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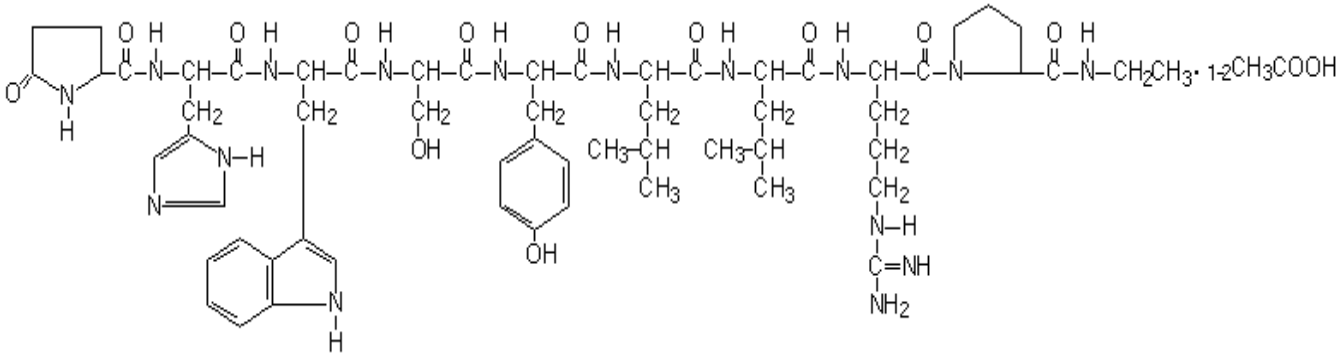
LUPRON®

(leuprolide acetate) Injection

DESCRIPTION

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

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, 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 circulation 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 all patients. 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. Bioavailability by subcutaneous administration is comparable to that by intravenous administration. Leuprolide acetate has a plasma half-life of approximately three hours. The metabolism, distribution and excretion of leuprolide acetate in man have not been determined.

INDICATIONS AND USAGE

LUPRON (leuprolide acetate) Injection is indicated in the palliative treatment of advanced prostatic cancer. It offers an alternative treatment of prostatic cancer when orchiectomy or estrogen administration are either not indicated or unacceptable to the patient. 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 treatment. The objective response to treatment was also similar for the two groups.

CONTRAINDICATIONS

A report of an anaphylactic reaction to synthetic GnRH (Factrel) has been reported in the medical literature.[1]

LUPRON 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 (1/600 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 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. 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.

WARNINGS

Isolated cases of worsening of signs and symptoms during the first weeks of treatment have been reported. Worsening of symptoms may contribute to paralysis with or without fatal complications.

PRECAUTIONS

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

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 "HOW SUPPLIED" section.

Laboratory Tests: Response to leuprolide acetate should be monitored by measuring serum levels of testosterone and acid phosphatase. 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. Transient increases in acid phosphatase levels occurred sometimes early in treatment. However, by the fourth week, the elevated levels usually decreased to values at or near baseline.

Drug Interactions: None have been reported.

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). 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 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 Category X. See "CONTRAINDICATIONS" section.

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

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 (leuprolide acetate) Injection 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.

	LUPRON (N=98)	DES (N=101)
	Number of Reports	
Cardiovascular System		
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
Gastrointestinal System		
Anorexia	6	5
Constipation	7	9
Nausea/vomiting	5	17
Endocrine System		
*Decreased testicular size	7	11
*Gynecomastia/breast tenderness or pain	7	63
*Hot flashes	55	12
*Impotence	4	12
Hemic and Lymphatic System		
Anemia	5	5
Musculoskeletal System		
Bone pain	5	2
Myalgia	3	9
Central/Peripheral Nervous System		
Dizziness/lightheadedness	5	7
General pain	13	13
Headache	7	4
Insomnia/sleep disorders	7	5
Respiratory System		
Dyspnea	2	8
Sinus congestion	5	6
Integumentary System		
Dermatitis	5	8
Urogenital System		
Frequency/urgency	6	8
Hematuria	6	4
Urinary tract infection	3	7
Miscellaneous		
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).

The following additional adverse reactions have been reported with LUPRON or LUPRON DEPOT (leuprolide acetate for depot suspension) during other clinical trials and/or during postmarketing surveillance. Reactions considered as nondrug related by the treating physician are excluded.

Cardiovascular System—Hypotension, Transient ischemic attack/stroke; *Gastrointestinal System*—Hepatic dysfunction; *Endocrine System*—Libido increase; *Hemic and Lymphatic System*—Decreased WBC, Hemoptysis; *Musculoskeletal System*—Ankylosing spondylosis, Pelvic fibrosis; *Central/ Peripheral Nervous System*—Hearing disorder, Peripheral neuropathy, Spinal fracture/paralysis; *Respiratory System*—Pulmonary infiltrate, Respiratory disorders; *Integumentary System*—Hair growth; *Urogenital System*—Penile swelling, Prostate pain; *Miscellaneous*—Hypoproteinemia, Hard nodule in throat, Weight gain, Increased uric acid.

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.

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

HOW SUPPLIED

LUPRON (leuprolide acetate) Injection is a sterile solution supplied in a 2.8 mL multiple-dose vial, NDC 0300-3612-28. Store below 77°F (25°C). Do not freeze. Protect from light—store vial in carton until use.

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.

Rx ONLY

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

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

WHAT IS LUPRON?

LUPRON (leuprolide acetate) Injection 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 (leuprolide acetate) Injection, 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 gray 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. Remove needle from bottle and lay syringe down. DO NOT TOUCH THE NEEDLE OR ALLOW THE NEEDLE TO TOUCH ANY SURFACE.

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.

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 (leuprolide acetate) Injection. 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.
- 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.
- 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, 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

® – Registered
(No. 3612)

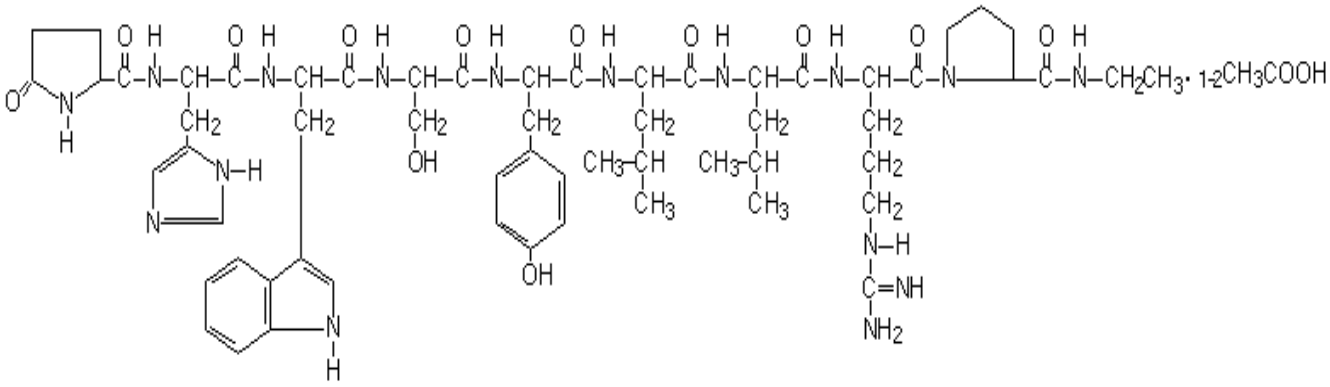
For Pediatric Use

LUPRON®

(leuprolide acetate) Injection

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.

- A 2.8 mL multiple dose vial contains leuprolide acetate (5 mg/mL), sodium chloride (6.3 mg/mL) for tonicity adjustment, benzyl alcohol as a preservative (9 mg/mL), and water for injection. The pH may have been adjusted with sodium hydroxide and/or acetic acid.

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. In adults, bioavailability by subcutaneous administration is comparable to that by intravenous administration; and leuprolide acetate has a plasma half-life of approximately three hours. The metabolism, distribution and excretion of leuprolide acetate in humans have not been determined. A pharmacokinetic study of leuprolide acetate in children has not been performed.

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 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 Injection 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 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. 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.[1]

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.

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: 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 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.

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.

- 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 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 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 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 labeling for LUPRON Injection for the pharmacokinetics, efficacy and safety of LUPRON in this population.

ADVERSE REACTIONS

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.

	Number of Patients N = 395	**(Percent)**
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.

See other 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.

For either 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.

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.

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

HOW SUPPLIED

LUPRON (leuprolide acetate) Injection is a sterile solution.

• A 2.8 mL multiple dose vial (NDC 0300-3612-28) contains leuprolide acetate (5 mg/mL), sodium chloride (6.3 mg/mL) for tonicity adjustment, benzyl alcohol as a preservative (9 mg/mL), and water for injection. The pH may have been adjusted with sodium hydroxide and/or acetic acid.
- 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. The volume of drug for the dose will vary depending on the syringe used and the concentration of drug.

Rx ONLY

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

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