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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-320

Approval Letter(s)



NDA 21-320

Praecis Pharmaceuticals, Incorporated
Attention: J.D. Bernardy, J.D.
Vice President, Regulatory Affairs & Quality Assurance
830 Winter Street
Waltham, MA 02451-1420

Dear Mr. Bernardy:

Please refer to your new drug application (NDA) dated December 11, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Plenaxis™ (abarelix for injectable suspension, 100mg).

We acknowledge receipt of your submissions dated January 5; March 13, 14, 15, 26, 27, 29, and 30; April 6, 9, 10, 13, 17, 19, 26, and 27(2); May 4, 7, 10, 22, 24, 25(2), and 29; June 14 and 15; and July 26, 2001; February 25, March 19 and 20; April 25(2); May 8 and 16(2); June 3, 5, 17, 19, 25, 27, and 30; July 9, 11, 14, 16, 17, 18, 29, and 31; August 8; September 10, 12, 17, 24, and 29; October 3, 14, 20, 24, and 30(2); and November 3, 4, 7, 11, 13, 16, 17, 18(2), 19, 21(2), and 24, 2003.

The February 25, 2003 submission constituted a complete response to our Not Approvable letter of June 11, 2001. The original submission was not approved because of the risk of serious allergic reactions, including anaphylaxis with hypotension and syncope, and because the risk of loss of efficacy over time. For your then proposed target population of men with local, regional, or advanced carcinoma of the prostate where androgen suppression is appropriate, the Agency determined that risks of Plenaxis™ exceeded its benefits.

This resubmission of the application provides for the use of Plenaxis™ (abarelix for injectable suspension, 100mg) for the palliative treatment of men with advanced symptomatic prostate cancer, in whom LHRH agonist therapy is not appropriate and who refuse surgical castration, and have one or more of the following: (1) risk of neurological compromise due to metastases, (2) ureteral or bladder outlet obstruction due to local encroachment or metastatic disease, or (3) severe bone pain from skeletal metastases persisting on narcotic analgesia.

The resubmitted application, considered for approval under 21 CFR Part 314, Subpart H at your request, narrows the originally proposed indication to use of the drug in a population for whom the benefits of the drug may outweigh the risks, but in whom the drug can be safely used only if distribution and/or use is restricted. The application provides for a risk management program that will help ensure the safe use of Plenaxis™ in the approved indicated population.

We completed our review of this application, as amended, and have concluded that adequate information has been presented to approve this application for Plenaxis™ (abarelix for injectable suspension, 100mg) under 21 CFR Part 314 Subpart H for the proposed indication in your resubmission. You have indicated your agreement with approval with restrictions to ensure safe use. Accordingly, this application is approved under 21 CFR Part 314, Subpart H. Approval is effective on the date of this letter. Marketing of this drug product and related activities are to be accordance with applicable provisions of the Act and FDA regulations, including the specific restrictions on distribution and use described below.

Plenaxis™ Risk Management Program

We remind you that your Plenaxis™ Risk Management Program is an important part of postmarketing risk management for Plenaxis™, and must include each of the following components in order to ensure distribution only to physicians with the training and experience necessary to assure safe use of the drug, and to ensure use of Plenaxis™ only in patients for whom the drug is indicated, as set forth in the INDICATIONS AND USAGE section of the FDA-approved labeling:

1. Enrollment of qualified physicians in a physician prescribing program that ensures that Plenaxis™ is distributed only to these enrolled physicians and that the use of Plenaxis™ is in the approved indicated population.
2. Implementation of a program to educate physicians, hospital pharmacists, patients, and distributors about the risks and benefits of Plenaxis™ and responsibilities of being part of the prescribing program.
3. Implementation of a reporting and collection system for serious adverse events associated with the use of Plenaxis™ that complies with the reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).
4. Implementation of a plan to evaluate the effectiveness of the Plenaxis™ Risk Management Program.

The Plenaxis™ Risk Management Program, as described in the attached documents, adequately addresses each of these requirements. Any change to the program must be discussed with the FDA prior to its institution and is subject to FDA approval. We expect your continued cooperation to resolve any problems regarding the Plenaxis™ Risk Management Program that may be identified following approval of your application.

Within the first year of the initiation of the Risk Management Program, and annually thereafter, you must provide the FDA with a report under 21 CFR 314.80(b)(2) that describes how each element of the program has been implemented, provides implementation data, and evaluates the success of the program using, among other available data, the studies, audits, and evaluations described in the Plenaxis™ Risk Management Program and postmarketing commitments #1, 2, 3, and 4 below.

We remind you of your specific reporting obligations regarding adverse events of patients who have received Plenaxis™. As set forth in the attached document, in addition to the usual postmarketing reporting of adverse drug experiences (21 CFR 314.80(c)), you will initiate a 15-day report for each of the following:

1. All spontaneous reports of anaphylaxis, anaphylactic reaction, anaphylactoid reaction, anaphylactic shock, angioedema of the throat, angioedema of the tongue, laryngeal obstruction,

- laryngeal angioedema, upper respiratory tract obstruction, systemic allergic reaction, immediate hypersensitivity reaction, acute bronchospasm, or wheezing.
2. All spontaneous reports of syncope, near-syncope, loss of consciousness, shock, or hypotension.
 3. All spontaneous reports involving treatment with epinephrine, parenteral antihistamine, inhaled bronchodilators, parenteral corticosteroids, intubation, tracheostomy, or cricothyroidotomy.
 4. All spontaneous reports of hospitalizations or emergency room visits for urticaria or angioedema.
 5. All spontaneous reports of death, regardless of causality.

Postmarketing Commitments

You have committed to conduct the postmarketing studies, specified in your submission dated November 21, 2003 that are listed below:

1. Conduct studies of a random sample of all enrolled prescribers as part of your risk management evaluation program to survey physician knowledge and understanding of risks and benefits of Plenaxis™ and responsibilities under the prescribing program. Praecis Pharmaceuticals Incorporated and FDA will review the study findings and agree to educational and/or other activities that may be needed to address observations.

Protocol Submission: by February 27, 2004
Study Start: by September 30, 2004
Final Report Submission: by September 30, 2008

2. Conduct a study ancillary to the 2000 patient "Plenaxis™ Experience Study" (see commitment #5) as part of the risk management evaluation program to evaluate use of Plenaxis™ by physicians in the approved, indicated population. Provide an assessment of the frequency of signed Patient Information signature pages filed in the patient's medical record, frequency of serum testosterone testing, and other physician responsibilities accepted as part of the Plenaxis™ Prescribing Program. Praecis Pharmaceuticals Incorporated and FDA will review study findings and agree to educational and/or other activities that may be needed to address observations.

Protocol Submission: by January 30, 2004
Study Start: by June 30, 2004
Final Report Submission: by September 30, 2008

3. Conduct a study involving use of Plenaxis™ through a case claims survey performed by a managed care organization. The survey will provide an assessment of whether Plenaxis™ is being used in the indicated population (e.g., review of formulary restrictions and patient information concerning age, sex, and diagnosis). Praecis Pharmaceuticals Incorporated and FDA will review study findings and agree to educational and/or other activities that may be needed to address observations.

Protocol Submission: by February 27, 2004
Study Start: by September 30, 2004
Final Report Submission: by September 30, 2008

4. Conduct a study as part of the risk management evaluation program to evaluate adherence to attested responsibilities of the prescribing program for hospital pharmacies. Praecis

Pharmaceuticals Incorporated and FDA will review study findings and agree to educational and/or other activities that may be needed to address observations.

Protocol Submission: by February 27, 2004
Study Start: by September 30, 2004
Final Report Submission: by September 30, 2008

5. Conduct a study of 2,000 patients to estimate the incidence of immediate-onset systemic allergic reactions (anaphylaxis, hypotension and/or syncope) in the indicated population receiving Plenaxis™ and to determine whether the hazard rate changes over time.

Protocol Submission: by January 30, 2004
Study Start: by June 30, 2004
Final Report Submission: by September 30, 2008

6. Conduct a clinical study to characterize Plenaxis™-induced immediate-onset system allergic reactions by evaluating skin test reactivity to Plenaxis™ and determining anti-abarelix IgG and IgE antibody levels for patients experiencing immediate-onset systemic allergic reactions.

Protocol Submission: by January 30, 2004
Study Start: by June 30, 2004
Final Report Submission: by September 30, 2008

7. Conduct a clinical study to assess the effectiveness of pre-treatment with oral antihistamine with or without oral steroids for patients who experience Plenaxis™-induced urticaria and/or pruritis within 2 hours of drug administration and continue Plenaxis™ therapy.

Protocol Submission: by January 30, 2004
Study Start: by June 30, 2004
Final Report Submission: by September 30, 2008

Submit your clinical study protocols to your IND for this product. We encourage you to submit your study protocols to the Division of Reproductive and Urologic Drug Products for review and comment prior to the initiation of your postmarketing studies. Submit nonclinical protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "Postmarketing Study Protocol", "Postmarketing Study Final Report", or "Postmarketing Study Correspondence."

The final printed labeling (FPL) must be identical to the enclosed agreed upon labeling text submitted on November 24, 2003, for the Product Information insert, the Patient Information form, and the Physician Attestation form; and identical to the immediate container and carton labels submitted on November 24, 2003. Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15

of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "FPL for approved NDA 21-320." Approval of this submission by FDA is not required before the labeling is used.

Under 21 CFR 314.550, after the initial 120 day period following approval, you must submit all promotional materials, including promotional labeling as well as advertisements, at least 30 days prior to the intended time of initial dissemination of the labeling or initial publication of the advertisement. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Reproductive and Urologic Drug Products and two copies of both the promotional materials and labeling directly to:

Division of Drug Marketing, Advertising,
and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

If you have any questions, please call Nenita Crisostomo, R.N., Regulatory Project Manager, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Florence Houn, MD MPH
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosures

Plenaxis™ RISK MANAGEMENT PROGRAM

A. Prescribing Program

1. Praecis Pharmaceuticals, Incorporated will enroll in a prescribing program physicians who meet all the following qualifications:
 - i. Ability to diagnose and manage the treatment of patients with advanced symptomatic prostate cancer
 - ii. Ability to diagnose and treat allergic reactions, including anaphylaxis
 - iii. Access to medication and equipment necessary to treat allergic reactions, including anaphylaxis
 - iv. Understanding of the risks and benefits of palliative treatment with Plenaxis™ for its approved indication, including the Package Insert, Patient Information, and Physician Attestation to Qualifications and Responsibilities

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

2. Praecis Pharmaceuticals, Incorporated will enroll in the prescribing program physicians who agree to do each of the following:

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

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

- ii. Report serious adverse events to Praecis Pharmaceuticals, Incorporated or to the Food and Drug Administration's (FDA) MedWatch Program.
- iii. Participate in a system that will identify for distributors of Plenaxis™ the physicians who are enrolled in Praecis Pharmaceuticals, Incorporated's Plenaxis™ prescribing program.

The Physician Attestation form will be used to demonstrate acceptance of these responsibilities by physicians.

3. Praecis Pharmaceuticals Incorporated will enroll in the prescribing program distributors that agree to do each of the following:

- i. Ship product only to enrolled physicians in the Plenaxis™ prescribing program listed in the Plenaxis™ Prescribers' Registry or hospital pharmacies that have accepted responsibilities and are enrolled under the Plenaxis™ prescribing program.

- ii. Permit Praecis Pharmaceuticals, Incorporated and the Food and Drug Administration to inspect records of distributors to verify compliance with the Plenaxis™ prescribing program
4. Physicians and hospital pharmacies may withdraw enrollment in the prescribing program by writing to Praecis Pharmaceuticals, Incorporated or Praecis Pharmaceuticals, Incorporated may withdraw physicians and hospital pharmacies from the prescribing program if agreed upon responsibilities are not met.
5. Praecis Pharmaceuticals, Incorporated will provide a way for distributors to identify physicians and hospital pharmacies that are enrolled in the Plenaxis™ prescribing program, and a way for hospital pharmacists to identify physicians who are enrolled in the Plenaxis™ prescribing program, that is secure and auditable.

B. Educational Program

Praecis Pharmaceuticals Incorporated will implement a program to educate physicians, distributors, hospital pharmacists, and patients about the risks and benefits of Plenaxis and responsibilities of being part of the prescribing program. Distributors and hospital pharmacists will be educated about their responsibility to verify that prescriptions were written by physicians enrolled in the prescribing program for Plenaxis™. The educational program will contain each of the following:

1. Educational opportunities will be provided to physicians to obtain prescribing qualifications and to carry out physician responsibilities under the Plenaxis™ prescribing program.
2. Distributors will be educated on the procedures for verifying that prescriptions were written by physicians and Authorized Buyers enrolled in the prescribing program for Plenaxis™.
3. Hospital pharmacists will be educated about the risks and benefits of Plenaxis™, information in the approved labeling (including the package insert and patient information), the prescribing program that enrolls qualified physicians and has hospital pharmacies verify that prescriptions were written by physicians enrolled in the prescribing program for Plenaxis™.
4. Patients will be educated on the risks associated with the use of Plenaxis™, the signs and symptoms of allergic reactions, including anaphylaxis, and Plenaxis™ approved indication.
5. Materials used for the educational program and promotion of Plenaxis™ will be submitted to the FDA for review and comment prior to use.

C. Adverse Event Reporting

Praecis Pharmaceuticals, Incorporated will implement a reporting and collection system for adverse events associated with the use of Plenaxis™ that complies with the reporting requirements for an approved NDA (21 CFR 314.80 and 314.81). Under 21 CFR 314.80(c), the following will be submitted to the FDA as 15-day reports, and a summary and discussion of the clinical significance of these events will be provided in the periodic report:

1. All spontaneous reports of anaphylaxis, anaphylactic reaction, anaphylactoid (or reaction), anaphylactic shock, angioedema of the throat, angioedema of the tongue, laryngeal obstruction,

laryngeal angioedema, upper respiratory tract obstruction, systemic allergic reaction, immediate hypersensitivity reaction, acute bronchospasm or wheezing

2. All spontaneous reports of syncope, near-syncope, loss of consciousness, shock, or hypotension
3. All spontaneous reports involving treatment with epinephrine, parenteral antihistamine, inhaled bronchodilator, parenteral corticosteroids, intubation, tracheostomy, or cricothyroidotomy
4. All spontaneous reports of hospitalizations or emergency room visits for urticaria or angioedema
5. All spontaneous reports of death, regardless of causality.

D. Risk Management Evaluation

Praecis Pharmaceuticals, Incorporated will implement a program to evaluate the effectiveness of the overall Risk Management Program in assuring Plenaxis™ is used safely. This information will allow the Agency to assess, on an ongoing basis, whether Plenaxis™ continues to be safe for use under the conditions of use upon which Plenaxis™ is being approved. The program will include each of the following elements:

1. Audits to evaluate whether physicians enrolled in the prescribing program are writing prescriptions and whether distributors and hospital pharmacists are providing Plenaxis™ or filling prescriptions to physicians not enrolled in the prescribing program.
2. Studies to evaluate whether physicians enrolled in the prescribing program are:
 - i. knowledgeable about the risks of Plenaxis™
 - ii. prescribing Plenaxis™ according to the approved indication
 - iii. comply with responsibilities agreed to in the prescribing program
3. Audits or studies to evaluate and ensure compliance with the Risk Management Program, including compliance of distributors and hospital pharmacies, that will occur quarterly.
4. Updates to FDA, including quarterly reports on the progress of the Risk Management Program, including ongoing evaluations, studies, audit information, and annual reports, submitted in accordance with 21 CFR 314.81(b)(2), beginning with the submission (within the first year of initiation of the Risk Management Program) of the annual report under that regulation, that summarizes how each element of the program has been implemented, provides implementation data, and evaluates the success of the program using, among other available data, the studies described in paragraph D1 and 2 above.

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/s/

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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-320

Approvable Letter (S)



NDA 21-320

Praecis Pharmaceuticals Inc.
Attention: JD Bernardy, J.D.
Vice President, Regulatory Affairs & Quality Assurance
830 Winter Street
Waltham, MA 02451-1420

Dear Mr. Bernardy:

Please refer to your new drug application (NDA) dated December 11, 2000, received December 12, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Plenaxis™ abarelix for injectable suspension).

We acknowledge receipt of your submissions dated December 22, 2000, January 5, March 9, 13, 14, 15, 19, 26, 27, 29, 30, April 6, 9, 10, 13, 17, 19 (3), 23, 24, 26, 27 (2), May 4, 7, 8, 10, 24, 25 (2), and 29, 2001.

We also refer to your submission dated May 22, 2001 (chemistry response). This submission has not been reviewed in the current review cycle. You may incorporate this submission by specific reference as part of your response to the deficiencies cited in this letter.

We have completed our review and find the information presented is inadequate, and the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies may be summarized as follows:

Clinical:

1. Sufficient information to support the safety of abarelix for use in the proposed population was not provided in the current application.
2. Abarelix is intended for chronic use and the data contained in the current application have not demonstrated sustained efficacy as assessed by serum testosterone levels. Moreover, in Study 149-99-03, abarelix was marginally inferior to Lupron Depot® in the percentage of patients who achieved and maintained castration from Day 29 through Day 85. This is worrisome given that more patients in this study were randomized to abarelix than in Studies 149-98-02 and 149-98-03 combined.

To address the above deficiencies, the following is required:

1. Conduct investigations to better clarify the nature of the severe systemic allergic reactions (e.g., reactions resulting in hypotension or syncope) that were reported in at least 0.4% of the population treated with abarelix. The ultimate objectives of these investigations should be either to decrease the actual incidence of systemic allergic reactions or to mitigate their consequences.

2. Provide additional data that demonstrate sustained efficacy of abarelix, and that demonstrate abarelix is not inferior to Lupron Depot® in the percentage of patients who achieve and maintain castration from Day 29 and beyond.
3. Propose a postmarketing risk management plan for abarelix that includes specific goals and methods to evaluate whether these goals are being met. This risk management plan should be developed after further data regarding the allergic reactions and lack of sustained efficacy over time have been obtained. This plan could include proposed labeling, physician and/or patient education, distribution options, or any additional proposals that would improve the risk-benefit profile of abarelix.

Chemistry:

Address the following deficiencies:

1. Justify _____
2. Justify why _____
3. Propose a specific optical rotation specification _____
4. Justify the wide range specification of carboxymethylcellulose (CMC) content in the abarelix CMC. It is recommended that the limits of specifications of the CMC content should be mean value of the batches \pm two standard deviations.
5. Provide justification for _____ coverage of abarelix _____ in the drug product.
6. The proposed _____ of expiration date of the drug product is not acceptable. Based on the available submitted data, an 18-month expiry can be granted.

Microbiology:

Address the following deficiencies:

Regarding components and in-process sterilization:

- a. Provide the _____ cited in the May 25, 2001, submission (microbiology response), page 1. Also, provide the _____
- b. DMF _____ is deficient and cannot support NDA approval at this time.
- c. DMF _____ is deficient and cannot support NDA approval at this time.

Facilities:

During recent inspections of the manufacturing facilities for your NDA, a number of deficiencies were noted and conveyed to you or your suppliers by the inspector. Satisfactory inspections will be required before this application may be approved.

Under 21 CFR 314.50(d)(5)(vi)(b), we request that you update your NDA by submitting all safety information you now have regarding your new drug. The safety update should include data from all nonclinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
 - Present tabulations of the new safety data combined with the original NDA data.
 - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
 - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
7. Provide English translations of current approved foreign labeling not previously submitted.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal meeting or telephone conference with the Division of Reproductive and Urologic Drug Products to discuss what further steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call Jeanine Best, M.S.N., R.N., Regulatory Project Manager, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Victor Raczkowski, M.D., M.Sc.
Deputy Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Victor Raczkowski
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