

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Approval Package for:**

***APPLICATION NUMBER:***  
**NDA 20-263/S-028**

***Name:*** Lupron Depot-PED  
7.5 mg, 11.25 mg, 15 mg  
(leuprolide acetate for depot suspension)  
&  
Lupron Injection  
(leuprolide acetate)

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

***Approval Date:*** February 16, 2006

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**NDA 20-263/S-028**

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**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*

**NDA 20-263/S-028**

**APPROVAL LETTER**



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 20-263/S-028

TAP Pharmaceutical Products, Inc.  
Attention: Tanya Haynes  
Regulatory Affairs Product Manager  
675 North Field Drive  
Lake Forest, IL 60045

Dear Ms. Haynes:

Please refer to your supplemental new drug application dated August 18, 2005, received August 19, 2005, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lupron (leuprolide acetate) Injection, 5 mg/ml (for pediatric use) and Lupron Depot-Ped (leuprolide acetate for depot suspension), 7.5, 11.25, and 15 mg prefilled syringes.

This supplemental new drug application provides for revision to the package inserts to add pituitary apoplexy to the **Postmarketing** subsection of the **ADVERSE REACTIONS** section.

We completed our review of this application and it is 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 enclosed labeling (text for the package inserts).

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved supplement NDA 20-263/S-028.**" Approval of this submission by FDA is not required before the labeling is used.

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  
Food and Drug Administration  
WO 22, Room 4447  
10903 New Hampshire Avenue  
Silver Spring, MD 20993-0002

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

If you have any questions, call Pat Madara, Regulatory Project Manager, at (301) 796-1249.

Sincerely,

*{See appended electronic signature page}*

Mary H. Parks, M.D.  
Acting Division Director  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center of Drug Evaluation and Research

Enclosures: draft package inserts:

1. Lupron Injection, 5 mg/mL (for pediatric use)
2. Lupron Depot-Ped, 7.5 mg, 11.25 mg and 15 mg, prefilled, dual-chamber syringes

**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*  
**NDA 20-263/S-028**

**FINAL PRINTED LABELING**

For Pediatric Use

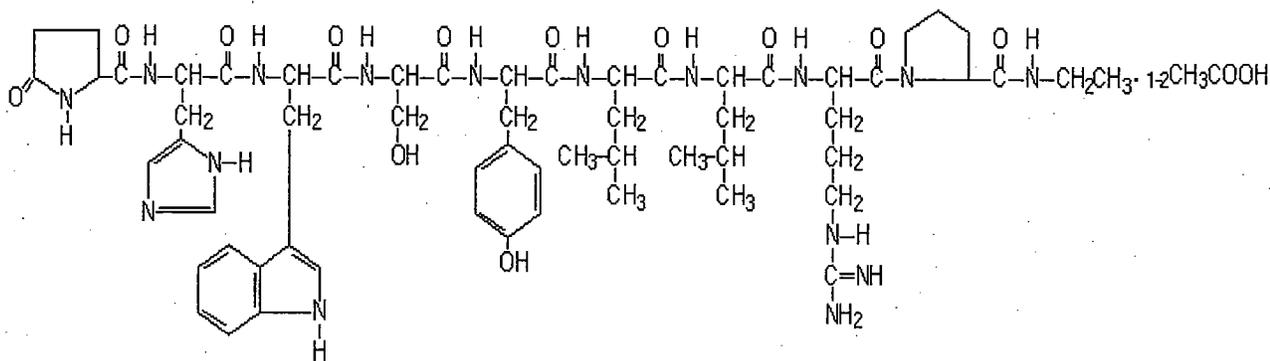
## LUPRON<sup>®</sup> INJECTION

(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

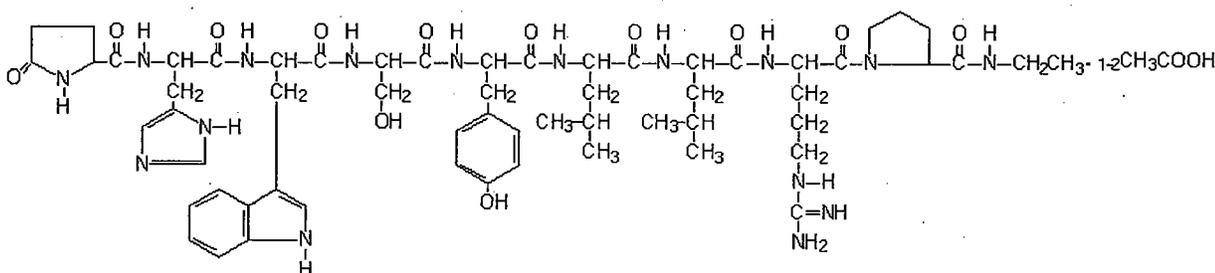
(No. 3612)

**LUPRON DEPOT-PED®**

(leuprolide acetate for depot suspension)

**7.5 mg, 11.25 mg and 15 mg****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 DEPOT-PED is available in a prefilled dual-chamber syringe containing sterile lyophilized microspheres which, when mixed with diluent, become a suspension intended as a single intramuscular injection.

The front chamber of LUPRON DEPOT-PED 7.5 mg, 11.25 mg, and 15 mg prefilled dual-chamber syringe contains leuprolide acetate (7.5/11.25/15 mg), purified gelatin (1.3/1.95/2.6 mg), DL-lactic and glycolic acids copolymer (66.2/99.3/132.4 mg), and D-mannitol (13.2/19.8/26.4 mg). The second chamber of diluent contains carboxymethylcellulose sodium (5 mg), D-mannitol (50 mg), polysorbate 80 (1 mg), water for injection, USP, and glacial acetic acid, USP to control pH.

During the manufacture of LUPRON DEPOT-PED, acetic acid is lost, leaving the peptide.

**CLINICAL PHARMACOLOGY**

Leuprolide acetate, a GnRH agonist, acts as a potent inhibitor of gonadotropin secretion when given continuously and in therapeutic doses. Human studies indicate that following an initial stimulation of gonadotropins, chronic stimulation with leuprolide acetate results in suppression or "downregulation" of these hormones and consequent suppression of ovarian and testicular steroidogenesis. These effects are reversible on discontinuation of drug therapy.

Leuprolide acetate is not active when given orally.

**Pharmacokinetics**

**Absorption** Following a single LUPRON DEPOT 7.5 mg injection to adult patients, mean peak leuprolide plasma concentration was almost 20 ng/mL at 4 hours and then declined to 0.36 ng/mL at 4 weeks. However, intact leuprolide and an inactive major metabolite could not be distinguished by the assay which was employed in the study. Nondetectable leuprolide plasma concentrations have been observed during chronic LUPRON DEPOT 7.5 mg administration, but testosterone levels appear to be maintained at castrate levels.

**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.

## 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.

In a study of 22 children with central precocious puberty, doses of LUPRON DEPOT were given every 4 weeks and plasma levels were determined according to weight categories as summarized below:

Patient Weight Range (kg)	Group Weight Average (kg)	Dose (mg)	Trough Plasma Leuprolide Level Mean $\pm$ SD (ng/mL)*
20.2 - 27.0	22.7	7.5	0.77 $\pm$ 0.033
28.4 - 36.8	32.5	11.25	1.25 $\pm$ 1.06
39.3 - 57.5	44.2	15.0	1.59 $\pm$ 0.65

\*Group average values determined at Week 4 immediately prior to leuprolide injection. Drug levels at 12 and 24 weeks were similar to respective 4 week levels.

## INDICATIONS AND USAGE

LUPRON DEPOT-PED 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 one 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

LUPRON DEPOT-PED is contraindicated in women who are or may become pregnant while receiving the drug. 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 of the human pediatric dose) to rabbits, LUPRON DEPOT 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 DEPOT in rabbits and with the highest dose in rats. The effects on fetal mortality are logical 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.

Leuprolide acetate is contraindicated in children demonstrating hypersensitivity to GnRH, GnRH agonist analogs, or any of the excipients.

A report of an anaphylactic reaction to synthetic GnRH (Factrel) has been reported in the medical literature.<sup>1</sup>

## 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

**Laboratory Tests** Response to LUPRON DEPOT-PED 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** No pharmacokinetic-based drug-drug interaction studies have been conducted. 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.

**Drug/Laboratory Test Interactions** Administration of LUPRON DEPOT 3.75 mg in women results in suppression of the pituitary-gonadal system. Normal function is usually restored within three months after treatment is discontinued. Therefore, diagnostic tests of pituitary gonadotropic and gonadal functions conducted during treatment and for up to three months after discontinuation of LUPRON DEPOT may be misleading.

**Information for Parents** Prior to starting therapy with LUPRON DEPOT-PED, the parent or guardian must be aware of the importance of continuous therapy. Adherence to 4 week drug administration schedules must be accepted if therapy is to be successful.

- 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.
- Report any unusual signs or symptoms to the physician.

**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 (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 leuprolide acetate-induced tumors or pituitary abnormalities were observed at a dose as high as 60 mg/kg for two years. 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.)

**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 also the labeling for LUPRON DEPOT 7.5 mg which is indicated for the palliative treatment of advanced prostate cancer. For LUPRON DEPOT-PED 11.25 mg and LUPRON DEPOT-PED 15 mg, no clinical information has been established for persons aged 65 and over.

## **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 which are not considered drug-related are excluded.

	Number of Patients	
	N = 395	(%)
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* - Emotional Lability, Nervousness, Personality Disorder, Somnolence; *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, the following adverse events were reported.

Symptoms consistent with an anaphylactoid or asthmatic process have been rarely reported. Rash, urticaria, and photosensitivity reactions have also been reported.

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

*Cardiovascular System* - Hypotension; *Hemic and Lymphatic System* - Decreased WBC; *Central/Peripheral Nervous System* - Peripheral neuropathy, Spinal fracture/paralysis; *Musculoskeletal System* - Tenosynovitis-like symptoms; *Urogenital System* - Prostate pain.

*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 different 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 DEPOT-PED must be administered under the supervision of a physician.*

The dose of LUPRON DEPOT-PED 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.

For each dosage form, 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.

Discontinuation of LUPRON DEPOT-PED should be considered before age 11 for females and age 12 for males.

The recommended starting dose is 0.3 mg/kg/4 weeks (minimum 7.5 mg) administered as a single intramuscular injection. The starting dose will be dictated by the child's weight.

≤ 25 kg	7.5 mg
> 25-37.5 kg	11.25 mg
> 37.5 kg	15 mg

If total downregulation is not achieved, the dose should be titrated upward in increments of 3.75 mg every 4 weeks. This dose will be considered the maintenance dose.

The lyophilized microspheres are to be reconstituted and administered as a single intramuscular injection. *For optimal performance of the prefilled dual chamber syringe (PDS), read and follow the following instructions:*

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.
2. To prepare for injection, screw the white plunger into the end stopper until the stopper begins to turn.

3. Hold the syringe UPRIGHT. Release the diluent by SLOWLY PUSHING (6 to 8 seconds) the plunger until the first stopper is at the blue line in the middle of the barrel.
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.
5. Hold the syringe UPRIGHT. With the opposite hand pull the needle cap upward without twisting.
6. Keep the syringe UPRIGHT. Advance the plunger to expel the air from the syringe.
7. Inject the entire contents of the syringe intramuscularly at the time of reconstitution. The suspension settles very quickly following reconstitution; therefore, LUPRON DEPOT should be mixed and used immediately.

NOTE: Aspirated blood would be visible just below the luer lock connection if a blood vessel is accidentally penetrated. If present, blood can be seen through the transparent LuproLoc™ safety device.

#### AFTER INJECTION

8. Withdraw the needle. Immediately activate the LuproLoc™ safety device by pushing the arrow forward with the thumb or finger until the device is fully extended and a CLICK is heard or felt.

Since the product does not contain a preservative, the suspension should be discarded if not used immediately.

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

#### HOW SUPPLIED

LUPRON DEPOT-PED is packaged as follows:

Kit with prefilled dual-chamber syringe	7.5 mg	NDC 0300-2108-01
Kit with prefilled dual-chamber syringe	11.25 mg	NDC 0300-2282-01
Kit with prefilled dual-chamber syringe	15 mg	NDC 0300-2440-01

Each syringe contains sterile lyophilized microspheres which is leuprolide incorporated in a biodegradable copolymer of lactic and glycolic acids. When mixed with diluent, LUPRON DEPOT-PED is administered as a single IM injection.

An information pamphlet for parents is included with the kit.

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [See USP Controlled Room Temperature]

**REFERENCE**

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

U.S. Patent Nos. 4,652,441; 4,677,191; 4,728,721; 4,849,228; 4,917,893; 5,330,767; 5,476,663; 5,823,997; 5,980,488; and 6,036,976. Other patents pending.



Manufactured for  
TAP Pharmaceuticals Inc.  
Lake Forest, IL 60045, U.S.A.  
by Takeda Pharmaceutical Company Limited  
Osaka, JAPAN 540-8645

<sup>TM</sup> -Trademark

® — Registered Trademark

(Nos. 2108, 2282, 2440)

TAPDN298-V2; Revised: MONTH, YEAR

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/s/

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Mary Parks  
2/16/2006 01:42:06 PM

**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*

**NDA 20-263/S-028**

**CORRESPONDENCE**

**Electronic Regulatory Submission for Archive**

March 16, 2006

Dr. Mary Parks, M.D., Acting Director  
Center for Drug Evaluation and Research  
Division of Metabolic and Endocrine Drug Products  
Electronic Document Room  
5901-B Ammendale Road  
Beltsville, MD 20705

**Attn: Pat Madera, Regulatory Project Manager**

RE: Lupron PED (leuprolide acetate/injection/depot suspension)  
Treatment of Central Precocious Puberty  
NDA 20-263

**FPL for Approved Supplement NDA 20-263/S-028**

Dear Dr. Parks:

TAP Pharmaceutical Products Inc. hereby submits the Final Printed Labeling (FPL) per the approval letter dated February 16, 2006 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 for Lupron<sup>®</sup> Injection in PDF format (Commodity Number: 03-5452-R5; Revision Date: October 2005)
- Module 1.14.2.2: Final Printed Labeling for Lupron Depot PED<sup>®</sup> in PDF format (Commodity Number: 03-5446-R14; Revision Date: February 2006)
- Module 1.14.2.3: Final Labeling Text for Lupron Depot PED<sup>®</sup> in SPL format

According to the "FDA SPL Implementation Guide for FDA Content of Labeling Submissions" dated January 2006, only one label per submission can be submitted to the Agency in SPL format. Therefore, this submission contains the Lupron Depot PED<sup>®</sup> package insert in SPL format and the Lupron<sup>®</sup> Injection package insert will be provided in SPL format within a later submission.

NDA 20-263  
Lupron PED (leuprolide acetate/injection/depot suspension)  
March 16, 2006  
Page 2 of 2

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 3 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.

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 20-263/S-028

PRIOR APPROVAL SUPPLEMENT

TAP Pharmaceutical Products Inc.  
Attn: Jessie Y. Lee, Ph.D., RAC  
Principal Regulatory Advisor  
675 North Field Drive  
Lake Forest, IL 60045

Dear Dr. Lee:

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

Name of Drug Product: Lupron PED (leuprolide acetate/injection/depot/suspension)

NDA Number: 20-263

Supplement number: S-028

Date of supplement: August 18, 2005

Date of receipt: August 19, 2005

This supplemental application provides for labeling revision to the package insert to add pituitary apoplexy to the Postmarketing subsection of the ADVERSE REACTIONS section.

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 19, 2006.

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service/Courier/Overnight Mail:  
Food and Drug Administration, CDER  
ATTN: Division of Metabolism and Endocrinology Products (DMEP)  
Central Document Room (CDR)  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

NDA 20-263/S-028

Page 2

If you have any questions, call me, at (301) 827-6380.

Sincerely,

*{See appended electronic signature page}*

Kati Johnson  
Chief, Project Management Staff  
Division of Metabolic & Endocrine Drug Products  
Office of Drug Evaluation II  
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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Kati Johnson  
9/1/2005 06:26:52 AM

**Electronic Regulatory Submission for Archive**

August 18, 2005

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Metabolic and Endocrine Drug Products, HFD#510  
Attention: CENTRAL DOCUMENT ROOM  
5901-B Ammendale Road  
Beltsville, Maryland 20715-1266

ATTENTION: David Orloff, M.D.  
Director

RE: NDA 20-263 Lupron PED (leuprolide acetate/injection/depot suspension)  
Sequence No.: 0004

**Prior Approval Labeling Supplement**

TAP Pharmaceutical Products Inc. hereby supplements the above-referenced NDA to provide for the labeling revision to the package insert of Lupron to include the serious post-marketing adverse event, pituitary apoplexy, which may occur in all gonadotropin-releasing hormone (GnRH) agonists, including LUPRON.

This is in response to an FDA letter dated May 11, 2005 (received on July 11, 2005) requesting the labeling revision within 30 days of receipt of the letter. The suggested labeling change was further clarified by the Agency and the revised wording was received on August 5, 2005. TAP's request to postpone the labeling submission from the original committed date of August 10, 2005 to August 24, 2005 was granted.

As requested, the package insert has been revised to add pituitary apoplexy, a serious adverse event, in the Postmarketing subsection of the Adverse Reaction section. Provided are electronic files (both PDF and MS Word) for the annotated and draft labeling per eCTD format.

The original signatures are provided on paper for the cover letter and FDA Form 356h. The PDF documents are provided in Adobe PDF 1.3 (Adobe 4.05) format. This submission is approximately 11 MB and is provided in one CD-ROM. The electronic files have been scanned for computer viruses using Virus Scan Enterprise version 7.0 and are virus free. The printed contents of the index-md5.txt are appended to this letter.

Dr. D. Orloff  
August 18, 2005  
Page 2

If there are any further questions, please feel free to contact Donna Helms, Director of TAP Regulatory Affairs, at (847) 582-4922.

Sincerely,

TAP Pharmaceutical Products Inc.

Jessie Y. Lee, Ph.D. RAC  
Principal Regulatory Advisor  
Phone: (847) 582-4924  
Fax: (847) 582-2880  
E-mail: [Jessie.Lee@TAP.com](mailto:Jessie.Lee@TAP.com)

JYL/jl

Attachment

C:08-2005FDA.JYL/20