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. 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 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 thoroughly to form a uniform suspension. LEUPROLIDE acetate (7.5/11.25/15 mg), purified gelatin...and glacial acetic acid, USP to control pH.

LUPRON DEPOT-PED must be administered under the supervision of a physician. LUPRON DEPOT-PED-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. Overdosage in rats, subcutaneous administration of 125 to 250 times the recommended human pediatric dose, expressed on a per body weight basis, resulted in...anastrozole, 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...despite the coexistence of ovarian and testicular steroidogenesis. These effects are reversible on discontinuation of drug therapy.

Lupron acetate is not active when given orally.
Pharmacokinetics
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/hr. with a terminal elimination half-life of approximately 3 hours based on a two compartment model.

In rats and dogs, administration of 14C-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 prepubertal 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. 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:

<table>
<thead>
<tr>
<th>Patient Weight Range (kg)</th>
<th>Group Weight Average (kg)</th>
<th>Dose (mg)</th>
<th>Trough Plasma Leuprolide Level Mean ± SD (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20.5 - 37.0</td>
<td>29.7</td>
<td>15</td>
<td>0.77 ± 0.009</td>
</tr>
<tr>
<td>28.4 - 36.8</td>
<td>32.5</td>
<td>11.25</td>
<td>1.25 ± 0.16</td>
</tr>
<tr>
<td>39.3 - 57.5</td>
<td>44.2</td>
<td>10.0</td>
<td>1.59 ± 0.05</td>
</tr>
</tbody>
</table>

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.

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 rats, 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.

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 retention of pubertal signs such as menarche, breast development, and testicular growth. The long-term consequences of inadequate control of gonadal steroid secretions 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 hepatic enzymes 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 gonadotropin 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 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 on 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.) 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 probable or possible relationship to drug as ascribed by the treating physician. Reactions which are not considered drug-related are excluded.

<table>
<thead>
<tr>
<th>Indication</th>
<th>Number of Patients N = 395 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body as a Whole</td>
<td>7 (2)</td>
</tr>
<tr>
<td>General Pain</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Integumentary System</td>
<td>21 (5)</td>
</tr>
<tr>
<td>Acne/Seborrhea</td>
<td>21 (5)</td>
</tr>
<tr>
<td>Injection Site Reactions</td>
<td>8 (2)</td>
</tr>
<tr>
<td>Including Abscess</td>
<td>8 (2)</td>
</tr>
<tr>
<td>Rash</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Including Abscess</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Vaginitis/Bleeding/Discharge</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Urinary System</td>
<td>7 (2)</td>
</tr>
</tbody>
</table>
INSTRUCTIONS
ON HOW TO
MIX AND
ADMINISTER

ADDITIONAL INFORMATION

- None of the components is hazardous; therefore, no special handling or disposal procedures are needed.
- Dispose of the syringe according to local regulations/procedures.

LuproLoc™
Other patents pending.

TAP Pharmaceuticals Inc.
Lake Forest, IL 60045

If you have any questions regarding the drug or the mixing/administration procedure, please call 1-800-622-2011 for further assistance.

NOTE: LUPRON DEPOT® and LUPRON DEPOT-PED® must be administered under the supervision of a physician.
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, as illustrated, until the device is fully extended and a CLICK is heard or felt.