin test these subjects for allergic responses to abarelix and CMC is acceptable
- the sponsor should also screen for antibodies and skin test any additional subjects who develop allergic reactions during treatment with abarelix in ongoing studies or other studies that were not included in the NDA; the sponsor may amend ongoing protocols to include these testing

Safety Outcome Measures in Sponsor's Proposed Studies:

- the sponsor's plans to assay IgG and IgE antibodies at screening, prior to each dose of abarelix, and temporal to the development of any severe allergic reaction to abarelix are acceptable
- the sponsor's plans to measure plasma histamine and tryptase (alpha and beta) temporal to the development of any severe allergic reaction to abarelix are acceptable
- patients who have had allergic reactions to abarelix should be skin tested, assuming that a skin test is developed

Proposed Indication

- the Agency prefers the proposed indication to be worded as follows:

[ ]

[ ]

Sponsor's Proposed Studies

- the Agency disagrees with the sponsor's definition of a failure during transition from abarelix to a GnRH agonist in the proposed clinical trials, because the benefit of abarelix is to avoid the initial testosterone (T) surge; therefore, to demonstrate this benefit, castrate levels (< 50 ng/dL) should be maintained at transition to a GnRH agonist
  - an increase in serum T above castrate levels (i.e., > 50 ng/dL) at transition would constitute a failure
  - the sponsor's proposal of using a T value of >140 ng/dL is not acceptable; the sponsor initially proposed using a similar definition of a failure as used in the pivotal phase 3 trials presented in the NDA to define an LH surge, that is an increase in 2 of the 3 T measurements >50 ng/dL in the first week of transition to a GnRH agonist would be considered a failure; the sponsor subsequently modified this proposal to be an increase in 2 of the 5 T values to > 50 ng/dL in the first month following transition to an agonist; the Agency told the sponsor to propose this definition and submit it with the statistical analysis plan for review and consideration
  - the serum T concentration on Days 14 and 28, as well as Days 1, 3, and 7, after the dose of GnRH analog should be considered in determining if the conversion was associated with a surge in T
  - subjects whose serum T levels are not suppressed to ≤ 50 ng/dL prior to dosing with the GnRH agonist and whose serum T levels increase after dosing with the GnRH agonist also will be classified as failures; a success will be considered for subjects whose serum T levels are not suppressed to ≤ 50 ng/dL prior to dosing with the GnRH agonist and whose serum T levels decrease to castrate levels after dosing with a GnRH agonist
  - the entire profile, not just one sample, will be needed for consideration of calling a patient a success; the sponsor concurred

Other Discussion:

- the sponsor answered that labeling **WARNINGS** would still appear regarding allergic reactions and the need for the in-office 30-minute observation period with the proposed limited dosing period
- [ ]
- the Agency raised the question in regard to the transition to a one-month or three-month GnRH agonist formulation because there is concern that a three-month agonist formulation may have a larger release at initial dosing; the sponsor responded that their plan now is to only transition to a one-month GnRH agonist formulation and they also said that the general Urology standard of care (per marketing research) is to initiate treatment with a one-month GnRH formulation; this issue, if not studied, can be addressed in labeling
- the sponsor asked if they would have a marketable product if the transition to a GnRH agonist is unsuccessful; the Agency responded that consideration for longer-term use in a restricted population (the highest risk group for flare complications) would be given with regular monitoring of T levels to observe for waning efficacy and a risk management program developed for handling possible allergic reactions; this could be achieved by a SubPart H approval with on-going studies to ultimately widen the approved population if possible; a second approach could be treatment with a dose of abarelix that would not be associated with the waning efficacy, along with an adequate risk management plan

for long-term monotherapy; the question regarding if increasing the dose, increases the rate of allergic reactions would need to be answered as well as overall safety of a higher dose
- the Agency responded that the process for addressing the safety and efficacy concerns that were identified in the NDA is going well and that the product would be useful for prostate cancer patients if the safety and efficacy concerns can be addressed and managed

Decisions:
- none

Action Items:
- the sponsor will submit proposals and statistical analysis plan for review and comment
- Meeting Minutes to the sponsor within 30 days

/S/

Minutes Preparer

/S/

Concurrence, Chair

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

cc:
Original NDA 21-320
HFD-580/DivFile
HFD-580/PM/Best
HFD-580/Shames/Hirsch/Monroe/Benson
HFD-570/Chowdhury/Lee
drafted:JAB/November 30, 2001
concurrence:Chowdhury,11.30.01/Benson,11.30.01/Lee,12.04.01/Monroe,12.10.01/Hirsch,12.10.01/Shames,12.12.01
final: JAB/December 12, 2001
MEETING MINUTES

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/s/

Jeanine Best
12/12/01 09:55:14 AM
CSO

Daniel A. Shames
12/12/01 12:54:29 PM
MEDICAL OFFICER

Meeting Minutes

Date: September 10, 2001 **Time:** 3:30-5:00 PM **Location:** Parklawn; Chesapeake Room

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

Indication: Palliative treatment of advanced prostate cancer

Sponsor: Praecis Pharmaceuticals, Inc.

Type of Meeting: End of Review Meeting

Meeting Chair: Dan Shames, M.D.

Meeting Recorder: Jeanine Best, M.S.N., R.N.

External Lead: JD Bernardy, J.D.

FDA Attendees:
Florence Houn, M.D., M.P.H., Office Director, Office of Drug Evaluation III (ODE III; HFD-103)
Dan Shames, M.D., Deputy Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Mark Hirsch, M.D., Urology Team Leader, DRUDP (HFD-580)
Scott Monroe, M.D., Medical Officer, DRUDP (HFD-580)
George Benson, M.D., Medical Officer, DRUDP (HFD-580)
Ashok Batra, M.D., Medical Officer, DRUDP (HFD-580)
Robert Meyer, M.D., Director, Division of Pulmonary Drug Products, (DPADP; HFD-570)
Badrul Chowdhury, M.D., Ph.D., Medical Team Leader, DPADP (HFD-570)
Charles Lee, M.D., Medical Officer, DPADP (HFD-570)
Moo-Jhong Rhee, Ph.D., Chemistry Team Leader, Division Of New Drug Chemistry II (DNDC II) @ DRUDP, (HFD-580)
Swapan De, Ph.D., Chemist, DNDC II @ DRUDP, (HFD-580)
Ameeta Parekh, Ph.D., Pharmacokinetics Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
DJ Chatterjee, Ph.D., Pharmacokinetics Reviewer, OCPB @ DRUDP (HFD-580)
Kate Meaker, M.S., Statistician, Division Of Biometrics II (DBII) @ DRUDP (HFD-580)
Stephen Langille, Ph.D., Microbiologist, Office of Pharmaceutical Science (OPS; HFD-805)
Jeanine Best, M.S.N, R.N., Senior Regulatory Associate, DRUDP (HFD-580)

External Participants:
Praecis Pharmaceuticals Inc.
Malcolm Gefter, Ph.D., Chief Executive Officer
Marc B. Garnick, M.D., Executive Vice President & Chief Medical Officer
Marilyn Campion M.S., Vice President, Clinical Operations & Biometrics
JD Bernardy, J.D., Vice President, Regulatory Affairs & Quality Assurance
Bruce Belanger, Ph.D., Manager, Biometrics

NDA 21-320
Meeting Minutes

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Consultants:

[

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Meeting Objective: To review and discuss the deficiencies that led to the Not Approvable Letter, June 11, 2001.

Background: This priority review NDA was submitted on December 11, 2000. Plenaxis™ (abarelix for injectable suspension) is a new molecular entity and is the first GnRH Antagonist to be reviewed for long-term therapeutic use (palliative treatment of advanced prostate cancer). The application contained deficiencies in Clinical, Chemistry, Microbiology, and Facilities, and was found to be not approvable by the Agency because of insufficient information to demonstrate the safe and effective use in the intended population.

Discussion:

- sponsor presentation, see attached slides **(Attachment 1)**
- the Agency told the sponsor that the broad indication _____ was not acceptable and had never been agreed upon; at most the indication (as agreed upon during IND drug development) would be the same as for the currently approved GnRH agonists

Question 1
Praecis has presented additional information to justify the importance of the avoidance of testosterone surge. Does the Agency concur with Praecis assessment?

- the Agency believes that in some patients (advanced prostate disease), avoidance of a testosterone flare (that occurs with the administration of GnRH agonists) is important; the Agency also believes that the importance of avoidance of a testosterone flare in all prostate cancer patients is theoretical and that a survival benefit is speculative and without supportive data at this time

Question 2
Praecis has proposed a risk management plan (safety) for use with Plenaxis™. Does Praecis' proposed plan adequately address the Agency's concerns?

- see attached slides for the DPADP response **(Attachment 2)**

- the Agency asserts that the allergic reactions seen in the clinical trials with Plenaxis were more immediate, more frequent, and more severe than those reaction that were reported with comparators in the clinical trials; comparing the frequency of severe allergic reactions seen with Plenaxis™ in the Plenaxis™ clinical program to those seen with other drugs (i.e., the comparator drugs used in the Plenaxis™ clinical program) seen in spontaneous postmarketing adverse reporting is not informative; the Agency believes that the number of allergic reactions associated with Plenaxis™ in the postmarketing period would be larger than with approved GnRH agonists
- the Agency is concerned that most urologists may not be fully knowledgeable and prepared to handle severe allergic reactions
- the risk management plan is not appropriate for the proposed [redacted] of prostate cancer patients; the risk may be acceptable in a much smaller population of prostate cancer patients with advanced disease or impending neurologic sequelae; the therapeutic index must be weighed against the risk/benefit analysis
- the Agency believes it is important to attempt to understand the etiology of the allergic reactions; even though it is acknowledged that additional information may not be discovered immediately and the treatment of the reaction may remain the same
- the Agency, as already stated in the June 11, 2001, Not Approvable letter, requests that the sponsor conduct investigations, pre NDA resubmission, to better clarify the nature of the allergic reactions, so that the incidence may be decreased or the consequences mitigated; the sponsor should investigate both the carboxymethylcellulose (CMC) excipient and the peptide; if the CMC is implicated, then a new formulation may be appropriate
- the Agency recommended that the sponsor should retrospectively test patients that had allergic reactions after receiving Plenaxis™ to study the nature of the allergic reaction
- the Agency stated that patients with any allergic reaction should not receive further doses of the product
- the Agency suggested that it could be possible to modify their IgG antibody test to look for IgE antibodies; a skin test should not be difficult to develop; the Agency stated that if such testing is predictive, then these tests may be used pre-dosing and patients that tested positive would not receive the product; the Agency acknowledged that developing these tests are often difficult, and may not always be successful, but the sponsor should start the program now to characterize these reactions; availability of a predictive skin tests, or a drug-specific IgE test, or both will be useful and may weigh in on the assessment of the dug product

Praecis has proposed a revised format for the Safety Update?

- the Division finds the format acceptable

Question 3
Praecis has provided support for efficacy risk management and revised labeling using current data for Agency consideration. Does the Agency concur that the NDA is approvable with:
- *The proposed risk management plan (efficacy)?*
- *The revised labeling?*
- *The proposed Phase 4 study plan?*

Does Praecis' proposed plan adequately address the Agency's concerns?

- the proposed plan is not acceptable
  - the sponsor should consider adding a weight restriction

- the decrease in efficacy demonstrated with increasing body weight is indicative of inadequate dose-finding
- [redacted]
- [redacted]
- the Division is concerned that the recommended measurement of the testosterone levels will not be conducted; the sponsor may consider ways to assure compliance in the risk management plan
- labeling may not be adequate to ensure that recommendations are heeded
- the sponsor needs to address the efficacy deficiency as outlined in the June 11, 2001, Not Approvable Letter; adequate information to address the deficiency must be generated pre-resubmission; the sponsor should present their approach for addressing the deficiency for consideration by the Division, before a NDA resubmission

- the Division asked the sponsor if there was a plan to [redacted] of Plenaxis™ over time; the sponsor did not provide a response

Question 4

The Chemistry questions in the Not Approvable Letter were addressed in NDA Amendment 028 of 22 May 2001. The Microbiology question (a) was answered in this document. DMF's [redacted] have been updated by the contractors, [redacted] respectively. Major facility inspections have been satisfactorily completed. Are there any other outstanding CMC issues?

- the CMC and Microbiology responses will be reviewed at the time of the NDA resubmission
- additional stability data should be submitted at the time of the resubmission
- [redacted]
- DMF's [redacted] and [redacted] have been updated and appear acceptable; a complete review will be done at the time of the NDA resubmission
- Facilities; the [redacted] site is not in cGMP compliance; the [redacted] site is to be inspected this week

Decisions made:

- the Agency reiterated that the deficiencies noted in the June 11, 2001, Not Approvable Letter must be addressed prior to resubmission of the NDA, not as postmarketing studies; the NDA resubmission must contain a complete response to the deficiencies
- the Agency reiterated that the proposed indication for Plenaxis cannot [redacted] already approved GnRH agonists
- the Agency stated that the current risk/benefit profile is unacceptable; the sponsor must decrease the risk profile or increase the benefit profile in order to gain approval for Plenaxis™

NDA 21-320
Meeting Minutes

Action Items:

- Meeting Minutes to sponsor within 30 Days

/S/

Minutes Preparer

/S/

Concurrence, Chair

Note to Sponsor:

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

Redacted 24

pages of trade

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commercial

information

NDA 21-320
Meeting Minutes

cc:
Original NDA 21-320
HFD-580/DivFile
HFD-580/PM/Best
HFD-580/Shames/Hirsch/Monroe/Benson/Batra/Rhee/De/Parekh/Chatterjee/De/Meaker
HFD-570/Meyer/Chowdhury/Lee
HFD-103/Houn
drafted:JAB/September 13, 2001
concurrence:Meyer,09.13.01/Benson,09.13.01/Rhee,09.13.01/De,09.13.01/Chatterjee,09.13.01/
Houn,09.13.01/Hirsch,09.13.01/Batra,09.14.01/Lee,09.18.01/Chowdhury,09.18.01/Parekh,09.20.01/
Monroe,09.24.01/Shames,09.24.01
final:JAB/October 1, 2001
MEETING MINUTES

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/s/

Daniel A. Shames
10/1/01 03:59:59 PM

Teleconference Meeting Minutes

Date: June 12, 2001 **Time**: 4:30-5:10 PM **Location:** PKLN; Room 17B-45

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

Indication:

Sponsor: Praecis Pharmaceuticals, Inc.

Type of Meeting: Guidance

Meeting Chair: Dan Shames, M.D..

External Lead: Marc Garnick, M.D.

Meeting Recorder: Jeanine Best, M.S.N., R.N.

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

External Participants (Praecis Pharmaceuticals, Inc.):
Marc Garnick, M.D., Executive Vice President, Chief Medical and Regulatory Affairs
JD Bernardy, J.D., Vice President, Regulatory Affairs and Quality Assurance

Meeting Objectives: To clarify clinical deficiencies noted in the Not Approvable Letter, issued June 11, 2001.

Background: This priority review NDA was submitted on December 11, 2000. Plenaxis™ (abarelix for injectable suspension) is a new molecular entity and is the first GnRH antagonist to be reviewed for long-term therapeutic use.

Discussion:

- the sponsor does not agree with the Agency that the allergic reactions observed with abarelix were any different that those observed with the GnRH agonists; and the sponsor believes that concerns with the allergic responses were addressed appropriately in responses submitted to their application; the Agency responded that the systemic allergic reactions occurring with the use of abarelix in the clinical trials were of a qualitative significant difference than those allergic reactions occurring with Lupron Depot® or Zoladex®; the rate of the observed allergic reactions was noted to be high when compared to other marketed drug products
- the sponsor does not believe that the allergic reactions can be reduced or mitigated; rather the sponsor believes the risk can be addressed through labeling alone; the Agency stated that the sponsor should investigate the systemic allergic reactions further and attempt to characterize the nature of the reactions;

anaphylaxis verses anaphylactoid, and to investigate whether abarelix or carboxymethycellulose is the basis of the allergic reactions

- the Agency stated that labeling alone is probably not enough to manage risk; the sponsor needs to develop an appropriate postmarketing risk management program to demonstrate the mitigation of the risk of allergic reactions
- the Agency stated that current data or reanalysis of this data may not be adequate to appropriately address the issue of allergic reactions; further data collection may be necessary
- the sponsor suggested an alternative indication , the Agency responded that approval for this indication could be considered, a possible approval might occur for example under SubPart H Regulations with a restricted distribution system in place to manage risk
- the Agency reported that efficacy of the abarelix was not maintained after 3 months, and that the dose and or dosing frequency should be investigated; abarelix should maintain castration as well as Lupron Depot®; the sponsor noted the decrease of efficacy and mainly noted it as related to body weight or age; the sponsor suggests addressing the efficacy concern with labeling for weight and age limitations or restricting use of abarelix for 6 months (to avoid a testosterone flare), and

Action Items:

- Meeting Minutes to sponsor within 30 days

Signature, minutes preparer

Concurrence, Chair

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

cc:
NDA 21-320:
HFD-580/Division File
HFD-580/ Shames
Concurrence: Shames,06.19.01
Final:JAB/June, 2001/N21320tcon061201.doc

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/s/

Daniel A. Shames
6/20/01 05:13:11 PM

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Teleconference Meeting Minutes

Date: June 11, 2001 **Time:** 4:30-4:45 PM **Location:** PKLN; Room 17B-45

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

Indication:

Sponsor: Praecis Pharmaceuticals, Inc.

Type of Meeting: Action Notification

Meeting Chair: Victor Raczkowski, M.D., M.Sc.

External Lead: Marc Garnick, M.D.

Meeting Recorder: Jeanine Best, M.S.N., R.N.

FDA Attendees:
Victor Raczkowski, M.D., M.Sc., Deputy Director, Office of Drug Evaluation III (ODE III; HFD-103)
Dan Shames, M.D., Deputy Director, Division of Reproductive and Urologic Drug Products DRUDP (HFD-580)
Jeanine Best, M.S.N., R.N., Regulatory Project Manager, DRUDP (HFD-580)

External Participants (Praecis Pharmaceuticals, Inc.):
Marc Garnick, M.D., Executive Vice President, Chief Medical and Regulatory Affairs
JD Bernardy, J.D., Vice President, regulatory Affairs and Quality Assurance

Meeting Objectives: To discuss the Not Approvable Action of this NDA with the sponsor.

Background: This priority review NDA was submitted on December 11, 2000. Plenaxis™ t (abarelix for injectable suspension) is a new molecular entity and is the first GnRH antagonist to be reviewed for long-term therapeutic use.

Discussion:

- the Not Approvable Action Letter is signed and will be faxed to the sponsor at the conclusion of the meeting
- this application was granted a priority review (because of product potential) and was reviewed carefully and thoroughly by the Division and Office; the application was also discussed more broadly with management in the Office of Review Management and CDER
- deficiencies were found in several areas: Clinical, Chemistry, Microbiology, and Facilities
- the clinical approvability issues have been discussed with the sponsor during the NDA review
- it is likely that additional data is required to respond to the clinical deficiencies; a reanalysis of the data is unlikely to remedy the situation

- it is speculative at this time to conclude that deficiencies could have been addressed during a standard review cycle of 10 to 12 months; the priority review needed to be completed in the assigned 6-month time-clock
- the sponsor may request an "End of Review" meeting (Type A Meeting) in order to further discuss the deficiencies and possible remedies; the sponsor may also refer to other options that are addressed in the Not Approvable Letter

Action Items:

- J. Best will fax Not Approvable (NA) Letter to the sponsor at the conclusion of this teleconference
- Meeting Minutes to sponsor within 30 days

/S/ /S/

Signature, minutes preparer

Concurrence, Chair

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

cc:
NDA 21-320:
HFD-580/Division File
HFD-580/ Shames/
HFD-103/Raczkowski
Concurrence: Shames,06.12.01/Raczkowski,06.13.01
Final:JAB/June 13, 2001/N21320tcon061101.doc

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/s/

Victor Raczkowski
6/13/01 11:58:10 AM

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MEMORANDUM OF TELECON

DATE: May 15, 2001

APPLICATION NUMBER: NDA 21-320

BETWEEN:

Name: J. D. Bernardy, J.D., Vice President Regulatory Affairs and Quality Assurance
Phone: (781) 795-4282
Representing: Praecis Pharmaceuticals, Inc.

AND

Name: Jeanine Best, M.S.N, R.N., Regulatory Project Manager
Division of Reproductive and Urologic Drug Products

SUBJECT: Biopharm Information Request

It appears that for some patients, vials other than those containing 100 mg were used in the clinical trials. Please respond to the following:

1. Clarify the vial contents (mg basis), and state the number of vials/doses that were used for each dosing in the centers conducting the controlled pivotal clinical trials.

2. State how the contents of the vials were reconstituted and mixed.

3. Following reconstitution, state how the doses were injected into the patients (especially for those vials that contained less than 100 mg/vial).

/S/

Jeanine Best, M.S.N., R.N.

cc:
Archival NDA 21-320
HFD-580/Division Files
HFD-580/Best

Drafted by: JAB/May 15, 2001
Final: JAB/May 15, 2001
Filename:N21320Tcon051501.doc

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/s/

Jeanine Best
5/15/01 04:30:24 PM
CSO

MEMORANDUM OF TELECON

DATE: April 24, 2001

APPLICATION NUMBER: NDA 21-320

BETWEEN:

Name: J. D. Bernardy, J.D., Vice President Regulatory Affairs and Quality Assurance
Phone: (617) 494-8400 x2282
Representing: Praecis Pharmaceuticals, Inc.

AND

Name: Jeanine Best, M.S.N, R.N., Regulatory Project Manager
Division of Reproductive and Urologic Drug Products

SUBJECT: Request for Additional Clinical Data

Please submit the following data:

Please provide the patient data listings of clinically notable laboratory values for Study 149-99-04 that is represented in Table 12.6.7, pages 249-251, of the Safety Update. The listing should include all values for each patient for the respective laboratory tests represented in the Table. For example, for a patient with one or more notable ALT value, please provide all ALT values for that patient in Study 149-99-04. Please use the format that was followed for Data Listing 15.29.1.1, page 426, of your March 27, 2001 submission (Amendment 008). In addition to identifying all clinically notable values (last column of Table 15.29.1.1), please also add a flag for each value that was above (H) or below (L) the limits of the normal range.

/s/

Jeanine Best, M.S.N., R.N.

cc:
Archival NDA 21-320
HFD-580/Division Files
HFD-580/Best

Drafted by: JAB/April 24, 2001
Final: JAB/April 24, 2001
Filename:N21320Tcon042401.doc

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/s/

Jeanine Best
4/24/01 03:08:32 PM
CSO

MEMORANDUM OF TELECON

DATE: April 20, 2001

APPLICATION NUMBER: NDA 21-320

BETWEEN:

Name: J. D. Bernardy, J.D., Vice President Regulatory Affairs and Quality Assurance
Phone: (617) 494-8400 x2282
Representing: Praecis Pharmaceuticals, Inc.

AND

Name: Jeanine Best, M.S.N, R.N., Regulatory Project Manager
Division of Reproductive and Urologic Drug Products

SUBJECT: Request for Additional Clinical Data

Please submit the following data:

Please generate a listing that will include all bilirubin values for all subjects who had one or more bilirubin values above the upper limit of normal. The list should be based on all studies with the depot formulation that were included in the ISS and Safety Update, namely 149-97-04, 149-98-02. 149-98-03, 149-98-04, 149-99-01, 149-99-03, and 149-99-04, and any other studies that may have relevance to this request. The listing should include for each subject:

1. the study number
2. the actual study day on which the sample was obtained with the day of dosing called Day 1
3. the value for bilirubin
4. the multiple of the upper limit of normal for each elevated bilirubin value

/S/

Jeanine Best, M.S.N., R.N.

cc:
Archival NDA 21-320
HFD-580/Division Files
HFD-580/Best

Drafted by: JAB/April 24, 2001
Final: JAB/April 24, 2001
Filename:N21320Tcon042001.doc

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/s/

Jeanine Best
4/24/01 09:16:11 AM
CSO

MEMORANDUM OF TELECON

DATE: April 17, 2001

APPLICATION NUMBER: NDA 21-320

BETWEEN:

Name: J. D. Bernardy, J.D., Vice President Regulatory Affairs and Quality Assurance
Phone: (617) 494-8400 x2282
Representing: Praecis Pharmaceuticals, Inc.

AND

Name: Jeanine Best, M.S.N, R.N., Regulatory Project Manager
Division of Reproductive and Urologic Drug Products

SUBJECT: Request for Additional Clinical Data and Clarification of Randomization in Studies

Please submit the following data:

1. Please provide the additional requested Financial Disclosure Data

2. Please provide laboratory data listings for subjects with clinically notable laboratory values in the Safety Update for Study 149-99-04; if this data has been submitted, please provide location in the NDA. Specifically, please provide a listing to support Table 12.6.7 in the Safety Update. The format of this new listing should be identical to that of Listing 15.29.1.1 on page 426 in Amendment 008.

3. Please provide narratives for Patients 350-2149 and 338-2164, both of whom withdrew from Study 149-99-04 because of elevated liver transaminases.

The sponsor clarified that randomization was done within Strata, not within Center, for Studies 98-02, 98-03, and 99-03.

Jeanine Best, M.S.N., R.N.

cc:
Archival NDA 21-320
HFD-580/Division Files
HFD-580/Best

Drafted by: JAB/April 24, 2001
Final: JAB/April 24, 2001
Filename:N21320Tcon041701.doc

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/s/

Jeanine Best
4/24/01 09:11:54 AM
CSO

Division of Reproductive and Urologic Drug Products

ADMINISTRATIVE REVIEW OF APPLICATION

Application Number: NDA 21-320

Name of Drug: **Plenaxis (abarelix for injectable suspension)**

Sponsor: **Praecis Pharmaceuticals, Inc.**

Material Reviewed:

Submission Date: **December 11, 2000**

Receipt Date: **December 12, 2000**

Filing Date: **February 10, 2001**

User-Fee Goal Date(s): June 12, 2001

Proposed Indication: Palliative treatment of advanced prostate cancer

Other Background Information: : This NDA will get a priority review. Abarelix represents the first antagonist and first sustained release formulation of a GnRH antagonist for the palliative treatment of advanced prostate cancer. The use of Abarelix acetate is related to the unique mechanism of action by which the initial surge of androgen is completely eliminated which results in the rapid onset of medical castration.

Review

PART I: OVERALL FORMATTING[a]

Y=Yes (Present), N=No (Absent)

	Y	N	COMMENTS (list volume & page numbers)
1. Cover Letter (original signature)	x		Vol. 1
2. Form FDA 356h (original signature)	x		Vol. 1
a. Reference to DMF(s) & Other Applications	x		Vol. 1
3. Patent information & certification	x		Vol. 1 pp. 265-349
4. Debarment certification (note: must have a definitive statement)	x		Vol. 1 p. 350

5. Financial Disclosure	x		Vol. 1 pp. 354-371
6. Comprehensive Index	x		Vol. 1
7. Pagination	x		Vol. 1
8. Summary Volume	x		Vol. 1
9. Review Volumes	x		Vol. 1 - 88
10. Labeling (PI, container, & carton labels)	x		Vol. 1 pp.51-71
a. unannotated PI			
b. annotated PI	x		
c. immediate container	x		
d. carton	x		
e. foreign labeling (English translation)		x	
11. Foreign Marketing History		x	
12. Case Report Tabulations (CRT) (paper or electronic) (by individual patient data listing or demographic)	x		Vol. 188
13. Case Report Forms (paper or electronic) (for death & dropouts due to adverse events)	x		Vol. 188

Y=Yes (Present), N=No (Absent)

PART II: SUMMARY[b]

Y=Yes (Present), N=No (Absent)

	Y	N	COMMENTS (list volume & page numbers)
1. Pharmacologic Class, Scientific Rationale, Intended Use, & Potential Clinical Benefits	x		Vol. 1 pp. 72-73
2. Summary of Each Technical Section	x		Vol. 1
a. Chemistry, Manufacturing, & Controls (CMC)	x		
b. Nonclinical Pharmacology/Toxicology	x		
c. Human Pharmacokinetic & Bioavailability	x		
d. Microbiology	x		Included in the CMC Section
e. Clinical Data & Results of Statistical Analysis	x		
3. Discussion of Benefit/Risk Relationship & Proposed Postmarketing Studies	x		Vol. 1 pp. 238-240
4. Summary of Safety	x		
5. Summary of Efficacy	x		

Y=Yes (Present), N=No (Absent)

PART III: CLINICAL/STATISTICAL SECTIONS[c]

Y=Yes (Present), N=No (Absent)

	Y	N	COMMENTS (list volume & page numbers)
1. List of Investigators	x		Vol. 1 pp. 357-371
2. Controlled Clinical Studies	x		Vol. 1 p. 354
a. Table of all studies	x		Vol. 1 p. 354
b. Synopsis, protocol, related publications, list of investigators, & integrated clinical & statistical report for each study (including completed, ongoing, & incomplete studies)	x		Vol. 1 pp. 241-263
c. Optional overall summary & evaluation of data from controlled clinical studies		x	
3. Integrated Summary of Efficacy (ISE)	x		Vol. 44
4. Integrated Summary of Safety (ISS)	x		Vol. 44
5. Drug Abuse & Overdosage Information	X		Vol. 44 p. 87
6. Integrated Summary of Benefits & Risks of the Drug	x		Vol. 44 p. 87
7. Gender/Race/Age Safety & Efficacy Analysis Studies		x	

Y=Yes (Present), N=No (Absent)

PART IV: MISCELLANEOUS

Y=Yes (Present), N=No (Absent)

	Y	N	COMMENTS (list volume & page numbers)
1. Written Documentation Regarding Drug Use in the Pediatric Population	x		Request for Pediatric Waiver Vol. 1 p. 373
2. Diskettes	x		
a. Proposed unannotated labeling in MS WORD 8.0			Annotated labeling in MS Word
b. Stability data in SAS data set format		x	Will be submitted in April 2001
c. Efficacy data in SAS data set format	x		
d. Biopharmacological information & study summaries in MS WORD 8.0	x		CD-ROM for Item 6 of the NDA
e. Animal tumorigenicity study data in SAS data set format		x	Will be submitted in March 2001 with the Safety Update
3. User-fee payment receipt	x		Vol. 1 p. 353

Y=Yes (Present), N=No (Absent)

[a]"GUIDELINE ON FORMATTING, ASSEMBLING, AND SUBMITTING NEW DRUG AND ANTIBIOTIC APPLICATIONS" (FEBRUARY 1987).

[b]"GUIDELINE FOR THE FORMAT AND CONTENT OF THE SUMMARY FOR NEW DRUG AND ANTIBIOTIC APPLICATIONS" (FEBRUARY 1987).

[c]"GUIDELINE FOR THE FORMAT AND CONTENT OF THE CLINICAL AND STATISTICAL SECTIONS OF NEW DRUG APPLICATIONS" (JULY 1988).

Additional Comments: Filing meeting was held on January 24, 2001.

Conclusions: This NDA is fileable.

/S/

Regulatory Health Project Manager

/S/

Concurrence, Chief, Project Management Staff

cc:
Original NDA
HFD-580/Div. Files
HFD-580/DeGuia/Rumble
final: DeGuia

ADMINISTRATIVE REVIEW

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/s/

Eufrecina deGuia
4/18/01 08:02:23 AM
CSO

Terri F. Rumble
4/19/01 04:41:01 PM
CSO
I concur.

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

Risk Management Plan submitted with the complete response on February 25, 2003.

APPEARS THIS WAY
ON ORIGINAL

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

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
OFFICE OF DRUG SAFETY (RM 15B-08, PKLN BLDG)
ATTENTION: SANDRA BIRDSONG

FROM: NITA CRISOSTOMO, PROJECT MANAGER
DIV. OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS, PH# 301-827-7260

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
AUG 15, 2003		21-320	N	Aug 7, 2003

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
PLENAXIS (ABARELIX SUSPENSION)	RUSH	GnRH ANTAGONIST	OCTOBER 30, 2003

NAME OF FIRM: PRAECIS PHARMACEUTICALS, INC.

REASON FOR REQUEST

I. GENERAL

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

II. BIOMETRICS

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

III. BIOPHARMACEUTICS

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

IV. DRUG EXPERIENCE

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

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Dear Ms. Birdsong,

This is a re-consultation with you for review of the revised Risk Management Plan, to include the Mandatory Restricted Distribution Plan. Attached, please find the copy of this document.

Thank you,
Nita

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

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

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Mail: ODS (Room 15B-08, PKLN Bldg.)
Attention: Sandra Birdsong

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

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
April 16, 2003		21-320	N	February 25, 2003

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Plenaxis (abarelix for inj. Suspension)	RUSH	GnRH Antagonist	May 16, 2003

NAME OF FIRM: Praecis Pharmaceuticals

REASON FOR REQUEST

I. GENERAL

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

II. BIOMETRICS

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

III. BIOPHARMACEUTICS

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

IV. DRUG EXPERIENCE

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

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: This is a consult request from Dr. Mark Hirsch, Urology Team Leader. Please assess the Risk Management Plan submitted by the sponsor. The User Fee Goal Date is August 27, 2003. This is an NME (New Molecular Entity) and will need an office sign off. Review package will be sent to ODS via interoffice mail.

Please call me if you have any questions.
Freshnie

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

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/s/

Eufrecina deGuia
4/17/03 04:19:48 PM

MEMORANDUM OF TELECON

DATE: April 11, 2001

APPLICATION NUMBER: NDA 21-320

BETWEEN:

Name: J. D. Bernardy, J.D., Vice President Regulatory Affairs and Quality Assurance
Phone: (617) 494-8400 x2282
Representing: Praecis Pharmaceuticals, Inc.

AND

Name: Jeanine Best, M.S.N, R.N., Regulatory Project Manager
Krishan Raheja, D.V.M., Ph.D., Pharmacologist
Division of Reproductive and Urologic Drug Products

SUBJECT: Request for Additional Pharmacology/Toxicology Data

Please submit the following data:

1. For Monkey Study N002059A, described in volume 10, plasma histamine data was presented as a graph but individual values were not included.

2. For Monkey Studies N002059C and N002059G, described in volumes 18 and 19, respectively, plasma was collected for histamine determination but no results were submitted.

The sponsor reported that the mouse carcinogenicity data would be submitted next week; there were no adverse findings; substance is similar to the rat carcinoginicity data.

/S/

Jeanine Best, M.S.N., R.N.

/s/

Jeanine Best
4/12/01 04:15:57 PM
CSO

Meeting Minutes

Date: April 11, 2001 **Time:** 2:00-3:00 PM **Location:** Parklawn; 17B-43

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

Indication: Palliative treatment of advanced prostate cancer

Sponsor: Praecis Pharmaceuticals, Inc.

Type of Meeting: Status Meeting

Meeting Chair: Susan Allen, M.D., M.P.H.

Meeting Recorder: Jeanine Best, M.S.N., R.N.

FDA Attendees:
Susan Allen, M.D., M.P.H., Director, Division of Reproductive and Urologic Drug Products
Mark Hirsch, M.D., Urology Team Leader, DRUDP (HFD-580)
Scott Monroe, M.D., Medical Officer, DRUDP (HFD-580)
George Benson, M.D., Medical Officer, DRUDP (HFD-580)
Ashok Batra, M.D., Medical Officer, DRUDP (HFD-580)
Marianne Mann, M.D., Deputy Director, Division of Pulmonary Drug Products, (DPDP; HFD-570)
Badrul Chowdhury, M.D., Medical Team Leader, DPDP (HFD-570)
Charles Lee, M.D., Medical Officer, DPDP (HFD-570)
Krishan Raheja, D.V.M., Ph.D., Pharmacologist, DRUDP (HFD-580)
Swapan De, Ph.D., Chemist, Division Of New Drug Chemistry II (DNDC II) @ DRUDP, (HFD-580)
DJ Chatterjee, Ph.D., Pharmacokinetics Reviewer, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Kate Meaker, M.S., Statistician, Division Of Biometrics II (DBII) @ DRUDP (HFD-580)
Stephen Langille, Ph.D., Microbiologist, Office of Pharmaceutical Science (OPS; HFD-805)
Barbara Chong, Ph.D., Regulatory Reviewer, Division of Drug Marketing, Advertising, and Communication, (DDMAC; HFD-42)
Eufrecina Deguia, Regulatory Project Manager, DRUDP (HFD-580)
Jeanine Best, M.S.N, R.N., Regulatory Project Manager, DRUDP (HFD-580)

Meeting Objective: To discuss the status of reviews and approvability of this new drug application.

Background: This priority review NDA was submitted on December 11, 2000. Plenaxis™ (abarelix for injectable suspension) is a new molecular entity and is the first GnRH Antagonist to be reviewed for long-term therapeutic use (palliative treatment of advanced prostate cancer). It may offer clinical benefit (to some advanced prostate cancer patients), over existing GnRH analogs because clinical trials have demonstrated that Plenaxis does not initially stimulate the secretion of testosterone and it suppresses testosterone to castrate levels more rapidly.

Discussion:
Clinical

- C. Lee from DPDP presented the DPDP allergy consult with regard to the allergic reactions that have been seen in the clinical trials with Plenaxis (see attached slides)
- there are increased allergic responses with products given intramuscularly and frequently (like Plenaxis)
- further discussion continued after the slide presentation with regard to the issue of management of potential allergic reactions and management of patients in the office with labeling guidelines; patients should remain in the office for observation for 1-hour post-injection; patients are observed for allergic reactions for 3-hours in some European countries post-injection
- the sponsor contends that there is no difference between their product and Lupron® Depot with regard to allergic reactions; this may be true in terms of cutaneous reactions but does not appear to apply to systemic reactions; the sponsor also attempts to diminish the rate of systemic allergic response to their product through manipulation of the denominator used by looking at patient year use
- there is some liver toxicity (transaminase elevation) demonstrated with use of the product in the clinical trials; some patients had increases in their liver function tests (LFTs) that they had to be removed from the study; LFTs were monitored monthly in the clinical trials; the product, if approved, will need to be labeled for regular measurement of LFTs during administration
- the sponsor presented further support (Study 9804) for use of this product in patients who are at risk for GnRH agonist therapy (may have a clinically significant complication); the Division's response is there is no contraindication for GnRH agonist therapy (other than sensitivity to the drug product) in many of these patients; instead, the risk/benefit usage is determined for an individual patient; the major concern is for the patient in whom a testosterone flare could lead to a clinically devastating event (i.e., a patient with asymptotic epidural metastasis)
- in light of the safety Update and stability data that were recently submitted to the NDA, the sponsor will be submitting a revised label; the Division has not made any labeling revisions to date

Clinical Pharmacology:

- there is a demonstrated efficacy diminution over time; there is a pharmacokinetic (PK) failure in efficacy of maintenance of testosterone suppression after 3-months of use; the PK profile is probably not too different between the 100 mg and the 150 mg doses (the 100 mg dose was the dose chosen by the sponsor)
- the sponsor claims that they have met their endpoint of suppression of testosterone and maintenance of testosterone at castrate levels for 3-months; the palliative treatment of advance prostate cancer with this product will be on-going and indefinite; for this reason, the Division is evaluating the efficacy of the product for a longer time-period; the sponsor agrees that efficacy of the product diminishes over time, but that this diminution is not clinically significant
- there is a demonstrated correlation between body weight and diminishing efficacy
- the sponsor is submitting additional supportive PK data for review this week

Pharmacology:

- cardiovascular toxicity effects were demonstrated with drug exposure in dog and monkey studies; one dog died from cardiac failure after drug exposure
- carcinogenicity study reports for the rat have been received; the mouse carcinogenicity study reports are still pending; the sponsor replied that reports will be submitted next week
- there were several monkey studies performed involving histamine release; in one study, results were presented as a graph but no detailed data was provided; in two other studies, blood was collected for

histamine release, but no results were submitted; the sponsor will be requested to provide these raw data values

Biometrics:

- it appears that the sponsor performed randomization within-strata but not within-center (sponsor will be asked to clarify); strata subgroups will be analyzed (strata for baseline testosterone level and body-weight)

Chemistry:

- there are no significant issues to date
- the 6-month stability data has been received; it might not support the sponsor's requested expiry date

Microbiology:

- there are a few deficiencies that will be conveyed in writing to the sponsor
  -
  - the sponsor referenced a DMF . but did not specify the location of the reference in this large DMF

DDMAC:

- . DDMAC has labeling comments that were not discussed at this meeting

Unresolved decisions:

- there was disagreement on whether or not the therapeutic benefit of this product out-weighs possible safety concerns; a GnRH agonist plus an anti-androgen (off-label use) may be equally efficacious, with a better safety profile.
- approvability of this NDA in view of the allergic safety issue and the diminution in efficacy over time; it is possible the product could be approved for a very limited indication (i.e., the palliative treatment of prostate cancer in men with asymptomatic epidural metastasis) or be approved under Subpart H with a limited distribution; there is a discomfort level in the Division
- labeling for the safe and effective use of the product

Decisions made:

- Office briefing is scheduled for May 7, 2001 at 2:00 PM
- Predecisional meeting is scheduled for May 29, 2001 at 1:30 PM

Action Items:

- J. Best and K. Raheja will call sponsor today and request missing monkey histamine data
- S. Languille will provide Micro deficiencies to J. Best to send to sponsor

/S/ /S/

Minutes Preparer

/S/

Concurrence, Chair

DPDP Consult

NDA 21-320

Pleanaxis (abarelix for suspension)

Reactions in 15 abarelix patients

- Consistent with systemic allergic reactions, including anaphylaxis
- Flushing, itching, urticaria, angioedema, hypotension, and syncope
- Rapid onset
- Abnormal respirations in one patient, treated with bronchodilator, bronchospasm?
- Anaphylaxis, with syncope or hypotension in six patients
- Reaction with the second or later dose in 14 of 15

Reactions in 2 leuprolide-treated patients

- Several days after the dose was given.
- One with first dose, other with third dose
- No circulatory or respiratory symptoms. not anaphylaxis

Anaphylaxis

- Gell and Coombs Type I immunologic reaction
- Immediate hypersensitivity reaction
- IgE-mediated process
- Previous immunologic sensitization is required, not with first exposure
- Penicillin, allergy immunotherapy extracts, anti-thymocyte globulin (ATG), tetanus antitoxin, and black widow antivenin

Anaphylactoid or psuedoallergic reaction

- Non-IgE mediated mast cell and basophil release
- Not an immune process
- May occur with the first exposure to the agent
- Symptoms and signs of anaphylactoid reactions otherwise mimic anaphylaxis
- Radiocontrast media (RCM), iron-dextran, and narcotics

Abarelix
- Decapeptide, molecular weight of 1416.06 D
- 96% to 99% binding to plasma protein
- Preclinical data
  - Direct histamine release
- Does not an IgE-mediated etiology
  - e.g., vancomycin

Patients
- Relatively ill, advanced prostate cancer
- None less than 64 years of age, some were older than 80 years
- Higher risk for poor outcome from anaphylaxis
- Despite the ages of these patients, no deaths from anaphylaxis were noted
- May be unreasonable to expect similar favorable outcomes outside of a clinical trial setting.

Concomitant medications as risk factors
- Beta blockers were concomitant medications in two patients
- ACE inhibitor in one patient

Frequency, abarelix
- 15 cases of systemic allergic reactions in 1141 abarelix exposed patients, 1.3%
- 6 cases of anaphylaxis with hypotension or syncope, 0.5%.

Frequency, leuprolide
- 2 cases of systemic allergic reactions in 367 leuprolide-exposed patients, 0.5%
- No anaphylaxis

Current product labeling

Goserelin.

- Allergic reactions are listed, frequency of 1% or greater in goserelin-treated women from all clinical trials

Leuprolide

- No mention in label of allergic reactions or anaphylaxis in clinical trials of leuprolide
- Reference to one case of anaphylaxis reported in the medical literature, and that symptoms consistent with an anaphylactoid or asthmatic process have been rarely reported (incidence rate of about 0.002%) reported.

Cetrorelix

- Reference is make to a single patient in a clinical study with cetrorelix with a severe anaphylactic reaction with cough, rash, and hypotension.

Nafarelin

- "in formal clinical trials of 1509 healthy adult patients, symptoms suggestive of drug sensitivity, such as shortness of breath, chest pain, urticaria, rash and pruritus occurred in 3 patients (approximately 0.2%)."

Frequency of anaphylaxis for abarelix is higher than the rate for the currently approved GnRH antagonists

Table 4. Rates of anaphylaxis/anaphylactoid events for certain drugs [MR&E, DrugDex®-Drug Evaluations]

Drug	Anaphylaxis, % of treatment courses	Fatal anaphylaxis, % of treatment courses
Penicillin	0.01 to 0.05	0.001-0.002
Low osmolar RCM	0.04	NA
Hyperosmolar RCM	0.22	0.009
Black widow spider antivenin	0.54	NA
Antithymocyte globulin	2	NA
Allergen immunotherapy	2	NA
Crotalidae antivenin	11 to 12	NA

Summary

- Frequent, severe, life-threatening reactions have been noted with abarelix
- Frequency of such events greater than those noted with currently marketed GnRH products
- Systemic allergic reaction in 1.3% of abarelix-treated patients
- Life-threatening anaphylaxis in 0.5%.
- Frequency of anaphylaxis with abarelix
  - Higher than the frequency with patients treated with penicillin or hyperosmolar RCM
  - Similar to the frequency seen with administration of black widow spider antivenin
- Elderly, ill patients, concomitant medications
- Chronic use for maintenance treatment

Additional evaluation

- Skin testing
- IgE ELISA

Manage with labeling?

Problems

- Skin test
- Prophylaxis
- Long-term administration, once every 28 days
- Off-label use

cc:
Original NDA 21-320
HFD-580/DivFile
HFD-580/PM/Best/Deguia
HFD-580/Allen/Hirsch/Monroe/Benson/Batra/Rumble/Raheja/Chatterjee/De/Meaker
HFD-570/Mann/Chowdhury/Lee
HFD-42/Chong
drafted:JAB/April 12, 2001
concurrence:Raheja,04.16.01/Rumble,04.16.01/Benson,04.16.01/Batra,04.17.01/Deguiae,04.17.01/
Meaker,04.17.01/Chatterjee,04.19.01/De,04.19.01/Hirsch,04.20.01/Monroe,04.23.01
final:JAB/May 10, 2001

MEETING MINUTES

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

/s/

Mark S. Hirsch
5/11/01 08:29:07 AM

MEMORANDUM OF TELECON

DATE: March 26, 2001

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

BETWEEN:

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

AND

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

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

Please provide the following additional analyses concerning the reduction of serum testosterone concentrations to ≤ 50 ng/dL by Day 29 and maintenance of these castrate levels in Studies 149-98-02, 149-98-03, and 149-99-03.

1. The requested analyses differ from those previously submitted in that:
   a) Subject failure should be based on failure to achieve and maintain castrate levels of testosterone. Subjects who terminated prematurely because of an adverse event (regardless of relationship of the AE to treatment with Study Drug) or other reason should be considered a treatment failure only if their serum testosterone was not ≤ 50 ng/dL.
   b) The period of assessment will also include the interval Day 1 through Day 365 for Studies 149-98-02 and 149-98-03.
2. For all analyses:
   a) The intent to treat population should be used.
   b) The analyses can be based on percentages with the last observation carried forward (LOCF) as was done in the original submission or by Kaplan Meier estimates if you prefer.
   c) For each analysis, please calculate the percent success in each treatment group, the difference in success between the 2 treatment groups in the respective Study, and the 95% two-sided confidence interval for the between-group difference.
3. For Study 149-98-02, please provide the following additional analyses. All analyses should treat premature withdrawals as described in Item 1a above.
   a) Achievement of medical castration by Day 29 and maintenance through day 85:
      1. Where failure is based on previously defined Efficacy Definition No. 2 (2 successive testosterone values within 14-day period >50 ng/mL);
      2. Where failure is based on previously defined Efficacy Definition No. 3 (testosterone values >50 ng/mL at the end of any 28-day treatment cycle).
   b) Achievement of medical castration by Day 29 and maintenance through Day 169:

1. Where failure is based on previously defined Efficacy Definition No. 5 (2 successive testosterone values within 14-day period >50 ng/mL);
2. Where failure is based on previously defined Efficacy Definition No. 6 (testosterone values >50 ng/mL at the end of any 28-day treatment cycle).

c) Achievement of medical castration by Day 29 and maintenance through Day 365:

1. Where failure is based on Efficacy Definition No. 5 through Day 169 and the testosterone value at the end of each 28-day treatment cycle from Day 197 through Day 365 (optional calculation);
2. Where failure is based on Efficacy Definition No. 6 modified to cover the period through Day 365.

4. For Study 149-98-03, please provide the same 7 or 8 additional analyses that are requested for Study 149-98-02.
5. For Study 149-99-03, please provide the following additional analyses. All analyses should treat premature withdrawals as described in Item 1a above.

a) Achievement of medical castration by Day 29 and maintenance through day 85:

1. Where failure is based on Efficacy Definition No. 2 (2 successive testosterone values within 14-day period >50 ng/mL);
2. Where failure is based on Efficacy Definition No. 3 (testosterone values >50 ng/mL at the end of any 28-day treatment cycle).

b) Achievement of medical castration by Day 29 and maintenance through Day 169:

Where failure is based on Efficacy Definition No. 6 (testosterone values >50 ng/mL at the end of any 28-day treatment cycle).

6. Please provide any additional analyses that you believe may be helpful to our review. For example, you may wish to include one or more analyses, using the definitions/requests listed above, based only on those subjects who achieved medical castration by Day 29, an analysis that you included in your original NDA submission.

Eufrecina DeGuia

Regulatory Project Manager