

PRODUCT MONOGRAPH

PrLUPRON[®]

leuprolide acetate injection
5 mg/mL

Multidose Vials
2.8 mL

PrLUPRON DEPOT[®]

leuprolide acetate for depot suspension

Prefilled dual-chamber syringe

7.5 mg/syringe (1-Month Slow Release) with Sterile Diluent

22.5 mg/syringe (3-Month Slow Release) with Sterile Diluent

30.0 mg/syringe (4-Month Slow Release) with Sterile Diluent

Gonadotropin-releasing hormone analog

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Date of Preparation:
March 11, 1999

Date of Latest Revision:
December 6, 2006

Date of Revision:
October 16, 2008

Submission Control No: 124763

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LUPRON[®]
leuprolide acetate injection

LUPRON DEPOT[®]
leuprolide acetate for depot suspension

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Subcutaneous	Multiple dose vial 5 mg/mL	LUPRON [®] Injection: acetic acid, benzyl alcohol, sodium chloride, sodium hydroxide
Intramuscular	Pre-filled dual chamber syringe containing sterile lyophilized microspheres 7.5 mg (1-Month SR), 22.5 mg (3-Month SR), 30.0 mg (4-Month SR)	LUPRON DEPOT [®] <u>1-Month SR</u> carboxymethylcellulose sodium, DL-lactic and glycolic acids copolymer, D-mannitol, glacial acetic acid, polysorbate 80, purified gelatin <u>3-Month SR and 4-Month SR</u> carboxymethylcellulose sodium, D-mannitol, glacial acetic acid, polylactic acid, polysorbate 80 <i>For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING section.</i>

INDICATIONS AND CLINICAL USE

LUPRON[®] (leuprolide acetate) Injection and LUPRON DEPOT[®] (leuprolide acetate for depot suspension) are indicated in

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

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

Geriatrics (> 65 years of age):

The majority of the patients studied in the clinical trials for LUPRON[®] Injection 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 LUPRON DEPOT[®] 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 DEPOT[®] 22.5 mg (3-Month SR) and LUPRON DEPOT[®] 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 component of the container. Isolated cases of anaphylaxis have been reported. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the Product Monograph.
- LUPRON[®] Injection and LUPRON DEPOT[®] are contraindicated in women who are or may become pregnant. The possibility exists that spontaneous abortion may occur if the drug is administered during pregnancy.
- It is not known whether leuprolide is excreted in human milk; therefore, LUPRON[®] Injection and LUPRON DEPOT[®] are contraindicated in patients who are breast-feeding.

WARNINGS AND PRECAUTIONS**General**

LUPRON[®] Injection and LUPRON DEPOT[®] (leuprolide acetate), like other LH-RH 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 LH-RH 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 therapy under close supervision.

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

Carcinogenesis and Mutagenesis

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

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

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

Dependence/Tolerance

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

Endocrine and Metabolism

Changes in Bone Density

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

Hypogonadism

Long-term administration of leuprolide 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.

Renal and Hepatic

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

Special Populations

Pregnant Women: LUPRON[®] Injection and LUPRON DEPOT[®] are not indicated for use in women. LUPRON DEPOT[®] treatment of women is covered in the LUPRON DEPOT[®] 3.75 mg and 11.25 mg “Endometriosis” Product Monograph.

Nursing Women: LUPRON[®] Injection and LUPRON DEPOT[®] 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.

Pediatrics (< 18 years of age): Safety and effectiveness of LUPRON DEPOT[®] 22.5 mg (3-Month SR) and LUPRON DEPOT[®] 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[®] Injection and LUPRON DEPOT[®] in children with central precocious puberty.

Geriatrics (> 65 years of age): In prostatic cancer clinical trials for LUPRON[®] Injection 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[®] Injection and LUPRON DEPOT[®] in this population.

Monitoring and Laboratory Tests

Response to LUPRON[®] Injection 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 on bone lesions may be monitored by bone scans, while its effects on prostatic lesions may be monitored by ultrasonography, and/or 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.

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 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.

Clinical Trial Adverse Drug Reactions

LUPRON[®] Injection and LUPRON DEPOT[®] 7.5 mg (1-M), 22.5 mg (3-M), 30 mg (4-M)

The following possibly or probably related systemic adverse reactions were reported by $\geq 5\%$ of the patients using LUPRON[®] Injection and LUPRON DEPOT[®] 7.5 mg, 22.5 mg and 30 mg in clinical studies. Reactions not considered drug related are excluded.

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

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)				
Body System	LUPRON DEPOT® 7.5 mg (1-M SR) N=56 (%)	LUPRON DEPOT® 22.5 mg (3-M SR)[§] Non-Orchiectomized N=94 (%)	LUPRON DEPOT® 30 mg (4-M SR) Non-Orchiectomized N=49 (%) Study 013	LUPRON DEPOT® 30 mg (4-M SR) Orchiectomized N=24 (%) Study 012
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)
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)

[§] The adverse reactions reported for LUPRON DEPOT® 22.5 mg (3-Month SR) are based on 2 clinical trials.

* Physiological effect of decreased testosterone

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

The following possibly or probably related systemic adverse reactions were reported by <5% of the patients using LUPRON[®] Injection and LUPRON DEPOT[®] 7.5 mg, 22.5 mg and 30 mg in clinical studies. Reactions not considered drug related are excluded.

LUPRON[®] Injection

<u>Cardiovascular System:</u>	congestive heart failure, ECG changes/ischemia, high blood pressure, hypotension, myocardial infarction, murmur, phlebitis/thrombosis, pulmonary emboli, transient ischemic attack/stroke, cardiac arrhythmias;
<u>Gastrointestinal System:</u>	constipation, dysphagia, gastrointestinal bleeding, gastrointestinal disturbance, hepatic dysfunction, peptic ulcer, rectal polyps, anorexia;
<u>Endocrine System:</u>	breast tenderness or pain, libido increase, thyroid enlargement, gynecomastia;
<u>Hemic and Lymphatic System:</u>	anemia, decreased WBC;
<u>Musculoskeletal System:</u>	ankylosing spondylosis, joint pain, pelvic fibrosis, myalgia, spasms;
<u>Central/Peripheral Nervous System:</u>	anxiety, blurred vision, dizziness/light-headedness, headache, hearing disorder, sleep disorders, lethargy, memory disorder, mood swings, nervousness, numbness, paresthesia, peripheral neuropathy, spinal fracture/paralysis, syncope/blackouts, taste disorders;
<u>Respiratory System:</u>	cough, pleural rub, pneumonia, pulmonary fibrosis, pulmonary infiltrate, respiratory disorders, sinus congestion;
<u>Integumentary System:</u>	carcinoma of skin/ear, dry skin, ecchymosis, hair loss, itching, pigmentation, skin lesions;
<u>Urogenital System:</u>	bladder spasms, incontinence, penile swelling, prostate pain, urinary obstruction, urinary tract infection, hematuria;
<u>Miscellaneous:</u>	depression, hypoglycemia, hypoproteinemia, increased BUN, increased creatinine, infection/inflammation, ophthalmologic disorders, swelling (temporal bone), asthenia, fatigue, fever.

LUPRON DEPOT[®] 7.5 mg (1-Month SR)

<u>Cardiovascular System:</u>	angina, cardiac arrhythmia;
<u>Endocrine System:</u>	gynecomastia, libido decrease;
<u>Gastrointestinal System:</u>	anorexia, diarrhea;
<u>Integumentary System:</u>	dermatitis, local skin reactions, hair growth;
<u>Musculoskeletal System:</u>	bone pain, myalgia;

Central/Peripheral Nervous

System:

paresthesia, insomnia;

Respiratory System:

dyspnea, hemoptysis;

Urogenital System:

dysuria, frequency/urgency, hematuria, testicular pain.

Miscellaneous:

asthenia, diabetes, fever/chills, hard nodule in throat, increased calcium, weight gain, increased uric acid, SGOT (greater than 2 times normal values).

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;

Digestive System:

anorexia, duodenal ulcer, increased appetite, thirst/dry mouth;

Hemic and Lymphatic System:

anemia, lymphedema;

Metabolic and Nutritional Disorders:

dehydration, edema;

Central/Peripheral Nervous System:

anxiety, delusions, depression, hypesthesia, libido decrease*, nervousness, paresthesia;

Respiratory System:

epistaxis, pharyngitis, pleural effusion, pneumonia;

Special Senses:

abnormal vision, amblyopia, dry eyes, tinnitus;

Urogenital System:

gynecomastia, impotence*, penis disorders, testis disorders.

* Physiologic effect 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.

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

Abnormal Hematologic and Clinical Chemistry Findings

Abnormalities of certain parameters were 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, 22.5 mg and 30.0 mg:

LUPRON DEPOT[®] 7.5 mg (1-Month SR)

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

LUPRON DEPOT[®] 22.5 mg (3-Month SR)

Increased BUN, hyperglycemia, hyperlipidemia (total cholesterol, 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/RBC, hyperlipidemia (total cholesterol, LDL-cholesterol, triglycerides), decreased HDL-cholesterol, eosinophilia, increased glucose, increased liver function tests (ALT, AST, GGTP, LDH), increased phosphorus. Additional laboratory abnormalities were reported: increased BUN and PT, leukopenia, thrombocytopenia, uricaciduria, urine abnormality.

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

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

Changes in Bone Density: Decreased bone density has been reported in the medical literature in men who have had orchiectomy or who have been treated with an LH-RH agonist analog. In a clinical trial, 25 men with prostate cancer, 12 of whom had been treated previously with leuprolide acetate for at least six months underwent bone density studies as a result of pain. The leuprolide-treated group had lower bone density scores than the 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 post-marketing surveillance, which includes other dosage forms and other patient populations, the following adverse events were reported:

<u>Cardiovascular System:</u>	hypotension;
<u>Hemic and Lymphatic System:</u>	decreased WBC;
<u>Central/Peripheral Nervous System:</u>	peripheral neuropathy, spinal fracture/paralysis;
<u>Integumentary System:</u>	rash, urticaria, photosensitivity reactions;
<u>Musculoskeletal System:</u>	tenosynovitis-like symptoms;
<u>Urogenital System:</u>	prostate pain;
<u>Miscellaneous:</u>	injection site reactions including pain, inflammation, sterile abscess, induration, and hematoma.

See the “Central Precocious Puberty” and “Endometriosis” LUPRON[®] Injection and LUPRON DEPOT[®] Product Monographs for other reported events.

DRUG INTERACTIONS

Overview

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

Drug-Drug Interactions

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

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory 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[®] therapy may therefore be misleading.

Effect on Clinical Laboratory Tests

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

DOSAGE AND ADMINISTRATION

Dosing Considerations

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

LUPRON DEPOT[®] 7.5, 22.5 and 30 mg administered intramuscularly is designed to provide continuous sustained release of leuprolide for 1, 3, and 4 months, respectively.

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

Recommended Dose and Dosage Adjustment

LUPRON[®] Injection

The recommended dose of LUPRON[®] Injection is 1 mg (0.2 mL), as a **single daily subcutaneous injection**. (See **CONSUMER INFORMATION** and **Administration**).

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 **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 **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 mg administered as a **single intramuscular injection once every four months (16 weeks)**, after reconstitution with the special diluent. See **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[®] Injection

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[®] Injection 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.

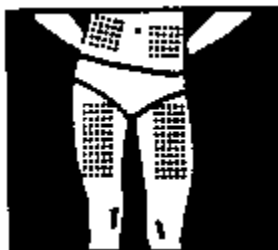
Administration

LUPRON[®] Injection

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

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

SUGGESTED ROTATION OF THE INJECTION SITE



Reconstitution

LUPRON DEPOT[®]

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

Due to different release characteristics, a fractional dose of the 3-month or 4-month depot formulation is not equivalent to the same dose of the monthly formulation and should not be given.

For LUPRON DEPOT[®] 7.5 mg (1-M SR), 22.5 mg (3-M SR) and 30 mg (4-M SR)

1. The LUPRON DEPOT[®] powder should be visually inspected and the syringe should **NOT BE USED** if clumping or caking is evident. A thin layer of powder on the wall of the syringe is considered normal. The diluent should appear clear.
2. To prepare for injection, screw the white plunger into the end stopper until the stopper begins to turn.
3. Remember to tighten the needle by twisting the needle cap clockwise. Do not overtighten.

4. Holding the syringe upright, release the diluent by **SLOWLY PUSHING** (6 - 8 seconds) the plunger until the first stopper is at the blue line in the middle of the barrel.
5. Keep the syringe upright. Gently shake the syringe to thoroughly mix the microspheres (powder) to form a uniform suspension. The suspension will appear milky.
6. If the microspheres adhere to the stopper or caking/clumping is present, tap the syringe against your finger to disperse. **DO NOT USE** if any of the powder has not gone into suspension.
7. Keep the syringe upright. With the opposite hand, remove the needle cap without twisting and advance the plunger to expel the air from the syringe.
8. At the time of reconstitution, inject the entire contents of the syringe intramuscularly. The suspension settles very quickly following reconstitution; therefore, LUPRON DEPOT[®] should be mixed and used immediately.

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

9. After injection, withdraw the needle. Immediately activate the LuproLoc* safety device by pushing the arrow forward with the thumb or finger until the device is fully extended and a CLICK is heard or felt.

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

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

OVERDOSAGE

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 for up to three years or 20 mg/day for up to two years.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Leuprolide 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 acts as a potent inhibitor of gonadotropin production. It is chemically unrelated to steroids.

Unlike steroid hormones, leuprolide 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 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 post-menopausal 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 5 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**).

Leuprolide is not active when given orally.

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 4 hours and then declined to 0.36 ng/mL at 4 weeks. However, intact leuprolide and an inactive major metabolite could not be distinguished by the assay used in the study. Undetectable leuprolide plasma concentrations have been observed during chronic LUPRON DEPOT[®] 7.5 mg (1-Month SR) administration, but testosterone levels appear to be maintained at 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 4 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 4 hours and the mean concentration then declined to 0.30 ng/mL at 16 weeks. The mean plasma concentration of leuprolide from weeks 3.5 to 16 was 0.44 ± 0.20 ng/mL (range: 0.20-1.06). Leuprolide appeared to be released at a constant rate following the onset of steady-state levels during the fourth week after dosing, providing steady plasma concentrations throughout the 16-week dosing interval. However, intact leuprolide and an inactive major metabolite could not be distinguished by the assay which was employed in the study. The initial burst, followed by the rapid decline to a steady-state level, was similar to the release pattern seen with the other depot formulations.

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 administered intravenously revealed that the mean systemic clearance was 7.6 L/h, with a terminal elimination half-life of approximately 3 hours based on a two compartment model.

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

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

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

Special Populations and Conditions

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

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

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

Multidose Vials

LUPRON[®] (leuprolide acetate) Injection 5 mg/mL: Keep refrigerated between 2 and 8°C (36-46°F).

Prefilled Dual-Chamber Syringes

LUPRON DEPOT[®] (leuprolide acetate for depot suspension) 7.5 mg/syringe (1-Month SR), 22.5 mg/syringe (3-Month SR), and 30.0 mg/syringe (4-Month SR): Store between 15 and 25°C (59-77°F). 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

Composition

LUPRON[®] Injection

In addition to **5 mg/mL of leuprolide acetate**, each 2.8 mL multiple-dose vial contains sodium chloride (6.3 mg/mL) for tonicity adjustment, benzyl alcohol as a preservative (9.0 mg/mL), and sterile water for injection USP. The pH may have been adjusted with sodium hydroxide and/or acetic acid.

LUPRON DEPOT[®]

LUPRON DEPOT[®] 7.5 mg (1-Month SR)

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

The front chamber of the prefilled dual-chamber syringe contains: leuprolide acetate (7.5 mg), purified gelatin (1.3 mg), DL-lactic and glycolic acids copolymer (66.2 mg), and D-mannitol (13.2 mg).

The rear chamber of diluent contains: carboxymethylcellulose sodium (5.0 mg), D-mannitol (50.0 mg), polysorbate 80 (1.0 mg), water for injection, USP and glacial acetic acid, USP to control pH.

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

LUPRON DEPOT[®] 22.5 mg (3-Month SR)

LUPRON DEPOT[®] 22.5 mg (3-Month SR) is available in a prefilled dual-chamber syringe containing sterile lyophilized microspheres composed of leuprolide acetate incorporated in a biodegradable polymer of polylactic acid.

The front chamber of the prefilled dual-chamber syringe contains: leuprolide acetate (22.5 mg), polylactic acid (198.6 mg) and D-mannitol (38.9 mg).

The rear chamber of diluent contains: carboxymethylcellulose sodium (7.5 mg), D-mannitol (75.0 mg), polysorbate 80 (1.5 mg), water for injection, USP and glacial acetic acid, USP to control pH.

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**.

LUPRON DEPOT[®] 30.0 mg (4-Month SR)

LUPRON DEPOT[®] 30.0 mg (4-Month SR) is available in a prefilled dual-chamber syringe containing sterile lyophilized microspheres composed of leuprolide acetate incorporated in a biodegradable polymer of polylactic acid.

The front chamber of the prefilled dual-chamber syringe contains: leuprolide acetate (30.0 mg), polylactic acid (264.8 mg) and D-mannitol (51.9 mg).

The rear chamber of diluent contains: carboxymethylcellulose sodium (7.5 mg), D-mannitol (75.0 mg), polysorbate 80 (1.5 mg), water for injection, USP and glacial acetic acid, USP to control pH.

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[®] (1-Month, 3-Month and 4-Month SR), acetic acid is lost, leaving the peptide.

Availability of Dosage Forms

LUPRON[®] Injection

LUPRON[®] Injection is supplied in sterile multidose vials of 2.8 mL for subcutaneous use.

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

LUPRON DEPOT[®]

LUPRON DEPOT[®] 7.5 mg (1-Month SR), LUPRON DEPOT[®] 22.5 mg (3-Month SR), and LUPRON DEPOT[®] 30.0 mg (4-Month SR) are supplied in single-dose kits containing one prefilled dual-chamber syringe with 23 G needle, two alcohol swabs, Patient Information Leaflet, Special Instructions for Use, and Package Insert.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

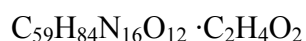
Proper name: leuprolide acetate

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

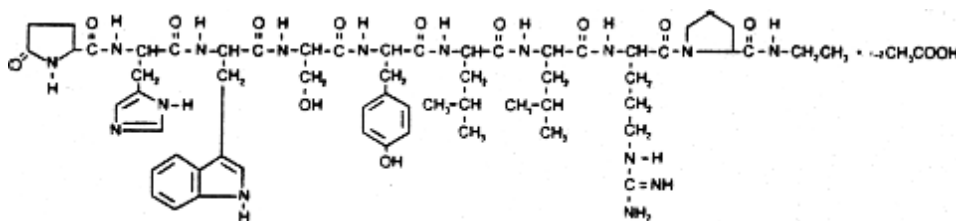
or: [D-Leu⁶, des-Gly-NH₂¹⁰, Proethylamide⁹] GnRH

Molecular formula and molecular mass:



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

LUPRON® Injection

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

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

Study 1

The first study was an open study with 118 patients randomly assigned to receive either 1 mg or 10 mg doses of leuprolide. 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. A summary of the trial design and patient demographics is shown in **Table 2**.

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Frequency of Injections
M80-036	Phase II, open, multicenter study	1 mg or 10 mg Subcutaneous 18 to 80 weeks	118 (111 had stage D ₂ disease)	~66 (42-93)	Once a day

The results of this study were as follows:

a) 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 3** below:

Table 3			
Summary of Survival (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 (\pm 6-10 weeks as standard errors).

b) Subjective Response

Bone pain: of 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.

c) 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.

d) Endocrine Evaluation

Plasma levels of FSH and LH increased markedly within four hours of the first dose of leuprolide 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.

e) 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 prestudy. None of the cardiovascular events were reported as drug-related. Relationship to therapy is unknown.

This study showed leuprolide 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 2

The second study was an open multicenter study with 202 previously untreated patients with Stage D₂ prostatic adenocarcinoma.

Patients were centrally randomized to receive either leuprolide 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, and 94 patients randomized to DES were evaluated.

The results of this study are as follows:

a) Objective Response

An overall favorable objective response to treatment (No Progression) occurred in 86% of the evaluable patients on leuprolide 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	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	67	49	36
DES	70	48	25

The summary of survival for leuprolide and DES is presented in **Table 4**:

Table 4 Summary of Survival						
Week of Follow-up	Leuprolide (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.

b) 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.

c) Endocrine Evaluation

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

d) Safety

During the first treatment period, the percentages of patients who experienced side effects differed significantly between the DES and the leuprolide groups. The incidence is presented in **Table 5**:

Table 5		
Incidence (%) of Adverse Reactions		
During First Treatment Period (199 patients)		
	DES (N=101)	Leuprolide (N=98)
Hot flashes	12	55
Peripheral edema	31	15
Nausea/vomiting	19	8
Impotence	14	4
Gynecomastia (Breastly 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 offers an important alternative to treatment with estrogens.

e) Efficacy

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

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

LUPRON DEPOT[®] 7.5 mg (1-Month SR)

A Phase III, open, multicenter study was carried out to determine whether leuprolide depot formulation 7.5 mg (1-Month SR) injected i.m. 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:

a) **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 solution reported in the previous study.

b) **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 solutions when an injection was delayed by 7-12 days; testosterone levels remained within the castrate range for the majority of patients.

LUPRON DEPOT[®] 22.5 mg (3-Month SR)

The efficacy of LUPRON DEPOT[®] 22.5 mg (3-Month SR) has been studied in 94 patients. The study design and patient demographics are seen in **Table 6**:

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)
M91-583 and M91-653	Phase III, open, multicenter study	22.5 mg LUPRON DEPOT [®] injected every 12 weeks Intramuscular Minimum 24 weeks	Study M91-583: 61* Study M91-653: 33*	Study M91-583: 71 (53-86) Study M91-653: 69 (55-82)

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

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

a) 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.

b) 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.

c) 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, WBC, % basophils, total-, HDL-, LDL-cholesterol,

triglycerides, 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.

d) 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 depot injection releases leuprolide 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.

LUPRON DEPOT[®] 30.0 mg (4-Month SR)

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 7**. The objectives were to determine whether a 30 mg depot formulation of leuprolide injected once every 16 weeks would reduce and maintain serum testosterone levels at castrate levels (≤ 50 ng/dL), and to assess the safety of the formulation. The study was divided into an initial 32-week treatment phase and a long-term treatment phase. Serum testosterone levels were determined biweekly or weekly during the first 32 weeks of treatment. Once the patient completed the initial 32-week treatment period, treatment continued at the investigator's discretion with serum testosterone levels being done every 4 months prior to the injection.

Table 7				
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)
M93-013	Phase III, open, multicenter study	30.0 mg LUPRON DEPOT [®] injected every 16 weeks Intramuscular Minimum 32 weeks	49	70 (54-84)

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

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

Animal Pharmacology

LUPRON[®] Injection

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.

LUPRON DEPOT[®]

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

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

- In a series of experiments with multiple administration (once every 4 weeks), serum testosterone levels in rats at a dose of 3 mg/kg and those in dogs at 1.5 mg/kg did not show any flare-up at the second and third injection, and continued to be maintained at the suppressed levels. This study demonstrates that leuprolide acetate for depot suspension releases the drug at a constant rate for one month and has a long acting potency.
- In another study, the effects of leuprolide acetate for depot suspension on accessory sex organ weights and hormone levels in adult male rats were compared to those produced by leuprolide acetate solution with subcutaneous administration. One group of rats were given 0.2, 1.0 and 5.0 mg/kg/day leuprolide acetate solution for 4 weeks; the other group received 0.6, 3.0 and 15 mg/kg leuprolide acetate for depot suspension once a week for 4 weeks. The reduction of organ weights and hormone levels was found more significant with the depot formulation than with the solution.
- In a third study with rats, the effects of a single administration of leuprolide acetate for depot suspension at doses of 0.03, 0.3 and 3 mg/kg intramuscular, and 3 mg/kg subcutaneously on genital organ weights, were compared to those of the subcutaneous daily injection of 100 mcg/kg/day of solution for two weeks. Results showed that at the beginning of treatment, there was a slight increase, but over the remaining two week treatment period, the organ weights decreased in dose-related fashion.

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

Human Pharmacology

General

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

After an initial transient increase in testosterone 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 and Metabolism

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

LUPRON[®] Injection

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 (S.C.) and by intravenous (I.V.) routes 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 S.C./I.V. was 0.94 with a range from 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 (i.m.). 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 85-100% 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 4 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 4 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

The safety assessment of leuprolide has been very extensive.

Acute Toxicity

LUPRON[®] Injection

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 deaths occurred. The LD₅₀ was concluded to be greater than 5 g/kg for intraperitoneal and subcutaneous routes and 2 g/kg for the intramuscular route.

Special Studies

LUPRON DEPOT[®]

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

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

- In a second irritation study, male rabbits were injected once or 4 successive times with leuprolide acetate for depot suspension (15% suspension) by intramuscular administration. Results were compared to those obtained with placebo-microcapsule or a

0.75% solution of acetic acid as the positive control. Deposition at injection sites, and slight irritation changes (hemorrhage, edema, inflammation) were noted: leuprolide acetate for depot suspension produced the same effects with the same degree as the placebo-microcapsule, but these were less than those of the positive control (0.75% acetic acid), and their severity were not potentiated by 4 repeated injections.

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

- Preliminary antigenicity study. Leuprolide acetate for depot suspension was given to guinea pigs at a dose of 123 mg/kg every 2 weeks by intramuscular route 4 times, and once by subcutaneous route 2 weeks after the last intramuscular dose. Results were compared to controls treated with placebo-microcapsule 122 mg/kg intraperitoneally, or with ovalbumin 5 mg/animal intravenously. No systemic anaphylactic reactions were observed with animals treated with leuprolide acetate for depot suspension and placebo-microcapsule, but some induced equivocal weak antibody production was noted.
- In a second study, the sensitization potential of leuprolide acetate for depot suspension at doses of 50 mg/animal/dosing by intramuscular (systemic anaphylaxis) or at doses of approximately 7.2 mg/animal/dosing (0.05 mL of a 144.23 mg/mL of suspension) intradermal (delayed hypersensitivity), were compared to those seen with gelatin, egg albumin or captan. No signs of anaphylactic reactions nor delayed hypersensitivity were observed for leuprolide acetate for depot suspension, while signs of anaphylactic reactions (such as nose scratching, sneezing, dyspnea or local irritation) were noted with other compounds.

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

Long Term Toxicity

LUPRON[®] Injection

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

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

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

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

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

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

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

LUPRON DEPOT[®]

Rats:

- Leuprolide acetate for depot suspension was administered intramuscularly to three groups of male rats at doses from 10, 30 and 100 mg/kg/week (corresponding to 0.8, 2.4 and 8.0 mg/kg/week of leuprolide acetate injection) once a week for 13 weeks. Rats dosed at 100 mg/kg/week showed atrophy of testes; in addition white spots were noted at the injection sites. The atrophy of the testes was reported to be due to the hormonal action of leuprolide acetate injection; the "no-toxic-effect" dose was considered to be 100 mg/kg/week.
- In another toxicity study, male rats were given leuprolide acetate for depot suspension subcutaneously once a week for 3 weeks, at doses of 30 mg/kg/week (corresponding to 2.4 mg/kg/week of leuprolide acetate injection). Atrophy of the testes, and a slight induration were noted. The "no-toxic effect" dose was considered to be 30 mg/kg/week.

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

Dogs:

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

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.

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.

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.

Mutagenicity

LUPRON[®] Injection

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

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PART III: CONSUMER INFORMATION

Pr LUPRON[®] leuprolide acetate injection

This leaflet is part III of a three-part "Product Monograph" published when LUPRON[®] Injection 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[®] Injection. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

LUPRON[®] (leuprolide acetate) Injection is 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 LH-RH) a hormone which occurs naturally in your body. Normally, your body releases small amounts of LH-RH and this leads to events which stimulate the production of sex hormones. However when you inject LUPRON[®] Injection, 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[®] Injection should not be used:

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

What the medicinal ingredient is:

Leuprolide acetate

What the important nonmedicinal ingredients are:

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

What dosage forms it comes in:

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

WARNINGS AND PRECAUTIONS

BEFORE you use LUPRON[®] Injection 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[®] Injection can cause thinning of the bone and may pose additional risk in patients with such a history.

During the first few weeks of treatment with LUPRON[®] Injection, 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 planning to take any other medicines, including non-prescription drugs (such as drug products for colds or nausea).

PROPER USE OF THIS MEDICATION

Usual dose:

The recommended dose of LUPRON[®] Injection is 1 mg (0.2 mL), as a single daily subcutaneous injection

Only a small amount of LUPRON[®] Injection 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



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[®] Injection keeps working for you.

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

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

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

In the first few weeks of taking LUPRON® Injection, 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.

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.

HOW TO STORE IT

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

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

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:

toll-free telephone: 866-234-2345
 toll-free fax 866-678-6789
 By email: cadrmpp@hc-sc.gc.ca

By regular mail:
 National AR Centre
 Marketed Health Products Safety and Effectiveness
 Information Division
 Marketed Health Products Directorate
 Tunney's Pasture, AL 0701C
 Ottawa ON K1A 0K9

NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.

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	
Uncommon	Abnormal swelling or numbness of limbs		✓	
	Severe bone pain		✓	
	Severe pain in chest or abdomen		✓	
	Vision Changes		✓	
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	✓			

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at: <http://www.abbott.ca> or by contacting the sponsor, Abbott Laboratories, Limited at: 1-800-361-7852.

This leaflet was prepared by Abbott Laboratories, Limited.

Last revised: October 16, 2008

PART III: CONSUMER INFORMATION

LUPRON DEPOT[®] **leuprolide acetate for depot suspension**

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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
- In women who are or may become pregnant.
- In women who are breast-feeding.

What the medicinal ingredient is:

Leuprolide acetate

What the important nonmedicinal ingredients are:

1-Month SR

Non-medicinal ingredients include: purified gelatin, DL-lactic and glycolic acids copolymer, and D-mannitol, carboxymethylcellulose sodium, polysorbate 80, water for injection, and glacial acetic acid.

3-Month SR and 4-Month SR

Non-medicinal ingredients include: polylactic acid, D-mannitol, carboxymethylcellulose sodium, polysorbate 80, water for injection, and glacial acetic acid.

What dosage forms it comes in:

LUPRON DEPOT[®] 7.5 mg (1-Month SR) is available in a prefilled dual-chamber syringe that contains 7.5 mg of leuprolide acetate as sustained-release microspheres and must be reconstituted with a special diluent prior to intramuscular administration once a month.

LUPRON DEPOT[®] 22.5 mg (3-Month SR) is available in a prefilled dual-chamber syringe that contains 22.5 mg leuprolide acetate as sustained-release microspheres and must be reconstituted with the appropriate diluent prior to intramuscular injection once every three months.

LUPRON DEPOT[®] 30.0 mg (4-Month SR) is available in a prefilled dual-chamber syringe that contains 30 mg leuprolide acetate as sustained-release microspheres and must be reconstituted with the appropriate diluent prior to intramuscular injection once every four months.

WARNINGS AND PRECAUTIONS

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.

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

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

PROPER USE OF THIS MEDICATION

Usual dose:

If you are taking LUPRON DEPOT[®] 7.5 mg (1-Month SR) report to your doctor **once every month** for your injection. If you are taking LUPRON DEPOT[®] 22.5 mg (3-Month SR), report to your doctor **once every three months** for your injection. If you are taking LUPRON DEPOT[®] 30.0 mg (4-Month SR), 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 visit.

If you need more information, ask your doctor.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

In the first few weeks of taking LUPRON DEPOT[®], 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.

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	
Uncommon	Abnormal swelling or numbness of limbs		✓	
	Severe bone pain		✓	
	Severe pain in chest or abdomen		✓	
	Vision Changes		✓	
Common	Decrease in testicular size		✓	
	Headache	✓		
	Hot flashes		✓	
	Impotence/ decrease in libido		✓	
	Itching Rash		✓	
	Skin reactions including reaction at site of injection		✓	

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 (59 -77°F). Protect from freezing.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:

toll-free telephone: 866-234-2345
 toll-free fax 866-678-6789
 By email: cadmp@hc-sc.gc.ca

By regular mail:
 National AR Centre
 Marketed Health Products Safety and Effectiveness
 Information Division
 Marketed Health Products Directorate
 Tunney's Pasture, AL 0701C
 Ottawa ON K1A 0K9

NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at: <http://www.abbott.ca> or by contacting the sponsor, Abbott Laboratories, Limited at: 1-800-361-7852.

This leaflet was prepared by Abbott Laboratories, Limited.

Last revised: October 16, 2008