

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19732/S012

FINAL PRINTED LABELING

(No. 3629)
03-4639-R5-Rev. Feb., 1996

LUPRON DEPOT® 7.5 mg

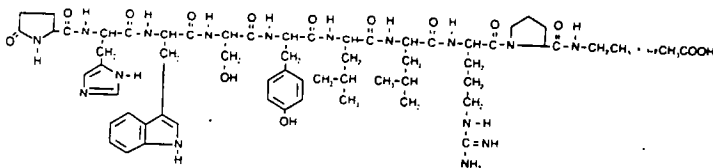
(leuprolide acetate for depot suspension)



034639

DESCRIPTION

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



LUPRON DEPOT is available in a vial containing sterile lyophilized microspheres, which when mixed with diluent, become a suspension which is intended as a monthly intramuscular injection.

The single-dose vial of LUPRON DEPOT 7.5 mg 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 accompanying ampule of diluent contains carboxymethylcellulose sodium (10 mg), D-mannitol (100 mg), polysorbate 80 (2 mg), water for injection, USP, and glacial acetic acid, USP to control pH.

During the manufacture of LUPRON DEPOT 7.5 mg, acetic acid is lost, leaving the peptide.

CLINICAL PHARMACOLOGY

Leuprolide acetate, an LH-RH agonist, acts as a potent inhibitor of gonadotropin secretion when given continuously and in therapeutic doses. Animal and human studies indicate that following an initial stimulation, chronic administration of leuprolide acetate results in suppression of ovarian and testicular steroidogenesis. This effect is reversible upon discontinuation of drug therapy. Administration of leuprolide acetate has resulted in inhibition of the growth of certain hormone dependent tumors (prostatic

tumors in Noble and Dunning male rats and DMBA-induced mammary tumors in female rats) as well as atrophy of the reproductive organs.

In humans, administration of leuprolide acetate results in an initial increase in circulating levels of luteinizing hormone (LH) and follicle stimulating hormone (FSH), leading to a transient increase in levels of the gonadal steroids (testosterone and dihydrotestosterone in males, and estrone and estradiol in premenopausal females). However, continuous administration of leuprolide acetate results in decreased levels of LH and FSH. In males, testosterone is reduced to castrate levels. In premenopausal females, estrogens are reduced to postmenopausal levels. These decreases occur within two to four weeks after initiation of treatment, and castrate levels of testosterone in prostate cancer patients have been demonstrated for more than five years.

Leuprolide acetate is not active when given orally.

PHARMACOKINETICS

Absorption: Following a single LUPRON DEPOT 7.5 mg injection to patients, mean peak leuprolide plasma concentration was almost 20 ng/mL at 4 hours and 0.36 ng/mL at 4 weeks. However, intact leuprolide and an inactive major metabolite could not be distinguished by the assay which was employed in the study. Nondetectable leuprolide plasma concentrations have been observed during chronic LUPRON DEPOT 7.5 mg administration, but testosterone levels

appear to be maintained at castrate levels.

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

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

Excretion: Following administration of LUPRON DEPOT 3.75 mg to 3 patients, less

than 5% of the dose was recovered as parent and M-I metabolite in the urine.

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

INDICATIONS AND USAGE

LUPRON DEPOT 7.5 mg is indicated in the palliative treatment of advanced prostatic cancer. It offers an alternative treatment of prostatic cancer when orchiectomy or estrogen administration are either not indicated or unacceptable to the patient. In clinical trials, the safety and efficacy of LUPRON DEPOT 7.5 mg does not differ from that of the original daily subcutaneous injection.

CONTRAINDICATIONS

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

LUPRON DEPOT is contraindicated in women who are or may become pregnant while receiving the drug. When administered on day 6 of pregnancy at test dosages of 0.00024, 0.0024, and 0.024 mg/kg (1/600 to 1/6 the human dose) to rabbits, LUPRON 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 in rats. The effects on fetal mortality are logical consequences of the alterations in hormonal levels brought about by this drug. Therefore, the possibility exists that spontaneous abortion may occur if the drug is administered during pregnancy.

WARNINGS

Isolated cases of worsening of signs and symptoms during the first weeks of treatment have been reported with LH-RH analogs. Worsening of symptoms may contribute to paralysis with or without fatal complications. For patients at risk, the physician may consider initiating therapy with daily LUPRON® (leuprolide acetate) Injection for the first two weeks to facilitate withdrawal of treatment if that is considered necessary.

PRECAUTIONS

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

Laboratory Tests: Response to LUPRON DEPOT 7.5 mg 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. Castrate levels were reached within two to four weeks and once achieved were maintained for as long as the patients received their injections. Transient increases in prostatic acid phosphatase levels may occur sometime early in treatment. However, by the fourth week, the elevated levels can be expected to decrease to values at or near baseline.

Drug Interactions: No pharmacokinetic-based drug-drug interaction studies have been conducted with LUPRON DEPOT. However, because leuprolide acetate is a peptide that is primarily degraded by peptidase and not by cytochrome P-450 enzymes as noted in specific studies, and the

drug is only about 46% bound to plasma proteins, drug interactions would not be expected to occur.

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

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

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

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

Pregnancy Category X. (See CONTRAINDICATIONS section.)

Pediatric Use: See LUPRON DEPOT-[®] (leuprolide acetate for depot suspension) labeling for the safety and effectiveness of the monthly formulation in children with central precocious puberty.

ADVERSE REACTIONS

In the majority of patients testosterone levels increased above baseline during the first week, declining thereafter to baseline levels or below by the end of the second week of treatment.

Potential exacerbations of signs and symptoms during the first few weeks of treatment is a concern in patients with vertebral metastases and/or urinary obstruction or hematuria which, if aggravated, may lead to neurological problems such as temporary weakness and/or paresthesia of the lower limbs or worsening of urinary symptoms (see WARNINGS section).

In a clinical trial of LUPRON DEPOT 7.5 mg, the following adverse reactions were reported to have a possible or probable relationship to drug as ascribed by the treating physician in 5% or more of the patients receiving the drug. Often, causality is difficult to assess in patients with metastatic prostate cancer. Reactions considered not drug-related are excluded.

LUPRON DEPOT 7.5 mg

	N=56	(Percent)
Cardiovascular System		
Edema	7	(12.5%)
Gastrointestinal System		
Nausea/vomiting	3	(5.4%)
Endocrine System		
*Decreased testicular size	3	(5.4%)
*Hot flashes/sweats	33	(58.9%)
*Impotence	3	(5.4%)
Central/Peripheral Nervous System		
General pain	4	(7.1%)
Respiratory System		
Dyspnea	3	(5.4%)
Miscellaneous		
Asthenia	3	(5.4%)
*Physiologic effect of testosterone.		decreased

Laboratory: Elevations of certain parameters were observed, but it is difficult to assess these abnormalities in this population.

SGOT (>2N)	4	(7.1%)
LDH (>2N)	11	(19.6%)
Alkaline phos (>1.5N)	4	(7.1%)

In this same study, the following adverse reactions were reported in less than 5% of the patients on LUPRON DEPOT 7.5 mg.

Cardiovascular System - Angina, Cardiac arrhythmia; **Gastrointestinal System** - Anorexia, Diarrhea; **Endocrine System** - Gynecomastia, Libido decrease; **Musculoskeletal System** - Bone pain, Myalgia; **Central/Peripheral Nervous System** - Paresthesia, Insomnia; **Respiratory System** - Hemoptysis; **Integumentary System** - Dermatitis, Local skin reactions, Hair growth; **Urogenital System** - Dysuria, Frequency/urgency, Hematuria, Testicular pain; **Miscellaneous** - Diabetes, Fever/chills, Hard nodule in throat, Increased calcium, Weight gain, Increased uric acid.

Postmarketing

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

Symptoms consistent with an anaphylactoid or asthmatic process have been rarely reported with GnRH analogs. Rash, urticaria, and photosensitivity reactions have also been reported.

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

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

See other LUPRON DEPOT and LUPRON Injection package inserts for other events reported in different patient populations.

OVERDOSAGE

In rats subcutaneous administration of 250 to 500 times the recommended human dose, expressed on a per body weight basis, resulted in dyspnea, decreased activity, and local irritation at the injection site. There is no evidence that there is a clinical counterpart of this phenomenon. In early clinical trials with daily subcutaneous leuprolide acetate, doses as high as

20 mg/day for up to two years caused no adverse effects differing from those observed with the 1 mg/day dose.

DOSAGE AND ADMINISTRATION

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

The recommended dose of LUPRON DEPOT is 7.5 mg, incorporated in a depot formulation. The lyophilized microspheres are to be reconstituted and administered monthly as a single intramuscular injection, in accord with the following directions:

- Using a syringe with a 23 gauge needle, withdraw 1 mL of diluent from the ampule, and inject it into the vial. (Extra diluent is provided; any remaining should be discarded.)
- Shake well to thoroughly disperse particles to obtain a uniform suspension. The suspension will appear milky.
- Withdraw the entire contents of the vial into the syringe and inject it at the time of reconstitution.

Although the potency of the reconstituted suspension has been shown to be stable for 24 hours, 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.

The vial of LUPRON DEPOT 7.5 mg and the ampule of diluent may be stored at room temperature.

HOW SUPPLIED

LUPRON DEPOT 7.5 mg is available in a single use kit (NDC 0300-3629-01) and in a six pack of drug only (NDC 0300-3629-06). Each vial contains sterile lyophilized microspheres which is leuprolide incorporated in a biodegradable copolymer of lactic and glycolic acids. When mixed with 1 mL of diluent, LUPRON DEPOT 7.5 mg is administered as a single monthly IM injection.

An information pamphlet for patients is included with the kit.

No refrigeration necessary. Protect from freezing.

Caution: Federal (U.S.A.) law prohibits dispensing without a prescription.

REFERENCE

- MacLeod TL, et al. Anaphylactic reaction to synthetic luteinizing hormone-releasing hormone. *Fertil Steril* 1987 Sept; 48(3):500-502.
- U.S. Patent Nos. 4,652,441; 4,677,191; 4,728,721; 4,849,228; 4,917,893; 4,954,298; 5,330,767; and 5,476,663.

TAP Pharmaceuticals Inc.
Deerfield, Illinois 60015-1595, U.S.A.
LUPRON DEPOT 7.5 mg manufactured by
Takeda Chemical Industries, Ltd.
Osaka, JAPAN 541

® - Registered trademark
Revised: February, 1996

Labeling: 342-217 ^{HE} Original

NDA No: 19732 86'd. 4.17.96

Reviewed by: CR 1/4/98

102
Manufactured by
Lupron Depot, Inc.
10000
10000
10000

U.S. Pat. 4,822,000
NDC 0300 7674 01
IMPROVED FORM
LUPRON
DEPOT 2.5mg
leuprolide acetate
for depot suspension

Injectable contains 2.5 mg
leuprolide acetate in 10 mL
of water. After mixing
with diluent, administered
intramuscularly. See
package insert for full
 prescribing information.
See package insert

Labeling: SLR-012 ^{AF} Original

NDA No: 19732 Rev. 4-17-96

Reviewed by: C. M. 1/8/98

22



**LUPRON
DEPOT[®] 7.5 mg**

leuprolide acetate
for depot suspension

Each vial contains:
leuprolide acetate, 7.5 mg;
purified gelatin, 1.3 mg;
DL-leucic & glycolic acids
copolymer, 86.2 mg;
D-mannitol, 13.2 mg

Usual Dose: After mixing with solvent,
administer entire contents of vial
by intramuscular injection once
a month under physician's
supervision. See enclosure for full
mixing and prescribing information.

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Manufactured for
TAP Pharmaceuticals Inc.
Deerfield, IL 60015
by Takeda Chemical Industries, Ltd.
Osaka, Japan 541



Exp. *Sample*
Lot.

131494



NDC 0300-3624-01
SINGLE DOSE

**LUPRON
DEPOT** 7.5 mg
leuprolide acetate
for depot suspension

Protect from freezing.
See bottom of carton for expiration
date and lot number.
Vial label bears coded expiration
date and lot number. Do not use
after first day of month/year
stamped.

13-1494-R7

leuprolide acetate 7.5 mg

For intramuscular injection
after mixing

CAUTION: Federal (U.S.A.)
law prohibits dispensing
without prescription

22

Labeling: SR-012 ^{AV} ORIGINAL
NDA No: 19732 Bo'd. 4-17-96
Reviewed by: CML 1/4/94

Sterile Diluent for
LUPRON
DEPOT

TAP Pharmaceuticals Inc.
Dearborn, MI 48115, U.S.A.

02-7770-21

Labeling: SLR-012 ^{AF} original
NDA No: 19732 Re'd. 4-17-96
Reviewed by: C. J. C. 1/2/97

NDC 0300-3647-01

Sterile Diluent
LUPRON
DEPOT

2 mL sterile diluent

dl

CAUTION: Federal (U.S.A.) law prohibits dispensing without prescription.

Exp. *Sample*
Lot



Ampule label bears coded expiration date and lot number. Do not use after first day of month/year stamped. Protect from freezing.
13-1537 R1

Sterile Diluent
LUPRON
DEPOT[®]

Each ampale contains: D-mannitol, 100 mg; carboxymethylcellulose sodium, 10 mg; polysorbate 80, 2 mg; water for injection, USP; and glacial acetic acid, USP to control pH.
Usual Dose: For use with Lupron Depot. See enclosure for full mixing directions.



Manufactured for TAP Pharmaceuticals Inc.
Deerfield, IL 60015
by Takeda Chemical Industries, Ltd.
Osaka, Japan 541



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Labeling: SLR-012 ^{HF} Original

NDA No: 19732 ^{File} 4-17-96

Reviewed by: C. J. C. 1/28/98

*Single Dose
Administration Kit
NDC 0300-3629-01*

CAUTION:
*Federal (USA) law prohibits
dispensing without prescription
NO REFRIGERATION NECESSARY
PROTECT FROM FREEZING*



- CJC* **Includes:**
- One Vial Lupron Depot®
NDC 0300-3624-01
(Leuprolide Acetate 7.5 mg)
 - One 2 mL Ampule Sterile
Diluent NDC 0300-3647-01
 - One Syringe with 23 Gauge
Needle
 - One 23 Gauge Needle

Sample
EXP.
LOT

LUPRON DEPOT®

7.5mg

02-7788-R3
Manufactured for
TAP Pharmaceuticals Inc.
Deerfield, IL 60015
by Takeda Chemical Industries, Ltd.
Osaka, Japan 541

LEUPROLIDE ACETATE FOR DEPOT SUSPENSION

Labeling: SLR-012 ^{AF} 0719121
NDA No: 19732 Bo'A. 4-17-96
Reviewed by: C 9/26 11/8/78

Single Dose
Administration Kit
NDC 0300-3629-00

CAUTION:
Federal (USA) law prohibits
dispensing without prescription
NO REFRIGERATION NECESSARY
PROTECT FROM FREEZING



Includes:

- One Vial Lupron Depot®
NDC 0300-3624-01
(Leuprolide Acetate 7.5 mg)
 - One 2 mL Ampule Sterile
Diluent NDC 0300-3647-01
 - One Syringe with 23 Gauge
Needle
 - One 23 Gauge Needle
- Physician Sample -
Not For Resale**

Sample
LUPRON DEPOT®

7.5mg

EXP.
LOT

02-7787-R3
Manufactured for
TAP Pharmaceuticals Inc.
Deerfield, IL 60015
by Takeda Chemical Industries, Ltd.
Osaka, Japan 541

LEUPROLIDE ACETATE FOR DEPOT SUSPENSION

Labeling: SLR-012^{AF} ORIGINAL 21

NDA No: 19732 Rev'd: 4-17-96

Reviewed by: C. M. 1/2/96

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YOUR
CHOICE FOR
TREATING
PROSTATE
CANCER

LUPRON DEPOT[®]

7.5 mg

LEUPROLIDE ACETATE FOR DEPOT SUSPENSION

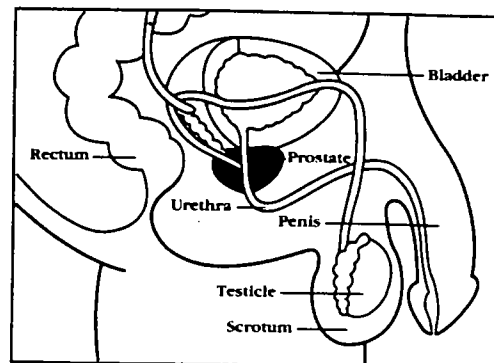
INTRODUCTION

This brochure has been created to answer your questions about prostate cancer and to help educate you about LUPRON DEPOT® 7.5 mg (leuprolide acetate for depot suspension), the drug you and your doctor have chosen to manage the disease.

According to the American Cancer Society, more than 100,000 men each year are diagnosed with prostate cancer. The risk of developing prostate cancer increases with age: it typically occurs in men age 40 and above.

WHAT IS THE PROSTATE?

The prostate is a chestnut-sized sex gland. It is located just below the bladder and surrounds part of the urethra, the canal that carries urine from the bladder during urination. The primary role of the prostate is to provide part of the fluid necessary for ejaculation.



WHAT CAUSES PROSTATE CANCER?

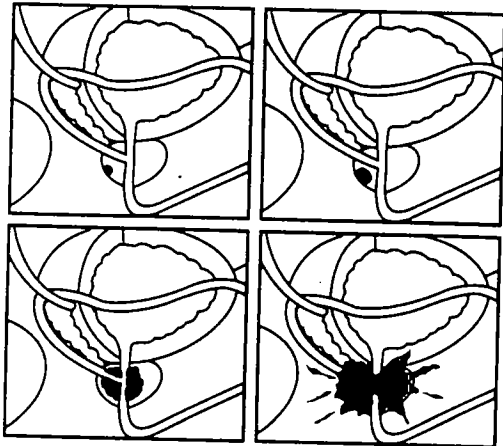
The exact cause of prostate cancer is unknown. What is known about the disease is that it begins with a group of cancerous cells (a tumor) within the prostate. Initially, the tumor may not cause any symptoms. However, as the cancer progresses, the tumor can enlarge and eventually put pressure on surrounding parts of the body such as the urethra. This process causes a block in the flow of urine from the bladder.

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HOW DOES PROSTATE CANCER SPREAD?

The growth and function of the normal prostate gland is dependent on the male hormone testosterone. Testosterone, which is produced almost entirely by the testicles, stimulates prostate cancer in much the same way kerosene fuels a fire. As long as the body produces testosterone, prostate cancer will continue to spread.

Prostate cancer can spread from the prostate to nearby lymph nodes, bones, or other organs. As a result, many men experience aches and pains in bones, joints or the back.



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HOW IS PROSTATE CANCER TREATED?

Because prostate cancer is fueled by testosterone, decreasing the body's supply of testosterone often controls the tumor's growth and relieves pain and difficulty in urinating. In most cases, it can slow or stop the growth of cancerous cells that spread to other parts of the body.

The treatment of prostate cancer depends on the stage of the tumor when it is discovered. A physician's objective when treating an advanced stage of prostate cancer (where the cancer has spread beyond the confines of the prostate) is to halt the spread of new tumor cells or shrink existing ones, and to relieve any symptoms they may be causing.

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LUPRON DEPOT® 7.5 mg (leuprolide acetate for depot suspension):

YOUR TREATMENT CHOICE

The treatment you and your doctor have chosen is LUPRON DEPOT, a member of

a class of drugs known as luteinizing hormone releasing-hormone analogs (LHRH analogs). LUPRON DEPOT works by shutting down testosterone produced by the testicles, which then decreases the amount of testosterone circulating in the body. Because LUPRON DEPOT lowers testosterone levels (the primary fuel for prostate cancer), the drug helps relieve the pain, difficulty in urinating and other symptoms associated with prostate cancer.

Once a month, you will visit your doctor's office to receive your injection of LUPRON DEPOT. The drug is released continuously and consistently over the next month. By receiving the injection in your physician's office, your doctor is able to monitor your progress and discuss any questions and concerns you might have about your condition.

The most common side effect associated with LUPRON DEPOT is hot flashes. Some men may also experience a temporary increase in their urinary symptoms or pain during the initial weeks of treatment. Like other treatment options, LUPRON DEPOT may cause impotence.



COMBINATION DRUG THERAPY


Your physician may have recommended that you take another drug along with LUPRON DEPOT 7.5 mg. These drugs, generally known as "antiandrogens," include Eulexin® (flutamide, Schering Corporation) and Casodex® (bicalutamide, Zeneca Pharmaceuticals). While LUPRON DEPOT 7.5 mg (leuprolide acetate for depot suspension) stops the production of testosterone by the testicles, antiandrogens block the small additional amount of testosterone produced by the adrenal glands.

Contact your doctor or pharmacist for additional information about Eulexin or Casodex.

This patient education brochure is not intended to be a substitute for information provided to you by your physician or provided to your physician by TAP Pharmaceuticals Inc.

You should discuss with your physician any questions you have about the diagnosis and treatment of prostate cancer.

This information is provided as a service of TAP Pharmaceuticals Inc.

 **TAP Pharmaceuticals Inc.**
2355 Waukegan Road
Deerfield, IL 60015

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034650

Labeling: SLR-012 ^{AF} ORIGINAL
NDA No: 19732 Re'd. 4-17-96
Reviewed by: C. G. C. 1/2/95



INSTRUCTIONS
ON HOW TO
MIX AND
ADMINISTER

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

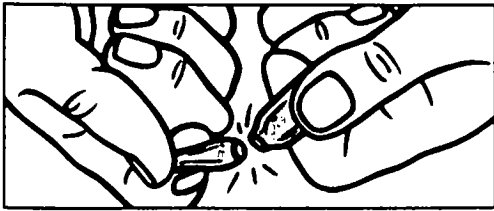
LUPRON DEPOT[®]

LEUPROLIDE ACETATE FOR DEPOT SUSPENSION

1. Use aseptic technique throughout. Assure

that all liquid is in the bottom section of the ampule of diluent by lightly flicking the top

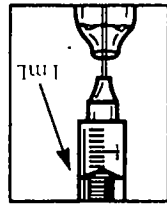
with your finger.



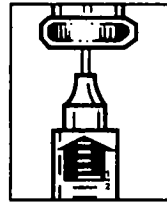
2. The top of this ampule is designed to break

off in any direction. To open, simply snap

the tip. Only moderate pressure is required.

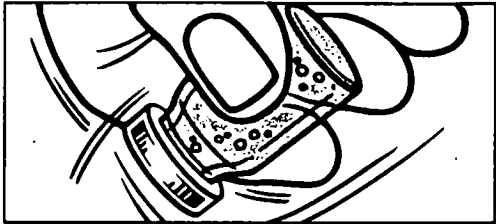


3. Use the syringe included in the kit or any syringe with at least a 23 gauge needle. Remember to tighten the luer lock mechanism by twisting the needle until it does not move. Withdraw 1 mL of diluent.



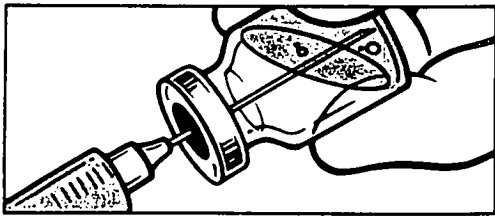
4. Remove the plastic cap from the vial and inject the diluent into the vial.

5. Shake the vial thoroughly to mix the particles to form a uniform suspension. The liquid will be milky.



6. Withdraw the entire contents of the vial

into the syringe used in step 3.



7. Immediately after reconstitution, inject the medication into any site usable for an intramuscular injection.

8. Discard the remainder of the diluent, the ampule, and the vial. None of the components is hazardous. No special handling or disposal procedures are needed.



SPECIAL INFORMATION

If you have any questions regarding the drug or this procedure, call 1-800-622-2011.

If the ampule of diluent should break or become unusable for any reason, do not substitute saline or sterile water. Contact TAP Pharmaceuticals for a replacement. Call 1-800-622-2011.



TR TAP Pharmaceuticals Inc.
2355 Waukegan Road
Deerfield, IL 60015

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034651

Labeling: SLR-012 AF 001911201
NDA No: 19732 Rev'd 4-17-96
Reviewed by: CML 1/9/94

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0300362906

NDC 0300-3629-06

**LUPRON
DEPOT[®] 7.5 mg**
leuprolide acetate
for depot suspension

Six Dose Package

No refrigeration necessary. Protect from freezing.

Exp.

Lot

Sample

Contains: Six Vials Lupron Depot[®] 7.5 mg NDC 0300-3624-01
Six 2 mL Ampules Sterile Diluent NDC 0300-3647-01
For Intramuscular injection after mixing.

CAUTION: Federal (U.S.A.) law prohibits dispensing without prescription



TP
Manufactured for
TAP Pharmaceuticals Inc.
Dearfield, IL 60015
By Takeda Chemical Industries, Ltd.
Osaka, Japan 541

Each single-dose vial contains:
leuprolide acetate, 7.5 mg; purified gelatin, 1.3 mg; D-l-leucine & glycocine
Each copolymer, 66.2 mg; D-mannitol, 13.2 mg
D-mannitol, 100 mg; carbon tetrachloride, 10 mg; polyoxalate
80.2 mg; water for injection, USP; and glacial acetic acid, USP to control pH.
See enclosure for full mixing and prescribing information.
By intramuscular injection once a month under physician's supervision.
Usual Dose: After mixing with diluent, administer entire contents of vial

13-1567-A3

LUPRON
DEPOT[®] 7.5 mg
leuprolide acetate
for depot suspension

NDC 0300-3629-06

90-629-06 NDC 0300

LUPRON
DEPOT[®] 7.5 mg
leuprolide acetate
for depot suspension
Six Dose Package