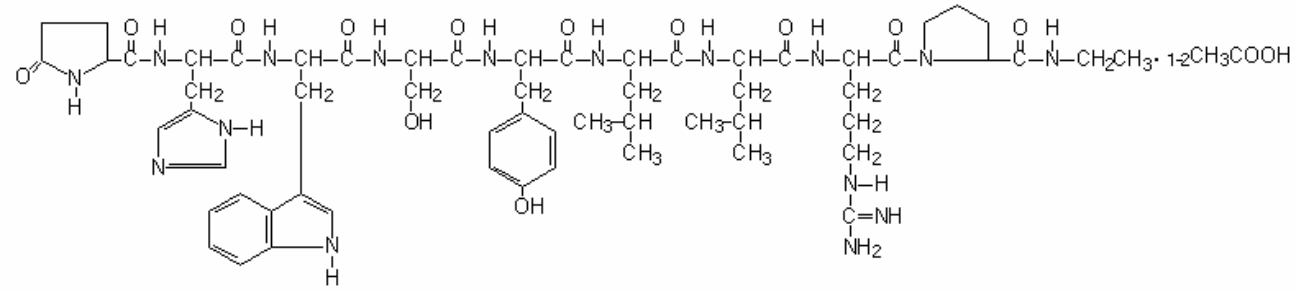
LUPRON DEPOT®– 4 Month 30 mg
(leuprolide acetate for depot suspension)

4-MONTH FORMULATION

Rx only

DESCRIPTION

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



LUPRON DEPOT-4 Month 30 mg is available in a prefilled dual-chamber syringe containing sterile lyophilized microspheres which, when mixed with diluent, become a suspension intended as an intramuscular injection to be given **ONCE EVERY FOUR MONTHS (16 weeks).**

The front chamber of LUPRON DEPOT-4 Month 30 mg prefilled dual-chamber syringe contains leuprolide acetate (30 mg), polylactic acid (264.8 mg) and D-mannitol (51.9 mg). The second chamber of diluent contains carboxymethylcellulose sodium (7.5 mg), D-mannitol (75.0 mg), polysorbate 80 (1.5 mg), water for injection, USP, and glacial acetic acid, USP to control pH.

During the manufacture of LUPRON DEPOT-4 Month 30 mg, acetic acid is lost, leaving the peptide.

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, administration of leuprolide acetate results in an initial increase in circulating levels of luteinizing hormone (LH) and follicle stimulating hormone (FSH), leading to a transient increase in levels of the gonadal steroids (testosterone and dihydrotestosterone in males, and

estrone and estradiol in premenopausal females). However, continuous administration of leuprolide acetate results in decreased levels of LH and FSH. In males, testosterone is reduced to castrate levels. In premenopausal females, estrogens are reduced to postmenopausal levels. These decreases occur within two to four weeks after initiation of treatment. Castrate levels of testosterone in prostatic cancer patients have been demonstrated for more than five years.

Leuprolide acetate is not active when given orally.

Pharmacokinetics

Absorption Following a single injection of LUPRON DEPOT-4 Month 30 mg in sixteen orchiectomized prostate cancer patients, mean plasma leuprolide concentration of 59.3 ng/mL was observed at 4 hours and the mean concentration then declined to 0.30 ng/mL at 16 weeks. The mean plasma concentration of leuprolide from weeks 3.5 to 16 was 0.44 ± 0.20 ng/mL (range: 0.20-1.06). Leuprolide appeared to be released at a constant rate following the onset of steady-state levels during the fourth week after dosing, providing steady plasma concentrations throughout the 16-week dosing interval. However, intact leuprolide and an inactive major metabolite could not be distinguished by the assay which was employed in the study. The initial burst, followed by the rapid decline to a steady-state level, was similar to the release pattern seen with the other depot formulations.

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

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

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

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

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

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

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

CLINICAL STUDIES

In an open-label, noncomparative, multicenter clinical study of LUPRON DEPOT-4 Month 30 mg, 49 patients with stage D2 prostatic adenocarcinoma (with no prior treatment) were enrolled. The objectives were to determine whether a 30 mg depot formulation of leuprolide injected once every 16 weeks would reduce and maintain serum testosterone levels at castrate levels (≤ 50 ng/dL), and to assess the safety of the formulation. The study was divided into an

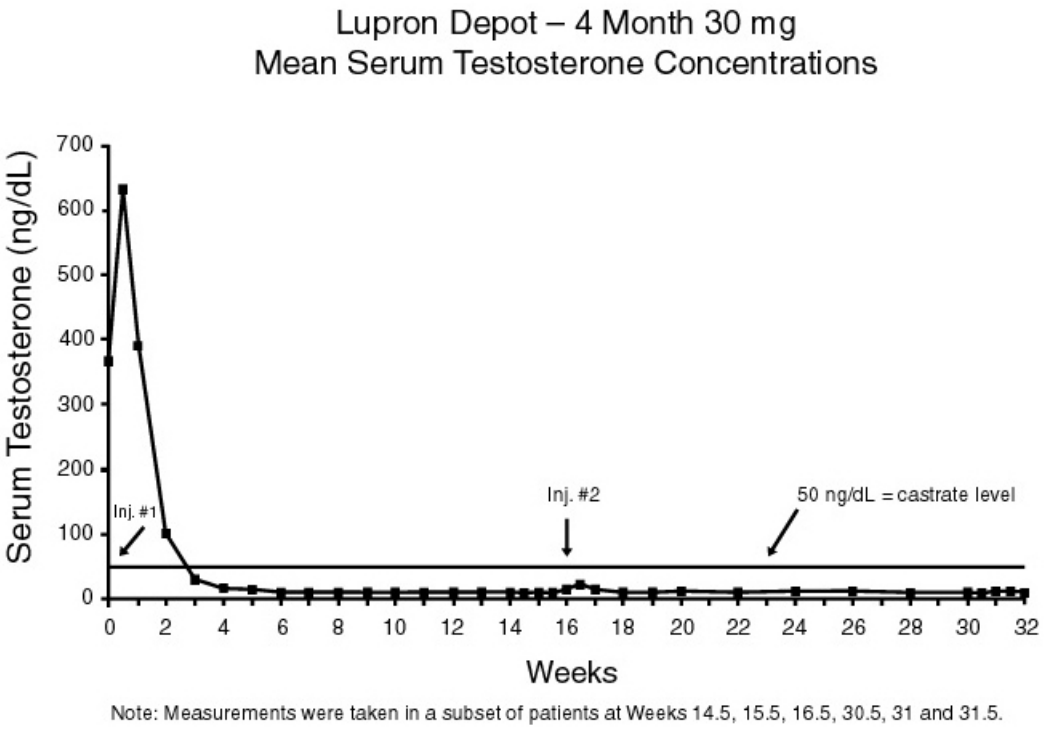
initial 32-week treatment phase and a long-term treatment phase. Serum testosterone levels were determined biweekly or weekly during the first 32 weeks of treatment. Once the patient completed the initial 32-week treatment period, treatment continued at the investigator's discretion with serum testosterone levels being done every 4 months prior to the injection.

In the majority of patients, testosterone levels increased 50% or more above the baseline during the first week of treatment. Mean serum testosterone subsequently suppressed to castrate levels within 30 days of the first injection in 94% of patients and within 43 days in all 49 patients during the initial 32-week treatment period. The median dosing interval between injections was 112 days. One escape from suppression (two consecutive testosterone values > 50 ng/dL after castrate levels achieved) was noted at Week 16. In this patient, serum testosterone increased to above the castrate range following the second depot injection (Week 16) but returned to the castrate level by Week 18. No adverse events were associated with this rise in serum testosterone. A second patient had a rise in testosterone at Week 17, then returned to the castrate level by Week 18 and remained there through Week 32. In the long-term treatment phase two patients experienced testosterone elevations, both at Week 48. Testosterone for one patient returned to the castrate range at Week 52, and one patient discontinued the study at Week 48 due to disease progression.

Secondary efficacy endpoints evaluated in the study were the objective tumor response as assessed by clinical evaluations of tumor burden (complete response, partial response, objectively stable and progression) and evaluations of changes in prostatic involvement and prostate-specific antigen (PSA). These evaluations were performed at Weeks 16 and 32 of the treatment phase. The long-term treatment phase monitored PSA at each visit (every 16 weeks). The objective tumor response analysis showed "no progression" (i.e. complete or partial response, or stable disease) in 86% (37/43) of patients at Week 16, and in 77% (37/48) of patients at Week 32. Local disease improved or remained stable in all patients evaluated at Week 16 and/or 32. For patients with elevated baseline PSA, 50% (23/46) had a normal PSA (< 4.0 ng/mL) at Week 16, and 51% (19/37) had a normal PSA at Week 32.

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

Using historical comparisons, the safety and efficacy of LUPRON DEPOT-4 Month 30 mg appear similar to the other LUPRON DEPOT formulations.



Note: Measurements were taken in a subset of patients at Weeks 14.5, 15.5, 16.5, 30.5, 31 and 31.5.

INDICATIONS AND USAGE

LUPRON DEPOT-4 Month 30 mg is indicated in the palliative treatment of advanced prostatic cancer.

CONTRAINDICATIONS

1. Hypersensitivity to GnRH, GnRH agonist analogs or any of the excipients in LUPRON DEPOT. Reports of anaphylactic reactions to synthetic GnRH (Factrel) or GnRH agonist analogs have been reported in the medical literature.
2. This formulation is not indicated for use in women. (See LUPRON DEPOT 3.75 mg and LUPRON DEPOT®–3 Month 11.25 mg package inserts.)
3. All formulations of LUPRON DEPOT are contraindicated in women who are or may become pregnant while receiving the drug. LUPRON DEPOT may cause fetal harm when administered to a pregnant woman. Major fetal abnormalities were observed in rabbits but not in rats after administration of LUPRON DEPOT throughout gestation. There was increased fetal mortality and decreased fetal weights in rats and rabbits. The effects on fetal mortality are expected consequences of the alterations in hormonal levels brought about by this drug. Therefore, the possibility exists that spontaneous abortion may occur. If this drug is used during pregnancy, or if the patient becomes pregnant while taking any formulation of LUPRON DEPOT, the patient should be apprised of the potential hazard to the fetus.

WARNINGS

Initially, LUPRON DEPOT, like other LH-RH agonists, causes increases in serum levels of testosterone to approximately 50% above baseline during the first week of treatment. Transient worsening of symptoms, or the occurrence of additional signs and symptoms of

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

For patients at risk, initiation of therapy with daily LUPRON® (leuprolide acetate) Injection (See **DOSAGE AND ADMINISTRATION** section in the LUPRON Injection labeling.) for the first two weeks to facilitate withdrawal of treatment may be considered. If spinal cord compression or renal impairment develops, standard treatment of these complications should be instituted.

PRECAUTIONS

Information for Patients An information pamphlet for patients is included with the product.

General Patients with metastatic vertebral lesions and/or with urinary tract obstruction should be closely observed during the first few weeks of therapy. (See **WARNINGS** section.)

Laboratory Tests Response to LUPRON DEPOT-4 Month 30 mg should be monitored by measuring serum levels of testosterone, as well as prostate-specific antigen. 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. Castrate levels were reached within two to four weeks and once achieved were maintained in most (45/49) patients for as long as the patients received their injections. (See **CLINICAL STUDIES** and **ADVERSE REACTIONS.)**

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

Drug/Laboratory Test Interactions Administration of LUPRON DEPOT in therapeutic doses results in suppression of the pituitary-gonadal system. Normal function is usually restored within three months after treatment is discontinued. Due to the suppression of the pituitary-gonadal system by LUPRON DEPOT, diagnostic tests of pituitary gonadotropic and gonadal functions conducted during treatment and for up to three months after discontinuation of LUPRON DEPOT may be affected.

Carcinogenesis, Mutagenesis, Impairment of Fertility Two-year carcinogenicity studies were conducted in rats and mice. In rats, a dose-related increase of benign pituitary hyperplasia and benign pituitary adenomas was noted at 24 months when the drug was administered subcutaneously at high daily doses (0.6 to 4 mg/kg). There was a significant but not dose-related increase of pancreatic islet-cell adenomas in females and of testicular interstitial cell adenomas in males (highest incidence in the low dose group). In mice no pituitary abnormalities were observed at a dose as high as 60 mg/kg for two years. Patients have been treated with leuprolide acetate for up to three years with doses as high as 10 mg/day and for two years with doses as high as 20 mg/day without demonstrable pituitary abnormalities.

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

Clinical and pharmacologic studies in adults (≥ 18 years) with leuprolide acetate and similar analogs have shown reversibility of fertility suppression when the drug is discontinued after continuous administration for periods of up to 24 weeks.

Pregnancy, Teratogenic Effects. Pregnancy Category X. (See **CONTRAINDICATIONS** section.)

Pediatric Use Safety and effectiveness of LUPRON DEPOT-4 Month 30 mg have not been established in pediatric patients. See LUPRON DEPOT-PED® (leuprolide acetate for depot suspension) labeling for the safety and effectiveness of the monthly formulation in children with central precocious puberty.

Geriatric Use In the clinical trials for LUPRON DEPOT – 4 Month 30 mg, the majority (79%) of the subjects studied were at least 65 years of age. Therefore, the labeling reflects the pharmacokinetics, efficacy and safety of LUPRON DEPOT in this population.

ADVERSE REACTIONS

Clinical Trials

The 4-month formulation of LUPRON DEPOT 30 mg was utilized in clinical trials that studied the drug in 49 nonorchiectomized prostate cancer patients for 32 weeks or longer and in 24 orchiectomized prostate cancer patients for 20 weeks.

In the majority of nonorchiectomized patients, testosterone levels increased 50% or more above baseline during the first week of treatment with LUPRON DEPOT, declining thereafter to baseline levels or below by the end of the second week of treatment. Therefore, potential exacerbations of signs and symptoms during the first few weeks of treatment are of concern in patients with vertebral metastases and/or urinary obstruction or hematuria which, if aggravated, may lead to neurological problems such as temporary weakness and/or paresthesia of the lower limbs or worsening of urinary symptoms. (See **WARNINGS** section.)

In the above described clinical trials, the following adverse reactions were reported in $\geq$ 5% of the patients during the treatment period regardless of causality.

Adverse Events Reported in ≥ 5% of Patients
Regardless of Causality
LUPRON DEPOT-4 Month 30 mg

	Nonorchiectomized, N = 49 Study 013		Orchiectomized, N = 24 Study 012	
	N	(%)	N	(%)
Body As a Whole				
Asthenia	6	(12.2)	1	(4.2)
Flu Syndrome	6	(12.2)	0	(0.0)
General Pain	16	(32.7)	1	(4.2)
Headache	5	(10.2)	1	(4.2)
Injection Site Reaction	4	(8.2)	9	(37.5)
Cardiovascular System				
Hot flashes/Sweats*	23	(46.9)	2	(8.3)
Digestive System				
GI Disorders	5	(10.2)	3	(12.5)
Metabolic and Nutritional Disorders				
Dehydration	4	(8.2)	0	(0.0)
Edema	4	(8.2)	5	(20.8)
Musculoskeletal System				
Joint Disorder	8	(16.3)	1	(4.2)
Myalgia	4	(8.2)	0	(0.0)
Nervous System				
Dizziness/Vertigo	3	(6.1)	2	(8.3)
Neuromuscular Disorders	3	(6.1)	1	(4.2)
Paresthesia	4	(8.2)	1	(4.2)
Respiratory System				
Respiratory Disorder	4	(8.2)	1	(4.2)
Skin and Appendages				
Skin Reaction	6	(12.2)	0	(0.0)
Urogenital System				
Urinary Disorders	5	(10.2)	4	(16.7)

In these same studies, the following adverse reactions were reported in less than 5% of the patients on LUPRON DEPOT-4 Month 30 mg.

Body As a Whole - Abscess, Accidental injury, Allergic reaction, Cyst, Fever, Generalized edema, Hernia, Neck pain, Neoplasm; *Cardiovascular System* - Atrial fibrillation, Deep thrombophlebitis, Hypertension; *Digestive System* - Anorexia, Eructation, Gastrointestinal hemorrhage, Gingivitis, Gum hemorrhage, Hepatomegaly, Increased appetite, Intestinal obstruction, Peridontal abscess; *Hemic and Lymphatic System* - Lymphadenopathy; *Metabolic and Nutritional Disorders* - Healing abnormal, Hypoxia, Weight loss; *Musculoskeletal System* - Leg cramps, Pathological fracture, Ptosis; *Nervous System* - Abnormal thinking, Amnesia, Confusion, Convulsion, Dementia, Depression, Insomnia/sleep disorders, Libido decreased*,

Neuropathy, Paralysis; *Respiratory System* - Asthma, Bronchitis, Hiccup, Lung disorder, Sinusitis, Voice alteration; *Skin and Appendages* - Herpes zoster, Melanosis; *Urogenital System* - Bladder carcinoma, Epididymitis, Impotence*, Prostate disorder, Testicular atrophy*, Urinary incontinence, Urinary tract infection.

* Due to the expected physiologic effects of decreased testosterone levels.

Laboratory: Abnormalities of certain parameters were observed, but their relationship to drug treatment is difficult to assess in this population. The following were recorded in ≥ 5% of patients: Decreased bicarbonate, Decreased hemoglobin/hematocrit/RBC, Hyperlipidemia (total cholesterol, LDL-cholesterol, triglycerides), Decreased HDL-cholesterol, Eosinophilia, Increased glucose, Increased liver function tests (ALT, AST, GGTP, LDH), Increased phosphorus. Additional laboratory abnormalities were reported: Increased BUN and PT, Leukopenia, Thrombocytopenia, Uricaciduria.

Postmarketing

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

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

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

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

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

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

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

See other LUPRON DEPOT and LUPRON Injection package inserts for other events reported in women and pediatric populations.

OVERDOSAGE

In clinical trials using daily subcutaneous leuprolide acetate in patients with prostate cancer, doses as high as 20 mg/day for up to two years caused no adverse effects differing from those observed with the 1 mg/day dose.

DOSAGE AND ADMINISTRATION

LUPRON DEPOT Must Be Administered Under The Supervision Of A Physician.

The recommended dose of LUPRON DEPOT-4 Month 30 mg to be administered is one injection **EVERY FOUR MONTHS (16 weeks).** Due to different release characteristics, a fractional dose of this 4-month depot formulation is not equivalent to the same dose of the monthly formulation and should not be given.

Incorporated in a depot formulation, the lyophilized microspheres are to be reconstituted and administered **EVERY FOUR MONTHS (16 weeks)** as a single intramuscular injection.

For optimal performance of the prefilled dual chamber syringe (PDS), read and follow the following instructions:

1. The LUPRON DEPOT powder should be visually inspected and the syringe should NOT BE USED if clumping or caking is evident. A thin layer of powder on the wall of the syringe is considered normal. The diluent should appear clear.
2. To prepare for injection, screw the white plunger into the end stopper until the stopper begins to turn.
3. Hold the syringe UPRIGHT. Release the diluent by SLOWLY PUSHING (6 to 8 seconds) the plunger until the first stopper is <u>at the blue line</u> in the middle of the barrel.
4. Keep the syringe UPRIGHT. Gently mix the microspheres (powder) thoroughly to form a uniform suspension. The suspension will appear milky. If the powder adheres to the stopper or caking/clumping is present, tap the syringe with your finger to disperse. DO NOT USE if any of the powder has not gone into suspension.
5. Hold the syringe UPRIGHT. With the opposite hand pull the needle cap upward without twisting.
6. Keep the syringe UPRIGHT. Advance the plunger to expel the air from the syringe.
7. Inject the entire contents of the syringe intramuscularly at the time of reconstitution. The suspension settles very quickly following reconstitution; therefore, LUPRON DEPOT should be mixed and used immediately.

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

AFTER INJECTION

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

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

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

HOW SUPPLIED
LUPRON DEPOT-4 Month 30 mg is packaged as follows:
Kit with prefilled dual-chamber syringe NDC 0300-3683-01

Each syringe contains sterile lyophilized microspheres which is leuprolide acetate incorporated in a biodegradable polymer of polylactic acid. When mixed with 1.5 mL of accompanying diluent, LUPRON DEPOT-4 Month 30 mg is administered as a single IM injection **EVERY FOUR MONTHS (16 weeks).**

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

U.S. Patent Nos. 4,728,721; 4,849,228; 5,330,767; 5,476,663; 5,480,656; 5,575,987; 5,631,020; 5,631,021; 5,643,607; 5,716,640; 5,814,342; 5,823,997; 5,980,488; and 6,036,976. Other patents pending.

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

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(No. 3683)
03-5449-R10; Revised: October, 2005