

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Approval Package for:**

***APPLICATION NUMBER:***  
**NDA 19-010/S-031**

***Name:*** Lupron Injection  
leuprolide acetate (5mg/ml)

***Sponsor:*** TAP Pharmaceuticals, Inc.

***Approval Date:*** September 15, 2005

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*  
**NDA 19-010/S-031**

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**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*

**NDA 19-010/S-031**

**APPROVAL LETTER**



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 19-732/S-027, S-029                      20-517/S-018, S-019  
19-010/S-031                                      20-708/S-020, S-021  
19-943/S-022, S-024                          20-011/S-029, S-031

TAP Pharmaceutical Products Inc.  
Attention: Tonya Haynes, M.P.H.  
Regulatory Product Manager  
675 North Field Drive  
Lake Forest, IL 60045

Dear Ms. Haynes:

Please refer to your supplemental new drug applications as listed below, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act:

NDA	Supplement	Name of Drug	Letter Date	Receipt Date
19-732	SCS-027	Lupron Depot (leuprolide acetate for depot suspension), 7.5mg	May 6, 2005	May 9, 2005
19-732	SLR-029	Lupron Depot (leuprolide acetate for depot suspension), 7.5mg	August 18, 2005	August 19, 2005
20-517	SCS-018	Lupron Depot (leuprolide acetate for depot suspension), 4-month, 30mg	May 6, 2005	May 9, 2005
20-517	SLR-019	Lupron Depot (leuprolide acetate for depot suspension), 4-month, 30mg	August 18, 2005	August 19, 2005
19-010	SLR-031	Lupron Injection (leuprolide acetate	August 18, 2005	August 19, 2005
20-708	SCS-020	Lupron Depot (leuprolide acetate for depot suspension), 3-month	May 6, 2005	May 9, 2005
20-708	SLR-021	Lupron Depot (leuprolide acetate for depot suspension), 3-month	August 18, 2005	August 19, 2005
19-943	SCS-022	Lupron Depot (leuprolide acetate for depot suspension), 3.75 mg	May 6, 2005	May 9, 2005
19-943	SLR-024	Lupron Depot (leuprolide acetate for depot suspension), 3.75 mg	August 18, 2005	August 19, 2005
20-011	SCS-029	Lupron Depot (leuprolide acetate for depot suspension), 3.75mg	May 6, 2005	May 9, 2005
20-011	SLR-031	Lupron Depot (leuprolide acetate for depot suspension), 3.75mg	August 18, 2005	August 19, 2005

The Prior Approval supplemental new drug applications dated August 18, 2005, provide for changes in the package insert to include text regarding pituitary apoplexy.

The "Changes Being Effected" supplemental new drug applications dated May 6, 2005, provide for the addition of an appearance test, and changes in the package insert and mixing instructions regarding the LUPRON recall.

We completed our review of these applications, they are approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the submitted labeling (package insert, mixing instructions) on August 18, 2005.

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 these submissions "FPL for approved supplement NDA ##-###/S-YYY, S-ZZZ", specific to the applications as listed above. Approval of these submissions by FDA is not required before the labeling is used.

In addition, submit three copies of the introductory promotional materials that you propose to use for this/these product(s). Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division/ the Division of DIVISION NAME and two copies of both the promotional materials and the package insert(s) directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42  
Food and Drug Administration  
Center for Drug Evaluation and Research  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410  
Food and Drug Administration  
Center for Drug Evaluation and Research  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

NDA's 19-732/S-027, S-029  
20-708/S-020, S-021

20-517/S-018, S-019  
19-943/S-022, S-024

19-010/S-031  
20-011/S-029, S-031

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If you have any questions, please call Nenita Crisostomo, R.N., Regulatory Health Project Manager, at (301) 827-7260.

Sincerely,

*{See appended electronic signature page}*

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

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

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Daniel A. Shames  
9/15/2005 12:02:51 PM

**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*

**NDA 19-010/S-031**

**FINAL PRINTED LABELING**

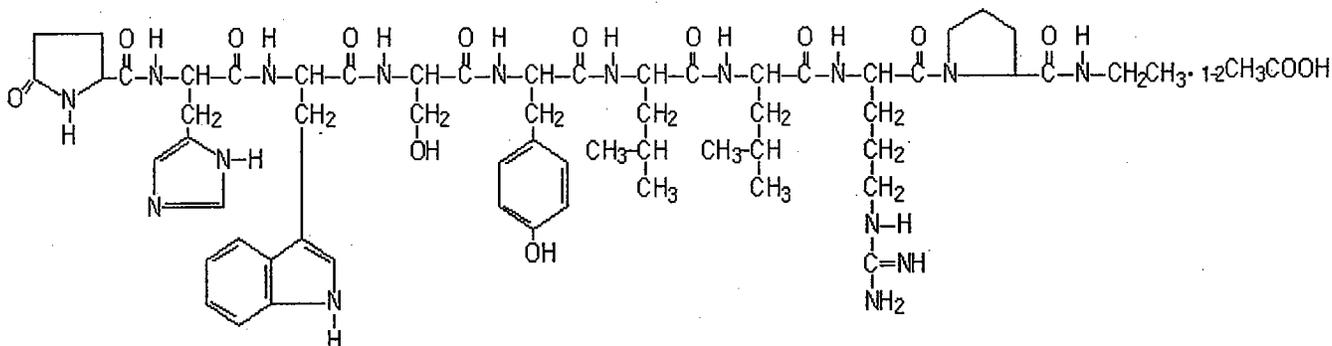
# LUPRON® INJECTION

(leuprolide acetate)

## Rx only

### DESCRIPTION

Leuprolide acetate is a synthetic nonapeptide analog of naturally occurring gonadotropin releasing hormone (GnRH or LH-RH). The analog possesses greater potency than the natural hormone. The chemical name is 5-oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-leucyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide acetate (salt) with the following structural formula:



LUPRON INJECTION is a sterile, aqueous solution intended for subcutaneous injection. It is available in a 2.8 mL multiple-dose vial containing leuprolide acetate (5 mg/mL), sodium chloride, USP (6.3 mg/mL) for tonicity adjustment, benzyl alcohol, NF as a preservative (9 mg/mL), and water for injection, USP. The pH may have been adjusted with sodium hydroxide, NF and/or acetic acid, NF.

### CLINICAL PHARMACOLOGY

Leuprolide acetate, an LH-RH agonist, acts as a potent inhibitor of gonadotropin secretion when given continuously and in therapeutic doses. Animal and human studies indicate that following an initial stimulation of gonadotropins, chronic administration of leuprolide acetate results in suppression of ovarian and testicular steroidogenesis. This effect is reversible upon discontinuation of drug therapy. Administration of leuprolide acetate has resulted in inhibition of the growth of certain hormone dependent tumors (prostatic tumors in Noble and Dunning male rats and DMBA-induced mammary tumors in female rats) as well as atrophy of the reproductive organs.

In humans, subcutaneous administration of single daily doses of leuprolide acetate results in an initial increase in circulating levels of luteinizing hormone (LH) and follicle stimulating hormone (FSH), leading to a transient increase in levels of the gonadal steroids (testosterone and dihydrotestosterone in males, and estrone and estradiol in pre-menopausal females). However, continuous daily administration of leuprolide acetate results in decreased levels of LH and FSH. In males, testosterone is reduced to castrate levels. In pre-menopausal females, estrogens are reduced to post-menopausal levels. These decreases occur within two to four weeks after initiation of treatment, and castrate levels of testosterone in prostatic cancer patients have been demonstrated for periods of up to five years.

Leuprolide acetate is not active when given orally.

### Pharmacokinetics

**Absorption** Bioavailability by subcutaneous administration is comparable to that by intravenous administration.

**Distribution** The mean steady-state volume of distribution of leuprolide following intravenous bolus administration to healthy male volunteers was 27 L. *In vitro* binding to human plasma proteins ranged from 43% to 49%.

**Metabolism** In healthy male volunteers, a 1 mg bolus of leuprolide administered intravenously revealed that the mean systemic clearance was 7.6 L/h, with a terminal elimination half-life of approximately 3 hours based on a two compartment model. In rats and dogs, administration of <sup>14</sup>C-labeled leuprolide was shown to be metabolized to smaller inactive peptides, a pentapeptide (Metabolite I), tripeptides (Metabolites II and III) and a dipeptide (Metabolite IV). These fragments may be further catabolized. The major metabolite (M-I) plasma concentrations measured in 5 prostate cancer patients reached maximum concentration 2 to 6 hours after dosing and were approximately 6% of the peak parent drug concentration. One week after dosing, mean plasma M-I concentrations were approximately 20% of mean leuprolide concentrations.

**Excretion** Following administration of LUPRON DEPOT 3.75 mg to 3 patients, less than 5% of the dose was recovered as parent and M-I metabolite in the urine.

**Special Populations** The pharmacokinetics of the drug in hepatically and renally impaired patients have not been determined.

**Drug Interactions** No pharmacokinetic-based drug-drug interaction studies have been conducted with leuprolide acetate. However, because leuprolide acetate is a peptide that is primarily degraded by peptidase and not by cytochrome P-450 enzymes as noted in specific studies, and the drug is only about 46% bound to plasma proteins, drug interactions would not be expected to occur.

## CLINICAL STUDIES

In a controlled study comparing LUPRON 1 mg/day given subcutaneously to DES (diethylstilbestrol), 3 mg/day, the survival rate for the two groups was comparable after two years of treatment. The objective response to treatment was also similar for the two groups.

## INDICATIONS AND USAGE

LUPRON INJECTION (leuprolide acetate) is indicated in the palliative treatment of advanced prostatic cancer.

## CONTRAINDICATIONS

1. LUPRON INJECTION is contraindicated in patients known to be hypersensitive to GnRH, GnRH agonist analogs or any of the excipients in LUPRON INJECTION: Reports of anaphylactic reactions to synthetic GnRH (Factrel) or GnRH agonist analogs have been reported in the medical literature.<sup>1</sup>
2. LUPRON is contraindicated in women who are or may become pregnant while receiving the drug. LUPRON may cause fetal harm when administered to a pregnant woman. Therefore, the possibility exists that spontaneous abortion may occur if the drug is administered during

pregnancy. If this drug is administered during pregnancy or if the patient becomes pregnant while taking any formulation of LUPRON, the patient should be apprised of the potential hazard to the fetus.

## **WARNINGS**

Initially, LUPRON, like other LH-RH agonists, causes increases in serum levels of testosterone. Transient worsening of symptoms, or the occurrence of additional signs and symptoms of prostate cancer, may occasionally develop during the first few weeks of LUPRON treatment. A small number of patients may experience a temporary increase in bone pain, which can be managed symptomatically. As with other LH-RH agonists, isolated cases of ureteral obstruction and spinal cord compression have been observed, which may contribute to paralysis with or without fatal complications.

Safe use of leuprolide acetate in pregnancy has not been established clinically. Before starting treatment with LUPRON, pregnancy must be excluded (see **CONTRAINDICATIONS** section).

Periodic monitoring of serum testosterone and prostate-specific antigen (PSA) levels is recommended, especially if the anticipated clinical or biochemical response to treatment has not been achieved. It should be noted that results of testosterone determinations are dependent on assay methodology. It is advisable to be aware of the type and precision of the assay methodology to make appropriate clinical and therapeutic decisions.

## **PRECAUTIONS**

Patients with metastatic vertebral lesions and/or with urinary tract obstruction should be closely observed during the first few weeks of therapy (see **WARNINGS** and **ADVERSE REACTIONS** sections).

Patients with known allergies to benzyl alcohol, an ingredient of the drug's vehicle, may present symptoms of hypersensitivity, usually local, in the form of erythema and induration at the injection site.

**Information for Patients:** See **INFORMATION FOR PATIENTS** which appears after the **REFERENCE** section.

**Laboratory Tests:** Response to leuprolide acetate should be monitored by measuring serum levels of testosterone and prostate-specific antigen (PSA). In the majority of patients, testosterone levels increased above baseline during the first week, declining thereafter to baseline levels or below by the end of the second week of treatment. Castrate levels were reached within two to four weeks and once attained were maintained for as long as drug administration continued.

**Drug Interactions:** See **CLINICAL PHARMACOLOGY, Pharmacokinetics** section.

**Drug/Laboratory Test Interactions:** Administration of leuprolide acetate in therapeutic doses results in suppression of the pituitary-gonadal system. Normal function is usually restored within 4 to 12 weeks after treatment is discontinued.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** Two-year carcinogenicity studies were conducted in rats and mice. In rats, a dose-related increase of benign pituitary hyperplasia and benign pituitary adenomas was noted at 24 months when the drug was administered subcutaneously at high daily doses (0.6 to 4 mg/kg). There was a significant but not dose-related increase of pancreatic islet-cell adenomas in females and of testicular interstitial cell adenomas in males (highest incidence in the low dose group). In mice no pituitary abnormalities were observed at a dose as high as 60 mg/kg for two years. Patients have been treated with leuprolide acetate for up to three years with doses as high as

10 mg/day and for two years with doses as high as 20 mg/day without demonstrable pituitary abnormalities.

Mutagenicity studies have been performed with leuprolide acetate using bacterial and mammalian systems. These studies provided no evidence of a mutagenic potential.

Clinical and pharmacologic studies in adults ( $\geq 18$  years) with leuprolide acetate and similar analogs have shown full reversibility of fertility suppression when the drug is discontinued after continuous administration for periods of up to 24 weeks. However, no clinical studies have been conducted with leuprolide acetate to assess the reversibility of fertility suppression.

**Pregnancy, Teratogenic Effects:** Pregnancy Category X (see **CONTRAINDICATIONS** and **WARNINGS** sections). When administered on day 6 of pregnancy at test dosages of 0.00024, 0.0024, and 0.024 mg/kg (1/600 to 1/6 the human dose) to rabbits, LUPRON produced a dose-related increase in major fetal abnormalities. Similar studies in rats failed to demonstrate an increase in major fetal malformations throughout gestation. There was increased fetal mortality and decreased fetal weights with the two higher doses of LUPRON in rabbits and with the highest dose in rats. The effects on fetal mortality are expected consequences of the alterations in hormonal levels brought about by this drug.

**Nursing Mothers:** It is not known whether leuprolide acetate is excreted in human milk. LUPRON should not be used by nursing mothers.

**Pediatric Use:** See labeling for LUPRON INJECTION for Pediatric Use for the safety and effectiveness in children with central precocious puberty.

**Geriatric Use:** In the clinical trials for LUPRON INJECTION, the majority (69%) of subjects studied were at least 65 years of age. Therefore, the labeling reflects the pharmacokinetics, efficacy and safety of LUPRON in this population.

## **ADVERSE REACTIONS**

### **Clinical Trials:**

In the majority of patients testosterone levels increased above baseline during the first week, declining thereafter to baseline levels or below by the end of the second week of treatment. This transient increase was occasionally associated with a temporary worsening of signs and symptoms, usually manifested by an increase in bone pain (see **WARNINGS** section). In a few cases a temporary worsening of existing hematuria and urinary tract obstruction occurred during the first week. Temporary weakness and paresthesia of the lower limbs have been reported in a few cases.

Potential exacerbations of signs and symptoms during the first few weeks of treatment is a concern in patients with vertebral metastases and/or urinary obstruction which, if aggravated, may lead to neurological problems or increase the obstruction.

In a comparative trial of LUPRON INJECTION (leuprolide acetate) versus DES, in 5% or more of the patients receiving either drug, the following adverse reactions were reported to have a possible or probable relationship to drug as ascribed by the treating physician. Often, causality is difficult to assess in patients with metastatic prostate cancer. Reactions considered not drug related are excluded.

	<b>LUPRON</b>	<b>DES</b>
	<b>(N=98)</b>	<b>(N=101)</b>
	<b><u>Number of Reports</u></b>	

<b>Cardiovascular System</b>		
Congestive heart failure	1	5
ECG changes/ischemia	19	22
High blood pressure	8	5
Murmur	3	8
Peripheral edema	12	30
Phlebitis/thrombosis	2	10
<b>Gastrointestinal System</b>		
Anorexia	6	5
Constipation	7	9
Nausea/vomiting	5	17
<b>Endocrine System</b>		
*Decreased testicular size	7	11
*Gynecomastia/breast tenderness or pain	7	63
*Hot flashes	55	12
*Impotence	4	12
<b>Hemic and Lymphatic System</b>		
Anemia	5	5
<b>Musculoskeletal System</b>		
Bone pain	5	2
Myalgia	3	9
<b>Central/Peripheral Nervous System</b>		
Dizziness/lightheadedness	5	7
General pain	13	13
Headache	7	4
Insomnia/sleep disorders	7	5
<b>Respiratory System</b>		
Dyspnea	2	8
Sinus congestion	5	6
<b>Integumentary System</b>		
Dermatitis	5	8
<b>Urogenital System</b>		
Frequency/urgency	6	8
Hematuria	6	4
Urinary tract infection	3	7
<b>Miscellaneous</b>		
Asthenia	10	10
*Physiologic effect of decreased testosterone.		

In this same study, the following adverse reactions were reported in less than 5% of the patients on LUPRON.

*Cardiovascular System*—Angina, Cardiac arrhythmias, Myocardial infarction, Pulmonary emboli; *Gastrointestinal System*—Diarrhea, Dysphagia, Gastrointestinal bleeding, Gastrointestinal disturbance, Peptic ulcer, Rectal polyps; *Endocrine System*—Libido decrease, Thyroid enlargement; *Musculoskeletal System*—Joint pain; *Central/Peripheral Nervous System*—Anxiety, Blurred vision, Lethargy, Memory disorder, Mood swings, Nervousness, Numbness, Paresthesia, Peripheral neuropathy, Syncope/blackouts, Taste disorders; *Respiratory System*—Cough, Pleural rub, Pneumonia, Pulmonary fibrosis; *Integumentary System*—Carcinoma of skin/ear, Dry skin, Ecchymosis, Hair loss, Itching, Local skin reactions, Pigmentation, Skin lesions; *Urogenital System*—Bladder spasms, Dysuria, Incontinence, Testicular pain, Urinary obstruction; *Miscellaneous*—Depression, Diabetes, Fatigue, Fever/chills, Hypoglycemia, Increased BUN, Increased calcium, Increased creatinine, Infection/inflammation, Ophthalmologic disorders, Swelling (temporal bone).

In an additional clinical trial and from long-term observation of both studies, the following additional adverse events (excluding those considered not drug related) were reported for patients receiving LUPRON.

*Cardiovascular System*—Bradycardia, Carotid bruit, Extrasystole, Palpitations, Perivascular cuffing (eyes), Ruptured aortic aneurysm, Stroke, Tachycardia, Transient ischemic attack; *Gastrointestinal System*—Flatus, Dryness of mouth and throat, Hepatitis, Hepatomegaly, Occult blood (rectal exam), Rectal fistula/erythema; *Endocrine System*—Libido increase, Thyroid nodule; *Musculoskeletal System*—Ankylosing spondylosis, Arthritis, Blurred disc margins, Bone fracture, Muscle stiffness, Muscle tenderness, Pelvic fibrosis, Spasms/cramps; *Central/Peripheral Nervous System*—Auditory hallucinations/tinnitus, Decreased hearing, Decreased reflexes, Euphoria, Hyperreflexia, Loss of smell, Motor deficiency; *Respiratory System*—Chest tightness, Decreased breathing sounds, Hemoptysis, Pleuritic chest pain, Pulmonary infiltrate, Rales/rhonchi, Rhinitis, Strep throat, Wheezing/bronchitis; *Integumentary System*—Boil (pubic), Bruises, Hives, Keratosis, Mole, Shingles, Spiders; *Urogenital System*—Blisters on penis, Inguinal hernia, Penile swelling, Post void residual, Prostatic pain, Pyuria; *Miscellaneous*—Abdominal distention, Facial swelling/edema, Feet burning, Flu, Eyelid growth, Hypoproteinemia, Accidental injury, Knee effusion, Mass, Pallid, Sallow, Weakness.

### **Postmarketing**

During postmarketing surveillance which includes other dosage forms and other patient populations, the following adverse events were reported.

Symptoms consistent with an anaphylactoid or asthmatic process have been rarely (incidence rate of about 0.002%) reported. Rash, urticaria, and photosensitivity reactions have also been reported.

Localized reactions including induration and abscess have been reported at the site of injection.

Symptoms consistent with fibromyalgia (e.g., joint and muscle pain, headaches, sleep disorders, gastrointestinal distress, and shortness of breath) have been reported individually and collectively.

*Cardiovascular System* – Hypotension; *Gastrointestinal System* – Hepatic dysfunction; *Hemic and Lymphatic System* – Decreased WBC; *Integumentary System* – Hair growth; *Central/Peripheral Nervous System* – Spinal fracture/paralysis, Hearing disorder; *Miscellaneous* – Hard nodule in throat, Weight gain, Increased uric acid; *Musculoskeletal System* – Tenosynovitis-like symptoms; *Respiratory System* – Respiratory disorders.

*Changes in Bone Density:* Decreased bone density has been reported in the medical literature in men who have had orchiectomy or who have been treated with an LH-RH agonist analog. In a clinical trial, 25 men with prostate cancer, 12 of whom had been treated previously with leuprolide acetate for at least six months, underwent bone density studies as a result of pain. The leuprolide-treated group had lower

bone density scores than the nontreated control group. It can be anticipated that long periods of medical castration in men will have effects on bone density.

**Pituitary apoplexy:** During post-marketing surveillance, rare cases of pituitary apoplexy (a clinical syndrome secondary to infarction of the pituitary gland) have been reported after the administration of gonadotropin-releasing hormone agonists. In a majority of these cases, a pituitary adenoma was diagnosed, with a majority of pituitary apoplexy cases occurring within 2 weeks of the first dose, and some within the first hour. In these cases, pituitary apoplexy has presented as sudden headache, vomiting, visual changes, ophthalmoplegia, altered mental status, and sometimes cardiovascular collapse. Immediate medical attention has been required.

See other LUPRON DEPOT and LUPRON INJECTION package inserts for other events reported in the same and different patient populations.

## **OVERDOSAGE**

In rats subcutaneous administration of 250 to 500 times the recommended human dose, expressed on a per body weight basis, resulted in dyspnea, decreased activity, and local irritation at the injection site. There is no evidence at present that there is a clinical counterpart of this phenomenon. In early clinical trials with leuprolide acetate doses as high as 20 mg/day for up to two years caused no adverse effects differing from those observed with the 1 mg/day dose.

## **DOSAGE AND ADMINISTRATION**

The recommended dose is 1 mg (0.2 mL or 20 unit mark) administered as a single daily subcutaneous injection. As with other drugs administered chronically by subcutaneous injection, the injection site should be varied periodically. Each 0.2 mL contains 1 mg of leuprolide acetate, sodium chloride for tonicity adjustment, 1.8 mg of benzyl alcohol as preservative and water for injection. The pH may have been adjusted with sodium hydroxide and/or acetic acid.

Follow the pictorial directions on the reverse side of this package insert for administration.

NOTE: As with all parenteral products, inspect the solution for discoloration and particulate matter before each use.

## **HOW SUPPLIED**

LUPRON INJECTION (leuprolide acetate) is a sterile solution supplied in a 2.8 mL multiple-dose vial. The vial is packaged as follows: 14 Day Patient Administration Kit with 14 disposable syringes and 28 alcohol swabs, NDC 0300-3612-28 and six-vial carton, NDC 0300-3612-24.

Store below 77°F (25°C). Do not freeze. Protect from light; store vial in carton until use.

U.S. Patent Nos. 4,005,063 and 4,005,194.

## **REFERENCE**

1. MacLeod TL, Eisen A, Sussman GL, et al: Anaphylactic reaction to synthetic luteinizing hormone-releasing hormone. *Fertil Steril* 1987 Sept;48(3):500-502.

## INFORMATION FOR PATIENTS

Be sure to consult your physician with any questions you may have or for information about LUPRON INJECTION (leuprolide acetate) and its use.

### WHAT IS LUPRON?

LUPRON INJECTION (leuprolide acetate) is chemically similar to gonadotropin releasing hormone (GnRH or LH-RH) a hormone which occurs naturally in your body.

Normally, your body releases small amounts of LH-RH and this leads to events which stimulate the production of sex hormones.

However, when you inject LUPRON INJECTION (leuprolide acetate), the normal events that lead to sex hormone production are interrupted and testosterone is no longer produced by the testes.

LUPRON must be injected because, like insulin which is injected by diabetics, LUPRON is inactive when taken by mouth.

If you were to discontinue the drug for any reason, your body would begin making testosterone again.

### DIRECTIONS FOR USING LUPRON

1. Wash hands thoroughly with soap and water.
2. If using a new bottle for the first time, flip off the plastic cover to expose the grey rubber stopper. Wipe metal ring and rubber stopper with an alcohol wipe each time you use LUPRON. Check the liquid in the container. If it is not clear or has particles in it, DO NOT USE IT. Exchange it at your pharmacy for another container.
3. Remove outer wrapping from one syringe. Pull plunger back until the tip of the plunger is at the 0.2 mL or 20 unit mark.
4. Take cover off needle. Push the needle through the center of the rubber stopper on the LUPRON bottle.
5. Push the plunger all the way in to inject air into the bottle.
6. Keep the needle in the bottle and turn the bottle upside down. Check to make sure the tip of the needle is in the liquid. Slowly pull back on the plunger, until the syringe fills to the 0.2 mL or 20 unit mark.
7. Toward the end of a two-week period, the amount of LUPRON left in the bottle will be small. Take special care to hold the bottle straight and to keep the needle tip in liquid while pulling back on the plunger.
8. Keeping the needle in the bottle and the bottle upside down, check for air bubbles in the syringe. If you see any, push the plunger *slowly* in to push the air bubble back into the bottle. Keep the tip of the needle in the liquid and pull the plunger back again to fill to the 0.2 mL or 20 unit mark.
9. Do this again if necessary to eliminate air bubbles.
10. To protect your skin, inject each daily dose at a different body spot.
11. Choose an injection spot. Cleanse the injection spot with another alcohol wipe.
12. Hold the syringe in one hand. Hold the skin taut, or pull up a little flesh with the other hand, as you were instructed.
13. Holding the syringe as you would a pencil, thrust the needle all the way into the skin at a 90° angle. Push the plunger to administer the injection.
14. Hold an alcohol wipe down on your skin where the needle is inserted and withdraw the needle at the same angle it was inserted.

15. Use the disposable syringe only once and dispose of it properly as you were instructed. Needles thrown into a garbage bag could accidentally stick someone. NEVER LEAVE SYRINGES, NEEDLES OR DRUGS WHERE CHILDREN CAN REACH THEM.

#### **SOME SPECIAL ADVICE**

- You may experience hot flashes when using LUPRON INJECTION (leuprolide acetate). During the first few weeks of treatment you may experience increased bone pain, increased difficulty in urinating, and less commonly but most importantly, you may experience the onset or aggravation of nerve symptoms. In any of these events, discuss the symptoms with your doctor. Like other treatment options, LUPRON may cause impotence. Notify your doctor if you develop new or worsened symptoms after beginning LUPRON treatment.
- You may experience some irritation at the injection site, such as burning, itching or swelling. These reactions are usually mild and go away. If they do not, tell your doctor.
- If you have experienced an allergic reaction to other drugs like LUPRON, you should not use this drug.
- Do not stop taking your injections because you feel better. You need an injection every day to make sure LUPRON keeps working for you.
- If you need to use an alternate to the syringe supplied with LUPRON, low-dose insulin syringes should be utilized.
- When the drug level gets low, take special care to hold the bottle straight up and down and to keep the needle tip in liquid while pulling back on the plunger.
- Do not try to get every last drop out of the bottle. This will increase the possibility of drawing air into the syringe and getting an incomplete dose. Some extra drug has been provided so that you can withdraw the recommended number of doses.
- Tell your pharmacist when you will need LUPRON so it will be at the pharmacy when you need it.
- Store below 77°F (25°C). Do not store near a radiator or other very warm place. Do not freeze. Protect from light; store vial in carton until use.
- Do not leave your drug or hypodermic syringes where anyone can pick them up.
- Keep this and all other medications out of reach of children.



Manufactured for  
TAP Pharmaceuticals Inc.  
Lake Forest, IL 60045, U.S.A.  
By Abbott Laboratories  
North Chicago, IL 60064, U.S.A.

® – Registered  
(No. 3612)

03-5452-R5, Rev. October, 2005

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## For Pediatric Use

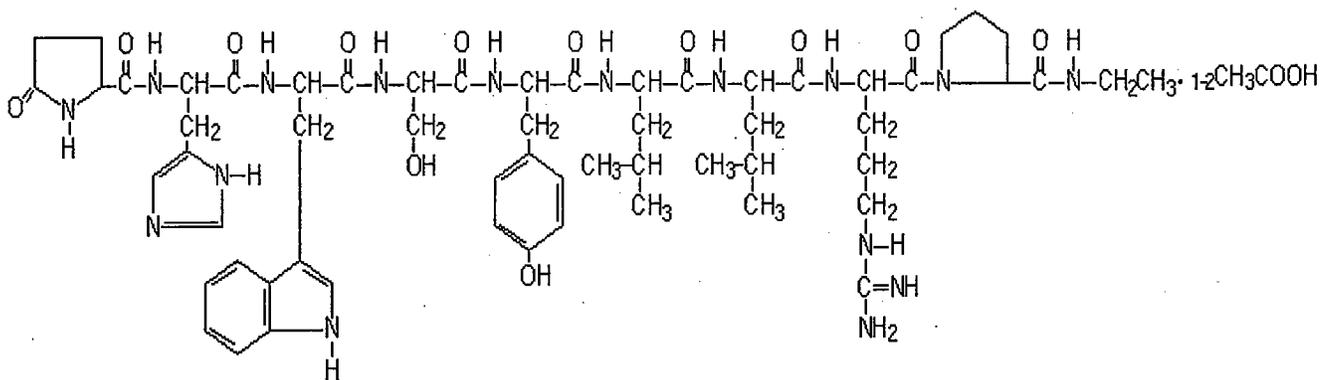
### LUPRON® INJECTION

(leuprolide acetate)

## Rx only

### DESCRIPTION

Leuprolide acetate is a synthetic nonapeptide analog of naturally occurring gonadotropin releasing hormone (GnRH or LH-RH). The analog possesses greater potency than the natural hormone. The chemical name is 5-oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-leucyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide acetate (salt) with the following structural formula:



LUPRON INJECTION is a sterile, aqueous solution intended for daily subcutaneous injection. It is available in a 2.8 mL multiple dose vial containing leuprolide acetate (5 mg/mL), sodium chloride, USP (6.3 mg/mL) for tonicity adjustment, benzyl alcohol, NF as a preservative (9 mg/mL), and water for injection, USP. The pH may have been adjusted with sodium hydroxide, NF and/or acetic acid, NF.

### CLINICAL PHARMACOLOGY

Leuprolide acetate, a GnRH agonist, acts as a potent inhibitor of gonadotropin secretion when given continuously and in therapeutic doses. Animal and human studies indicate that following an initial stimulation of gonadotropins, chronic administration of leuprolide acetate results in suppression of ovarian and testicular steroidogenesis. This effect is reversible upon discontinuation of drug therapy.

Leuprolide acetate is not active when given orally.

### Pharmacokinetics

A pharmacokinetic study of leuprolide acetate in children has not been performed.

**Absorption:** In adults, bioavailability by subcutaneous administration is comparable to that by intravenous administration.

**Distribution:** The mean steady-state volume of distribution of leuprolide following intravenous bolus administration to healthy adult male volunteers was 27 L. *In vitro* binding to human plasma proteins ranged from 43% to 49%.

**Metabolism:** In healthy adult male volunteers, a 1 mg bolus of leuprolide administered intravenously revealed that the mean systemic clearance was 7.6 L/h, with a terminal elimination half-life of approximately 3 hours based on a two compartment model.

In rats and dogs, administration of <sup>14</sup>C-labeled leuprolide was shown to be metabolized to smaller inactive peptides, a pentapeptide (Metabolite I), tripeptides (Metabolites II and III) and a dipeptide (Metabolite IV). These fragments may be further catabolized.

The major metabolite (M-I) plasma concentrations measured in 5 prostate cancer patients reached maximum concentration 2 to 6 hours after dosing and were approximately 6% of the peak parent drug concentration. One week after dosing, mean plasma M-I concentrations were approximately 20% of mean leuprolide concentrations.

**Excretion:** Following administration of LUPRON DEPOT 3.75 mg to three adult patients, less than 5% of the dose was recovered as parent and M-I metabolite in the urine.

**Special Populations:** The pharmacokinetics of the drug in hepatically and renally impaired patients has not been determined.

**Drug Interactions:** No pharmacokinetic-based drug-drug interaction studies have been conducted with leuprolide acetate. However, because leuprolide acetate is a peptide that is primarily degraded by peptidase and the drug is only about 46% bound to plasma proteins, drug interactions would not be expected to occur.

## CLINICAL STUDIES

In children with central precocious puberty (CPP), stimulated and basal gonadotropins are reduced to prepubertal levels. Testosterone and estradiol are reduced to prepubertal levels in males and females respectively. Reduction of gonadotropins will allow for normal physical and psychological growth and development. Natural maturation occurs when gonadotropins return to pubertal levels following discontinuation of leuprolide acetate.

The following physiologic effects have been noted with the chronic administration of leuprolide acetate in this patient population.

1. **Skeletal Growth.** A measurable increase in body length can be noted since the epiphyseal plates will not close prematurely.
2. **Organ Growth.** Reproductive organs will return to a prepubertal state.
3. **Menses.** Menses, if present, will cease.

## INDICATIONS AND USAGE

LUPRON INJECTION is indicated in the treatment of children with central precocious puberty. Children should be selected using the following criteria:

1. Clinical diagnosis of CPP (idiopathic or neurogenic) with onset of secondary sexual characteristics earlier than 8 years in females and 9 years in males.
2. Clinical diagnosis should be confirmed prior to initiation of therapy:
  - Confirmation of diagnosis by a pubertal response to a GnRH stimulation test. The sensitivity and methodology of this assay must be understood.
  - Bone age advanced 1 year beyond the chronological age.
3. Baseline evaluation should also include:

- Height and weight measurements.
- Sex steroid levels.
- Adrenal steroid level to exclude congenital adrenal hyperplasia.
- Beta human chorionic gonadotropin level to rule out a chorionic gonadotropin secreting tumor.
- Pelvic/adrenal/testicular ultrasound to rule out a steroid secreting tumor.
- Computerized tomography of the head to rule out intracranial tumor.

## CONTRAINDICATIONS

1. Hypersensitivity to GnRH, GnRH agonist analogs or any of the excipients in LUPRON INJECTION. Reports of anaphylactic reactions to synthetic GnRH (Factrel) or GnRH agonist analogs have been reported in the medical literature<sup>1</sup>.
2. LUPRON is contraindicated in women who are or may become pregnant while receiving the drug. LUPRON may cause fetal harm when administered to a pregnant woman. Major fetal abnormalities were observed in rabbits but not in rats after administration of leuprolide acetate throughout gestation. There was increased fetal mortality and decreased fetal weights in rats and rabbits. (See **PRECAUTIONS, Pregnancy, Teratogenic Effects** section.) The effects on fetal mortality are expected consequences of the alterations in hormonal levels brought about by this drug. Therefore, the possibility exists that spontaneous abortion may occur if the drug is administered during pregnancy. If this drug is administered during pregnancy or if the patient becomes pregnant while taking any formulation of LUPRON, the patient should be apprised of the potential hazard to the fetus.

## WARNINGS

During the early phase of therapy, gonadotropins and sex steroids rise above baseline because of the natural stimulatory effect of the drug. Therefore, an increase in clinical signs and symptoms may be observed (see **CLINICAL PHARMACOLOGY** section).

Noncompliance with drug regimen or inadequate dosing may result in inadequate control of the pubertal process. The consequences of poor control include the return of pubertal signs such as menses, breast development, and testicular growth. The long-term consequences of inadequate control of gonadal steroid secretion are unknown, but may include a further compromise of adult stature.

## PRECAUTIONS

Patients with known allergies to benzyl alcohol, an ingredient of the vehicle of LUPRON INJECTION, may present symptoms of hypersensitivity, usually local, in the form of erythema and induration at the injection site.

### Information for Parents:

Prior to starting therapy with LUPRON INJECTION, the parent or guardian must be aware of the importance of continuous therapy. Adherence to daily drug administration schedules must be accepted if therapy is to be successful. Irregular dosing could restart the maturation process.

- During the first 2 months of therapy, a female may experience menses or spotting. If bleeding continues beyond the second month, notify the physician.
- Any irritation at the injection site should be reported to the physician immediately. If the child has experienced an allergic reaction to other drugs like LUPRON, this drug should not be used.

- Report any unusual signs or symptoms to the physician, like continued pubertal changes, substantial mood swings or behavioral changes.

**Laboratory Tests:** Response to leuprolide acetate should be monitored 1-2 months after the start of therapy with a GnRH stimulation test and sex steroid levels. Measurement of bone age for advancement should be done every 6-12 months.

Sex steroids may increase or rise above prepubertal levels if the dose is inadequate (see **WARNINGS** section). Once a therapeutic dose has been established, gonadotropin and sex steroid levels will decline to prepubertal levels.

**Drug Interactions:** See **CLINICAL PHARMACOLOGY, Pharmacokinetics** section.

**Drug/Laboratory Test Interactions:** Administration of leuprolide acetate in therapeutic doses results in suppression of the pituitary-gonadal system. Normal function is usually restored within 4 to 12 weeks after treatment is discontinued.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** A two-year carcinogenicity study was conducted in rats and mice. In rats, a dose-related increase of benign pituitary hyperplasia and benign pituitary adenomas was noted at 24 months when the drug was administered subcutaneously at high daily doses of 0.6 to 4 mg/kg (>100 times the clinical doses of 7.5 to 15 mg/month based on body surface area). There was a significant but not dose-related increase of pancreatic islet-cell adenomas in females and of testes interstitial cell adenomas in males (highest incidence in the low dose group). In mice, no leuprolide acetate-induced tumors or pituitary abnormalities were observed at daily dose as high as 60 mg/kg (>5000 times the clinical doses based on body surface area). Adult patients have been treated with leuprolide acetate for up to three years with doses as high as 10 mg/day and for two years with doses as high as 20 mg/day without demonstrable pituitary abnormalities.

Although no clinical studies have been completed in children to assess the full reversibility of fertility suppression, animal studies (prepubertal and adult rats and monkeys) with leuprolide acetate and other GnRH analogs have shown functional recovery. However, following a study with leuprolide acetate, immature male rats demonstrated tubular degeneration in the testes even after a recovery period. In spite of the failure to recover histologically, the treated males proved to be as fertile as the controls. Also, no histologic changes were observed in the female rats following the same protocol. In both sexes, the offspring of the treated animals appeared normal. The effect of the treatment of the parents on the reproductive performance of the F1 generation was not tested. The clinical significance of these findings is unknown.

**Pregnancy, Teratogenic Effects:** Pregnancy Category X (see **CONTRAINDICATIONS** section). When administered on day 6 of pregnancy at test dosages of 0.00024, 0.0024, and 0.024 mg/kg (1/1200 to 1/12 the human pediatric dose) to rabbits, LUPRON produced a dose-related increase in major fetal abnormalities. Similar studies in rats failed to demonstrate an increase in fetal malformations. There was increased fetal mortality and decreased fetal weights with the two higher doses of LUPRON in rabbits and with the highest dose in rats.

**Nursing Mothers:** It is not known whether leuprolide acetate is excreted in human milk. LUPRON should not be used by nursing mothers.

**Geriatric Use:** See labeling for LUPRON INJECTION for the pharmacokinetics, efficacy and safety of LUPRON in this population.

## ADVERSE REACTIONS

### Clinical Trials:

Potential exacerbation of signs and symptoms during the first few weeks of treatment (see **PRECAUTIONS** section) is a concern in patients with rapidly advancing central precocious puberty.

In two studies of children with central precocious puberty, in 2% or more of the patients receiving the drug, the following adverse reactions were reported to have a possible or probable relationship to drug as ascribed by the treating physician. Reactions considered not drug related are excluded.

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	<u>Number of Patients</u> <u>N = 395 (Percent)</u>	
Body as a Whole		
General Pain	7	(2)
Integumentary System		
Acne/Seborrhea	7	(2)
Injection Site Reactions		
Including Abscess	21	(5)
Rash Including		
Erythema Multiforme	8	(2)
Urogenital System		
Vaginitis/Bleeding/ Discharge	7	(2)

In those same studies, the following adverse reactions were reported in less than 2% of the patients.

*Body as a Whole* - Body Odor, Fever, Headache, Infection; *Cardiovascular System* - Syncope, Vasodilation; *Digestive System* - Dysphagia, Gingivitis, Nausea/Vomiting; *Endocrine System* - Accelerated Sexual Maturity; *Metabolic and Nutritional Disorders* - Peripheral Edema, Weight Gain; *Nervous System* - Nervousness, Personality Disorder, Somnolence, Emotional Lability; *Respiratory System* - Epistaxis; *Integumentary System* - Alopecia, Skin Striae; *Urogenital System* - Cervix Disorder, Gynecomastia/Breast Disorders, Urinary Incontinence.

## **Postmarketing**

During postmarketing surveillance, which includes other dosage forms and other patient populations, the following adverse events were reported.

Symptoms consistent with an anaphylactoid or asthmatic process have been rarely (incidence rate of about 0.002%) reported. Rash, urticaria, and photosensitivity reactions have also been reported. Localized reactions including induration and abscess have been reported at the site of injection. Symptoms consistent with fibromyalgia (e.g., joint and muscle pain, headaches, sleep disorders, gastrointestinal distress, and shortness of breath) have been reported individually and collectively.

*Cardiovascular System* – Hypotension, Pulmonary embolism; *Gastrointestinal System* – Hepatic dysfunction; *Hemic and Lymphatic System* – Decreased WBC; *Integumentary System* – Hair growth; *Central/Peripheral Nervous System* – Peripheral neuropathy, Spinal fracture/paralysis, Hearing disorder; *Miscellaneous* – Hard nodule in throat, Weight gain, Increased uric acid; *Musculoskeletal System* – Tenosynovitis-like symptoms; *Respiratory System* – Respiratory disorders; *Urogenital System* – Prostate pain.

*Changes in Bone Density:* Decreased bone density has been reported in the medical literature in men who have had orchiectomy or who have been treated with an LH-RH agonist analog. In a clinical trial, 25 men with prostate cancer, 12 of whom had been treated previously with leuprolide acetate for at least six months, underwent bone density studies as a result of pain. The leuprolide-treated group had lower bone density scores than the nontreated control group. The effects on bone density in children are unknown.

*Pituitary apoplexy:* During post-marketing surveillance, rare cases of pituitary apoplexy (a clinical syndrome secondary to infarction of the pituitary gland) have been reported after the administration of gonadotropin-releasing hormone agonists. In a majority of these cases, a pituitary adenoma was diagnosed, with a majority of pituitary apoplexy cases occurring within 2 weeks of the first dose, and some within the first hour. In these cases, pituitary apoplexy has presented as sudden headache, vomiting, visual changes, ophthalmoplegia, altered mental status, and sometimes cardiovascular collapse. Immediate medical attention has been required.

See other LUPRON INJECTION and LUPRON DEPOT package inserts for adverse events reported in other patient populations.

## **OVERDOSAGE**

In rats, subcutaneous administration of 125 to 250 times the recommended human pediatric dose, expressed on a per body weight basis, resulted in dyspnea, decreased activity, and local irritation at the injection site. There is no evidence at present that there is a clinical counterpart of this phenomenon. In early clinical trials using leuprolide acetate in adult patients, doses as high as 20 mg/day for up to two years caused no adverse effects differing from those observed with the 1 mg/day dose.

## **DOSAGE AND ADMINISTRATION**

LUPRON INJECTION can be administered by a patient/parent or health care professional.

The dose of LUPRON INJECTION must be individualized for each child. The dose is based on a mg/kg ratio of drug to body weight. Younger children require higher doses on a mg/kg ratio.

After 1-2 months of initiating therapy or changing doses, the child must be monitored with a GnRH stimulation test, sex steroids, and Tanner staging to confirm downregulation. Measurements of bone age

for advancement should be monitored every 6-12 months. The dose should be titrated upward until no progression of the condition is noted either clinically and/or by laboratory parameters.

The first dose found to result in adequate downregulation can probably be maintained for the duration of therapy in most children. However, there are insufficient data to guide dosage adjustment as patients move into higher weight categories after beginning therapy at very young ages and low dosages. It is recommended that adequate downregulation be verified in such patients whose weight has increased significantly while on therapy.

As with other drugs administered by injection, the injection site should be varied periodically.

Discontinuation of LUPRON INJECTION should be considered before age 11 for females and age 12 for males.

The recommended starting dose is 50 mcg/kg/day administered as a single subcutaneous injection. If total downregulation is not achieved, the dose should be titrated upward by 10 mcg/kg/day. This dose will be considered the maintenance dose.

Follow the pictorial directions on the reverse side of this package insert for administration.

NOTE: As with other parenteral products, inspect the solution for discoloration and particulate matter before each use.

## HOW SUPPLIED

LUPRON INJECTION (leuprolide acetate) is a sterile solution supplied in a 2.8 mL multiple-dose vial. The vial is packaged as follows:

- 14 Day Patient Administration Kit with 14 disposable syringes and 28 alcohol swabs, NDC 0300-3612-28.
- Six-vial carton, NDC 0300-3612-24.
- Store below 77°F (25°C). Do not freeze. Protect from light; store vial in carton until use.
- Use the syringes supplied with LUPRON INJECTION. Insulin syringes may be substituted for use with LUPRON INJECTION.

U.S. Patent Nos. 4,005,063; 4,005,194.

## REFERENCE

1. MacLeod TL, et al. Anaphylactic reaction to synthetic luteinizing hormone-releasing hormone. *Fertil Steril* 1987 Sept;48(3):500-502.

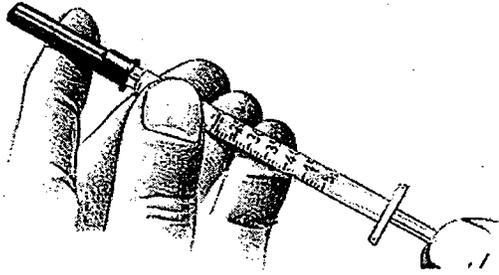


Manufactured for  
TAP Pharmaceuticals Inc.  
Lake Forest, IL 60045, U.S.A.  
By Abbott Laboratories  
North Chicago, IL 60064, U.S.A.

® – Registered

(No. 3612)

## ADMINISTERING THE INJECTION



Read this booklet before  
injecting the medication.  
Read the complete  
instructions for injection.



TAP Pharmaceutical Products Inc.  
Lake Forest, IL 60045, U.S.A.

(No. 3612)

03-5452-R5; Rev. October, 2005

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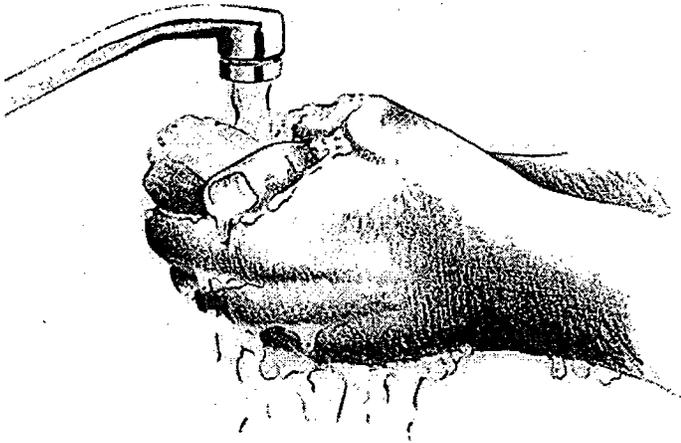
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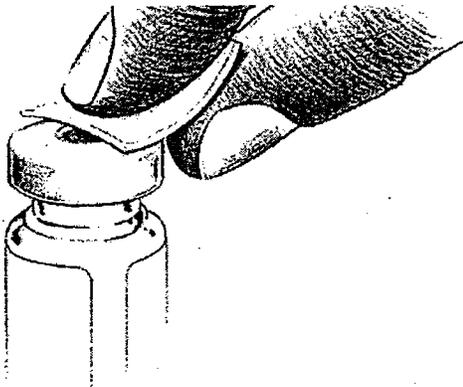
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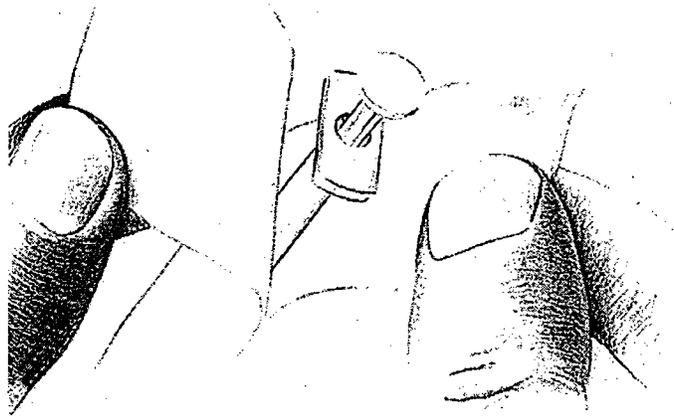
## ADMINISTERING THE INJECTION



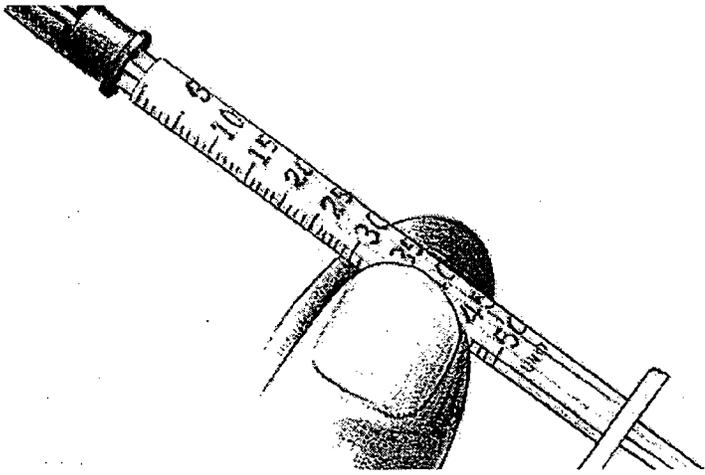
**1. Wash hands thoroughly.**



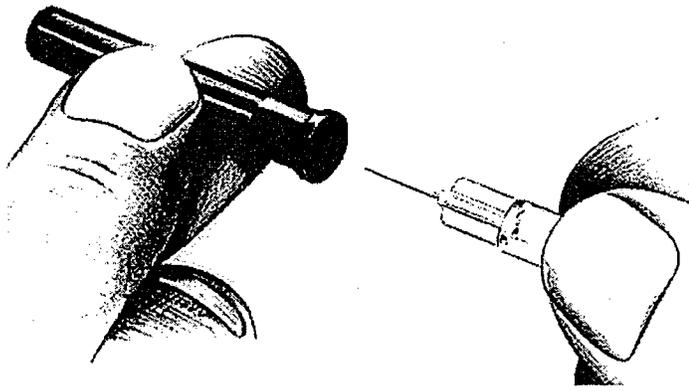
**2. Check the liquid in the container. It should look clear. DO NOT USE if it is not clear or if it has particles in it. If using a new bottle, flip off the plastic cover to expose the grey rubber stopper. Use an alcohol swab to cleanse the metal ring and rubber stopper on medication bottle every day, just before you use it.**



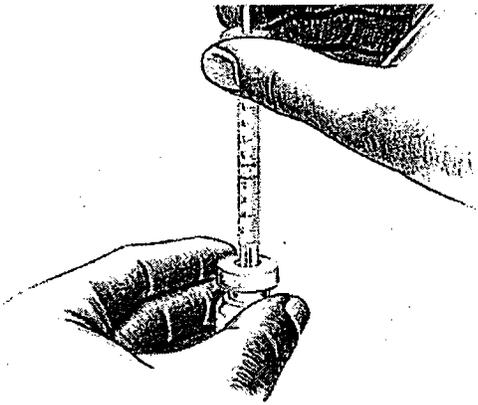
**3. Remove outer wrapping from one syringe.**



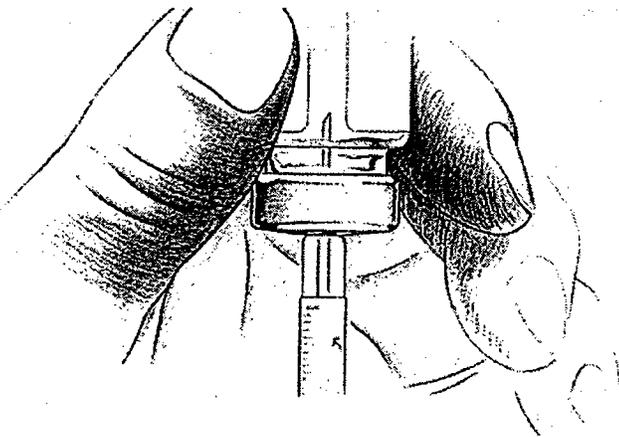
**4. Pull the syringe plunger back until its tip is at the proper mark.**



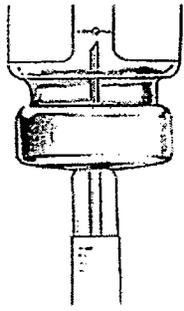
**5. Uncover needle. Do not touch the needle.**



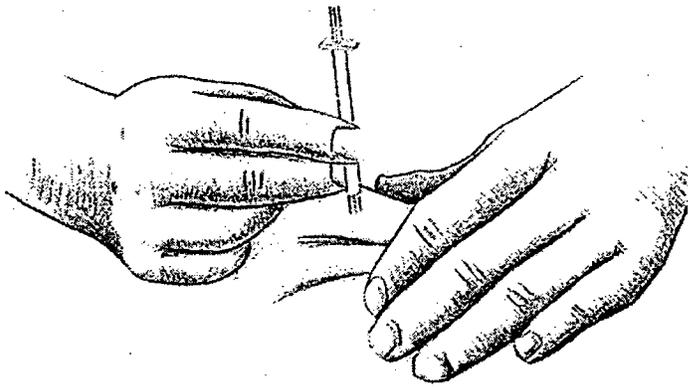
**6. Place the bottle on a clean, flat surface and push the needle through the center of the rubber stopper on the bottle. Push the plunger all the way in to inject air into the bottle.**



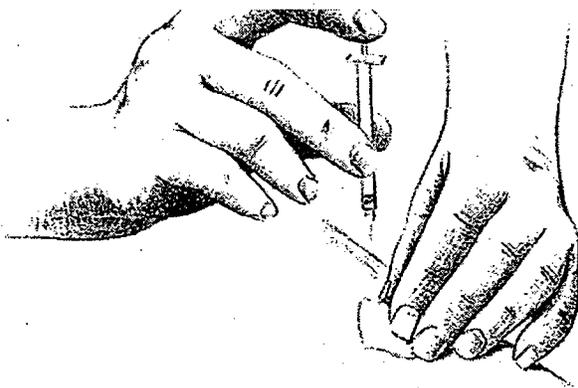
**7. Keep the needle in the bottle. Lift the bottle and turn it straight upside down. Check to see that the needle tip is in the liquid.**



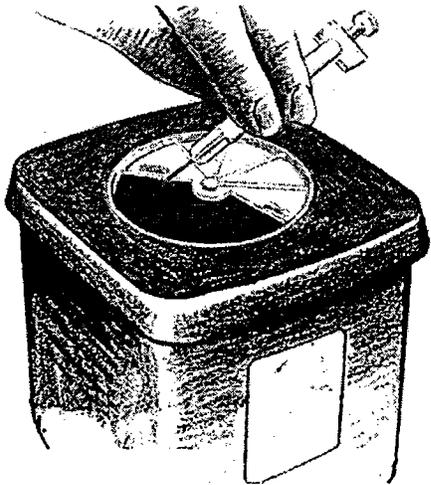
- 8. With the needle tip in the liquid, slowly pull back the plunger until syringe fills to the proper mark.  
If any bubbles appear in the syringe, remove them by pushing the plunger up slowly.  
With the needle tip still in the liquid, pull the plunger until it is once more at the proper mark.**



- 9. Choose a different injection site each day.  
Cleanse the injection site with a new alcohol swab.  
Hold the skin the way you were instructed.  
Slide the needle quickly all the way through the skin, into the subcutaneous tissue, at a 90° angle.**



- 10. Push the plunger to inject the medication.  
Withdraw the needle at the same angle it was inserted (90°).  
Wipe the skin with an alcohol swab.**



- 11. Dispose of the syringe and alcohol swabs as you were instructed.  
Remember: use the disposable syringe only once.**

**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*

**NDA 19-010/S-031**

**ADMINISTRATIVE**

## Division of Reproductive and Urologic Drug Products

### REGULATORY PROJECT MANAGER REVIEW

**Applicant:** TAP Pharmaceutical Products, Inc.

**Materials Reviewed:**

NDA	Supplement	Name of Drug	Letter Date	Receipt Date
19-732	SCS-027	Lupron Depot (leuprolide acetate for depot suspension), 7.5mg	May 6, 2005	May 9, 2005
19-732	SLR-029	Lupron Depot (leuprolide acetate for depot suspension), 7.5mg	August 18, 2005	August 19, 2005
20-517	SCS-018	Lupron Depot (leuprolide acetate for depot suspension), 4-month, 30mg	May 6, 2005	May 9, 2005
20-517	SLR-019	Lupron Depot (leuprolide acetate for depot suspension), 4-month, 30mg	August 18, 2005	August 19, 2005
19-010	SLR-031	Lupron Injection (leuprolide acetate	August 18, 2005	August 19, 2005
20-708	SCS-020	Lupron Depot (leuprolide acetate for depot suspension), 3-month	May 6, 2005	May 9, 2005
20-708	SLR-021	Lupron Depot (leuprolide acetate for depot suspension), 3-month	August 18, 2005	August 19, 2005
19-943	SCS-022	Lupron Depot (leuprolide acetate for depot suspension), 3.75 mg	May 6, 2005	May 9, 2005
19-943	SLR-024	Lupron Depot (leuprolide acetate for depot suspension), 3.75 mg	August 18, 2005	August 19, 2005
20-011	SCS-029	Lupron Depot (leuprolide acetate for depot suspension), 3.75mg	May 6, 2005	May 9, 2005
20-011	SLR-031	Lupron Depot (leuprolide acetate for depot suspension), 3.75mg	August 18, 2005	August 19, 2005

### Background and Summary

In January 5, 2005, TAP issued a Dear Healthcare Professional letter and a Voluntary Recall of two particular lots from NDAs 20-517 and 20-708 where complaints of clumping were reported by healthcare professionals to TAP. In addition to TAP's initiation on investigating on the issue, they proposed changes to the labeling as a corrective action to the reported issue. Furthermore, the Sponsor proposes to revise the "Appearance" section of their drug product specification---as a chemistry supplement. These changes affects all of the Lupron Depot drug products with pre-

filled syringes and therefore, the changes are being proposed for all of the NDAs listed above, except for NDA 19-010 (does not have a pre-filled syringe).

In addition, on October 18, 2004, the Office of Drug Safety reviewed the MedWatch reports with significant adverse events of pituitary apoplexy following the administration of GnRH agonists. This review was followed by a Prior Approval supplement request letter dated May 11, 2005, issued by the Division of Reproductive and Urologic Drug Products to all of the sponsors of GnRH agonists, including all of the listed NDAs above, containing the following verbiage:



The above paragraph was further revised by the Division, concluding the final version which was conveyed to the Sponsor on July 15, 2005 prior to submitting the supplement, as follows:

*Pituitary apoplexy:* During post-marketing surveillance, rare cases of pituitary apoplexy (a clinical syndrome secondary to infarction of the pituitary gland) have been reported after the administration of gonadotropin-releasing hormone agonists. In a majority of these cases, a pituitary adenoma was diagnosed with a majority of pituitary apoplexy cases occurring within 2 weeks of the first dose, and some within the first hour. In these cases, pituitary apoplexy has presented as sudden headache, vomiting, visual changes, ophthalmoplegia, altered mental status, and sometimes cardiovascular collapse. Immediate medical attention has been required.

### REVIEW

Of the Lupron Recall changes, the labeling portion of the chemistry supplement was reviewed. See Chemistry review for the changes in the Appearance section of the specification. Listed below are the Sponsor's proposed changes containing the verbiage to the labels:

#### A. LUPRON RECALL:

- 1) In the Package Insert, under the DOSAGE AND ADMINISTRATION section, and in the INSTRUCTIONS ON HOW TO MIX AND ADMINISTER pamphlet:
  - a. The sponsor proposed to add the following statement as item #1:

The LUPRON DEPOT powder should be visually inspected and the syringe should NOT BE USED if clumping or caking is evident. A thin layer of powder on the wall of the syringe is considered normal. The diluent should appear clear.

b. The sponsor proposed to add the following statement to add onto item #4:

Keep the syringe UPRIGHT. Gently mix the microspheres ( [ ] powder) thoroughly to form a uniform suspension. The suspension will appear milky. If the powder adheres to the stopper or caking/clumping is present, tap the syringe with your finger to disperse. DO NOT USE if any of the powder has not gone into suspension.

B. PITUITARY APOPLEXY: The following text was inserted under the Postmarketing subsection of the Adverse Events section of the Package Insert:

*Pituitary apoplexy:* During post-marketing surveillance, rare cases of pituitary apoplexy (a clinical syndrome secondary to infarction of the pituitary gland) have been reported after the administration of gonadotropin-releasing hormone agonists. In a majority of these cases, a pituitary adenoma was diagnosed, with a majority of pituitary apoplexy cases occurring within 2 weeks of the first dose, and some within the first hour. In these cases, pituitary apoplexy has presented as sudden headache, vomiting, visual changes, ophthalmoplegia, altered mental status, and sometimes cardiovascular collapse. Immediate medical attention has been required.

A. PACKAGE INSERT: In addition to the changes listed below, all of the NDAs listed

The manufacturing company changed from Takeda Chemical Industries, Ltd. Osaka, Japan 541 to Takeda Pharmaceutical Company Limited Osaka, Japan 540-8645.

NDA	Lupron Recall	Pituitary Apoplexy	Other Changes
	Text inserted is as proposed andn requested for all of the supplements listed below.		
19-732	SCS-027: Acceptable	SLR-029: Acceptable	1. The labeling revision code and date changed from [ ] to <u>TAPDN295-V2; Revised: Month, Year</u> 2. Copyright year changed from [ ] to <u>1988- Year</u>
20-517, 3 mo	SCS-018: Acceptable	SLR-019: Acceptable	1. The labeling revision code and date changed from [ ] to <u>TAPDN293-V2; Revised: Month, Year</u> 2. Copyright year changed from [ ] to <u>1995 - Year</u>

20-517, 4 mo	SCS-018 Acceptable	SLR-019 Acceptable	<ol style="list-style-type: none"> <li>The labeling revision code and date changed from <input type="checkbox"/> to <u>TAPDN294-V2</u>; Revised: <u>Month, Year</u></li> <li>Copyright year changed from <input type="checkbox"/> to <u>1997 - Year</u></li> </ol>
20-011	SCS-029 Acceptable	SLR-031 Acceptable	<p>NDA 20-11 &amp; 19-943 share the same label, therefore this portion of the review applies to both applications:</p> <ol style="list-style-type: none"> <li><u>Rx only</u> is moved from the end of the label to the beginning—before DESCRIPTION section.</li> <li>The labeling revision code and date changed from <input type="checkbox"/> to <u>TAPDN296-V2</u>; Revised: <u>Month, Year</u></li> <li>Copyright year changed from <input type="checkbox"/> to <u>1990 - Year</u></li> </ol>
19-943	SCS-022 Acceptable	SLR-024 Acceptable	
19-010		SLR 031, Adult & Pediatric Use sections are Acceptable.	<ol style="list-style-type: none"> <li>The labeling revision code and date changed from <input type="checkbox"/> to <u>TAPDN299-V2, Rev. Month, Year</u></li> <li>Copyright year changed from <input type="checkbox"/> to <u>© 1993 - Year</u></li> </ol>
20-708	SCS-020 Acceptable	SLR-021 Acceptable	<ol style="list-style-type: none"> <li>"Rx only" is moved from the end of the label to the beginning</li> <li>The labeling revision code and date changed from <input type="checkbox"/> to <u>TAPDN297-V2, Revised: MONTH, YEAR</u></li> <li>Copyright year changed from <input type="checkbox"/> to <u>© 1993 - YEAR</u></li> </ol>

B. MIXING INSTRUCTIONS: Text inserted in items #1 & #4 are as proposed for all the supplements listed below and are acceptable.

20-708	SCS-020	<p>The following changes are in addition to the changes regarding Lupron Recall and are acceptable:</p> <ol style="list-style-type: none"> <li>The Sponsor inserted the exact verbiage of the agreed-upon text in all of these supplements on the Mixing Instructions leaflet, as indicated above.</li> <li>In addition, the Sponsor added the following:</li> </ol> <div style="text-align: center;">  <p><b>REVIEW REVISED MIXING INSTRUCTIONS</b></p> </div>
19-943	SCS-022	
20-011	SCS-029	
20-517, 3mo & 4mo	SCS-018	
19-732	SCS-027	

**Conclusions**

Based on this labeling review, these supplemental applications are recommended for approval, as concurred by Chemistry and Clinical.

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Nenita Crisostomo, R.N.  
Regulatory Health Project Manager

Supervisory Comment/Concurrence:

*{see appended electronic signature}*

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Jennifer Mercier  
Chief, Project Management Staff

PM Labeling Review: Lupron Recall & Apoplexy  
Page 6 of 6

Drafted: NIC/9.5.05  
Revised/Initialed: AGassman9.9.05, MHirsch9.9.05, SDe9.9.05, JMercier  
Finalized: DFS/NCrisostomo/9.9.05  
Filename: review.SLR.apoplexy.Recall

**CSO LABELING REVIEW**

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

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Nenita Crisostomo  
9/9/2005 04:11:28 PM  
CSO

Jennifer L. Mercier  
9/19/2005 04:48:47 PM  
CSO

**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*

**NDA 19-010/S-031**

**CORRESPONDENCE**

**Electronic Regulatory Submission for Archive**

October 28, 2005

Dr. Daniel Shames, MD, Division Director  
Division of Reproductive and Urologic Drug Products, HFD-580  
Center for Drug Evaluation and Research  
Electronic Document Room  
5901-B Ammendale Road  
Beltsville, MD 20705

**Attn: Nenita Crisostomo, RN, Regulatory Project Manager**

**RE: Lupron<sup>®</sup> Injection (leuprolide acetate)**  
Prostate cancer  
NDA 19-010

**FPL for Approved Supplement NDA 19-010/S-031**

Dear Dr. Shames:

TAP Pharmaceutical Products Inc. hereby submits the Final Printed Labeling (FPL) per the approval letter dated September 15, 2005 for the above-referenced supplemental New Drug Application. The FPL is identical to the submitted labeling on August 18, 2005.

**The following information is included in this submission:**

- Module 1.14.2.2: Final Printed Labeling in PDF format (Commodity Number: 03-5452-R5; Revision Date: October 2005)
- Module 1.14.2.3: Final Labeling Text in MS Word format

This submission is provided in an electronic Common Technical Document (eCTD) format. The only exception from electronic format is signatures, originals of which are provided on paper. Electronic documents are provided in Adobe PDF 1.3 (Adobe 4.05b) format. This submission is approximately 5 megabytes and is provided on one CD-ROM. This submission has been checked for viruses using McAfee Virus Scan Enterprise 7.1.0, and is virus free.

The printed contents of the index-md5.txt file are appended to this letter.

NDA 19-010  
Lupron® Injection (leuprolide acetate)  
October 28, 2005  
Page 2 of 2

Should you have any questions or comments, please contact me at the information provided below.

Sincerely,

Tonya Haynes  
Regulatory Product Manager  
TAP Pharmaceutical Products Inc.  
675 N. Field Drive  
Lake Forest, IL 60045  
Tel: (847) 582-2633  
Fax: (847) 582-2880



NDA 20-517/S-019    NDA 20-011/S-031  
NDA 20-708/S-021    NDA 19-732/S-029  
NDA 19-010/S-031    NDA 19-943/S-024

**PRIOR APPROVAL SUPPLEMENT**

TAP Pharmaceutical Products Inc.  
Attention: Tonya Haynes, M.P.H.  
Regulatory Product Manager  
675 North Field Drive  
Lake Forest, IL 60045

Dear Ms. Hayes:

We have received your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product	NDA#	Supplement number	Date of Supplement	Date of Receipt
Lupron Depot (leuprolide acetate for depot suspension), 3-Month, 22.5 mg, <i>and</i> ,  Lupron Depot (leuprolide acetate for depot suspension), 4-Month, 30 mg	20-517	S-019	August 18, 2005	August 19, 2005
Lupron Depot (leuprolide acetate for depot suspension), 3.75 mg	20-011	S-031	August 18, 2005	August 19, 2005
Lupron Depot (leuprolide acetate for depot suspension), 7.5 mg	19-732	S-029	August 18, 2005	August 19, 2005
Lupron Depot (leuprolide acetate for depot suspension), 3-Month, 11.25 mg	20-708	S-021	August 18, 2005	August 19, 2005
Lupron Injection (leuprolide acetate)	19-010	S-031	August 18, 2005	August 19, 2005
Lupron Depot (leuprolide acetate for depot suspension), 3.75 mg	19-943	S-024	August 18, 2005	August 19, 2005

NDA 20-517/S-019    NDA 20-011/S-031  
NDA 20-708/S-021    NDA 19-732/S-029  
NDA 19-010/S-031    NDA 19-943/S-024  
Page 2

These supplemental applications propose the revision to the Postmarketing subsection of the Adverse Reaction section in the package insert to add information regarding pituitary apoplexy.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on October 18, 2005, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be February 17, 2006.

Please cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Reproductive and Urologic Drug Products, HFD-580  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

If you have any question, please call me, at (301) 827-7260.

Sincerely,

*{See appended electronic signature page}*

Nenita Crisostomo, R.N.  
Regulatory Health Project Manager  
Division of Reproductive and Urologic Drug  
Products, HFD-580  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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

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Nenita Crisostomo  
9/1/2005 07:14:45 PM