

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

7.5 mg/syringe (1-Month slow release), 22.5 mg/syringe (3-Month slow release),

30.0 mg/syringe (4-Month slow release)

Gonadotropin-releasing hormone analog

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PrLUPRON
leuprolide acetate injection

PrLUPRON 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^a
LUPRON		
subcutaneous	sterile solution supplied in a 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 / 7.5 mg (1-Month SR)	carboxymethylcellulose sodium, DL-lactic and glycolic acids copolymer, D-mannitol, gelatin, glacial acetic acid, polysorbate 80
	pre-filled dual-chamber syringe containing sterile lyophilized microspheres / 22.5 mg (3-Month SR)	carboxymethylcellulose sodium, D-mannitol, glacial acetic acid, polylactic acid, polysorbate 80
	pre-filled dual-chamber syringe containing sterile lyophilized microspheres / 30.0 mg (4-Month SR)	carboxymethylcellulose sodium, D-mannitol, glacial acetic acid, polylactic acid, polysorbate 80
Definition: SR = Slow Release a. For a complete listing, see DOSAGE FORMS, COMPOSITION AND PACKAGING .		

INDICATIONS AND CLINICAL USE

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

- the palliative treatment of sex hormone responsive advanced (stage D2) carcinoma of the prostate.

LUPRON DEPOT must be administered under the supervision of a health professional.

Geriatrics (> 65 years of age):

The majority of the patients studied in the clinical trials for LUPRON and LUPRON DEPOT were 65 years and older. See **CLINICAL TRIALS**.

Pediatrics (< 18 years of age):

LUPRON DEPOT 22.5 mg (3-Month SR) and 30.0 mg (4-Month SR) are not indicated for use in children. LUPRON DEPOT treatment of children is covered in the LUPRON DEPOT 3.75 mg and 7.5 mg “Central Precocious Puberty” Product Monograph.

Women (> 18 years of age):

LUPRON and LUPRON DEPOT 7.5 mg (1-Month SR), 22.5 mg (3-Month SR) and 30.0 mg (4-Month SR) 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.

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 administered on Day 6 of pregnancy at test dosages of 0.00024, 0.0024, and 0.024 mg/kg (1/300 to 1/3 the 3.75 mg LUPRON DEPOT human 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 is excreted in human milk; therefore, LUPRON and LUPRON DEPOT are contraindicated in patients who are breast-feeding.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- LUPRON and LUPRON DEPOT should be prescribed by a qualified physician experienced in the use of hormonal therapy in prostate cancer. LUPRON and LUPRON DEPOT should be administered under the supervision of a health professional. The following are clinically significant adverse events:
 - Clinical testosterone flare reaction in men with prostate cancer. See **General**.
 - Osteoporosis. See **WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Changes in Bone Density**.

General

LUPRON (leuprolide acetate injection) and LUPRON DEPOT (leuprolide acetate for depot suspension), like other gonadotropin-releasing hormone (LHRH) agonists, causes a transient increase in serum concentration of testosterone during the first weeks of treatment. Patients may experience worsening of symptoms or onset of new symptoms, including bone pain, neuropathy, hematuria, or ureteral or bladder outlet obstruction. Cases of spinal cord compression, which may contribute to paralysis with or without fatal complications, have been reported with LHRH agonists. If spinal cord compression or renal impairment due to ureteral obstruction develops, standard treatment of these complications should be instituted.

Patients with metastatic vertebral lesions and/or with urinary tract obstruction should begin leuprolide acetate therapy under close supervision.

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 selective serotonin reuptake inhibitors (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/day). Also in rat, there was a significant but not a 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/day 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**.

Cardiovascular

Increased risk of developing myocardial infarction, sudden cardiac death and stroke has been reported in association with use of gonadotropin-releasing hormone (GnRH) agonists in men. The risk should be evaluated carefully along with cardiovascular risk factors when determining a treatment for patients with prostate cancer. Patients receiving GnRH agonists should be monitored for symptoms and signs suggestive of development of cardiovascular disease and be managed according to current clinical practice. See **WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests**.

Effect on QT/QTc Interval

Androgen deprivation therapy has the potential to prolong QT/QTc interval on an ECG. Physicians should consider whether the benefits of androgen deprivation therapy outweigh the potential risk in patients with congenital long QT syndrome, electrolyte abnormalities, or congestive heart failure and in patients taking Class IA (e.g. quinidine, procainamide), Class III (e.g., amiodarone, sotalol, dofetilide, ibutilide), or Class IC (e.g., flecainide, propafenone) antiarrhythmic medications.

In a randomized, active-controlled trial to compare leuprolide acetate 7.5 mg with an LHRH antagonist in patients with prostate cancer, periodic electrocardiograms were collected and evaluated. In the leuprolide cohort, a mean QTcF increase of 17 msec from baseline was reported. The percentage of subjects who experienced maximum QTcF changes of > 30 to < 60 msec and \geq 60 msec was 41 and 4%, respectively.

Dependence/Tolerance

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

Endocrine and Metabolism

Changes in Bone Density

Decreased bone mineral density can be anticipated with long-term use of an LHRH agonist. Androgen deprivation therapy is associated with increased risks of osteoporosis and skeletal bone fractures. The risk of skeletal fracture increases with the duration of androgen deprivation therapy. Assessment of osteoporosis risk and management according to clinical practice and guidelines should be considered.

In patients with significant risk factors for decreased bone mineral content and/or bone mass such as chronic alcohol and/or tobacco use, presumed or strong family history of osteoporosis or chronic use of drugs that can reduce bone mass such as anticonvulsants or corticosteroids, leuprolide acetate may pose an additional risk. In these patients, risk versus benefit must be weighed carefully before therapy with LUPRON or LUPRON DEPOT is instituted.

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.

Reduction in Glucose Tolerance

A reduction in glucose tolerance and an increased risk in developing diabetes have been reported in men treated with androgen deprivation therapy. Patients treated with LUPRON or LUPRON DEPOT should undergo periodic monitoring of blood glucose. Diabetic patients may require more frequent monitoring when receiving LUPRON or LUPRON DEPOT.

Hematologic

Anemia is a known physiologic consequence of testosterone suppression. Assessment of anemia risk and management according to local clinical practice and guidelines should be considered.

Hepatic/Biliary/Pancreatic

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

In the postmarketing setting, cases of serious liver injury (including reports of fatal cases) have been described in which a causal association with leuprolide acetate therapy is suspected. Elevations in alanine aminotransferase (ALT) in patients receiving LUPRON DEPOT in clinical trials have been reported. Monitoring of liver function in patients treated with LUPRON or LUPRON DEPOT should be considered.

Psychiatric

Like other drugs in this class, mood swings, including depression, have been reported with LUPRON and LUPRON DEPOT (see **ADVERSE REACTIONS, Clinical Trial Adverse Drug Reactions**). There have been reports of suicidal ideations and attempt (see **ADVERSE REACTIONS, Post-market Adverse Reactions**). Patients should be counseled on the possibility of development or worsening of depression during treatment with LUPRON or LUPRON DEPOT.

Renal

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

Special Populations

Pregnant Women

LUPRON and LUPRON DEPOT 7.5 mg (1-Month SR), 22.5 mg (3-Month SR) and 30.0 mg (4-Month SR) 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 (1-Month SR) and 11.25 mg (3-Month SR) “Endometriosis” Product Monograph.

Nursing Women

LUPRON and LUPRON DEPOT 7.5 mg (1-Month SR), 22.5 mg (3-Month SR) and 30.0 mg (4-Month SR) 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 (1-Month SR) and 11.25 mg (3-Month SR) “Endometriosis” Product Monograph.

Pediatrics (< 18 years of age)

Safety and effectiveness of LUPRON DEPOT 22.5 mg (3-Month SR) and 30.0 mg (4-Month SR) have not been established in pediatric patients. See “Central Precocious Puberty” Product Monograph for the safety and effectiveness of LUPRON and LUPRON DEPOT in children with central precocious puberty.

Geriatrics (> 65 years of age)

In prostatic cancer clinical trials for LUPRON and LUPRON DEPOT, the majority of subjects studied were at least 65 years of age. The labelling therefore reflects the pharmacokinetics, efficacy and safety of LUPRON and LUPRON DEPOT in this population.

Monitoring and Laboratory Tests

Response to LUPRON and LUPRON DEPOT should be monitored by measuring serum levels of testosterone, as well as prostate-specific antigen and prostatic acid phosphatase. In the majority of patients, testosterone levels increased above baseline during the first week, declining thereafter to baseline levels or below by the end of the second week. In the LUPRON DEPOT 30.0 mg (4-Month SR) study, castrate levels were reached within two to four weeks, and once achieved, were maintained in most patients (45/49) for as long as the patients received their injections. See **CLINICAL TRIALS**.

The effects of leuprolide acetate on bone lesions may be monitored by bone scans, while its effects on prostatic lesions may be monitored by ultrasonography and/or computed tomography (CT) scan in addition to digital rectal examination.

Intravenous pyelogram, ultrasonography, or CT scan may also be utilized to diagnose or assess the status of obstructive uropathy.

Periodic monitoring of serum testosterone and Prostatic Specific Antigen (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.

Baseline risk factors of cardiovascular diseases should be assessed. Patients receiving LUPRON or LUPRON DEPOT should be monitored periodically for risk factors, signs and symptoms of cardiovascular diseases. In addition, baseline ECG recording and serum potassium, calcium, and magnesium levels are recommended. Monitoring of ECG and serum electrolyte levels during treatment should also be considered for those at risk for electrolyte abnormality and QTc prolongation.

Blood glucose levels and/or glycosylated hemoglobin (HbA1c) should be checked periodically in patients treated with LUPRON or LUPRON DEPOT and more frequently in diabetic patients. See **WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Reduction in Glucose Tolerance**.

Monitoring of liver function in patients treated with LUPRON or LUPRON DEPOT should be considered.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

In clinical studies, an initial rise in serum testosterone levels usually occurred in non-orchietomized patients during the first week of treatment.

This occasionally was associated with a worsening of signs and symptoms, usually an increase in bone pain. See **WARNINGS AND PRECAUTIONS**. In some cases, temporary renal impairment was accompanied by mental confusion, joint pain, nausea and vomiting. In each case, leuprolide acetate administration was continued and the symptom(s) subsided in one to two weeks.

The potential for exacerbation of signs and symptoms during the first few weeks of treatment is a concern in patients with vertebral metastases and/or in patients with severe obstructive uropathy which, if aggravated, may lead to neurological problems such as temporary weakness and/or paresthesia of the lower limbs or worsening of urinary symptoms, such as hematuria and urinary tract obstruction.

Interstitial lung disease has been reported with a variable time to onset in the postmarketing reports of patients treated with leuprolide acetate. Although a direct causal relationship between leuprolide acetate therapy and interstitial lung disease has not been established on the basis of the prostate cancer treatment, discontinuation of leuprolide acetate to allow for a potential resolution of the interstitial lung disease should be considered.

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.

LUPRON and LUPRON DEPOT 7.5 mg (1-Month SR), 22.5 mg (3-Month SR), 30.0 mg (4-Month SR)

The following possibly or probably related systemic adverse reactions were reported by $\geq 5\%$ of the patients using LUPRON (leuprolide acetate injection) and LUPRON DEPOT (leuprolide acetate for depot suspension) 7.5 mg, 22.5 mg and 30.0 mg in clinical studies. Reactions not considered drug related are excluded.

In two clinical studies with LUPRON, hot flashes (49 to 55%), impotence/decrease in libido (3 to 10%), local reactions at injection site/ecchymosis/erythema (4 to 15%), decrease in testicular size/atrophic genitalia (7 to 13%), and itching rash (3%) were reported.

Adverse reactions reported by $\geq 5\%$ of the patients using LUPRON DEPOT formulations are summarized in **Table 1**.

Table 1. Incidence (%) of Possibly or Probably Related Systemic Adverse Reactions Reported by ≥ 5% of Patients Treated with LUPRON DEPOT 7.5 mg (1 injection every month), LUPRON DEPOT 22.5 mg (1 injection every 3 months) and LUPRON DEPOT 30 mg (1 injection every 4 months)

	LUPRON DEPOT 7.5 mg (1-Month SR) N=56 (%) Study M85-097	LUPRON DEPOT 22.5 mg (3-Month SR)¹ Non- Orchiectomized N=94 (%) Studies M91-583 and M91-653	LUPRON DEPOT 30.0 mg (4-Month SR) Non- Orchiectomized N=49 (%) Study M93-013	LUPRON DEPOT 30.0 mg (4-Month SR) Orchiectomized N=24 (%) Study M93-012²
Body as a Whole				
Asthenia	3 (5.4)	7 (7.4)	6 (12.2)	1 (4.2)
Flu syndrome			6 (12.2)	0 (0.0)
General pain	4 (7.1)	25 (26.6)	16 (32.7)	1 (4.2)
Headache		6 (6.4)	5 (10.2)	1 (4.2)
Injection site reaction		13 (13.8)	4 (8.2)	9 (37.5)
Cardiovascular System				
Hot flashes/sweats*	33 (58.9)	55 (58.5)	23 (46.9)	2 (8.3)
Gastrointestinal System				
Nausea/vomiting	3 (5.4)			
GI disorder		15 (16.0)	5 (10.2)	3 (12.5)
Metabolic and Nutritional Disorders				
Dehydration			4 (8.2)	0 (0.0)
Edema	7 (12.5)		4 (8.2)	5 (20.8)
Musculoskeletal System				
Joint disorder		11 (11.7)	8 (16.3)	1 (4.2)
Myalgia			4 (8.2)	0 (0.0)
Central/Peripheral Nervous System				
Dizziness/Vertigo		6 (6.4)	3 (6.1)	2 (8.3)
Insomnia/Sleep disorders		8 (8.5)		
Neuromuscular disorders		9 (9.6)	3 (6.1)	1 (4.2)
Paresthesia			4 (8.2)	1 (4.2)
Respiratory System				
Dyspnea	3 (5.4)			
Respiratory disorders		6 (6.4)	4 (8.2)	1 (4.2)

	LUPRON DEPOT 7.5 mg (1-Month SR) N=56 (%) Study M85-097	LUPRON DEPOT 22.5 mg (3-Month SR)¹ Non- Orchiectomized N=94 (%) Studies M91-583 and M91-653	LUPRON DEPOT 30.0 mg (4-Month SR) Non- Orchiectomized N=49 (%) Study M93-013	LUPRON DEPOT 30.0 mg (4-Month SR) Orchiectomized N=24 (%) Study M93-012²
Skin and Appendages				
Skin reaction		8 (8.5)	6 (12.2)	0 (0.0)
Urogenital System				
Testicular atrophy*	3 (5.4)	19 (20.2)		
Impotence*	3 (5.4)	0 (0.0)		
Urinary disorders		14 (14.9)	5 (10.2)	4 (16.7)

* Physiological effects of decreased testosterone.

1: The adverse reactions reported for LUPRON DEPOT 22.5 mg (3-Month SR) are based on two clinical trials.

2: Study M93-012 was a multicenter, open-label study designed to characterize the pharmacokinetic profile of LUPRON DEPOT 30.0 mg (4-Month SR) following a single intramuscular injection and to assess the safety of the formulation in prostatic cancer patients.

Less Common Clinical Trial Adverse Drug Reactions (< 5%)

The following possibly or probably related systemic adverse reactions were reported by less than 5% of the patients using LUPRON and LUPRON DEPOT 7.5 mg (1-Month SR), 22.5 mg (3-Month SR) and 30.0 mg (4-Month SR) in clinical studies. Reactions not considered drug-related are excluded.

LUPRON

Cardiovascular System:	cardiac arrhythmias, congestive heart failure, electrocardiogram (ECG) changes/ischemia, high blood pressure, hypotension, myocardial infarction, murmur, phlebitis/thrombosis, pulmonary emboli, transient ischemic attack/stroke
Central/Peripheral Nervous System:	anxiety, blurred vision, dizziness/light-headedness, headache, hearing disorder, lethargy, memory disorder, mood swings, nervousness, numbness, paresthesia, peripheral neuropathy, sleep disorders, spinal fracture/paralysis, syncope/blackouts, taste disorders
Endocrine System:	breast tenderness or pain, gynecomastia, libido increase, thyroid enlargement
Gastrointestinal System:	anorexia, constipation, dysphagia, gastrointestinal bleeding, gastrointestinal disturbance, hepatic dysfunction, peptic ulcer, rectal polyps

Hemic and Lymphatic System:	anemia, decreased white blood cell (WBC)
Integumentary System:	carcinoma of skin/ear, dry skin, ecchymosis, hair loss, itching, pigmentation, skin lesions
Musculoskeletal System:	ankylosing spondylosis, joint pain, myalgia, pelvic fibrosis, spasms
Respiratory System:	cough, pleural rub, pneumonia, pulmonary fibrosis, pulmonary infiltrate, respiratory disorders, sinus congestion
Urogenital System:	bladder spasms, hematuria, incontinence, penile swelling, prostate pain, urinary obstruction, urinary tract infection
Miscellaneous:	asthenia, depression, fatigue, fever, hypoglycemia, hypoproteinemia, increased blood urea nitrogen (BUN), increased creatinine, infection/inflammation, ophthalmologic disorders, swelling (temporal bone)

LUPRON DEPOT 7.5 mg (1-Month SR)

Cardiovascular System:	angina, cardiac arrhythmia
Central/Peripheral Nervous System:	insomnia, paresthesia
Endocrine System:	gynecomastia, libido decrease
Gastrointestinal System:	anorexia, diarrhea
Integumentary System:	dermatitis, local skin reactions, hair growth
Musculoskeletal System:	bone pain, myalgia
Respiratory System:	dyspnea, hemoptysis
Urogenital System:	dysuria, frequency/urgency, hematuria, testicular pain
Miscellaneous:	asthenia, diabetes, fever/chills, hard nodule in throat, increased calcium, increased uric acid, serum glutamic oxaloacetic transaminase (SGOT) (> 2 times normal values), weight gain

LUPRON DEPOT 22.5 mg (3-Month SR)

Body as a Whole:	enlarged abdomen, fever
Cardiovascular System:	arrhythmia, bradycardia, heart failure, hypertension, hypotension, varicose vein
Central/Peripheral Nervous System:	anxiety, delusions, depression, hypesthesia, libido decrease*, nervousness, paresthesia
Digestive System:	anorexia, duodenal ulcer, increased appetite, thirst/dry mouth

Hemic and Lymphatic System:	anemia, lymphedema
Metabolic and Nutritional Disorders:	dehydration, edema
Respiratory System:	epistaxis, pharyngitis, pleural effusion, pneumonia
Special Senses:	abnormal vision, amblyopia, dry eyes, tinnitus
Urogenital System:	gynecomastia, impotence*, penis disorders, testis disorders

* Physiologic effects of decreased testosterone

LUPRON DEPOT 30.0 mg (4-Month SR)

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, periodontal 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

[†] Physiologic effects of decreased testosterone.

Abnormal Hematologic and Clinical Chemistry Findings

Abnormalities of certain parameters observed in hematologic and clinical chemistry determinations were recorded, but relationship to drug is difficult to assess in this population.

The following were recorded in $\geq 5\%$ of patients in clinical studies with LUPRON DEPOT 7.5 mg (1-Month SR), 22.5 mg (3-Month SR) and 30.0 mg (4-Month SR):

LUPRON DEPOT 7.5 mg (1-Month SR)

Lactate dehydrogenase (LDH) (> 2 times normal values), alkaline phosphatase (> 1.5 times normal values).

In the Phase 3, open-label, multicenter 24-week study of previously untreated patients with stage D2 prostate cancer (Study M85-097), treated with LUPRON DEPOT 7.5 mg (1-Month SR) injected monthly, 1/56 (2%) patients had an asymptomatic elevation of aspartate aminotransferase (AST) $> 3X$ ULN. This patient did not have a concomitant elevation in bilirubin. Alanine aminotransferase (ALT) was not measured in this study.

LUPRON DEPOT 22.5 mg (3-Month SR)

Increased BUN, hyperglycemia, hyperlipidemia [total cholesterol, low-density lipoprotein (LDL)-cholesterol, triglycerides], hyperphosphatemia, abnormal liver function tests, increased PT, increased PTT. Additional laboratory abnormalities reported were: decreased platelets, decreased potassium and increased WBC.

LUPRON DEPOT 30.0 mg (4-Month SR)

Abnormalities of certain parameters were observed, but their relationship to drug treatment are difficult to assess in this population. The following were recorded in $\geq 5\%$ of patients: decreased bicarbonate, decreased hemoglobin/hematocrit/red blood cell (RBC), hyperlipidemia (total cholesterol, LDL-cholesterol, triglycerides), decreased high-density lipoprotein (HDL)-cholesterol, eosinophilia, increased glucose, increased liver function tests [alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transpeptidase (GGTP), lactate dehydrogenase (LDH)], and increased phosphorus. Additional laboratory abnormalities were reported: increased BUN and PT, leukopenia, thrombocytopenia, uricaciduria, urine abnormality.

See **DRUG INTERACTIONS**, **Drug-Laboratory Test Interactions** section for more details.

Post-Market Adverse Drug Reactions

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

There have been reports of suicidal ideation and attempt. Many, but not all, of these patients had a history of depression or other psychiatric illness.

Pituitary Apoplexy

During postmarketing 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 two 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.

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 LHRH 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 acetate-treated group had lower bone density scores than the non-treated control group. From another case report, two additional men, one 64 and the other 70 years, respectively, receiving goserelin acetate, were observed to have collapsed vertebrae thought to be due to decreased bone mineral density. It can be anticipated that long periods of medical castration in men will have effects on bone density.

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

Cardiovascular System:	cardiac arrest, hypotension, myocardial infarction, and sudden cardiac death
Central/Peripheral Nervous System:	convulsion, peripheral neuropathy, spinal fracture/paralysis
Hemic and Lymphatic System:	decreased WBC
Hepatobiliary Disorders:	serious liver injury (including fatal cases)
Integumentary System:	photosensitivity reactions, rash, urticaria
Musculoskeletal System:	tenosynovitis-like symptoms
Urogenital System:	prostate pain
Miscellaneous:	hematoma, induration, inflammation, injection site reactions including pain, sterile abscess
Respiratory System:	interstitial lung disease, pulmonary fibrosis

See the “Central Precocious Puberty” 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.

Since androgen deprivation treatment may prolong the QTc interval, the concomitant use of leuprolide acetate with medicinal products known to prolong the QTc interval or medicinal products able to induce torsades de pointes should be carefully evaluated. Such medicinal products include but are not limited to the examples that follow: Class IA (e.g. quinidine, disopyramide), Class III (e.g. amiodarone, dronedarone, sotalol, dofetilide, ibutilide), or Class IC (e.g. flecainide, propafenone) antiarrhythmic medicinal products, antipsychotics (e.g. chlorpromazine), antidepressants (e.g. amitriptyline, nortriptyline), opioids (e.g. methadone), macrolide antibiotics and analogues (e.g. erythromycin, clarithromycin, azithromycin), quinolone antibiotics (e.g. moxifloxacin), antimalarials (e.g. quinine), azole antifungals, 5-hydroxytryptamine (5-HT₃) receptor antagonists (e.g. ondansetron), and beta-2 adrenoceptor agonists (e.g. salbutamol).

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 leuprolide acetate in therapeutic doses results in suppression of the pituitary-gonadal system. Normal function is usually restored within 4 to 12 weeks after treatment is discontinued. Diagnostic tests of pituitary-gonadal function conducted during treatment and within 4 to 8 weeks after discontinuation of LUPRON DEPOT (leuprolide acetate for depot suspension) therapy may therefore be misleading.

As expected, 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. See **DETAILED PHARMACOLOGY**. 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 health professional.
- LUPRON DEPOT 7.5 mg (1-Month SR), 22.5 mg (3-Month SR) and 30.0 mg (4-Month SR) administered intramuscularly is designed to provide continuous sustained release of leuprolide for one, three, and four months, respectively.
- In patients treated with GnRH analogues for prostate cancer, treatment is usually continued upon development of castration-resistant prostate cancer. Reference should be made to relevant guidelines.

Recommended Dose and Dosage Adjustment

LUPRON

The recommended dose of LUPRON (leuprolide acetate injection) is 1 mg (0.2 mL), as a **single daily subcutaneous injection**. See **DOSAGE AND ADMINISTRATION**, **Administration** and **CONSUMER INFORMATION**.

LUPRON DEPOT

The recommended dose of LUPRON DEPOT (1-Month SR) is 7.5 mg administered **monthly** as a **single intramuscular injection**, after reconstitution with the special diluent. See **DOSAGE AND ADMINISTRATION**, **Administration** and **CONSUMER INFORMATION**.

The recommended dose of LUPRON DEPOT (3-Month SR) is 22.5 mg administered as a **single intramuscular injection once every three months (12 weeks)**, after reconstitution with the special diluent. See **DOSAGE AND ADMINISTRATION**, **Administration** and **CONSUMER INFORMATION**. Due to different release characteristics, a fractional dose of this 3-Month depot formulation is not equivalent to the same dose of the monthly formulation and should therefore not be given.

The recommended dose of LUPRON DEPOT (4-Month SR) is 30.0 mg administered as a **single intramuscular injection once every four months (16 weeks)**, after reconstitution with the special diluent. See **DOSAGE AND ADMINISTRATION**, **Administration** and **CONSUMER INFORMATION**. 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 therefore not be given.

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

Maintaining testosterone suppression is important in treating the symptoms of hormone-dependent prostate cancer. Missing an appointment by a few days should not disrupt the benefits of treatment, but keeping a consistent schedule of LUPRON DEPOT injection is an important part of treatment.

Administration

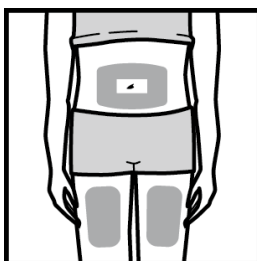
As with all parenteral products, inspect container's solution for discoloration and particulate matter before each use.

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

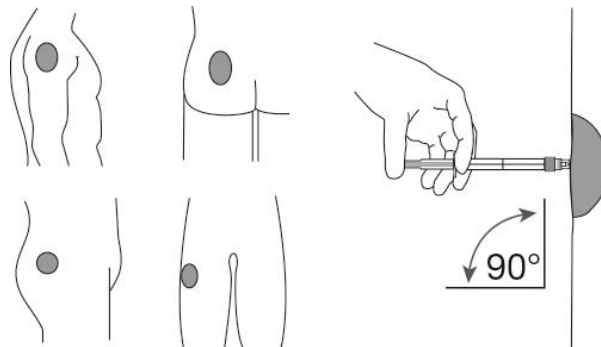


Reconstitution

LUPRON DEPOT 7.5 mg (1-Month SR), 22.5 mg (3-Month SR) and 30.0 mg (4-Month SR)

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

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** (six to eight 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 by inserting the needle at a 90 degree angle into the gluteal area, anterior thigh, or deltoid; injection sites should be alternated.



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. If blood is present remove the needle immediately. Do not inject the medication.

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 approximately 133 times the recommended human dose, expressed on a per body weight basis, resulted in dyspnea, decreased activity, and local irritation at the injection site.

There is no 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.

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

General

Animal and human studies indicate that, following an initial stimulation, chronic administration of leuprolide acetate results in the inhibition of gonadotropin production. Consequently, ovarian or testicular steroidogenesis is suppressed. The therapeutic effect of leuprolide acetate in the treatment of hormone-dependent tumors, such as in prostatic cancer, results from the reduction in serum gonadotropins and gonadal steroids.

Chronic administration of leuprolide acetate has resulted in inhibition of tumor growth (prostatic tumors in Noble and Dunning male rats, 7-12-dimethylbenz[α]-anthracene (DMBA)-induced mammary tumors in female rats) as well as atrophy of the reproductive organs. An additional mechanism of action, a direct effect on the gonads by downregulation of the gonadotropin receptors, is suggested in some animal studies.

In humans, subcutaneous administration of single daily doses 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 the levels of the gonadal steroids (testosterone and dihydrotestosterone in males and estrone and estradiol in premenopausal females). However, continuous administration results in decreased levels of LH and FSH in all patients. 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, and are maintained as long as treatment continues. Castrate levels of testosterone in prostatic cancer patients have been demonstrated for periods of up to five years.

Pharmacokinetics

Intramuscular injections of LUPRON DEPOT (leuprolide acetate for depot suspension) 7.5 mg (1-Month SR), 22.5 mg (3-Month SR), and 30.0 mg (4-Month SR) provide plasma concentrations of leuprolide acetate over a period of one, three, and four months, respectively. See **DETAILED PHARMACOLOGY**.

Absorption

Following a single LUPRON DEPOT 7.5 mg (1-Month SR) injection to adult patients, the mean peak leuprolide plasma concentration was almost 20 ng/mL at four hours and then declined to 0.36 ng/mL at four 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 castrate levels.

The pharmacokinetic profile of LUPRON DEPOT 22.5 mg (3-Month SR) was characterized in 23 orchiectomized prostate cancer patients. Following a single injection of the three-month

formulation of LUPRON DEPOT 22.5 mg (3-Month SR), a mean peak plasma leuprolide concentration of 48.9 ng/mL was observed at four hours and then declined to 0.67 ng/mL at 12 weeks. Leuprolide appeared to be released at a constant rate following the onset of steady-state level during the third week after dosing, providing steady plasma concentrations through the 12-week dosing interval. Detectable levels of leuprolide were present at all measurement points in all patients during this 12-week period. The initial burst, followed by the rapid decline to a steady-state level, was similar to the release pattern seen with the monthly formulation.

Following a single injection of LUPRON DEPOT 30.0 mg (4-Month SR) in sixteen orchiectomized prostate cancer patients, a mean plasma leuprolide concentration of 59.3 ng/mL was observed at four 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 to 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.

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 three 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 five prostate cancer patients reached mean maximum concentration two to six 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 three 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.

Geriatrics

See **WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics** section.

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. Protect from light. Keep in carton until use.

LUPRON DEPOT

Store LUPRON DEPOT (leuprolide acetate for depot suspension) 7.5 mg (1-Month SR), 22.5 mg (3-Month SR), and 30.0 mg (4-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 (leuprolide acetate injection) is available as a sterile solution supplied in a multiple dose vial of 2.8 mL. Each multiple-dose vial contains 5 mg/mL leuprolide acetate for subcutaneous use.

LUPRON is supplied as a 14-day kit. Each 14-day Patient Administration Kit contains one vial of LUPRON, 14 syringes, two indication-specific **Consumer Information** leaflets and one **Instructions for Use** leaflet.

LUPRON DEPOT

LUPRON DEPOT (leuprolide acetate for depot suspension) is available three strengths: 7.5 mg (1-Month SR), 22.5 mg (3-Month SR) and 30.0 mg (4-Month SR).

LUPRON DEPOT 7.5 mg (1-Month SR), 22.5 mg (3-Month SR) and 30.0 mg (4-Month SR) are supplied in single dose kits containing one pre-filled dual-chamber syringe with 23 G needle and one booklet including indication-specific **Consumer Information** as well as **Special Instructions for Use**.

Listing of Non-Medicinal Ingredients

LUPRON

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

LUPRON DEPOT 7.5 mg (1-Month SR)

The front chamber of the LUPRON DEPOT 7.5 mg (1-Month SR) pre-filled dual-chamber syringe contains 7.5 mg leuprolide acetate with the following non-medicinal ingredients: DL-lactic and glycolic acids copolymer, D-mannitol and gelatin.

The rear chamber of diluent contains the following non-medicinal ingredients: carboxymethylcellulose sodium, D-mannitol, glacial acetic acid (to control pH), polysorbate 80 and water for injection.

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.

LUPRON DEPOT 22.5 mg (3-Month SR)

The front chamber of the LUPRON DEPOT 22.5 mg (3-Month SR) pre-filled dual-chamber syringe contains 22.5 mg leuprolide acetate, with the following non-medicinal ingredients: D-mannitol and polylactic acid.

The rear chamber of diluent contains the following non-medicinal ingredients: carboxymethylcellulose sodium, D-mannitol, glacial acetic acid (to control pH), polysorbate 80 and water for injection.

When mixed with diluent, the sterile lyophilized microspheres become a suspension, which is intended as an intramuscular injection to be given **once every three months**.

During the manufacturing process of LUPRON DEPOT (3-Month SR), acetic acid is lost, leaving the leuprolide peptide.

LUPRON DEPOT 30.0 mg (4-Month SR)

The front chamber of the LUPRON DEPOT 30.0 mg (4-Month SR) pre-filled dual-chamber syringe contains: 30.0 mg leuprolide acetate, with the following non-medicinal ingredients: D-mannitol and polylactic acid.

The rear chamber of diluent contains the following non-medicinal ingredients: carboxymethylcellulose sodium, D-mannitol, glacial acetic acid (to control pH), polysorbate 80 and water for injection.

When mixed with diluent, the sterile lyophilized microspheres become a suspension, which is intended as an intramuscular injection to be given **once every four months**.

During the manufacturing process of LUPRON DEPOT (4-Month SR), acetic acid is lost, leaving the leuprolide peptide.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Proper name: leuprolide acetate

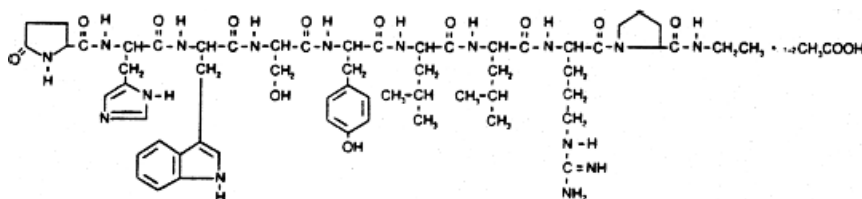
Chemical name: 5-oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-Leucyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide acetate.

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

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

Molecular formula and molecular mass: $C_{59}H_{84}N_{16}O_{12} \cdot C_2H_4O_2$ 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 2. Summary of Patient Demographics for Clinical Trials in Prostatic Cancer

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)
M80-036*	Phase 2, open-label, multicenter study	LUPRON 1 mg or 10 mg once daily Subcutaneous 18 to 80 weeks	118 (111 had stage D ₂ disease)	~66 years (42-93 years)
M81-017†	Open-label multicenter study	LUPRON or DES (diethylstilbesterol) 1 mg three times daily	202 (93 had stage D ₂ disease)	--

* Retrospective control for this study was obtained from the National Prostatic Cancer Project (NPCP), Protocol No. 1300 which consisted of two treatment arms: DES (diethylstilbesterol) or orchiectomy.

† Retrospective comparison of the results of Study M80-036 carried out by the NPCP. Patients received either DES or orchiectomy.

LUPRON DEPOT

Table 3. Summary of Patient Demographics for Clinical Trials with LUPRON DEPOT in Prostatic Cancer

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)
M85-097	Phase III, open-label, multicenter study	7.5 mg LUPRON DEPOT injected every 4 weeks Intramuscular 24 weeks	53	--
M91-583	Phase III, open-label, multicenter study	22.5 mg LUPRON DEPOT injected every 12 weeks Intramuscular Minimum 24 weeks	61*	71 years (53 to 86 years)
M91-653	Phase III, open-label, multicenter study	22.5 mg LUPRON DEPOT injected every 12 weeks Intramuscular Minimum 24 weeks	33*	69 years (55 to 82 years)
M93-013	Phase III, open-label, multicenter study	30.0 mg LUPRON DEPOT injected every 16 weeks Intramuscular Minimum 32 weeks	49	70 years (54 to 84 years)

* Two patients (one from each study) were excluded from the efficacy analysis. Hence a total of 94 patients were studied.

Study Results

LUPRON

Two controlled multicenter studies were conducted to evaluate the safety, efficacy, and endocrine effects of leuprolide acetate in advanced prostatic cancer patients (Stage D₂).

A further objective was to compare the efficacy of leuprolide acetate with that of DES (diethylstilbestrol).

Study M80-036

The first study was an open study with 118 patients randomly assigned to receive either 1 mg or 10 mg doses of leuprolide acetate. Retrospective control for this study was obtained from the National Prostatic Cancer Project (NPCP), Protocol No. 1300 which consisted of two treatment arms: DES or orchiectomy.

Objective Response

For evaluation, patients were divided in three groups by prior treatment as shown below, and the NPCP criterion was used to assess the response.

Evaluable including D₁ N = 100 patients	Evaluable, D₂ only No Progression	Estimated Median Time for First Progression
Group 1 = previously untreated	72%	76 weeks
Group 2 = previously hormone-treated	48%	49 weeks
Group 3 = orchiectomized	23%	43 weeks

A summary of survival for this study is presented in **Table 4** below:

Table 4. Summary of Survival for Study M80-036 (N=47)

Week of Follow-Up	Dead	Alive	Censored*
30	1	46	0
60	5	42	0
90	12	34	1
120	22	24	1
150	29	17	1
180	31	15	1
210	32	14	1
240	33	12	2
270	35	9	3
300	36	8	3
330	37	5	5
360	38	4	5
390	38	1	8
After Last Data: (Week 395)	38	0	9

* "Censored" includes patients who was lost to follow-up.

The median survival is estimated as 121 weeks (± 6 to 10 weeks as standard errors).

Subjective Response

Bone pain: Of the 94 evaluable stage D₂ patients, 26 reported no bone pain throughout the study. Of the remaining 68 patients, only one (1%) reported worsening of bone pain while 55 (81%) reported improvement, and 12 patients (18%) reported no change.

Nine patients reported normal performance status throughout the study. Of the remaining 85 patients, 44 (52%) improved, 34 (40%) reported no change, and only 7 (8%) worsened.

Dose-response Relationship

Orchiectomized patients who received 10 mg/day showed a somewhat higher subjective response rate than those receiving 1 mg/day; however, the difference was not statistically significant. Furthermore, the suppression of testosterone level was similar in the two-dose groups.

Endocrine Evaluation

Plasma levels of FSH and LH increased markedly within four hours of the first dose of leuprolide acetate in all three treatment groups. However, from Day 8 and on, FSH and LH levels had decreased significantly for all three groups.

Testosterone (T) and dihydrotestosterone (DHT) followed a similar pattern. By Day 4, T and DHT had increased markedly in both the previously untreated and hormone-treated groups, but subsequently declined to minimal levels by Week 2 and continued at those levels (identical to the minimal testosterone levels of the orchiectomized patients) for the duration of the treatment.

Safety

The most common side effects reported were hot flashes (41%), and sexual dysfunction (14%) with decrease in libido and impotence. Cardiovascular-related effects were noted in few patients. Three out of four patients had cardiovascular disease at pre-study. None of the cardiovascular events were reported as drug-related. Relationship to therapy is unknown.

This study showed leuprolide acetate to be a safe and effective drug for the treatment of advanced prostatic cancer.

Previously untreated patients achieved a better response than previously treated patients.

Study M81-017

Study M81-017 was an open multicenter study with 202 previously untreated patients with Stage D₂ prostatic adenocarcinoma.

Patients were centrally randomized to receive either leuprolide acetate or diethylstilbestrol (DES); those with definite evidence of progression or intolerable side effects on their initial treatment were crossed-over to the other treatment.

Ninety-two (92) patients randomized to leuprolide acetate, and 94 patients randomized to DES were evaluated.

Objective Response

An overall favourable objective response to treatment (No Progression) occurred in 86% of the evaluable patients on leuprolide acetate and 85% of the evaluable patients on DES.

There was no significant difference between the two treatment groups in time to first progression or time to treatment failure.

Time to first progression was analyzed for evaluable patients who had a best response of "no progression". The following are the estimated quartiles (in weeks):

Group	25th	Median	75th
Leuprolide acetate	75	60	43
DES	--	61	42

Treatment failure was defined as time to first progression or to termination of study because of an adverse reaction. The following are the estimated quartiles (in weeks):

Group	25th	Median	75th
Leuprolide acetate	67	49	36
DES	70	48	25

The summary of survival for leuprolide acetate and DES is presented in **Table 5**.

Table 5. Summary of Survival in Study M81-017

Week of Follow-up	Leuprolide acetate (N=94)			DES (N=99)		
	Dead	Alive	Censored*	Dead	Alive	Censored*
30	3	90	1	11	87	1
60	14	76	4	25	72	2
90	29	60	5	33	64	2
120	42	46	6	40	56	3
150	50	36	8	53	42	4
180	56	29	9	58	36	5
210	62	22	10	60	34	5
240	68	15	11	65	28	6
270	70	13	11	67	25	7
300	72	11	11	69	23	7
330	73	10	11	70	21	8
360	73	4	17	74	10	15
390	74	0	20	76	0	23
After Last Death Time of Last Death (weeks)		(358)			(364)	

* "Censored" includes patients who were lost to follow-up prior to the number of weeks shown, or who are alive but have not yet completed that number of weeks.

Subjective Response

Patients from both groups had a significant reduction in bone pain and in use of analgesics. There was no difference in overall subjective response, performance status, urinary symptoms, or mood changes in patients from both groups.

Endocrine Evaluation

By Week 4, testosterone and dihydrotestosterone from both groups reached castrate levels and remained there for the duration of the study.

Safety

During the first treatment period, the percentages of patients who experienced side effects differed significantly between the DES and the leuprolide acetate groups. The incidence is presented in **Table 6**.

Table 6. Incidence (%) of Adverse Reactions During First Treatment Period (199 patients)

	DES (N=101)	Leuprolide acetate (N=98)
Hot flashes	12	55
Peripheral edema	31	15
Nausea/vomiting	19	8
Impotence	14	4
Gynecomastia (Breast pain)	63	8
Bone Pain	2	5
Musculoskeletal spasms	9	1

Since prostatic cancer patients are already at high risk for developing thromboembolic and other cardiovascular diseases because of age and existing malignancy, leuprolide acetate offers an important alternative to treatment with estrogens.

Efficacy

Eighty-six percent (86%) of the patients on leuprolide acetate and 85% of the patients on DES had a favorable response to treatment.

In summary, this study showed that leuprolide acetate is a safe and effective treatment of Stage D₂ prostatic cancer.

LUPRON DEPOT

Study M85-097

A Phase 3, open, multicenter study was carried out to determine whether the LUPRON DEPOT 7.5 mg (1-Month SR) injected intramuscularly once every four weeks would reduce testosterone to, and maintain it at, castrate levels (≤ 50 ng/dL) in 56 previously untreated prostate cancer patients, and to evaluate objective clinical response.

The results are as follows:

Objective response

Best objective response was determined over a period of 24 weeks for 53 evaluable patients. Eighty one percent (81%) of the patients responded favourable (no progression) to treatment at some time. This result was not significantly different from the response rate of 86% observed for patients receiving the daily subcutaneous injection of leuprolide acetate solution reported in the previous study.

Testosterone levels

The median time to onset of castrate levels of testosterone for 53 evaluable patients was 21 days, and mean testosterone levels fell within the castrate range by Week 3 of treatment. After the onset of castrate levels, there were no escapes of testosterone values, provided that patients received their monthly injections on time. The pattern of testosterone release over the first 24 weeks of treatment did not differ from that observed in patients receiving the daily subcutaneous injection of leuprolide acetate solutions when an injection was delayed by 7 to 12 days; testosterone levels remained within the castrate range for the majority of patients.

Studies M91-583 and M91-653

LUPRON DEPOT 22.5 mg (3-Month SR) was found to be effective in suppressing serum testosterone and maintaining it at the castrate level.

Serum testosterone

Following the initial depot injection, the characteristic increase in mean testosterone over the pretreatment level occurred on Day 4, followed by a steady decline to the castrate range by Week 3. The median time to onset of castrate levels was 22 days. Testosterone suppression was sustained throughout each 12-week dosing interval. After falling into the castrate range, mean testosterone remained well within the castrate range throughout the 12-week interval.

As expected elevated pretreatment levels of alkaline phosphatase (AP) and prostatic specific antigen (PSA) reflected the presence of bony metastatic disease and the general prostatic cancer status respectively. Decreases and/or normalization (in AP and PSA) during treatment reflected the continuing presence of, and presumably the treatment related reduction in bony metastatic disease and/or improvement in the general prostatic cancer status.

Objective response

According to the tumour response rating of the patients, an 85% "no progression" rate (based on best objective response) was achieved during the 24-week treatment period. Complete response was achieved in 1% of the patients, 37% patients had a partial response and 47% patients showed a stable condition.

Eighty (85%) patients responded favourably to the treatment.

Of the 83% of the patients who completed the first 24 weeks of treatment, and continued with the long-term phase of the study, only 17% of the patients discontinued from the study prior to receiving the third injection. Four (4%) patients received only the first injection, 12 (13%) patients received only two injections and 78 (83%) patients received the third injection. Only six patients prematurely terminated the treatment at least in part due to an adverse event. Among those, adverse event was not the primary reason to stop the treatment in four patients. Only one patient discontinued the treatment due to intolerable hot flashes which was, according to the investigator, treatment related.

Laboratory values

LUPRON DEPOT (3-Month SR) has not clinically affected the mean systolic or diastolic blood pressure. Nor the effect on the mean pulse rate is indicative of a clinically significant trend. However, mean body weight significantly increased ($p < 0.001$) during the treatment. These results were not unexpected, since patients generally showed clinical improvement with treatment during the study. The effect on clinical laboratory determinations [hemogram, white blood cell (WBC), % basophils, total-, high-density lipoprotein (HDL)-, low-density lipoprotein (LDL)-cholesterol, triglycerides, serum glutamate pyruvate transaminase (SGPT), phosphorus, sodium and glucose) were often attributed, by the investigator, to the underlying disease state, to non-fasting blood collection, or as being consistent with the age and status of the patient population studied. As expected, pretreatment levels of alkaline phosphatase reflected the presence of bony metastatic disease. Changes during treatment reflected the continuing presence of, and presumably the treatment-related reduction, in bony metastatic disease.

Safety

Ninety (96%) patients reported adverse events. The most common adverse event was vasodilatation or hot flashes, occurring in 59% of the patients. Among the 94 evaluable patients, only 25% patients classified the adverse event as severe. The overall incidence of severe events (excluding those judged by the investigator as definitely not treatment-related) was low (8 patients, 9%).

The increase in serum testosterone at the beginning of the treatment which has been seen with both the daily injection and the monthly depot formulation, may theoretically result in a transient exacerbation of disease-related symptoms, especially bone pain. Forty-six (49%) of the patients experienced one or more adverse events during the initial two weeks of treatment. Hot flashes was again the most frequently (13%) reported event during this time. Seven (7%) patients reported severe events during this time.

In summary, the leuprolide acetate depot injection releases leuprolide acetate at an apparently steady state; its efficacy in the treatment of advanced prostatic cancer does not differ from the efficacy of the daily subcutaneous injection.

Study M93-013

In an open-label, non-comparative, multicenter clinical study using LUPRON DEPOT 30.0 mg (4-Month SR), 49 patients with stage D₂ prostatic adenocarcinoma (with no prior treatment) were enrolled. The study design and patient demographics is shown in **Table 3**. The objectives were to determine whether a 30.0 mg depot formulation of leuprolide acetate 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 four 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 transiently 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 elevations of changes in prostatic involvement and 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.

Using historical comparisons, the safety and efficacy of LUPRON DEPOT 30.0 mg (4-Month SR), appear similar to the other depot formulations.

DETAILED PHARMACOLOGY

Leuprolide acetate is an analog of gonadotropin-releasing hormone (GnRH). 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 six weeks.

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

In a series of experiments with multiple administration (once every four 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 four weeks; the other group received 0.6, 3.0 and 15 mg/kg leuprolide acetate for depot suspension once a week for four 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 three-month period when LUPRON DEPOT (3-Month SR) formulation was studied in rats and dogs.

Human Pharmacology

Pharmacodynamics

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. See **CLINICAL TRIALS**.

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.

The pharmacokinetic profile of LUPRON DEPOT 22.5 mg (3-Month SR) was characterized in 23 orchiectomized prostate cancer patients. Following a single injection of the three-month formulation of LUPRON DEPOT 22.5 mg (3-Month SR), a mean peak plasma leuprolide concentration of 48.9 ng/mL was observed at four hours and then declined to 0.67 ng/mL at 12 weeks. Leuprolide appeared to be released at a constant rate following the onset of steady-state level during the third week after dosing, providing steady plasma concentrations through the 12-week dosing interval. Detectable levels of leuprolide were present at all measurement points in all patients during this 12-week period. The initial burst, followed by the rapid decline to a steady-state level, was similar to the release pattern seen with the monthly formulation.

The pharmacokinetic profile of LUPRON DEPOT 30.0 mg (4-Month SR) was characterized in 16 orchiectomized prostate cancer patients. Following a single injection of the four month formulation of LUPRON DEPOT 30.0 mg (4-Month SR), a mean peak plasma leuprolide concentration of 59.3 ng/mL was observed at four hours and the mean concentration then declined to 0.30 ng/mL at 16 weeks.

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 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.

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.

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.

Mouse

Maximum tolerated dose studies (prelude to carcinogenicity studies) were conducted in mice. The mice were dosed subcutaneously with 0, 20, 60, 200 and 600 mg/kg/day. 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.

Rat

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.

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

Monkey

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 acetate 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.

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 three 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 include 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.

Special Studies

LUPRON DEPOT

Rabbit

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 four 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 same the degree as the placebo-microcapsule, but these are less than those of the positive control (0.75% acetic acid), and their severity were not potentiated by four 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 two 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 Pig

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 two weeks by intramuscular route four times, and once by subcutaneous route two 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.

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

P^rLUPRON[®] 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 is used in the palliative treatment of prostate cancer. Palliative treatment is the relief of symptoms associated with a disease; it is not a cure.

What it does:

Leuprolide acetate is chemically similar to gonadotropin-releasing hormone (GnRH or LHRH); a hormone which occurs naturally in your body. Normally, your body releases small amounts of LHRH and this leads to events which stimulate the production of sex hormones. However, when you inject LUPRON, the normal events that lead to sex hormone production are interrupted and testosterone is no longer produced by the testes. Decreasing the levels of testosterone leads to decreased symptoms associated with prostate cancer.

When it should not be used:

LUPRON should not be used:

- if you are allergic to leuprolide acetate, any similar nonapeptides (e.g., histrelin, desorelin), or any of the non-medicinal ingredients in LUPRON
- in women who are or may become pregnant
- in women who are breast-feeding

What the medicinal ingredient is:

leuprolide acetate

What the 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

Serious Warnings and Precautions

LUPRON should be prescribed by a doctor experienced with this type of drug.

LUPRON may cause:

- worsening of symptoms of prostate cancer at the beginning of the treatment
- bone thinning (osteoporosis)

BEFORE you use LUPRON talk to your doctor or pharmacist if:

- You are allergic to any component of the medication.
- You have previous history of obstructive uropathy (difficulty urinating due to a block in the urinary tract).
- You have family history of osteoporosis or are 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.
- You have had or are suspected of having seizures, epilepsy, cerebrovascular disorder, central nervous system anomalies, or brain tumor.
- You are taking other medication(s) that have been associated with convulsions or seizures such as bupropion and any selective serotonin reuptake inhibitor (SSRI) medication for depression.
- You have a history of heart disease or disorders, or have a genetic heart condition called "long QT syndrome".
- You have high blood sugar (diabetes). LUPRON may affect your blood sugar and you may need to test your blood sugar more frequently while receiving treatment with LUPRON.
- You have low red blood cell counts. LUPRON may cause a decrease in red blood cells (anemia).

During the first few weeks of treatment with LUPRON, you may experience worsening of symptoms or onset of new symptoms; including bone pain, presence of blood in the urine or difficulty urinating.

INTERACTIONS WITH THIS MEDICATION

Tell your doctor and pharmacist if you are taking, have been taking, or are planning to take any other medicines, including nonprescription drugs (such as drug products for colds or nausea).

In particular, if you take the following medicines:

- medicines used to correct heart rhythm such as quinidine, disopyramide, amiodarone, dronedarone, sotalol, dofetilide, ibutilide (e.g., Corvert[®]), flecainide (e.g., Tambocor[®]), propafenone (e.g., Rythmol[®])

- medicines used to treat schizophrenia such as chlorpromazine
- medicines to treat depression such as amitriptyline, nortriptyline
- morphine-like medicines (e.g., methadone)
- certain antibiotics and antimicrobials such as erythromycin, clarithromycin (e.g., Biaxin®), azithromycin (e.g., Zithromax®), moxifloxacin (e.g., Avelox®)
- antimalarials (e.g., quinine)
- antifungals
- medicines used to prevent nausea and vomiting caused by cancer chemotherapy, radiation therapy and surgery such as ondansetron (e.g., Zofran®)
- medicines used for the relief of bronchospasm in conditions like asthma and chronic obstructive pulmonary disease such as salbutamol (e.g., Ventolin®)

PROPER USE OF THIS MEDICATION

Usual dose:

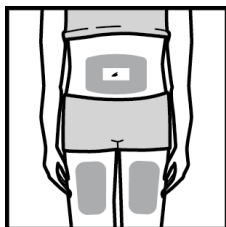
The recommended dose of LUPRON is 1 mg (0.2 mL), as a single daily subcutaneous injection.

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 healthcare 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 doctor: if you miss an injection at the usual time, take it as soon as you remember, if you remember on the same day. If not, do not take the missed dose at all. Simply wait until it is time for your next dose. Do not take two doses at once.

Do not stop your daily injections because you feel better. You need one injection a day to make sure LUPRON keeps working for you.

It is very important that your doctor check your progress at regular medical visits.

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 testosterone levels will initially increase and then decline over several weeks. During this period some patients may experience worsening of urinary symptoms and/or a temporary increase in bone pain. **Should this occur, contact your doctor immediately.**

The following side effects are commonly experienced after the initial rise and occur due to decreasing levels of testosterone in the body:

- general pain or flu-like symptoms
- hot flashes/sweats
- joint and muscle pain
- emotional changes such as feeling depressed
- worsening urinary symptoms

Should these side effects persist or if they are severe, contact your doctor immediately.

Notify your doctor if you develop new or worsened symptoms of depression after beginning LUPRON treatment

A local 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	Decrease in testicular size		√	
	Difficulty urinating		√	
	Headache	√		
	Hot flashes		√	
	Impotence/ decrease in libido		√	
	Itching rash		√	
	Skin reactions including reaction at site of injection		√	
	Vomiting/nausea	√		
Uncommon	Abnormal swelling or numbness of limbs		√	
	Convulsion		√	
	Severe bone pain		√	
	Severe pain in chest or abdomen		√	
	Vision changes		√	
Reported from postmarketing with unknown frequency	New onset or worsening of shortness of breath, especially with exertion; dry cough/interstitial lung disease, an inflammation of lung tissue		√	
	Serious liver injury (yellow skin, yellow eyes, nausea/vomiting, decreased or loss of appetite, fatigue, itching, abdominal pain and bleeding and bruising)		√	√

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 SIDE EFFECTS

You can report any suspected side effects associated with the use of health products to Health Canada by:

- **Visiting the Web page on Adverse Reaction Reporting (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html>) for information on how to report online, by mail or by fax; or**
- **Calling toll-free at 1-866-234-2345.**

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

The most recent version of this document plus the full Product Monograph, prepared for health professionals, can be found at:

www.abbvie.ca

or by contacting the sponsor, AbbVie Corporation, Saint-Laurent, Qc H4S 1Z1 at: 1-888-704-8271.

This leaflet was prepared by AbbVie Corporation.

Last revised: June 20, 2019

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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 is used in the palliative treatment of prostate cancer. Palliative treatment is the relief of symptoms associated with a disease; it is not a cure.

What it does:

Leuprolide acetate is chemically similar to gonadotropin-releasing hormone (GnRH or LHRH); a hormone which occurs naturally in your body. Normally, your body releases small amounts of LHRH and this leads to events which stimulate the production of sex hormones. However when you inject LUPRON DEPOT, the normal events that lead to sex hormone production are interrupted and testosterone is no longer produced by the testes. Decreasing the levels of testosterone leads to decreased symptoms associated with prostate cancer.

When it should not be used:

LUPRON DEPOT should not be used:

- if you are 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 or may become pregnant
- in women who are breast-feeding

What the medicinal ingredient is:

leuprolide acetate

What the non-medicinal ingredients are:

LUPRON DEPOT 7.5 mg (1-Month slow release) also contains: carboxymethylcellulose sodium, DL-lactic and glycolic acids copolymer, D-mannitol, glacial acetic acid, polysorbate 80, gelatin, and water for injection.

LUPRON DEPOT 22.5 mg (3-Month slow release) and 30.0 mg (4-month slow release) also contain: carboxymethylcellulose sodium, D-mannitol, glacial acetic acid, polylactic 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 three strengths: 7.5 mg (1-Month slow release), 22.5 mg (3-Month slow release) and 30.0 mg (4-Month slow release).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

LUPRON DEPOT should be prescribed by a doctor experienced with this type of drug.

LUPRON DEPOT may cause:

- worsening of symptoms of prostate cancer at the beginning of the treatment
- bone thinning (osteoporosis)

BEFORE you use LUPRON DEPOT talk to your doctor or pharmacist if:

- You are allergic to any component of the medication.
- You have previous history of obstructive uropathy (difficulty urinating due to a block in the urinary tract).
- You have family history of osteoporosis or are 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.
- You have had or are suspected of having seizures, epilepsy, cerebrovascular disorder, central nervous system anomalies, or brain tumor.
- You are taking other medication(s) that have been associated with convulsions or seizures such as bupropion and any selective serotonin reuptake inhibitor (SSRI) medication for depression.
- You have a history of heart disease or disorders, or have a genetic heart condition called "long QT syndrome".
- You have high blood sugar (diabetes). LUPRON DEPOT may affect your blood sugar and you may need to test your blood sugar more frequently while receiving treatment with LUPRON DEPOT.
- You have low red blood cell counts. LUPRON DEPOT may cause a decrease in red blood cells (anemia).

During the first few weeks of treatment with LUPRON DEPOT, you may experience worsening of symptoms or onset of new symptoms, including bone pain, presence of blood in the urine or difficulty urinating.

INTERACTIONS WITH THIS MEDICATION

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In particular, if you take the following medicines:

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- medicines used to treat schizophrenia such as chlorpromazine
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- certain antibiotics and antimicrobials such as erythromycin, clarithromycin (e.g., Biaxin[®]), azithromycin (e.g., Zithromax[®]), moxifloxacin (e.g., Avelox[®])
- antimalarials (e.g., quinine)
- antifungals
- medicines used to prevent nausea and vomiting caused by cancer chemotherapy, radiation therapy and surgery such as ondansetron (e.g., Zofran[®])
- medicines used for the relief of bronchospasm in conditions like asthma and chronic obstructive pulmonary disease such as salbutamol (e.g., Ventolin[®])

PROPER USE OF THIS MEDICATION

Usual dose:

If you are taking LUPRON DEPOT 7.5 mg (1-Month slow release) report to your doctor **once every month** for your injection.

If you are taking LUPRON DEPOT 22.5 mg (3-Month slow release), report to your doctor **once every three months** for your injection.

If you are taking LUPRON DEPOT 30.0 mg (4-Month slow release), report to your doctor **once every four months** for your injection.

It is very important that your doctor check your progress at regular medical visits. Your doctor, or healthcare provider, will administer LUPRON DEPOT for you during your scheduled visits.

If you need more information, ask your doctor.

Overdose:

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

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.

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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	Decrease in testicular size		√	
	Headache	√		
	Hot flashes		√	
	Impotence/ decrease in libido		√	
	Itching rash		√	
	Skin reactions including reaction at site of injection		√	
Uncommon	Abnormal swelling or numbness of limbs		√	
	Convulsion		√	
	Severe bone pain		√	
	Severe pain in chest or abdomen		√	
	Vision changes		√	
Reported from postmarketing with unknown frequency	New onset or worsening of shortness of breath, especially with exertion; dry cough/interstitial lung disease, an inflammation of lung tissue		√	
	Serious liver injury (yellow skin, yellow eyes, nausea/vomiting, decreased or loss of appetite, fatigue, itching, abdominal pain and bleeding and bruising)		√	√

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 SIDE EFFECTS

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

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