

PRODUCT MONOGRAPH

Pr LUPRON[®]
leuprolide acetate injection

5 mg/mL

Pr LUPRON DEPOT[®]
leuprolide acetate for depot suspension
pre-filled dual chamber syringe containing sterile lyophilized microspheres
3.75 mg/syringe (1-Month slow release), 7.5 mg/syringe (1-Month slow release), 11.25
mg/syringe (1-Month slow release), 15 mg/syringe (1-Month slow release)

Gonadotropin-releasing hormone analog

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Pr LUPRON®

leuprolide acetate injection

Pr LUPRON DEPOT®

leuprolide acetate for depot suspension

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form/Strength	Clinically Relevant Non-medicinal Ingredients
LUPRON®		
subcutaneous	multiple-dose vial / 5 mg/mL	acetic acid, benzyl alcohol, sodium chloride, sodium hydroxide
LUPRON DEPOT®		
intramuscular	pre-filled dual chamber syringe containing sterile lyophilized microspheres 3.75 mg (1-Month SR), 7.5 mg (1-Month SR), 11.25 mg (1-Month SR), and 15.0 mg (1-Month SR)	carboxymethylcellulose sodium, DL-lactic and glycolic acids copolymer, D-mannitol, gelatin, glacial acetic acid, polysorbate 80 <i>For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING section.</i>
Definition: SR = slow release		

INDICATIONS AND CLINICAL USE

LUPRON[®] (leuprolide acetate injection) and LUPRON DEPOT[®] (leuprolide acetate for depot suspension) are indicated for:

- 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 as follows:
 - (a) Confirmation of diagnosis by a pubertal response to a GnRH stimulation test. The sensitivity and methodology of this assay must be understood.
 - (b) Bone age advanced one year beyond the chronological age.
3. Baseline evaluation should also include:
 - (a) Height and weight measurements
 - (b) Sex steroid levels
 - (c) Adrenal steroid level to exclude congenital adrenal hyperplasia
 - (d) Beta human chorionic gonadotropin level to rule out a chorionic gonadotropin secreting tumor
 - (e) Pelvic/adrenal/testicular ultrasound to rule out a steroid secreting tumor
 - (f) Computerized tomography of the head to rule out intracranial tumor

LUPRON DEPOT[®] must be administered under the supervision of a physician.

Geriatrics (> 65 years of age):

Refer to the “Prostatic Cancer” Product Monograph for the efficacy and safety of LUPRON[®] and LUPRON DEPOT[®] in this population.

CONTRAINDICATIONS

- LUPRON[®] (leuprolide acetate injection) and LUPRON DEPOT[®] (leuprolide acetate for depot suspension) are contraindicated in patients with hypersensitivity to the drug or its components or similar nonapeptides or components of the container. Isolated cases of anaphylaxis have been reported. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section.
- LUPRON[®] and LUPRON DEPOT[®] are contraindicated in women who are or may become pregnant. When LUPRON DEPOT[®] was 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 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 (0.024 mg/kg) 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.

Patients treated with LUPRON[®] and LUPRON DEPOT[®] should use non-hormonal methods of contraception.

- It is not known whether leuprolide acetate is excreted in human milk; therefore, LUPRON[®] and LUPRON DEPOT[®] are contraindicated in patients who are breast-feeding.

WARNINGS AND PRECAUTIONS

General

Postmarketing reports of convulsions have been observed in patients on leuprolide acetate therapy. These included patients in the female and pediatric populations, patients with a history of seizures, epilepsy, cerebrovascular disorders, central nervous system anomalies or tumors, and in patients on concomitant medications that have been associated with convulsions such as bupropion and SSRIs. Convulsions have also been reported in patients in the absence of any of the conditions mentioned above.

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

Carcinogenesis and Mutagenesis

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

Patients have been treated with leuprolide acetate for up to three years with doses as high as 10 mg/day and for two years with doses as high as 20 mg/day without demonstrable pituitary abnormalities.

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

Central Precocious Puberty

During the early phase of therapy, gonadotropins and sex steroids rise above baseline because of the natural stimulatory effect of the drug. An increase in clinical signs and symptoms may therefore be observed. See **DETAILED PHARMACOLOGY**.

Non-compliance with the 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.

Dependence/Tolerance

No drug-dependence has been reported with the use of leuprolide acetate.

Endocrine and Metabolism

Changes in Bone Density

Bone loss can be expected as part of natural aging and can also be anticipated during the hypoandrogenic state caused by long-term use of leuprolide acetate. In patients with significant risk factors for decreased bone mineral content and/or bone mass such as family history of osteoporosis, chronic use of corticosteroids or anticonvulsants or chronic abuse of alcohol or tobacco, leuprolide acetate may pose additional risk. In these patients, risk versus benefit must be weighed carefully before initiation of leuprolide acetate therapy.

Hypogonadism

Long-term administration of leuprolide acetate will cause suppression of pituitary gonadotropins and gonadal hormone production with clinical symptoms of hypogonadism. These changes have

been observed to reverse on discontinuation of therapy. However, whether the clinical symptoms of induced hypogonadism will reverse in all patients has not yet been established.

Hepatic/Biliary/Pancreatic

The pharmacokinetics of the drug in patients with hepatic, biliary or pancreatic impairment have not been determined.

Renal

The pharmacokinetics of the drug in patients with renal impairment have not been determined.

Special Populations

Pregnant Women

The paediatric products LUPRON[®] and LUPRON DEPOT[®] described in this Product Monograph are not indicated for use in women. LUPRON DEPOT[®] treatment of women is covered in the LUPRON DEPOT[®] 3.75 mg and 11.25 mg “Endometriosis” Product Monograph.

Nursing Women

It is not known whether leuprolide acetate is excreted in human milk; therefore LUPRON[®] and LUPRON DEPOT[®] are contraindicated in patients who are breastfeeding. LUPRON DEPOT[®] treatment of women is covered in the LUPRON DEPOT[®] 3.75 mg and 11.25 mg “Endometriosis” Product Monograph.

Geriatrics (> 65 years of age)

Refer to the “Prostatic Cancer” Product Monograph for the efficacy and safety of LUPRON[®] and LUPRON DEPOT[®] in this population.

Monitoring and Laboratory Tests

Response to LUPRON[®] and LUPRON DEPOT[®] should be monitored 1 to 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 to 12 months.

Sex steroids may increase or rise above prepubertal levels if the dose is inadequate. See **WARNINGS AND PRECAUTIONS, Endocrine and Metabolism**. Once a therapeutic dose has been established, gonadotropin and sex steroid levels will decline to prepubertal levels.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Potential exacerbation of signs and symptoms during the first few weeks of treatment is a concern in patients with rapidly advancing central precocious puberty. See **WARNINGS AND PRECAUTIONS**.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

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 (see **Table 1**). Reactions considered not drug related are excluded.

Table 1. Adverse Reactions Reported Having a Possible or Probable Relationship to Drug in 2% or more of Patients Receiving the Drug

	Number of Patients N = 421(%)
Body as a Whole	
General pain	12 (3)
Headache	11 (3)
Injection site reaction including abscess*	37 (9)
Cardiovascular System	
Vasodilatation	9 (2)
Integumentary System	
Acne/Seborrhea	8(2)
Rash including erythema multiforme	12 (3)
Nervous System	
Emotional lability	19 (5)
Urogenital System	
Vaginitis/vaginal bleeding/ vaginal discharge	13 (3)

* Most events were mild or moderate in severity.

Less Common Clinical Trial Adverse Drug Reactions (< 2%)

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

Body as a Whole:	Aggravation of pre-existing tumor and decreased vision, allergic reaction, body odor, fever, flu syndrome, infection, hypertrophy.
Cardiovascular System:	Bradycardia, hypertension, peripheral vascular disorder, syncope.
Digestive System:	Constipation, dyspepsia, dysphagia, gingivitis, increased appetite, nausea/vomiting.
Endocrine System:	Accelerated sexual maturity, feminization, goiter.
Hemic and Lymphatic System:	Purpura.
Metabolic and Nutritional Disorders:	Growth retarded, peripheral edema, weight gain.
Musculoskeletal System:	Arthralgia, joint disorder, myalgia, myopathy.
Nervous System:	Depression, hyperkinesia, nervousness, somnolence.
Respiratory System:	Asthma, epistaxis, pharyngitis, rhinitis, sinusitis.
Integumentary System:	Alopecia, hair disorder, hirsutism, leukoedema, nail disorder, skin hypertrophy, urticaria.
Urogenital System:	Cervix disorder/neoplasm, dysmenorrhea, gynecomastia/breast disorders, menstrual disorder, urinary incontinence.

Abnormal Hematologic and Clinical Chemistry Findings

The following laboratory events were recorded as adverse reactions: antinuclear antibody present and increased sedimentation rate.

See **Effect on Clinical Laboratory Tests** under the **DRUG INTERACTIONS** section.

Post-Market Adverse Drug Reactions

Isolated cases of anaphylaxis have been reported. Symptoms consistent with an anaphylactoid or asthmatic process have been rarely reported.

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.

During post-marketing surveillance, which includes other dosage forms and other patient populations, the following adverse events were reported:

Cardiovascular System:	Hot flush, hypertension, hypotension, flushing.
Digestive System:	Abdominal pain, nausea, vomiting.
Hemic and Lymphatic System:	Decreased WBC.
Central/Peripheral Nervous System:	Convulsion, peripheral neuropathy, spinal fracture/paralysis.
Integumentary System:	Hyperhidrosis, photosensitivity reactions, rash, urticaria.
Metabolic and Nutritional Disorders:	Diabetes mellitus, weight increased
Musculoskeletal System:	Tenosynovitis-like symptoms.
Respiratory System:	Chest pain.
Urogenital System:	Prostate pain.
Miscellaneous:	Injection site reactions including pain, inflammation, sterile abscess, induration and hematoma.

See the “Prostate Cancer” and “Endometriosis” LUPRON[®] and LUPRON DEPOT[®] Product Monographs for other reported events.

DRUG INTERACTIONS

Overview

Leuprolide being approximately 46% bound to plasma proteins, and a peptide that is primarily degraded by peptidase and not by cytochrome P-450 enzymes as noted in specific studies, drug interactions would not be expected to occur.

Drug-Drug Interactions

No pharmacokinetic-based drug-drug interaction studies have been conducted.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Test Interactions

Administration of LUPRON DEPOT[®] at therapeutic doses results in suppression of the pituitary-gonadal system. Normal function is usually restored within 4 to 12 weeks after treatment is discontinued. Diagnostic tests of pituitary-gonadal function conducted during treatment and within 4 to 8 weeks after discontinuation of LUPRON DEPOT[®] therapy may therefore be misleading.

As expected, (see **DETAILED PHARMACOLOGY**) leuprolide acetate administration will initially affect selected serum and urine parameters in the first week of treatment: elevation of BUN, creatinine, acid phosphatase, testosterone and dihydrotestosterone can be expected. With chronic administration, these high values will usually return to normal, or drop below baseline in the case of testosterone, dihydrotestosterone and acid phosphatase.

DOSAGE AND ADMINISTRATION

Dosing Considerations

- LUPRON DEPOT[®] (leuprolide acetate for depot suspension) must be administered under the supervision of a physician.
- LUPRON DEPOT[®] 3.75 mg (1-Month SR), 7.5 mg (1-Month SR), 11.25 mg (1-Month SR) and 15 mg (1-Month SR) administered intramuscularly is designed to provide continuous sustained release of leuprolide for 1 month.

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

Use in Central Precocious Puberty

The dose of leuprolide acetate 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 to 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 to 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 adjustments 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 LEUPROLIDE ACETATE SHOULD BE CONSIDERED BEFORE AGE 11 FOR FEMALES AND AGE 12 FOR MALES.

Recommended Dose and Dosage Adjustment

LUPRON[®]

The recommended starting dose is 50 mcg/kg/day administered as a **single daily subcutaneous injection**. If total downregulation is not achieved, the dose should be titrated upward by 10 mcg/kg/day to a maximum of 100 mcg/kg/day. This dose will be considered the maintenance dose.

LUPRON DEPOT[®]

The recommended starting dose is 0.3 mg/kg/4 weeks (minimum 7.5 mg) administered as a **single intramuscular injection**, after reconstitution with the special diluent. See **DOSAGE AND ADMINISTRATION, Administration**. The starting dose will be dictated by the child's weight.

Child's Weight	Total Dose
≤ 25 kg	7.5 mg
> 25 to ≤ 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 to a maximum of 15 mg per month. This dose will be considered the maintenance dose.

Missed Dose

LUPRON[®]

If the patient forgets to take the injection at the usual time, they should take it as soon as they remember, if they remember on the same day. If not, they should not take the missed dose at all; they should wait until it is time for their next dose. The patient should not take two doses at once.

The patient should not stop taking LUPRON[®] simply because they feel better.

LUPRON DEPOT[®]

Regular injections are important. Adherence to 4-week drug administration schedules must be accepted if therapy is to be successful. If a shot is missed or is administered a week late, the child's pubertal development could begin again. See **WARNINGS AND PRECAUTIONS, General** and **WARNINGS AND PRECAUTIONS, Central Precocious Puberty**.

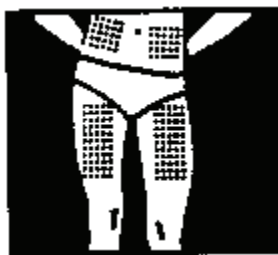
Administration

LUPRON[®]

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

As a guide, the usual sites of injection are indicated below:

SUGGESTED ROTATION OF THE INJECTION SITE



Reconstitution

LUPRON DEPOT[®]

The lyophilized microspheres contained in the front chamber of the prefilled dual-chamber syringe are to be reconstituted prior to intramuscular administration, in accord with the following directions:

Due to different release characteristics, a fractional dose of the 3-month depot formulation is not equivalent to the same dose of the monthly formulation and should not be given.

For LUPRON DEPOT[®] 3.75, 7.5, 11.25 and 15.0 mg (1-Month SR)

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. Remember to tighten the needle by twisting the needle cap clockwise. Do not overtighten.
4. Holding 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.
5. Keep the syringe upright. Gently shake the syringe to thoroughly mix the microspheres (powder) to form a uniform suspension. The suspension will appear milky.
6. If the microspheres adhere to the stopper or caking/clumping is present, tap the syringe against your finger to disperse. **DO NOT USE** if any of the powder has not gone into suspension.
7. Keep the syringe upright. With the opposite hand, remove the needle cap without twisting and advance the plunger to expel the air from the syringe.
8. At the time of reconstitution, inject the entire contents of the syringe intramuscularly. 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.

9. After injection, 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.

Although the suspension has been shown to be stable for 24 hours following reconstitution, 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.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

In rats, subcutaneous administration of leuprolide acetate as a single dose 333 times the recommended human pediatric dose, expressed on a per body weight basis, resulted in dyspnea, decreased activity, and excessive scratching.

There is no clinical experience with the effects of an acute overdose. Because the acute animal toxicity of the drug is low, adverse effects are not expected. No difference in adverse reactions was observed in patients who received either 1 or 10 mg/day leuprolide acetate for up to three years or 20 mg/day for up to two years.

In cases of overdosage, the patients should be monitored closely and management should be symptomatic and supportive.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Leuprolide acetate is a synthetic nonapeptide analog of naturally-occurring gonadotropin-releasing hormone (GnRH or LHRH). The analog possesses greater potency than the natural hormone. When administered as indicated, leuprolide acetate acts as a potent inhibitor of gonadotropin production. It is chemically unrelated to steroids.

Unlike steroid hormones, leuprolide acetate exerts specific action on the pituitary gonadotrophs and the human reproductive tract.

This specificity reduces the likelihood of secondary adverse effects such as gynecomastia, thromboembolism, edema, liver and gallbladder involvement.

Pharmacodynamics

Human studies indicated 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.

Central Precocious Puberty

Two chronic studies involving the treatment of children with central precocious puberty (CPP), demonstrated that following the administration of LUPRON[®] (leuprolide acetate) injection and/or LUPRON DEPOT[®] (leuprolide acetate for depot suspension), stimulated and basal gonadotropins are reduced to prepubertal levels. Testosterone and estradiol are reduced to

prepubertal levels in males and females, respectively, and a 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 physiological effects have been noted with the chronic administration of leuprolide acetate in CPP patients.

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

Intramuscular injection of LUPRON DEPOT[®] provides plasma concentrations of leuprolide acetate over a period of one month.

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 in **Table 2**.

Table 2. Determination of Leuprolide Plasma Levels According to Weight Categories in Children with Central Precocious Puberty

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

Pharmacokinetics

Intramuscular injections of LUPRON DEPOT[®] (leuprolide acetate for depot suspension) 3.75 mg (1-Month SR), 7.5 mg (1-Month SR), 11.25 mg (1-Month SR) and 15 mg (1-Month SR) provide plasma concentrations of leuprolide acetate over a period of one month. See **DETAILED PHARMACOLOGY**.

Leuprolide is not active when given orally.

Absorption

A single dose of LUPRON DEPOT[®] 3.75 mg (1-Month SR) was administered by intramuscular injection to healthy adult female volunteers. The absorption of leuprolide was characterized by an initial increase in plasma concentration, with peak concentration ranging from 4.6 to 10.2 ng/mL at four hours post-dosing. However, intact leuprolide and an inactive metabolite could not be distinguished by the assay used in the study. Following the initial rise, leuprolide concentrations started to plateau within two days after dosing and remained relatively stable for about four to five weeks with plasma concentrations of about 0.30 ng/mL.

Following a single LUPRON DEPOT[®] 7.5 mg (1-Month SR) intramuscular injection to adult patients, the 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 used in the study. Undetectable leuprolide plasma concentrations have been observed during chronic LUPRON DEPOT[®] 7.5 mg (1-Month SR) administration, but testosterone levels appear to be maintained at castrated levels.

In adults, bioavailability by subcutaneous administration is comparable to that by intravenous administration. Leuprolide acetate has a plasma half-life of 2.9 hours. See **DETAILED PHARMACOLOGY**.

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 acetate 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 ¹⁴C-labelled leuprolide was shown to be metabolized to smaller inactive peptides, pentapeptide (Metabolite I), tripeptides (Metabolites II and III) and dipeptide (Metabolite IV). These fragments may be further catabolized.

The major metabolite (M-I) plasma concentrations measured in 5 prostate cancer patients reached mean 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 leuprolide concentrations.

Excretion

Following administration of LUPRON DEPOT[®] 3.75 mg (1-Month SR) to 3 patients, less than 5% of the dose was recovered as parent and M-I metabolite in the urine.

Special Populations and Conditions

Pediatrics

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

Hepatic Insufficiency

The pharmacokinetics of the drug in patients with hepatic impairment have not been determined.

Renal Insufficiency

The pharmacokinetics of the drug in patients with renal impairment have not been determined.

STORAGE AND STABILITY

LUPRON[®]

Store LUPRON[®] (leuprolide acetate injection) 5 mg/mL between 2 and 8°C.

LUPRON DEPOT[®]

Store LUPRON DEPOT[®] (leuprolide acetate for depot suspension) 3.75 mg (1-Month SR), 7.5 mg (1-Month SR), 11.25 mg (1-Month SR) and 15 mg (1-Month SR) between 15 and 25°C. Protect from freezing.

Although the suspension has been shown to be stable for 24 hours following reconstitution, since the product does not contain a preservative, the suspension should be discarded if not used immediately.

SPECIAL HANDLING INSTRUCTIONS

It is very important to activate the LuproLoc[®] safety device immediately after injection. This is done by pushing the arrow forward with the thumb or finger until the device is fully extended and a CLICK is heard or felt. See **DOSAGE AND ADMINISTRATION, Administration, Reconstitution**.

DOSAGE FORMS, COMPOSITION AND PACKAGING

LUPRON[®]

LUPRON[®] is available in sterile multiple-dose vials of 2.8 mL for subcutaneous use, containing 5 mg/mL leuprolide acetate.

LUPRON[®] is supplied as a 14-day kit. Each 14-day Patient Administration Kit contains one vial of LUPRON[®], twenty-eight swabs and fourteen syringes, and one Patient Information/Instructions for Use Leaflet.

Listing of Non-Medicinal Ingredients

In addition to 5 mg/mL of leuprolide acetate, each 2.8 mL multiple dose vial contains sodium chloride for tonicity adjustment, benzyl alcohol as a preservative, and sterile water for injection, USP. The pH may have been adjusted with sodium hydroxide and/or acetic acid.

LUPRON DEPOT[®]

LUPRON DEPOT[®] (leuprolide acetate for depot suspension) is available in four strengths: 3.75 mg (1-Month SR), 7.5 mg (1-Month SR), 11.25 mg (1-Month SR) and 15 mg (1-Month SR).

LUPRON DEPOT[®] (1-Month SR) is supplied in single-dose kits containing one prefilled dual-chamber syringe with 23 G needle, two alcohol swabs, Patient Information Leaflet, Special Instructions for Use, and Package Insert.

Listing of Non-Medicinal Ingredients

LUPRON DEPOT[®] 3.75 mg (1-Month SR)

LUPRON DEPOT[®] 3.75 mg (1-Month SR) is available in a prefilled dual-chamber syringe containing sterile lyophilized microspheres composed of leuprolide acetate incorporated in a biodegradable copolymer of lactic and glycolic acids.

The front chamber of the prefilled dual-chamber syringe contains: leuprolide acetate, purified gelatin, DL-lactic and glycolic acids copolymer, and D-mannitol.

The rear chamber of diluent contains: carboxymethylcellulose sodium, D-mannitol, polysorbate 80, water for injection, USP and glacial acetic acid, USP to control pH.

LUPRON DEPOT[®] 7.5 mg (1-Month SR)

LUPRON DEPOT[®] 7.5 mg (1-Month SR) is available in a prefilled dual-chamber syringe containing sterile lyophilized microspheres composed of leuprolide acetate incorporated in a biodegradable copolymer of lactic and glycolic acids.

The front chamber of the prefilled dual-chamber syringe contains: leuprolide acetate, purified gelatin, DL-lactic and glycolic acids copolymer, and D-mannitol.

The rear chamber of diluent contains: carboxymethylcellulose sodium, D-mannitol, polysorbate 80, water for injection, USP and glacial acetic acid, USP to control pH.

LUPRON DEPOT[®] 11.25 mg (1-Month SR)

LUPRON DEPOT[®] 11.25 mg (1-Month SR) is available in a prefilled dual-chamber syringe containing sterile lyophilized microspheres composed of leuprolide acetate incorporated in a biodegradable copolymer of lactic and glycolic acids.

The front chamber of the prefilled dual-chamber syringe contains: leuprolide acetate, purified gelatin, DL-lactic and glycolic acids copolymer, and D-mannitol.

The rear chamber of diluent contains: carboxymethylcellulose sodium, D-mannitol, polysorbate 80, water for injection, USP and glacial acetic acid, USP to control pH.

LUPRON DEPOT[®] 15.0 mg (1-Month SR)

LUPRON DEPOT[®] 15.0 mg (1-Month SR) is available in a prefilled dual-chamber syringe containing sterile lyophilized microspheres composed of leuprolide acetate incorporated in a biodegradable copolymer of lactic and glycolic acids.

The front chamber of the prefilled dual-chamber syringe contains: leuprolide acetate, purified gelatin, DL-lactic and glycolic acids copolymer, and D-mannitol.

The rear chamber of diluent contains: carboxymethylcellulose sodium, D-mannitol, polysorbate 80, water for injection, USP and glacial acetic acid, USP to control pH.

When mixed with diluent, the sterile lyophilized microspheres become a suspension, which is intended as an intramuscular injection to be given **ONCE EVERY MONTH**.

During the manufacturing process of LUPRON DEPOT[®] (1-Month SR), acetic acid is lost, leaving the leuprolide peptide.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Proper name: leuprolide acetate

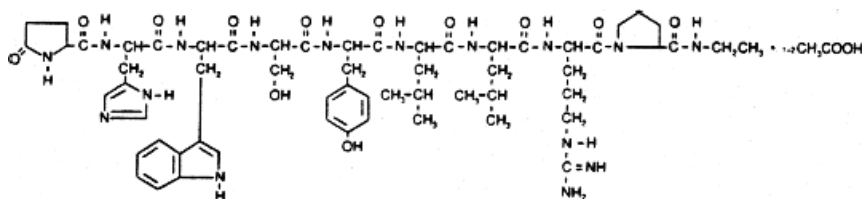
Chemical name: 5-oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-Leucyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide acetate.

or: des-Glycine¹⁰, [D-Leucine⁶] LH-RH ethylamide acetate.

or: [D-Leu⁶, des-Gly-NH₂¹⁰, Proethylamide⁹] GnRH.

Molecular formula and molecular mass: C₅₉H₈₄N₁₆O₁₂ · C₂H₄O₂ 1209.41 as free base

Structural formula:



Physicochemical properties: Leuprolide acetate is a fine or fluffy, white to off-white powder, very soluble in water, ethanol and propylene glycol; pKa = 9.6.

CLINICAL TRIALS

Study Demographics and Trial Design

LUPRON[®]

Table 3. Summary of Patient Demographics for Clinical Trials in Patients with Central Precocious Puberty

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
I	Phase 3, open, multicenter study	LUPRON DEPOT [®] 7.5, 11.25 or 15 mg based on body weight Intramuscular Drug is discontinued when an age appropriate for puberty is attained	22	6.9 years (1.1 - 8.9 years)	2 M, 20 F

Definitions: M = male, F = female.

Study Results

In an open, multicenter study, LUPRON DEPOT[®] (leuprolide acetate for depot suspension) was shown to be safe and effective in the therapeutic management of children with central precocious puberty (CPP). Successful suppression of gonadotropins and sex steroids to prepubertal levels was achieved in 95% of the children by Week 4. In addition, the majority of these children demonstrated decreases or stabilization in Tanner staging of breast, pubic hair, and genitalia compared with baseline. Menses ceased in all females by the end of the second therapeutic month, and growth rates were reduced.

Table 4. Results of Study I in Patients with Central Precocious Puberty

Primary Endpoints	Associated value and statistical significance for LUPRON DEPOT [®]
The criteria for effectiveness include: 1) Height, weight, growth rate 2) Bone age and predicted height 3) Tanner Staging (Breast, Pubic Hair, Genitalia) 4) Menses 5) Hormone Determinations (Gonadotropins, Sex Steroids)	Successful suppression of gonadotropins and sex steroids to prepubertal levels was achieved in 95% of the children by week 4.

In an open, non-comparative, multi-centre study involving LUPRON[®] (leuprolide acetate injection) and LUPRON DEPOT[®] (leuprolide acetate for depot suspension), once adequate suppression of the pituitary-gonadal axis was achieved, the children demonstrated both physical and psychological regression of sexual maturation, slowing of linear growth velocity, and a decrease in the ratio of bone age to chronological age.

LUPRON[®]/LUPRON DEPOT[®]

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.

DETAILED PHARMACOLOGY

Leuprolide acetate is an analog of gonadotropin-releasing hormone (Gn-RH). It was found to have antireproductive properties on chronic administration at high doses, interfering with gonadal steroidogenesis. It produces a reversible regression of steroid-dependent reproductive tissues in both male and female, in a manner analogous to that produced by gonadectomy or by antiandrogenic and antiestrogenic drugs.

Animal Pharmacology

Pharmacodynamics

LUPRON[®]

Several studies in rats were conducted to determine the effects of prolonged administration of leuprolide.

In two non-tumor studies, leuprolide showed in male rats a marked reduction of LH and FSH, accompanied by decreased plasma testosterone at 20 mcg/twice a day for 106 days in the first study and at 20 and 100 mcg/twice a day for 160 days in the second study.

In a tumor study, in male rats implanted with R3327-G prostatic carcinoma, a daily dose of leuprolide at 1, 50 or 1000 mcg/kg for 20 days showed a significant reduction in the tumor growth rate, and enhanced the survival of the animals.

Leuprolide has also been tested in female rats having mammary tumors induced by the administration of 7-12-dimethylbenz[α]-anthracene (DMBA). Doses of leuprolide used ranged from 0.01 mcg to 10 mcg twice a day, up to 31 days. Except for 0.01 mcg which was a "no-effect-dose", leuprolide produced regression of tumor growth similar to the effects seen in the castrate control.

Pharmacokinetics

LUPRON DEPOT[®]

Pharmacokinetic behaviors of leuprolide acetate for depot suspension were studied in rats and dogs.

In rats, release kinetics after subcutaneous and intramuscular injections, exhibited a pseudo-zero-order kinetics for one month in a dose ranging from 3 to 30 mg/kg; the release rate at a dose of 3 mg/kg was 2.8% of dose/day. Serum levels for leuprolide showed a sharp increase immediately after injection, result of an initial burst of the drug, accompanied by an initial flare up of testosterone level. Serum level for leuprolide and testosterone decreased to below normal level, and were sustained at a suppressed level for over 6 weeks.

In dogs, serum level profiles showed essentially the same pattern.

In a series of experiments with multiple administration (once every 4 weeks), serum testosterone levels in rats at a dose of 3 mg/kg and those in dogs at 1.5 mg/kg did not show any flare-up at the second and third injection, and continued to be maintained at the suppressed levels. This study demonstrates that leuprolide acetate for depot suspension releases the drug at a constant rate for one month and has a long acting potency.

In another study, the effects of leuprolide acetate for depot suspension on accessory sex organ weights and hormone levels in adult male rats were compared to those produced by leuprolide acetate solution with subcutaneous administration. One group of rats were given 0.2, 1.0 and 5.0 mg/kg/day leuprolide acetate solution for 4 weeks; the other group received 0.6, 3.0 and 15 mg/kg leuprolide acetate for depot suspension once a week for 4 weeks. The reduction of organ weights and hormone levels was found more significant with the depot formulation than with the solution.

In another study with rats, the effects of a single administration of leuprolide acetate for depot suspension at doses of 0.03, 0.3 and 3 mg/kg intramuscular, and 3 mg/kg subcutaneously on genital organ weights, were compared to those of the subcutaneous daily injection of 100 mcg/kg/day of solution for two weeks. Results showed that at the beginning of treatment, there was a slight increase, but over the remaining two-week treatment period, the organ weights decreased in dose-related fashion.

Sustained serum drug level, inhibition of steroidogenesis, drastic suppression of the growth of the reproductive organs were observed over a 3-Month period when LUPRON DEPOT[®] (3-Month SR) formulation was studied in rats and dogs.

Human Pharmacology

Pharmacodynamics

General

With chronic administration, leuprolide had demonstrated a reduction in gonadotropins and sex steroids.

After an initial transient increase in testosterone or estradiol level, leuprolide produces a marked suppression of these levels as well as an inhibition of mammary and prostate tumor growth, and atrophy of the reproductive organs.

This decrease is maintained at castrate levels, as long as treatment continues.

There was no evidence of a dose-response relationship in the testosterone level with doses of 1 mg or 10 mg/day.

Central Precocious Puberty

With chronic administration, LUPRON[®] and LUPRON DEPOT[®] demonstrated a reduction of gonadotropins and sex steroids to prepubertal levels, and a slowing of linear growth velocity, as long as treatment continued at therapeutic doses.

Pharmacokinetics

The absorption, metabolism, distribution, and excretion of leuprolide acetate in humans have not been fully established. See **ACTION AND CLINICAL PHARMACOLOGY**.

Absorption

LUPRON[®]

The pharmacokinetic profile of leuprolide has been characterized in a single-dose, randomized, two-period, cross-over bioavailability study after administration of 1 mg doses by subcutaneous and by intravenous route in healthy male volunteers. Mean leuprolide plasma level curves were characteristic for each route. Mean levels during earlier sampling times were generally higher after the intravenous regimen, while levels during the later sampling times were generally higher after the subcutaneous regimen. The absolute bioavailability based on the ratio of the mean area under the curve (AUC) for subcutaneous/intravenous was 0.94 with a range of 0.70 to 1.24.

The mean plasma half-life was 2.9 hours. The study demonstrates that the bioavailability of leuprolide after subcutaneous administration was comparable to that of intravenous administration.

LUPRON DEPOT[®]

The pharmacokinetic profile of LUPRON DEPOT[®] has been characterized in an open, single-dose study in 10 orchiectomized prostatic cancer patients given 7.5 mg (1-Month SR) intramuscularly. Blood plasma levels were measured over an 8-week period.

After an initial burst, mean plasma leuprolide acetate concentrations declined to approximately 0.8 ng/mL within four days after the injection and remained basically stable for 2.5 weeks. Prolonged plasma concentrations were achieved with all but one patient with detectable plasma levels up to 4 weeks. Approximately 85 to 100% of the observed 8-week AUC was obtained for each patient after the first four weeks. After 8 weeks, plasma levels were essentially undetectable in all patients.

An estimate of the absolute bioavailability from this dosage form was approximately 90% when compared to an equivalent intravenous solution dose used in another study.

TOXICOLOGY

Acute Toxicity

LUPRON[®]

Acute studies were conducted in rats and mice at 100 mg/kg/day. Only signs of decreased motor activity, dyspnea, and excessive scratching were reported; the LD₅₀ is greater than 100 mg/kg/day in rats and mice.

LUPRON DEPOT[®]

Mice and rats were given leuprolide acetate for depot suspension with different routes of administration: oral, intraperitoneal and subcutaneous (doses of 5 g/kg) and intramuscular (doses of 2 g/kg). No death occurred. The LD₅₀ was concluded to be greater than 5 g/kg for intraperitoneal and subcutaneous routes and 2 g/kg for the intramuscular route.

Special Studies

LUPRON DEPOT[®]

Rabbits

In a preliminary study, male rabbits were given single injections (1 mL/animal) of a 15% suspension of leuprolide acetate for depot suspension into the subcutaneous tissue of the abdomen to assess local irritation.

Deposition of the test drug at site of injection was noted at 2 and 14 days after the injection, along with slight hemorrhage and dilatation of capillaries at 50 days after the injection. Leuprolide acetate for depot suspension was reported not to produce significant subcutaneous irritation in rabbits in this study.

In a second irritation study, male rabbits were injected once or 4 successive times with leuprolide acetate for depot suspension (15% suspension) by intramuscular administration. Results were compared to those obtained with placebo-microcapsule or a 0.75% solution of acetic acid as the positive control. Deposition at injection sites, and slight irritation changes (hemorrhage, edema, inflammation) were noted: leuprolide acetate for depot suspension produced the same effects with the same degree as the placebo-microcapsule, but these were less than those of the positive control (0.75% acetic acid), and their severity were not potentiated by 4 repeated injections.

The injection-site toxicity and irritation effects of LUPRON DEPOT[®] (3-Month SR) were studied in rabbits. The rabbits were administered with intramuscular and subcutaneous injections at doses of 11.25 mg/mL for intramuscular injection and 5.64 mg/mL for subcutaneous injection. Intramuscular injection was in the left vastus lateralis muscle, and subcutaneous injection was in the abdominal region. Only mild irritative changes such as mild hemorrhage and degeneration of the muscle fiber were seen 2 days after the injection. Moreover, granulation tissue composed of macrophages and multinucleated giant cells was observed. The size of granulation tissue observed was decreased 13 weeks after the injection. Therefore, these changes were characterized mainly by foreign body reactions caused by the persistence of the microcapsule formulation.

Guinea Pigs

Two studies were performed to evaluate the potential of leuprolide acetate for depot suspension to produce either systemic anaphylaxis or delayed hypersensitivity reactions in guinea pigs.

Preliminary antigenicity study. Leuprolide acetate for depot suspension was given to guinea pigs at a dose of 123 mg/kg every 2 weeks by intramuscular route 4 times, and once by subcutaneous route 2 weeks after the last intramuscular dose. Results were compared to controls treated with placebo-microcapsule 122 mg/kg intraperitoneally, or with ovalbumin 5 mg/animal intravenously. No systemic anaphylactic reactions were observed with animals treated with leuprolide acetate for depot suspension and placebo-microcapsule, but some induced equivocal weak antibody production was noted.

In a second study, the sensitization potential of leuprolide acetate for depot suspension at doses of 50 mg/animal/dosing by intramuscular (systemic anaphylaxis) or at doses of approximately 7.2 mg/animal/dosing (0.05 mL of a 144.23 mg/mL of suspension) intradermal (delayed hypersensitivity), were compared to those seen with gelatin, egg albumin or captan. No signs of anaphylactic reactions nor delayed hypersensitivity were observed for leuprolide acetate for depot suspension, while signs of anaphylactic reactions (such as nose scratching, sneezing, dyspnea or local irritation) were noted with other compounds

Long-Term Toxicity

LUPRON[®]

A series of subchronic and chronic toxicity studies conducted in mice, rats, and monkeys with daily subcutaneous injections of leuprolide acetate resulted in atrophy of the sex organs in both male and female animals. Reduced serum levels of gonadotropin hormones were observed in rats and monkeys following administration of leuprolide for 90 days.

Marked pharmacologic effects consisting of atrophy of primary and secondary sex organs in both sexes were observed in rats dosed with 1 to 4 mg/kg/day of leuprolide for 90 days. No overt toxic effects were observed. The "no-toxic-effect" dosage was 4 mg/kg/day.

Rhesus monkeys dosed subcutaneously with 0, 1, 2 and 4 mg/kg/day for 90 days exhibited marked atrophy of the primary and secondary sex organs of both sexes. The reproductive effects were consistent with the pharmacologic action of the drug. The "no-toxic-effect" dosage was 4 mg/kg/day as no overt toxicity was observed.

Leuprolide was administered subcutaneously to cynomolgus monkeys once daily at dosages of 0, 0.6, 4.0 and 10 mg/kg/day for one year. Atrophy of sex organs of both sexes was the principal finding. These changes were ascribed to the pharmacologic activity of the drug. The "no-toxic-effect" dose was 10 mg/kg/day.

Maximum tolerated dose studies (prelude to carcinogenicity studies) were conducted in rats and mice. Rats were dosed subcutaneously with 0, 10, 30, 100 and 300 mg/kg/day for 90 days while mice received 0, 20, 60, 200 and 600 mg/kg/day.

Drug related pituitary hyperplasia and hypertrophy, atrophy of sex organs (both sexes) and marked skin irritation at the injection sites were observed in rats. As a result, no maximum tolerated dose was established by the study.

Marked skin irritation at injection sites was observed in mice dosed with 200 and 600 mg/kg/day. Hypertrophy of anterior pituitary cells were observed in female mice dosed with 200 mg/kg/day but not at 600 mg/kg/day. Sex organ atrophy, secondary to the drug pharmacologic effects, were observed in all treated male and female mice. The maximum tolerated dose in mice was 60 mg/kg/day.

LUPRON DEPOT[®]

Rat

Leuprolide acetate for depot suspension was administered intramuscularly to three groups of male rats at doses from 10, 30 and 100 mg/kg/week (corresponding to 0.8, 2.4 and 8.0 mg/kg/week of leuprolide acetate injection) once a week for 13 weeks. Rats dosed at

100 mg/kg/week showed atrophy of testes; in addition white spots were noted at the injection sites. The atrophy of the testes was reported to be due to the hormonal action of leuprolide acetate injection; the "no-toxic-effect" dose was considered to be 100 mg/kg/week.

In another toxicity study, male rats were given leuprolide acetate for depot suspension subcutaneously once a week for 3 weeks, at doses of 30 mg/kg/week (corresponding to 2.4 mg/kg/week of leuprolide acetate injection). Atrophy of the testes, and a slight induration were noted. The "no-toxic effect" dose was considered to be 30 mg/kg/week.

In a third study, leuprolide acetate for depot suspension was given subcutaneously to groups of male and female rats, at doses of 0, 10, 30 and 100 mg/kg/week once a week for 13 weeks (corresponding to 0, 0.8, 2.4 and 8 mg/kg/week of leuprolide acetate injection). Atrophy of the testes was noted, with induration at injection site; in female rats, the vagina failed to open throughout the dosing period. Leuprolide acetate for depot suspension produced changes related to the expected pharmacologic effects. The "no-toxic-effect" dose was considered to be 100 mg/kg/week.

Dog

In two different studies, female and male beagle dogs were given leuprolide acetate for depot suspension subcutaneously for 13 weeks, once a week at doses of 10, 30, 100 mg/kg/week, corresponding to 0.8, 2.4 and 8 mg/kg/week leuprolide acetate injection. No death was reported. Signs and symptoms included inflammatory lesions at the injection sites, and atrophic changes of the primary and accessory sex glands. The injection site change, seen in both control and test groups, was induced by the microcapsule, not leuprolide, and was reversible.

Mutagenicity and Carcinogenicity

Mutagenicity

***LUPRON*[®]**

Leuprolide has been studied *in vitro* and *in vivo*, using bacterial and mammalian systems.

In vitro assays using *Salmonella* and *Saccharomyces* with and without the presence of liver microsomal enzyme from Aroclor-1254 induced rats, no signs of mutagenicity have been observed.

Leuprolide was non-mutagenic *in vivo* cytogenic assay in rats or in the Mouse Dominant Lethal assay at doses of 0, 1, 2 and 4 mg/kg administered subcutaneously.

Both *in vitro* and *in vivo* studies have provided no evidence of a mutagenic potential of leuprolide.

***LUPRON DEPOT*[®]**

In the Ames Test, using *S. typhimurium*, strains TA 98, TA 100, TA 1535 and TA 1537, and *E. coli* strain WP2hcr, leuprolide acetate for depot suspension was found not mutagenic at dosing

ranging from 0.03 to 10 mg/plate, irrespective of treatment with mammalian metabolic activation system (S-9 mix).

Carcinogenicity

LUPRON DEPOT[®]

Two rodent carcinogenicity studies were conducted for two years with daily doses of 0.6, 1.5, and 4 mg/kg/day in the rat, and with 0.6, 6, and 60 mg/kg/day in the mouse.

In rats, a dose-related incidence of pituitary hyperplasia, hypertrophy and benign pituitary adenomas were noted at 12 month necropsy, while a statistically significant dose-related incidence of benign pituitary adenomas was observed in both male and female rats after 24 months when the drug was administered subcutaneously at high daily doses (0.6 to 4 mg/kg).

In mice, no drug-induced neoplastic changes or pituitary abnormalities were observed at doses as high as 60 mg/kg for two years.

Patients have been treated with leuprolide 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. Clinical signs of pituitary abnormalities have not been observed in any of these patients.

Reproduction and Teratology

Fertility and Reproduction

LUPRON DEPOT[®]

Fertility and reproductive performance studies cannot be conducted with leuprolide, because the compound affects the pituitary-gonadal axis and influences endocrine reproductive organs. As a result, there would be a decrease in fertility and reproduction.

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.

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.

Teratology

LUPRON DEPOT[®]

Leuprolide administered to pregnant rats at dosages of 0, 1, 3 and 10 mcg/kg/day from gestational day 6 to gestational day 15 (major period of organogenesis) was not teratogenic. At 10 mcg/kg/day, leuprolide increased the incidence of resorptions; surviving fetuses showed no abnormalities. The "no-toxic-effect" dosage was 3 mcg/kg/day.

Leuprolide increased the incidence of embryonic resorptions in pregnant rabbits when dosed with 0, 0.1, 0.3 or 1.0 mcg/kg/day during the period of major organogenesis, i.e., gestational day 6 through gestational day 18. Surviving fetuses showed no abnormalities.

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PART III: CONSUMER INFORMATION

Pr LUPRON[®] leuprolide acetate injection

This leaflet is PART III of a three-part "Product Monograph" published when LUPRON[®] was approved for sale in Canada and is designed specifically for consumers. This leaflet is a summary and will not tell you everything about LUPRON[®]. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

- LUPRON[®] (leuprolide acetate injection) is indicated in the treatment of children with central precocious puberty.

What is precocious puberty?

Precocious puberty occurs when girls under the age of 8 or boys under the age of 9 begin to develop signs of sexual maturity.

Signs and symptoms:

- Girls develop breasts and may have monthly periods.
- The penis and testicles of boys grow larger.
- Behavior may change; children may become aggressive or moody.
- Pubic hair grows in both sexes.
- Children may have oily skin and/or acne.
- Children may be the tallest in the class; there is a sudden growth spurt like that usually seen in teenagers.

Why does it happen:

In most cases, there is no special reason for this early development. It is not caused by anything we do and is not necessarily passed on from parents to children. However, there may be some physical problem, like a tumor, causing precocious puberty; this would require other treatment. A doctor will need to perform tests to rule out some possible physical causes.

What the medication does:

LUPRON[®] is a hormone-like agent. It is given by injection once a day to adjust your child's body clock (monthly injections are also available).

- Your child will stop making some hormones at adult levels.
- Pubertal changes (pubic hair, girl's period, breasts, etc.) should stop and may even become less obvious.
- Growth rate becomes more normal.
- When it's right for your child, your child's doctor will stop administering the shots and puberty will begin again.

When it should not be used:

LUPRON[®] should not be used:

- If your child is allergic to leuprolide acetate, any similar nonapeptides (e.g., histrelin, desorelin), or any of the non-medicinal ingredients in LUPRON[®].
- In women who are pregnant or may become pregnant.
- In women who are breast-feeding.

What the medicinal ingredient is:

leuprolide acetate

What the important non-medicinal ingredients are:

Each 2.8 mL multiple-dose vial contains **benzyl alcohol**, sodium chloride, and sterile water for injection. Each vial also contains sodium hydroxide and/or acetic acid.

What dosage forms it comes in:

LUPRON[®] is a drug which contains 5 mg of leuprolide acetate per mL. It comes in 2.8 mL multiple-dose vials. LUPRON[®] is supplied as a 14-day kit.

WARNINGS AND PRECAUTIONS

Before your child takes LUPRON[®] tell your child's doctor if:

- Your child is allergic to any component of the medication
- Your child has a family history of osteoporosis or is a chronic user of drugs that can reduce bone mass such as anticonvulsants, corticosteroids, alcohol and/or tobacco. LUPRON[®] can cause thinning of the bone and may pose additional risk in patients with such a history.
- Your child has had or is suspected of having seizures, epilepsy, cerebrovascular disorder, central nervous system anomalies, or brain tumor.
- Your child is taking other medication(s) that have been associated with convulsions or seizures such as bupropion and any SSRI medication for depression.

INTERACTIONS WITH THIS MEDICATION

Tell your child's doctor and pharmacist if your child is taking, has been taking, or planning to take any other medicines, including non-prescription drugs (such as drug products for colds or nausea).

PROPER USE OF THIS MEDICATION

Usual Dose:

Your child needs one injection a day, as prescribed by your child’s doctor.

It is very important that the doctor check your child’s progress at regular medical visits.

Only a small amount of LUPRON® is needed once a day. Use the recommended ½ cc presterilized disposable syringe (see Instructions for Use Leaflet). Syringes are provided in the Patient Administration Kit.

Change the site of injection as instructed by your doctor.

As a guide, the usual sites of injection are indicated below:

SUGGESTED ROTATION OF THE INJECTION SITE



Overdose:

In case of overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

Follow these instructions unless instructed otherwise by your child’s doctor: if your child misses an injection at the usual time, give it to him/her as soon as you remember, if you remember on the same day. If not, do not give him/her the missed dose at all. Simply wait until it is time for your child’s next dose. Do not give two doses at once. If you need more information, ask your child’s doctor.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Postmarketing reports of convulsions have been observed in patients taking LUPRON®. These included patients in the female and pediatric populations, patients with a history of seizures, epilepsy, cerebrovascular disorders, central nervous system anomalies or tumors, and in patients on concomitant medications that have been associated with convulsions such as bupropion and SSRIs. Convulsions have also been reported in patients in the absence of any of the conditions mentioned above.

In the first few weeks of taking LUPRON®, your child’s hormone levels will initially increase and then decline over several weeks. During this period some patients may experience worsening of symptoms.

The following items are not necessarily problems, but your child’s doctor will want to know about them. Call your child’s doctor or tell the doctor at your child’s next appointment if:

- Pubertal changes continue.
- Your daughter has a period, especially after the first month of treatment with LUPRON®.
- Your child has substantial mood swings (write down the date this happens).
- You observe any behavioural changes in your child (boys may become aggressive; girls may become moody).

A skin reaction may occur: itching, redness, burning, and/or swelling at the injection site. These reactions usually are mild and disappear after a few days. If they persist or worsen, tell your child’s doctor.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom/effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common	Abnormal swelling or numbness of limbs		✓	
	Convulsion		✓	
	Severe bone pain		✓	
	Severe pain in chest or abdomen		✓	
	Vision changes		✓	
Uncommon	Headache	✓		
	Itching rash		✓	
	Skin reactions including reaction at site of injection		✓	
	Vomiting /nausea	✓		

This is not a complete list of side effects. For any unexpected effects while taking LUPRON®, contact your doctor or pharmacist.

HOW TO STORE IT

Store LUPRON® vials or kits in the refrigerator (2 to 8°C) and protect from light (keep in carton until use).

As with other medications, KEEP OUT OF REACH OF CHILDREN.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report on line at:**
www.healthcanada.gc.ca/medeffect
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
 - **Fax toll-free to 1-866-678-6789**
 - **Mail to: Canada Vigilance Program**
Health Canada
Postal Locator 0701C
Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at <http://www.healthcanada.gc.ca/medeffect>

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be obtained by contacting the sponsor, AbbVie Corporation at 1-800-699-9948.

This leaflet was prepared by AbbVie Corporation.

Last revised: November 1, 2012

PART III: CONSUMER INFORMATION

Pr LUPRON DEPOT[®] leuprolide acetate for depot suspension

This leaflet is PART III of a three-part "Product Monograph" published when LUPRON DEPOT[®] was approved for sale in Canada and is designed specifically for consumers. This leaflet is a summary and will not tell you everything about LUPRON DEPOT[®]. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

- LUPRON DEPOT[®] (leuprolide acetate injection) is indicated in the treatment of children with central precocious puberty.

What is precocious puberty?

Precocious puberty occurs when girls under the age of 8 or boys under the age of 9 begin to develop signs of sexual maturity.

Signs and symptoms:

- Girls develop breasts and may have monthly periods.
- The penis and testicles of boys grow larger.
- Behavior may change; children may become aggressive or moody.
- Pubic hair grows in both sexes.
- Children may have oily skin and/or acne.
- Children may be the tallest in the class; there is a sudden growth spurt like that usually seen in teenagers.

Why does it happen:

In most cases, there is no special reason for this early development. It is not caused by anything we do and is not necessarily passed on from parents to children. However, there may be some physical problem, like a tumor, causing precocious puberty; this would require other treatment. A doctor will need to perform tests to rule out some possible physical causes.

What the medication does:

LUPRON DEPOT[®] is a hormone-like agent. It is given by injection **once a month** to adjust your child's body clock (daily injections are also available).

- Your child will stop making some hormones at adult levels.
- Pubertal changes (pubic hair, girl's period, breasts, etc.) should stop and may even become less obvious.
- Growth rate becomes more normal.
- When it's right for your child, your child's doctor will stop administering the shots and puberty will begin again.

When it should not be used:

LUPRON DEPOT[®] should not be used:

- If your child is allergic to leuprolide acetate, any similar nonapeptides (e.g., histrelin, desorelin), or any of the non-medicinal ingredients in LUPRON DEPOT[®].
- In women who are pregnant or may become pregnant.
- In women who are breast-feeding.

What the medicinal ingredient is:

leuprolide acetate

What the important non-medicinal ingredients are:

Carboxymethylcellulose sodium, DL-lactic and glycolic acids copolymer, and D-mannitol, gelatine, glacial acetic acid, polysorbate 80 and water for injection..

What dosage forms it comes in:

LUPRON DEPOT[®] is available in a pre-filled dual-chamber syringe containing leuprolide acetate as sustained-release microspheres and must be reconstituted with a special diluent prior to intramuscular injection. LUPRON DEPOT[®] is available in four strengths: 3.75, 7.5, 11.25 and 15.0 mg (1-Month SR) and is supplied in single-dose kits containing one prefilled dual-chamber syringe with 23 G needle, two alcohol swabs, Patient Information Leaflet, Special Instructions for Use, and Package Insert.

WARNINGS AND PRECAUTIONS

BEFORE your child takes LUPRON DEPOT[®] tell your child's doctor if:

- Your child is allergic to any component of the medication
- Your child has a family history of osteoporosis or is a chronic user of drugs that can reduce bone mass such as anticonvulsants, corticosteroids, alcohol and/or tobacco. LUPRON DEPOT[®] can cause thinning of the bone and may pose additional risk in patients with such a history.
- Your child has had or is suspected of having seizures, epilepsy, cerebrovascular disorder, central nervous system anomalies, or brain tumor.
- Your child is taking other medication(s) that have been associated with convulsions or seizures such as bupropion and any SSRI medication for depression.

INTERACTIONS WITH THIS MEDICATION

Tell your child’s doctor and pharmacist if your child is taking, has been taking, or planning to take any other medicines, including non-prescription drugs (such as drug products for colds or nausea).

PROPER USE OF THIS MEDICATION

Usual Dose:

Your child only needs **one injection a month**, as prescribed by your child’s doctor. It is very important that the doctor check your child’s progress at regular medical visits. Your child’s doctor, or healthcare provider, will administer LUPRON DEPOT® during your child’s scheduled visit.

Overdose:

In case of overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

Adherence to 4-week drug administration schedules must be accepted if therapy is to be successful. For best results, your child should have the right amount of LUPRON DEPOT® in his or her body at all times. If your child misses a dose, the pubertal development could restart.

If you need more information, ask your doctor.

Regular injections are important!

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Postmarketing reports of convulsions have been observed in patients taking LUPRON DEPOT®. These included patients in the female and pediatric populations, patients with a history of seizures, epilepsy, cerebrovascular disorders, central nervous system anomalies or tumors, and in patients on concomitant medications that have been associated with convulsions such as bupropion and SSRIs. Convulsions have also been reported in patients in the absence of any of the conditions mentioned above.

In the first few weeks of taking LUPRON DEPOT®, your child’s hormone levels will initially increase and then decline over several weeks. During this period, some patients may experience worsening of symptoms.

The following items are not necessarily problems, but your child’s doctor will want to know about them. Call your child’s doctor or tell the doctor at your child’s next appointment if:

- Pubertal changes continue.
- Your daughter has a period, especially after the first month of treatment with LUPRON DEPOT®.
- Your child has substantial mood swings (write down the date this happens).
- You observe any behavioural changes in your child (boys may become aggressive; girls may become moody).

A skin reaction may occur: itching, redness, burning, and/or swelling at the injection site. These reactions usually are mild and disappear after a few days. If they persist or worsen, tell your doctor.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom/effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common	Abnormal swelling or numbness of limbs		✓	
	Convulsion		✓	
	Severe bone pain		✓	
	Severe pain in chest or abdomen		✓	
	Vision changes		✓	
	Skin reactions including reaction at site of injection		✓	
Uncommon	Headache	✓		
	Itching rash		✓	
	Skin reactions including reaction at site of injection		✓	
	Vomiting /nausea	✓		

This is not a complete list of side effects. For any unexpected effects while taking LUPRON DEPOT®, contact your doctor or pharmacist.

HOW TO STORE IT

Store between 15 and 25°C. Protect from freezing.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report on line at:
www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
 - Fax toll-free to 1-866-678-6789
 - Mail to: Canada Vigilance Program
Health Canada
Postal Locator 0701C
Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at <http://www.healthcanada.gc.ca/medeffect>

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be obtained by contacting the sponsor, AbbVie Corporation at 1-800-699-9948.

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