CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-320

Approved Labeling

Physician Package Insert

Plenaxis™
(abarelix for injectable suspension)

WARNING

Immediate-onset systemic allergic reactions, some resulting in hypotension and syncope, have occurred after administration of Plenaxis™. These immediate-onset reactions have been reported to occur following any administration of Plenaxis™, including after the initial dose. The cumulative risk of such a reaction increases with the duration of treatment (see WARNINGS). Following each injection of Plenaxis™, patients should be observed for at least 30 minutes in the office and in the event of an allergic reaction, managed appropriately.

- **Only physicians who have enrolled in the Plenaxis™ PLUS Program (Plenaxis™ User Safety Program), based on their attestation of qualifications and acceptance of prescribing responsibilities, may prescribe Plenaxis™ (See DOSAGE AND ADMINISTRATION and HOW SUPPLIED).**
- **Plenaxis™ is indicated for the palliative treatment of men with advanced symptomatic prostate cancer, in whom LHRH agonist therapy is not appropriate and who refuse surgical castration, and have one or more of the following: (1) risk of neurological compromise due to metastases, (2) ureteral or bladder outlet obstruction due to local encroachment or metastatic disease, or (3) severe bone pain from skeletal metastases persisting on narcotic analgesia.**
- **The effectiveness of Plenaxis™ in suppressing serum testosterone to castrate levels decreases with continued dosing in some patients (see CLINICAL PHARMACOLOGY, Pharmacodynamics). Effectiveness beyond 12 months has not been established. Treatment failure can be detected by measuring serum total testosterone concentrations just prior to administration on Day 29 and every 8 weeks thereafter (see WARNINGS).**

DESCRIPTION

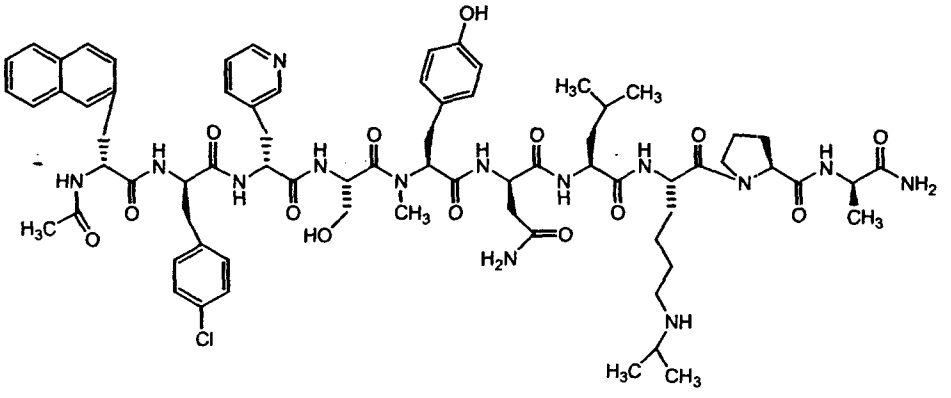
Abarelix for injectable suspension (Plenaxis™) is a synthetic decapeptide with potent antagonistic activity against naturally occurring gonadotropin releasing-hormone (GnRH).

Plenaxis™ inhibits gonadotropin and related androgen production by directly and competitively blocking GnRH receptors in the pituitary.

Abarelix is chemically described as acetyl-D-β-naphthylalanyl-D-4-chlorophenylalanyl-D-3-pyridylalanyl-L-seryl-L-N-methyl-tyrosyl-D-asparagyl-L-leucyl-L-N(ε)-isopropyl-

lysyl-L-prolyl-D-alanyl-amide. It is initially manufactured as an acetate water complex and converted to a carboxymethylcellulose (CMC) water complex in manufacturing the drug product. The molecular weight for abarelix anhydrous free base is 1416.06.

The structural formula for abarelix peptide is:



Abarelix for injectable suspension is supplied as a white to off-white sterile dry powder which, when mixed with the diluent, 0.9% Sodium Chloride Injection, USP, becomes a depot suspension intended for intramuscular (IM) injection.

The single-dose vial contains 113 mg of anhydrous free base abarelix peptide (net) supplied in an abarelix CMC complex. This complex also contains 19.1 to 31 mg of CMC. After the vial is reconstituted with 2.2 mL of 0.9% sodium chloride injection, 2 mL is administered to deliver a dose of 100 mg of abarelix (net) as the abarelix CMC complex at a pH of 5±1.

CLINICAL PHARMACOLOGY

Mechanism of Action

Abarelix exerts its pharmacological action by directly suppressing luteinizing hormone (LH) and follicle stimulating hormone (FSH) secretion and thereby reducing the secretion of testosterone by the testes. Due to the direct inhibition of the secretion of LH by abarelix, there is no initial increase in serum testosterone concentrations.

Saturation binding studies revealed that [^{125}I]-abarelix has a very high affinity (K_D = 0.1 nM) for the rat pituitary LHRH receptor.

PHARMACOKINETICS

A single dose (100 mg IM) of Plenaxis™ was given to 14 healthy male volunteers 52 to 75 years of age, with body weight of 61.6 to 110.5 kg, and the pharmacokinetic information is provided in Table 1:

Table 1. Mean ± SD Pharmacokinetic Parameter Values of 100 mg of Plenaxis™ Following a Single IM Injection (n = 14)

C_{max} (ng/mL)	T_{max} (days)	$AUC_{0-\infty}$ (ng • day/mL)	CL/F (L/day)	$t_{1/2}$ (days)
43.4 ± 32.3	3.0 ± 2.9	500 ± 96	208 ± 48	13.2 ± 3.2

Absorption

Following IM administration of 100 mg of Plenaxis™, abarelix is absorbed slowly with a mean peak concentration of 43.4 ng/mL observed approximately 3 days after the injection.

Distribution

The apparent volume of distribution during the terminal phase determined after IM administration of Plenaxis™ was 4040 ± 1607 liters, implying that abarelix probably distributes extensively within the body.

Metabolism

In vitro hepatocyte (rat, monkey, human) studies and *in vivo* studies in rats and monkeys showed that the major metabolites of abarelix were formed via hydrolysis of peptide bonds. No significant oxidative or conjugated metabolites of abarelix were found either *in vitro* or *in vivo*. There is no evidence of cytochrome P-450 involvement in the metabolism of abarelix.

Excretion

In humans, approximately 13% of unchanged abarelix was recovered in urine after a 15 µg/kg IM injection; there were no detectable metabolites in urine. Renal clearance of abarelix was 14.4 L/day (or 10 mL/min) after administration of 100 mg Plenaxis™.

Pharmacodynamics:

Effects of Plenaxis™ on Serum Testosterone: The effectiveness of Plenaxis™ in suppressing serum testosterone was studied in two randomized, open-label, active-comparator trials. Patients were not those with advanced symptomatic prostate cancer. They were randomized in a 2:1 ratio to Plenaxis™ 100 mg IM versus LHRH agonist (Study 1) or to Plenaxis™ versus LHRH agonist + nonsteroidal antiandrogen (Study 2). Plenaxis™ was administered IM on Days 1, 15, 29 (Week 4), then every 4 weeks

thereafter for at least 6 months (24 weeks). LHRH agonist and nonsteroidal antiandrogen were administered in standard fashion. After completing 6 months of treatment, patients could continue randomized treatment for an additional 6 months.

Avoidance of testosterone surge: In both studies combined, 100% (348/348) of Plenaxis™ patients and 16% (28/172) of comparator patients avoided a testosterone surge.

Attainment of medical castration: The percentage of patients who attained serum testosterone concentration ≤50 ng/dL on Study Days 2, 8, 15 and 29 are summarized in the table below:

Table 2. Percentage of patients who attained medical castration (serum testosterone concentration ≤50 ng/dL) in Studies 1 and 2.

	Plenaxis™	
Day	Total N	% Castrate
2	339	24
4	333	56
8	348	70
15	347	73
29	347	94

Attainment and maintenance of medical castration: Successful response ~~was~~ defined as attainment of medical castration on Day 29 and maintenance through Day 85 (where no **two** consecutive serum testosterone concentrations between Days 29 and 85 were greater than 50 ng/dL). In Study 1, 92% on Plenaxis™ patients responded and 96% of LHRH agonist patients responded. In Study 2, 93% of Plenaxis™ patients and 95% of LHRH agonist + nonsteroidal antiandrogen patients responded.

However, when failure was defined as any observed serum testosterone > 50 ng/dL (including transient elevations) just prior to dosing on Day 29 and every 28 days thereafter, effectiveness of testosterone suppression decreased over time. Results of this analysis are summarized in Table 3.

Table 3. Percentage of patients who attained and maintained medical castration; [no serum testosterone >50 ng/dL just prior to dosing on Day 29 and every 28 days thereafter]

	Study 1	N		Study 2	N
Day	Plenaxis™			Plenaxis™	
85	84%	176		92%	164
169	75%	166		87%	155
365	62%	93		71%	86

Effects of Plenaxis™ on Cardiac Electrophysiology: In a single, active-controlled, clinical study comparing Plenaxis™ to LHRH agonist + nonsteroidal antiandrogen, periodic electrocardiograms were performed. Both therapies prolonged the mean Fridericia-corrected QT interval by >10 msec from baseline. In approximately 20% of patients in both groups, there were either changes from baseline QTc of >30 msec, or

end-of-treatment QTc values exceeding 450 msec. Similar results were observed in 2 other Phase 3 studies with Plenaxis™ and the active-control treatments. It is unclear whether these changes were directly related to study drugs, to androgen deprivation therapy, or to other variables.

Special Populations

Race

Data from Hispanics, Blacks and Caucasians demonstrated that race appeared to have no influence on the pharmacokinetics of Plenaxis™.

Renal and Hepatic Insufficiency

The pharmacokinetics of Plenaxis™ in hepatically and/or renally impaired patients have not been determined.

Pediatric Use

There have been no studies of Plenaxis™ in pediatric patients.

CLINICAL STUDIES

One study of Plenaxis™ was conducted in 81 men with advanced symptomatic prostate cancer who were at risk for clinical exacerbation ("clinical flare") if treated with an LHRH agonist. The objective of this open-label, multicenter, uncontrolled, single-arm study was to demonstrate that such patients could avoid orchiectomy through at least

12 weeks of treatment. In this trial, treatment was to be given for at least 6 months with the option to continue treatment in an extension trial.

Of the 81 patients who enrolled, 9 patients from one site were excluded from the efficacy analysis due to inadequate documentation by the study investigator. The specific reasons given for enrollment of the 72 patients were: bone pain from prostate cancer skeletal metastases (n = 31); an enlarged prostate gland or pelvic mass causing bladder neck outlet obstruction (n = 25); bilateral retroperitoneal adenopathy with ureteral obstruction (n = 9); impending neurological compromise from spinal, spinal cord, or epidural metastases (n = 6); or other (n = 1). The median age was 73 years, range 40 to 94 years. There were 62 Caucasians, 6 African Americans and 4 Hispanics.

Plenaxis™ 100 mg was administered via IM injection on Days 1, 15 and 29, then every 4 weeks thereafter. Twelve patients discontinued prior to Day 169 for the following reasons: adverse event (n=2), voluntary withdrawal (n=3), death (n=4), and "other" (n=3). Sixty patients were treated for at least 24 weeks; in the extension phase, 33 patients for at least 48 weeks and 15 patients for at least 96 weeks. None (0%) of the 72 patients required orchiectomy while being treated with Plenaxis™, including the extension phase (median combined duration of therapy was 40 weeks). However, 2 patients were withdrawn before week 12 for treatment-related adverse events (immediate-onset systemic allergic reactions consisting of urticaria, and urticaria and pruritis, respectively) and received alternate therapy. In this trial, medical castration (defined as serum total testosterone concentration $\leq$50 ng/dL) was achieved in 57 of the 72 patients (79%) by Day 8, and by 68 of 71 patients (96%) by Week 4.

Although the study was not designed to assess specific clinical outcomes, the following were observed:

- None (0) of 8 patients with vertebral or epidural metastases and without neurological symptoms developed neurological symptoms.
- Ten of 13 patients with bladder outlet obstruction and a bladder drainage catheter had the catheter removed by 12 weeks.
- Eleven of 15 patients with pain due to skeletal metastases were able to reduce the potency, dose and/or frequency of narcotic analgesia at 12 weeks.

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

Plenaxis™ is contraindicated in those patients with a known hypersensitivity to any of the components in abarelix for injectable suspension.

Plenaxis™ is not indicated in women or pediatric patients. In addition, Plenaxis™ may cause fetal harm if administered to a pregnant woman.

WARNINGS

Immediate-Onset Systemic Allergic Reactions (See Boxed Warnings)

In the clinical trial of patients with advanced, symptomatic prostate cancer, 3 of 81 (3.7%) patients experienced an immediate-onset systemic allergic reaction within minutes of receiving Plenaxis™. The allergic reactions were urticaria (Day 15), urticaria and pruritis (Day 29), and hypotension and syncope (Day 141). Patients should be monitored for at least 30 minutes after each injection of Plenaxis™. In the event of an allergic reaction associated with hypotension and/or syncope, appropriate supportive measures such as leg elevation, oxygen, IV fluids, antihistamines, corticosteroids, and epinephrine (alone or in combination) should be employed.

From all the prostate cancer clinical trials with Plenaxis™ (mostly in men without advanced, symptomatic disease), immediate-onset systemic allergic reactions (occurring within 30 minutes of dosing), were observed in 1.1% (15/1397) of patients dosed with Plenaxis™. In 14/15 patients who experienced an allergic reaction, each developed symptoms within 8 minutes of injection. The cumulative risk of such a reaction increased with duration of treatment. The cumulative rates (and 95% confidence intervals) on Days 56, 141, 365 and 676 were 0.51%, (0.13%, 0.88%) 0.80% (0.30%, 1.29%), 1.24% (0.43%, 2.04%) and 2.91% (0.87, 4.95%), respectively. Seven patients experienced hypotension or syncope as part of their allergic reaction, representing 0.5% of all patients. The cumulative rates (and 95% confidence intervals) for these types of reactions on Days 56, 141, 365, and 617 after the initial dose were 0.22% (0.0%, 0.46%), 0.32% (0.0%, 0.64%), 0.61% (0.0%, 1.24%) and 1.67% (0.07, 3.28%), respectively.

Decrease in Effectiveness With Continued Dosing

A decrease in overall effectiveness with increased duration of treatment, as measured by failure to maintain suppression of serum testosterone below 50 ng/dL, was noted (**see Clinical Pharmacology, Pharmacodynamics**). Treatment failure can be detected by measuring serum total testosterone concentrations just prior to administration on Day 29 after the initial dose and every 8 weeks thereafter.

Prolongation of the QT Interval

Because Plenaxis™ may prolong the QT interval (**see Clinical Pharmacology, Pharmacodynamics**), physicians should carefully consider whether the risks of Plenaxis™ outweigh the benefits in patients with baseline QTc values >450 msec (e.g. congenital QT prolongation) and in patients taking Class IA (e.g. quinidine, procainamide) or Class III (e.g. amiodarone, sotalol) antiarrhythmic medications.

PRECAUTIONS

General

Decreased effectiveness in patients >225 pounds: The decrease in overall effectiveness of Plenaxis™ with increased duration of treatment is greater in patients who weigh more than 225 pounds. Strict monitoring of serum testosterone in these patients is warranted.

Monitoring of liver function: Clinically meaningful transaminase elevations were observed in some patients who received Plenaxis™ or comparator drugs. Serum transaminase levels should be obtained before starting treatment with Plenaxis™ and periodically during treatment (**see Adverse Reactions**).

Decrease in bone mineral density: Extended treatment with GnRH antagonists and LHRH agonists may result in a decrease in bone mineral density.

Drug Interactions

No formal drug/drug interaction studies with Plenaxis™ were performed. Cytochrome P-450 is not known to be involved in the metabolism of Plenaxis™. Plenaxis™ is highly bound to plasma proteins (96 to 99%).

Laboratory Tests

Response to Plenaxis™ should be monitored by measuring serum total testosterone concentrations just prior to administration on Day 29 and every 8 weeks thereafter (**see WARNINGS**). Serum transaminase levels should be obtained before starting treatment with Plenaxis™ and periodically during treatment. Periodic measurement of serum PSA levels may also be considered.

Geriatric Use

Prostate cancer occurs primarily in an older patient population. Clinical studies with Plenaxis™ have been conducted primarily in patients ≥ 65 years of age. No difference in the safety profile, when examined as a function of age, was apparent.

Pediatric Use

The safety and effectiveness of Plenaxis™ in pediatric patients have not been studied. Plenaxis™ is not indicated for use in pediatric patients.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Plenaxis™ was not carcinogenic to mice or rats when administered as a subcutaneous depot every 28 days for 2 years at doses up to 300 mg/kg in mice and 100 mg/kg in rats. Systemic drug exposures, as measured by mean C_{max}, were approximately 210-278-fold for mice and 21-32-fold for rats the human exposure following subcutaneous depot administration of 100 mg.

Plenaxis™ was not mutagenic in the *in vitro* bacterial Ames assay or forward mutation assay in mouse lymphoma, or clastogenic in the *in vivo* mouse micronucleus assay.

No effects on mating or fertility in male and female rats given 1 mg/kg subcutaneous Plenaxis™, a dose 0.114-fold the human therapeutic dose of 100 mg based on body surface area. Mating and fertility were significantly decreased at doses of 3 and 10 mg/kg (0.34-fold and 1.135-fold, respectively, the human therapeutic dose of 100 mg based on body surface area), but the effects were reversible.

Pregnancy Category X

(see **CONTRAINDICATIONS**)

Embryolethality occurred in pregnant rats administered a single subcutaneous dose of Plenaxis™ up to 3 mg/kg (0.228-fold the human therapeutic dose of 100 mg based on body surface area). In rabbits a dose-related increase in fetal resorptions and reduced viability was observed at doses up to 30 mg/kg (6.81-fold the human therapeutic dose of 100 mg based on body surface area). No teratogenic effects were observed in rats or rabbits up to doses of 3 mg/kg or 30 mg/kg, respectively. A no-observable-adverse-

effect-level (NOAEL) dose was 0.3 mg/kg (approximately 0.034-fold the human therapeutic dose of 100 mg based on body surface area) in rats and <0.01 mg/kg (<0.0023-fold the human therapeutic dose of 100 mg based on body surface area) in rabbits.

Nursing Mothers

It is not known whether Plenaxis™ is excreted in human milk. Because many drugs are excreted in human milk, and because the effects of Plenaxis™ on lactation and/or the breastfed child have not been determined, Plenaxis™ should not be used by nursing mothers.

ADVERSE REACTIONS

Immediate-Onset Systemic Allergic Reactions: See BOXED WARNINGS and WARNINGS

In the single study of Plenaxis™ conducted in men with advanced symptomatic prostate cancer, adverse events reported by ≥10% of patients are listed in Table 4. Adverse events are listed without regard to causality. Causality is often difficult to assess in elderly patients with multiple co-morbidities and prostate cancer.

Table 4. Adverse Events in ≥10% of Patients in the Advanced Symptomatic Prostate Cancer Study (without regard for causality).

Preferred Term	Plenaxis™ N=81 n (%)
Hot flushes*	64 (79)
Sleep disturbance*	36 (44)
Pain	25 (31)
Breast enlargement*	24 (30)
Breast pain/nipple tenderness*	16 (20)
Back pain	14 (17)
Constipation	12 (15)
Peripheral edema	12 (15)
Dizziness	10 (12)
Headache	10 (12)
Upper respiratory tract infection	10 (12)
Diarrhea	9 (11)
Dysuria	8 (10)
Fatigue	8 (10)
Micturition frequency	8 (10)
Nausea	8 (10)
Urinary retention	8 (10)
Urinary tract infection	8 (10)

* Pharmacological consequence of androgen deprivation

Changes in Laboratory Values

Clinically meaningful increases in serum transaminases were seen in a small percentage of patients in both treatment groups in each active-controlled Plenaxis™ study. In Study 1 and Study 2 combined, the percentage of Plenaxis™ patients reporting serum ALT >2.5 times upper limit of normal or >200 U./L was 8.2% and 1.8%, respectively. The percentage reporting serum AST >2.5 times upper limit of normal or >200 U/L was 3.1% and 0.8%, respectively. Similar results were reported for active comparators.

Slight decrease in hemoglobin, a pharmacological consequence of castration, were observed in patients receiving Plenaxis™ and active comparator. Mean increases in serum triglycerides of approximately 10% were seen in Plenaxis™-treated patients.

OVERDOSAGE

The maximum tolerated dose of Plenaxis™ has not been determined. The maximum dose used in clinical studies was 150 mg. There have been no reports of accidental overdose with Plenaxis™.

DOSAGE AND ADMINISTRATION

For safety reasons, Plenaxis™ is approved with marketing restrictions. Only physicians who attest to the following qualifications and accept the following responsibilities, and on that basis enroll in PRAECIS PHARMACEUTICALS INCORPORATED's Plenaxis™ **PLUS** Program should prescribe Plenaxis™. PRAECIS PHARMACEUTICALS INCORPORATED and its agents will provide Plenaxis™ to physicians enrolled in the Plenaxis™ **PLUS** Program.

To enroll, physicians must attest that they are able and willing to:

- diagnose and manage advanced symptomatic prostate cancer.
- diagnose and treat allergic reactions, including anaphylaxis.
- have access to medication and equipment necessary to treat allergic reactions, including anaphylaxis.
- have patients observed for development of allergic reactions for 30 minutes following each administration of Plenaxis™.
- understand the risks and benefits of palliative treatment with Plenaxis™, including information from the Package Insert, Patient Information, and the Physician Attestation.
- educate the patients on the risks and benefits of treatment with Plenaxis™ and obtain the patient's signature on the Patient Information signature page, sign it, and 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.
- report serious adverse events, such as any immediate-onset systemic allergic event (including anaphylaxis, hypotension, and syncope) as soon as possible to PRAECIS PHARMACEUTICALS INCORPORATED at 1-866-PLENAXIS (1-866-753-6294) or to the Food and Drug Administration's MedWatch Program at 1-800-FDA-1088.

- understand that they may withdraw their enrollment in the Plenaxis™ Prescribing Program by a written statement submitted to PRAECIS PHARMACEUTICALS INCORPORATED (contact information below) or that PRAECIS PHARMACEUTICALS INCORPORATED may withdraw physicians from the Plenaxis™ **PLUS** Program if they do not meet the agreed upon responsibilities.

To enroll in the Plenaxis™ Prescribing Program call 1-866-PLENAXIS (1-866-753-6294) or visit www.plenaxisplus.com.

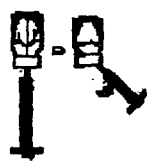
Dose: The recommended dose of Plenaxis™ is 100 mg administered intramuscularly to the buttock on Day 1, 15, 29 (week 4) and every 4 weeks thereafter. Treatment failure can be detected by measuring serum testosterone concentrations just prior to Plenaxis™ administration, beginning on Day 29 and every 8 weeks thereafter.

Directions for Reconstituting and Administering Plenaxis™

Read the instructions completely before performing reconstitution.

The sterile powder for suspension is to be reconstituted in accordance with the following directions:

Reconstitution Instructions for 1 Vial of Plenaxis™ to Provide a 100 mg (50 mg/mL) Dose as a Single IM Injection

1	Use aseptic technique throughout. Prior to reconstitution, gently shake the vial of Plenaxis™ (abarelix for injectable suspension). Hold the vial at an angle (45 degrees) and tap lightly on table to break up any caking. Withdraw 2.2 mL of 0.9% Sodium Chloride Inj., USP using the enclosed 18 G x 1 ½" needle and a 3 cc syringe. Discard the remaining diluent. **(Picture 1)**
2	Keeping the vial **upright**, insert the needle all the way into the vial and inject the diluent **quickly**. Before withdrawing the needle, remove **2.2** mL of air. Shake immediately. **(Picture 2)**
3	**Shake** for approximately 15 seconds. Allow the vial to stand for approximately 2 minutes. Tap the vial to **reduce foaming** and swirl the vial occasionally. Again, **shake** for approximately 15 seconds. Allow the vial to stand for approximately 2 minutes. Tap the vial to **reduce foaming** and swirl the vial occasionally. **(Picture 3)**
4 	**Do not reinject the air into the vial**. Locate **a second injection spot** on the stopper, and then insert the 18 G needle. Invert the vial and draw up some of the suspension into the syringe and **without removing the needle from the vial reinject it at any remaining solids in the vial. Repeat the process until all solids are dispersed**. Swirl the vial before withdrawal and withdraw **the entire contents (at least 2 mL)** by positioning the needle at a 45 degree angle as shown in the picture. **(Picture 4)**

5	Pull the plunger back to recover the residual suspension in the 18 G x1½" needle. Exchange the 18 G x 1 ½" needle with the enclosed 22 G x 1½" Safety Glide™ injection needle. **(Picture 5)**
6	Insert the needle at the desired injection site, pull the plunger back to check for back-flow of blood. If blood flows into the syringe, do not inject at this site. Select another injection site. Deliver the entire reconstituted suspension intramuscularly **immediately**. **(Picture 6)** **Observe the patient after injection for 30 minutes for any sign of an allergic-type response.**

Plenaxis™ does not contain a preservative and should be administered within 1 hour following reconstitution.

STORAGE

Store at 25°C (77°F), excursions permitted to 15-30°C (59-86°F), USP Controlled Room Temperature.

HOW SUPPLIED

The physician must attest to meeting the qualifications and accepting the responsibilities in the **DOSAGE AND ADMINISTRATION** section of this package insert by submitting the Physician's Attestation form to PRAECIS PHARMACEUTICALS INCORPORATED to be enrolled in the Plenaxis™ **PLUS** Program. PRAECIS PHARMACEUTICALS INCORPORATED and its agents will only provide Plenaxis™

to physicians enrolled in the Plenaxis™ Prescribing Program. Plenaxis™ vials are not to be resold or redistributed.

Plenaxis™ (abarelix for injectable suspension) is supplied as a single-dose, preservative-free vial containing 113 mg of abarelix (anhydrous free base peptide) as an abarelix CMC complex, a sterile powder (NDC 68158-149-01) which, when reconstituted with 2.2 mL of 0.9% sodium chloride solution, yields a 2 mL delivered dose of 100 mg (50 mg/mL). Each single use dispensing pack also contains: a single-use 10 mL diluent vial of 0.9% Sodium Chloride Injection, USP, one 3 cc syringe with an 18 gauge 1½ inch needle and one 22 gauge 1½ inch Safety Glide™ injection needle.

PRAECIS

PRAECIS PHARMACEUTICALS INCORPORATED
830 Winter Street
Waltham, MA 02451-1420
1-877-PRAECIS (1-877-772-3247)

02-01
Issue Date

Patient Information

Patient Information
Plenaxis™
(plen·AK·sis)
(abarelix for injectable suspension)

Read the Patient Information that comes with Plenaxis™ before you start getting injections. Sign the last page if you agree with treatment with Plenaxis™. (Your signature will be required to start treatment.)

What is the most important information I should know about Plenaxis™?

- **Plenaxis™ can cause serious or life threatening allergic reactions that may need emergency medical treatment right away.** These serious reactions may include:
  - low blood pressure and fainting (shock)
  - swelling of your face, eyelids, tongue, or throat
  - asthma, wheezing, or other breathing problems such as chest tightness or shortness of breath

Your chances of getting a serious or life threatening allergic reaction may increase with each Plenaxis™ injection that you get.

If a serious or life threatening allergic reaction happens, it is usually soon after getting a Plenaxis™ injection. **Therefore, you must wait in your doctor's office or health care facility for 30 minutes after each Plenaxis™ injection.** Tell your doctor right away if you feel any warmth, redness, light-headedness, swelling or thickness in your throat. This could mean you are having a serious allergic reaction.

- **Only doctors signed up with PRAECIS PHARMACEUTICALS INCORPORATED can prescribe Plenaxis™ because they know about treating prostate cancer and allergic reactions from Plenaxis™.**

- **Plenaxis™ is only for treating advanced prostate cancer when a patient cannot have or refuses other treatments for prostate cancer, such as other hormone treatments or surgery to remove the testicles, and there are serious symptoms from the prostate cancer such as the cancer is near or pressing on the spinal cord, causing problems urinating or blockage of urine from the kidneys or bladder, or there is very bad bone pain even when taking narcotic pain medicines.**

- **Plenaxis™ may not keep working for everyone over time, so doctors should do blood tests about every 8 weeks to make sure Plenaxis™ is working by keeping your testosterone hormone level low.**

What is Plenaxis™?
Plenaxis™ is a type of medicine called a gonadotropin-releasing hormone (GnRH) antagonist that lowers the male hormone testosterone in your blood. Testosterone makes most prostate cancers grow. Other ways to treat your prostate cancer are taking other hormone medicines to lower testosterone or surgery to remove your testicles. Plenaxis™ is used when these other ways to treat prostate cancer cannot be used or are refused.

Who should not take Plenaxis™?

Do not take Plenaxis™ if you are:

- **a woman.** There is no approved use of Plenaxis™ in women. Plenaxis™ can cause serious allergic reactions. Plenaxis™ can cause the death of an unborn child in a pregnant woman. Plenaxis™ may also pass into breast milk.
- **a child under the age of 18 years.** There are no studies that show that Plenaxis™ is safe or effective for use in children for any condition.
- **allergic to any of the ingredients in Plenaxis™.** The ingredients include abarelix and carboxymethylcellulose. The mixing solution contains sodium chloride.

Tell your doctor before taking a Plenaxis™ injection:

- if you or any family members have a rare heart condition known as prolongation of the QTc interval

- about all the medicines you take including prescription and nonprescription medicines, vitamins and herbal supplements. Plenaxis™ has not been studied with other medicines. Plenaxis™ and some of your other medicines may affect each other and could cause side effects.

How do I take Plenaxis™?

Plenaxis™ is only prescribed by doctors who are part of the Plenaxis™ **PLUS** Program (Plenaxis™ User Safety Program) run by PRAECIS PHARMACEUTICALS INCORPORATED.

- Plenaxis™ is given as an injection in your buttocks. Your doctor or nurse gives a Plenaxis™ injection every two weeks for the first month, and then every four weeks (every 28 days). It is important that you keep your appointment with your doctor's office for the times when your injection is due.

Always wait in your doctor's office for **30 minutes** after getting each Plenaxis™ injection. (See "What is the most important information I should know about Plenaxis™?")

Your doctor should do regular blood tests about every 8 weeks to check your testosterone level to see if Plenaxis™ is working for you. If you weigh more than 225 pounds, there

may be a greater chance that Plenaxis™ may stop working. Your doctor should also do blood tests to check on your liver because Plenaxis™ may cause changes in your liver tests.

What are the possible side effects of Plenaxis™?

Plenaxis™ can cause:

- **serious allergic or life threatening reactions.** (See "What is the most important information I should know about Plenaxis™?")

- **allergic skin reactions** such as a rash, hives, itching, tingling, and redness (flushing). A skin reaction may happen right away after injection with Plenaxis™ or several days later. Tell your doctor right away if you get an allergic skin reaction or rash after a Plenaxis™ injection.

- **a change in heart rhythm called prolongation of the QTc interval.** This condition may change the way your heart beats, cause fainting and even death in some patients.

- **changes in liver function, which usually go away after you stop taking Plenaxis™.** Your doctor should do blood tests to check your liver function before you start getting Plenaxis™ and during your treatment with it.

- **loss in bone mineral density with extended treatment.** Low bone mineral density can lead to thinning of the bones (osteoporosis).

The most common side effects of Plenaxis™ are:

- hot flashes
- problems sleeping
- pain, including back pain
- breast enlargement or breast pain
- constipation

Talk to your doctor if you get a side effect that bothers you.

These are not all the possible side effects of Plenaxis™. For more information ask your doctor.

General Information about Plenaxis™

This leaflet summarizes the most important information about Plenaxis™. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider for information about Plenaxis™ that is written for health professionals.

Patient Signature for Treatment with Plenaxis™

- I have read and understood the Patient Information leaflet. My doctor has answered my questions about treatment with Plenaxis™ for treating advanced prostate cancer.

- I cannot have or refuse treatments for my prostate cancer, such as other hormone treatments or surgery to remove my testicles, and my doctor has told me I have serious signs and/or symptoms from my prostate cancer such as the cancer is near or pressing on the spinal cord, or it is causing problems urinating or blockage of urine from the kidneys or bladder, or I have very bad bone pain even when taking narcotic pain medicines.

- Plenaxis™ can cause serious allergic reactions right after an injection. Therefore, after each injection I will wait in my doctor's office or health care facility for 30 minutes so if I have a serious allergic reaction, I can be treated.

- I know that my doctor should be getting blood tests to check my testosterone level about every 8 weeks to check if Plenaxis™ is working for me.

- I understand that I can only get Plenaxis™ from doctors who have signed up with the company that makes Plenaxis™.

My signature shows that I have read, understood and agree with **all** the statements above. I allow my doctor to begin treatment with Plenaxis™. I only need to sign this page one time to start my treatment.

Name of Patient (Print):_____

Signature of Patient:_____Date:_____

Name of Physician (Print):_____

Signature of Physician _____Date:_____

Instructions to Physician:

As part of beginning Plenaxis™ treatment, give the patient a copy of the entire leaflet with the signed page, and put the original patient signature page in the patient's medical chart.

This information leaflet has been approved by the U.S. Food and Drug Administration.

PRAECIS PHARMACEUTICALS INCORPORATED
830 Winter Street
Waltham, MA 02451-1420
Date of most recent revision: 03-01

Physician Attestation

PHYSICIAN ATTESTATION of QUALIFICATIONS and ACCEPTANCE of PRESCRIBING RESPONSIBILITIES

Plenaxis™ PLUS Program

I wish to participate in the Plenaxis™ **PLUS** Program (Plenaxis™ User Safety Program) and by my signature below, attest that I have the qualifications and accept the responsibilities described below.

RISKS AND BENEFITS OF Plenaxis™ *AND APPROPRIATE USE*

- I understand that for safety reasons Plenaxis™ (abarelix) is approved with marketing restrictions of which the **PLUS** Program for Plenaxis™ is a required element. I will not distribute Plenaxis™ to other physicians or facilities. By my signature below, I attest that I have the qualifications and accept the prescribing responsibilities described in this document.
- I understand that because of the risk of immediate-onset systemic allergic reaction, including hypotension and/or syncope, and because of the risk of loss of effectiveness over time, Plenaxis™ is only indicated for the palliative treatment of men with advanced symptomatic prostate cancer, in whom LHRH agonist therapy is not appropriate and who refuse surgical castration, and have one or more of the following: (1) risk of neurological compromise due to metastases, (2) ureteral or bladder outlet obstruction due to local encroachment or metastatic disease, or (3) severe bone pain from skeletal metastases persisting on narcotic analgesia.
- I understand that the effectiveness of Plenaxis™ in suppressing serum testosterone to castrate levels decreases with continued dosing in some patients, and effectiveness beyond 12 months has not been established. Treatment failure can be detected by measuring serum testosterone concentrations just prior to administration on Day 29 and every 8 weeks thereafter.
- I understand that Plenaxis™ is not indicated in women or children.

QUALIFICATION OF PRESCRIBING PHYSICIANS

- I can diagnose and manage advanced symptomatic prostate cancer.
- I can diagnose and treat allergic reactions, including anaphylaxis.
- I have access to medication and equipment necessary to treat these reactions, including anaphylaxis.
- I have reviewed the complete Package Insert for Plenaxis™ and I am thoroughly familiar with the important information in the Boxed Warning, Indication and Usage, Contraindications, Warnings, Precautions, Adverse Reactions, Dosage and Administration, and Patient Information sections.

RESPONSIBILITIES OF PRESCRIBING PHYSICIANS

- I will have patients observed for development of allergic reactions for 30 minutes following each administration of Plenaxis™.
- I understand the risks and benefits of palliative treatment with Plenaxis™, including information from the Package Insert, Patient Information, and this Attestation.
- I will educate the patients I am considering for treatment with Plenaxis™ on the risks and benefits of treatment with Plenaxis™, obtain the patient's signature on the Patient Information leaflet's signature page, sign the form myself, 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.

- I will give any patient who is considering treatment with Plenaxis™ a copy of the Patient Information leaflet, and instruct the patient to read it and to ask any questions the patient may have, as a preliminary step to signing the Patient Information leaflet's signature page.
- I will report serious adverse events, such as any immediate-onset systemic allergic event (anaphylaxis, hypotension and syncope) to PRAECIS PHARMACEUTICALS INCORPORATED at 1-866 PLENAXIS (1-866-753-6294) or the Food and Drug Administration's MEDWATCH Program at 1-800-FDA-1088.
- I understand that I may withdraw as a prescriber of Plenaxis™ by a written statement submitted to PRAECIS PHARMACEUTICALS INCORPORATED (contact information below), or that PRAECIS PHARMACEUTICALS INCORPORATED may withdraw me from the Plenaxis™ **PLUS** Program if I do not meet the agreed upon responsibilities.

By signing, I acknowledge receipt of the Plenaxis™ full prescribing information, agree that I meet the qualifications and will follow the listed conditions for use described above.

_____ _____
Name (typed or printed) Date

_____
Signature

_____
Title

UPIN/Medicare#_____

Specialty (circle one) Urologist Oncologist Internist Other _____
(Specify specialty)

Office Name _____
Address _____ E-mail _____
City _____ State _____ Zip _____
Phone Number _____ Fax Number _____
State License Number _____

Second Office or Hospital Name _____
Address _____ E-mail _____
City _____ State _____ Zip _____
Phone Number _____ Fax Number _____

Fax completed and signed PHYSICIAN'S ATTESTATION to:

PRAECIS PHARMACEUTICALS INCORPORATED
Attention: Plenaxis™ **PLUS** Program
c/o SENTRX
Overlook at Great Notch
150 Clove Road
Little Falls, New Jersey 07424
Fax: 1-800-648-8180

You may also complete this form online by visting www.plenaxisplus.com. Then print, sign and fax the Attestation to PRAECIS.

Request Additional Materials:
Package Inserts Patient Information forms Physician Attestations Hospital Pharmacy Agreements

08-01

Hospital Pharmacy Agreement

HOSPITAL PHARMACY'S ACCEPTANCE OF RESPONSIBILITIES

Plenaxis™ PLUS Program

For safety reasons, the marketing of Plenaxis™ is restricted. The Plenaxis™ **PLUS** Program (Plenaxis™ User Safety Program) ensures hospital pharmacies understand that only physicians who are enrolled with PRAECIS PHARMACEUTICALS INCORPORATED and are listed in the Plenaxis™ Prescriber's Registry should prescribe Plenaxis™. Hospital pharmacies must accept the responsibilities below to receive Plenaxis™ from PRAECIS PHARMACEUTICALS INCORPORATED or its distributors.

- I understand that because of the risk of immediate-onset systemic allergic reactions, including hypotension and syncope, and because of the risk of loss of effectiveness over time, Plenaxis™ is only indicated for the palliative treatment of men with advanced symptomatic prostate cancer, in whom LHRH agonist therapy is not appropriate and who refuse surgical castration, and have one or more of the following: (1) risk of neurological compromise due to metastases, (2) ureteral or bladder outlet obstruction due to local encroachment or metastastic disease, or (3) severe bone pain from skeletal metastases persisting on narcotic analgesia.

- Hospital pharmacists will:
  - Verify that each prescriber has been confirmed in the Plenaxis™ Prescribers' Registry before dispensing Plenaxis™. Confirmation of registry participants can be accomplished via the interactive voice response (IVR) telephone number, 1-866-PLENAXIS (1-866-753-6294).
  - Dispense all doses of Plenaxis™ with Patient Information.

I understand that I may withdraw my enrollment in the Plenaxis™ **PLUS** Program by a written statement submitted to PRAECIS PHARMACEUTICALS INCORPORATED (contact information below) or that PRAECIS PHARMACEUTICAS INCORPORATED may withdraw this pharmacy from the Plenaxis™ **PLUS** Program if they do not meet the agreed upon responsibilities.

By signing below, I acknowledge and accept the above responsibilities.

Print Name _____ Signature _____

Title _____ Date _____

Hospital Pharmacy License #_____

Hospital Pharmacy Name _____

Shipping Address _____

City _____ State/Zip _____

Billing Address _____

City _____ State/Zip _____

Phone _____ Fax _____

E-mail _____

You may also complete this form online by visting www.plenaxisplus.com

Fax completed and signed form to: **PRAECIS PHARMACEUTICALS INCORPORATED**

Attention: Plenaxis™ **PLUS** Program
c/o SENTRX
Overlook at Great Notch
150 Clove Road
Little Falls, New Jersey 07424
Fax Number: 1-800-648-8180

Request additional materials
Package Inserts
Patient Information
Physician Attestations

09-01

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

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

The Package Insert will require major revisions; the review was deferred to the next review cycle.

5/14/01

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

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

Sponsor's revised Package Insert, May 29, 2001.

ISI

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

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

Sponsor Revised Package Insert, April 13, 2001.

/S/

5/7/01

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

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

Sponsor Original Package Insert, December 11, 2000.

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

Sponsor Original Package Insert, December 11, 2000.

ISI

5/7/01

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

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

Label for Antagon™ (ganirelix for injectable suspension), the first GnRH Antagonist approved in the U.S.

/S/

5/7/01

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

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

Label for Trelstar™ Depot (triptorelin pamoate for injectable suspension), a GnRH Agonist approved for the palliative treatment of advanced prostate cancer.

/S/

5/7/01

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

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

Label for Viadur™ (leprolide acetate implant), a GnRH Agonist approved for the palliative treatment of advanced prostate cancer.

/S/

S17L51

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