PRODUCT MONOGRAPH

Pr LUPRON DEPOT®

leuprolide acetate for depot suspension

Prefilled dual-chamber syringe

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

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

Gonadotropin-releasing hormone analog

Abbott Laboratories, Limited
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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
Intramuscular	Pre-filled dual chamber syringe containing sterile lyophilized microspheres 3.75 mg (1-month), 11.25 mg (3-Month)	1-Month SR carboxymethylcellulose sodium, DL-lactic and glycolic acids copolymer, D-mannitol, glacial acetic acid, polysorbate 80, purified gelatin 3-Month SR carboxymethylcellulose sodium, D-mannitol, glacial acetic acid, polylactic acid, polysorbate 80 *For a complete listing see **DOSAGE FORMS, COMPOSITION AND PACKAGING** section.*

INDICATIONS AND CLINICAL USE

Both LUPRON DEPOT® (leuprolide acetate for depot suspension) 3.75 mg (1-Month SR) and 11.25 mg (3-Month SR) are indicated in

- the treatment of endometriosis, including pain relief and reduction of endometriosis lesions, for a period of six months.

LUPRON DEPOT® can be used as sole therapy where it may provide symptomatic relief for women close to menopause who do not desire surgery, or as an adjunct to surgery.

Experience with LUPRON DEPOT® for the management of endometriosis has been limited to women 18 years of age and older.

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

Geriatrics (> 65 years of age):
LUPRON DEPOT® 3.75 mg (1-Month SR) and 11.25 mg (3-Month SR) are not indicated for women over 65 years of age.

Pediatrics (< 18 years of age):
LUPRON DEPOT® 11.25 mg (3-Month SR) is not indicated for pediatric use. LUPRON DEPOT® treatment of children is covered in the LUPRON DEPOT® 3.75 mg and 7.5 mg, "Central Precocious Puberty" Product Monograph.

CONTRAINDICATIONS

- LUPRON DEPOT® (leuprolide acetate for depot suspension) is 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 DEPOT® is contraindicated in women who are or may become pregnant. When administered on day 6 of pregnancy at test dosages of 0.00024, 0.0024, and 0.024 mg/kg (1/300 to 1/3 the 3.75 mg LUPRON DEPOT® human dose) to rabbits, LUPRON DEPOT® produced a dose-related increase in major fetal abnormalities. Similar studies in rats failed to demonstrate an increase in fetal malformations. There was increased fetal mortality and decreased fetal weights with the two higher doses of LUPRON DEPOT® in rabbits and with the highest dose (0.024 mg/kg) in rats. The effects on fetal mortality are logical consequences of the alterations in hormonal levels brought about by this drug. Therefore, the possibility exists that spontaneous abortion may occur if the drug is administered during pregnancy.

  Patients treated with LUPRON DEPOT® should use nonhormonal methods of contraception.

- LUPRON DEPOT® is also contraindicated in patients with undiagnosed abnormal vaginal bleeding.

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

WARNINGS AND PRECAUTIONS

General

Isolated cases of short-term worsening of signs and symptoms have been reported during initiation of leuprolide therapy. They are sometimes, but not necessarily, associated with a stimulation of the pituitary gland and an initial increase in the levels of circulating gonadal hormones.

During the early phase of therapy, sex steroids temporarily rise above baseline because of the physiologic effect of the drug. Therefore, an increase in clinical signs and symptoms may be observed during the initial days of therapy, but these will dissipate with continued therapy at adequate doses.

Worsening of the clinical condition may occasionally require discontinuation of therapy and/or surgical intervention.

Before initiating treatment with LUPRON DEPOT® (leuprolide acetate for depot suspension), pregnancy must be ruled out (see **WARNINGS AND PRECAUTIONS, Special Populations, Pregnant Women**).

Patients on leuprolide therapy should be assessed on a regular basis by their attending physician.

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

Since bone loss can be anticipated as part of natural menopause, it may also be expected to occur during the medically induced hypoestrogenic state caused by the long-term use of LUPRON DEPOT® (leuprolide acetate for depot suspension). For a period of up to six months, this bone loss should not be important.

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.

Re-treatment cannot be recommended since safety data for re-treatment are not available. If the symptoms of endometriosis recur after a course of therapy, and further treatment with LUPRON DEPOT® is contemplated, it is recommended that bone density be assessed before re-treatment begins to ensure that values are within normal limits.

A controlled study in endometriosis patients showed that vertebral bone density, as measured by dual energy X-ray absorptiometry (DEXA), decreased by an average of 4.1% at six months compared with the pretreatment value.

For those patients who were tested at six or twelve months after discontinuation of therapy, the mean bone density returned to -2.6% of pretreatment.

Earlier studies in endometriosis patients, utilizing quantitative computed tomography (QCT), demonstrated that in the few patients who were retested at six and twelve months, partial to complete recovery of bone density was recorded in the posttreatment period. Use of LUPRON DEPOT® for longer than six months or in the presence of other known risk factors for decreased bone mineral content may cause additional bone loss.

The safety of re-treatment as well as treatment beyond 6 months with LUPRON DEPOT® has not been established.

Adverse events occurring in clinical studies with LUPRON DEPOT® that are associated with hypoestrogenism include: hot flashes, headaches, emotional lability, decreased libido, acne, myalgia, reduction in breast size, and vaginal dryness. Estrogen levels returned to normal after treatment was discontinued.

Renal and Hepatic

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

Special Populations

Pregnant Women: Safe use of the drug in pregnancy has not been established; therefore a nonhormonal method of contraception should be used during treatment. Patients should be advised that if they miss or postpone a dose of LUPRON DEPOT®, ovulation may occur with the potential for conception. If a patient becomes pregnant during treatment, she should discontinue treatment and consult her physician.

Since menstruation should stop with effective doses of LUPRON DEPOT®, the patient should notify her physician if regular menstruation persists. Patients missing successive doses of LUPRON DEPOT® may experience breakthrough bleeding.

Before initiating treatment with LUPRON DEPOT®, pregnancy must be ruled out.

Nursing Women: It is not known whether leuprolide is excreted in human milk; therefore, LUPRON DEPOT® is contraindicated in patients who are breast-feeding.

Pediatrics (< 18 years of age): Safety and effectiveness of LUPRON DEPOT® 11.25 mg (3-Month SR) have not been established in pediatric patients. See "Central Precocious Puberty" Product Monograph for the safety and effectiveness of LUPRON DEPOT® 3.75 mg (1-Month SR) in children with central precocious puberty.

Geriatrics (> 65 years of age): LUPRON DEPOT® 3.75 mg (1-Month SR) and 11.25 mg (3-Month SR) has not been studied in women over 65 years of age and is not indicated in this population.

Monitoring and Laboratory Tests

Changes in Laboratory Values During Treatment

Plasma Enzymes: During clinical trials with LUPRON DEPOT®, regular laboratory monitoring revealed that SGOT levels were more than twice the upper limit of normal in only one patient. There was no other clinical or laboratory evidence of abnormal liver function.

Hematology: Slight decreases in hemoglobin and hematocrit values to below normal were noted with receipt of LUPRON DEPOT® 11.25 mg (3-Month SR), but none were considered clinically significant.

Lipids: At enrollment, 4% of LUPRON DEPOT® 3.75 mg (1-Month SR) patients and 1% of the danazol patients had total cholesterol values above the normal range. These patients also had cholesterol values above the normal range at the end of treatment. Of those patients whose pretreatment cholesterol values were in the normal range, 7% of the LUPRON DEPOT® patients and 9% of the danazol patients had posttreatment values above the normal range.

The mean (+ SEM) pretreatment values for total cholesterol from all patients were 4.63 (0.08) mmol/L in the LUPRON DEPOT® 3.75 mg (1-Month SR) group and 4.54 (0.08) mmol/L in the danazol group. At the end of treatment, the mean values for total cholesterol from all patients were 5.01 mmol/L in the LUPRON DEPOT® group and 5.03 mmol/L in the danazol group. These increases from the pretreatment values were statistically significant ($p<0.03$) in both groups.

Triglycerides were increased above the upper limit of normal in 12% of the patients who received LUPRON DEPOT® 3.75 mg (1-Month SR) and in 6% of the patients who received danazol.

At the end of treatment, HDL cholesterol fractions decreased below the lower limit of the normal range in 2% of the LUPRON DEPOT® 3.75 mg (1-Month SR) patients compared with 54% of those receiving danazol. LDL cholesterol fractions increased above the upper limit of the normal range in 6% of the patients receiving LUPRON DEPOT® 3.75 mg (1-Month SR) compared with 23% of those receiving danazol. There was no increase in the LDL/HDL ratio in patients receiving LUPRON DEPOT® 3.75 mg (1-Month SR), but there was approximately a two-fold increase in the LDL/HDL ratio in patients receiving danazol. The clinical implication of these changes in this patient population for a restricted therapeutic period is unclear.

Isolated elevations of SGOT were observed in leuprolide acetate- and danazol-treated patients.

In subjects receiving LUPRON DEPOT® 11.25 mg (3-Month SR), triglycerides were slightly elevated (range 142-210 mg/dL) in 32% of the subjects who had demonstrated normal baseline values.

Other Changes: In comparative studies, the following changes were seen in approximately 5% to 8% of patients. LUPRON DEPOT® was associated with elevations of LDH and phosphorus, and decreases in WBC counts, and danazol therapy was associated with increases in hematocrit, platelet count, and LDH.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Estradiol levels may increase during the first weeks following the initial injection, but then decline to basal levels. This transient increase in estradiol can be associated with a temporary worsening of signs and symptoms (see **WARNINGS AND PRECAUTIONS**).

Clinical Trial Adverse Drug Reactions

LUPRON DEPOT® 3.75 mg (1-Month SR)

In two controlled clinical trials treating endometriosis, one comparing LUPRON DEPOT® 3.75 mg (1-Month SR) with danazol (800 mg/day) and the other with placebo, the following adverse reactions were reported to have a possible or probable relationship to study drugs as ascribed by the treating physician in 5% or more of the patients receiving the drug (see **Table 1**).

Table 1
Adverse Reactions Reported Having a Possible or Probable Relationship to Study Drugs in 5% or More of Patients Receiving LUPRON DEPOT® 3.75 mg (1-Month SR) versus Danazol (800 mg/day) and LUPRON DEPOT® 3.75 mg (1-Month SR) versus Placebo

BODY SYSTEM	LUPRON DEPOT® 3.75 mg (1-Month SR) N=166 (%)	Danazol 800 mg/day N=136 (%)	Placebo N=31 (%)
	Number of Reports (%)		
Cardiovascular System			
Edema	12 (7)	17 (13)	1 (3)
Gastrointestinal System			
Nausea/vomiting	21 (13)	17 (13)	1 (3)
GI disturbances*	11 (7)	8 (6)	1 (3)
Endocrine System			
Hot flashes/sweats*	139 (84)	77 (57)	9 (29)
Breast changes, tenderness/pain*	10 (6)	12 (9)	0 (0)
Decreased libido*	19 (11)	6 (4)	0 (0)
Androgen-like effects	22 (13)	44 (32)**	1 (3)
Virilism	0 (0)	1 (1)	0 (0)
Acne	17 (10)	27 (20)	0 (0)
Seborrhea	2 (1)	5 (4)	0 (0)
Hirsutism	2 (1)	9 (7)	1 (3)
Voice alteration	1 (1)	2 (1)	0 (0)
Musculoskeletal System			
Myalgia*	1 (1)	7 (5)	0 (0)
Joint disorder*	14 (8)	11 (8)	0 (0)

Table 1 Adverse Reactions Reported Having a Possible or Probable Relationship to Study Drugs in 5% or More of Patients Receiving LUPRON DEPOT® 3.75 mg (1-Month SR) versus Danazol (800 mg/day) and LUPRON DEPOT® 3.75 mg (1-Month SR) versus Placebo			
BODY SYSTEM	**LUPRON DEPOT® 3.75 mg (1-Month SR) N=166 (%)**	**Danazol 800 mg/day N=136 (%)**	**Placebo N=31 (%)**
	Number of Reports (%)		
Central/Peripheral Nervous System			
Depression/emotional lability*	36 (22)	27 (20)	1 (3)
Headaches*	53 (32)	30 (22)	2 (6)
Dizziness	19 (11)	4 (3)	0 (0)
Insomnia/sleep disorders*	2 (1)	4 (3)	0 (0)
General pain	31 (19)	22 (16)	1 (3)
Neuromuscular disorders*	11 (7)	17 (13)	0 (0)
Nervousness*	8 (5)	11 (8)	0 (0)
Paresthesias	12 (7)	11 (8)	0 (0)
Integumentary System			
Skin reactions	17 (10)	20 (15)	1 (3)
Urogenital System			
Vaginitis*	46 (28)	23 (17)	0 (0)
Miscellaneous			
Asthenia	5 (3)	9 (7)	0 (0)
Weight gain/loss	22 (13)	36 (26)	0 (0)
* Physiologic effect of decreased estrogen. ** Individual percentages equal 33% due to rounding. Reactions considered not drug-related are excluded.			

In these same studies, the following were reported in less than 5% of patients receiving LUPRON DEPOT®:

Body as a Whole: body odor, flu syndrome, injection site reactions;
Cardiovascular System: palpitations, syncope, tachycardia;
Gastrointestinal System: dry mouth, thirst, appetite changes;
Central/Peripheral Nervous System: anxiety*, personality disorder, memory disorder, delusions, insomnia/sleep disorders*;
Endocrine System: androgen-like effects;
Skin and Appendages: alopecia, hair disorder, nail disorder;
Hemic and Lymphatic Systems: ecchymosis, lymphadenopathy;
Respiratory System: rhinitis;
Special Senses: ophthalmologic disorders*, conjunctivitis, taste perversion;
Urogenital System: dysuria*, lactation, menstrual disorders;

* Physiologic effect of decreased estrogen.

LUPRON DEPOT® 11.25 mg (3-Month SR)

In a pharmacokinetic trial involving 20 healthy female subjects receiving LUPRON DEPOT® 11.25 mg (3-Month SR), a few adverse events were reported with this formulation that were not reported previously. These included face edema, agitation, laryngitis and ear pain, and are noted in **Table 2**.

Table 2
Adverse Events Reported by 20 Healthy Female Subjects Receiving LUPRON DEPOT® 11.25 mg (3-Month SR) in a Pharmacokinetic Trial

BODY SYSTEM	LUPRON DEPOT® 11.25 (3-Month SR) N=20 (%)
Body as a Whole	
Asthenia	1 (5.0)
Face edema	1 (5.0)
General pain	4 (20.0)
Headache/migraine*	16 (80.0)
Cardiovascular System	
Hot flashes/sweats*	13 (65.0)
Digestive System	
GI disturbance*	2 (10.0)
Liver function test abnormal	1 (5.0)
Nausea/vomiting	2 (10.0)
Metabolic and Nutritional Disorders	
Edema	1 (5.0)
Musculoskeletal System	
Myalgia*	2 (10.0)
Nervous System	
Agitation	1 (5.0)
Depression/emotional lability*	1 (5.0)
Dizziness/vertigo	1 (5.0)
Insomnia/sleep disorders*	2 (10.0)
Neuromuscular disorders*	1 (5.0)
Respiratory System	
Laryngitis	1 (5.0)
Special Senses	
Ear pain	1 (5.0)
Urogenital System	
Dysmenorrhea	1 (5.0)

* Physiologic effect of the drug.

Abnormal Hematologic and Clinical Chemistry Findings

See **Monitoring and Laboratory Tests** under **WARNINGS AND PRECAUTIONS**.

Post-Market Adverse Drug Reactions

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

Like other drugs in this class, mood swings, including depression, have been reported as a physiologic effect of decreased sex steroids. There have been very rare reports of suicidal ideation and attempt. Many, but not all, of these patients had a history of depression or other psychiatric illness. Patients should be counselled on the possibility of worsening of depression.

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.

Symptoms consistent with fibromyalgia (e.g., joint and muscle pain, headaches, sleep disorders, gastrointestinal distress, and shortness of breath) have been reported individually and collectively. The relationship of any of these symptoms to leuprolide acetate has not been established.

The following events have been reported during post-marketing surveillance:

Cardiovascular System:	hypotension, pulmonary embolism;
Gastrointestinal System:	hepatic dysfunction;
Hemic and Lymphatic System:	decreased WBC;
Central/Peripheral Nervous System:	peripheral neuropathy, spinal fracture/paralysis;
Respiratory System:	dyspnea;
Integumentary System:	rash, urticaria, photosensitivity reactions;
Musculoskeletal System:	tenosynovitis-like symptoms;
Urogenital System:	menstrual disorders;
Miscellaneous:	injection site reactions including pain, inflammation, sterile abscess, induration and hematoma.

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

DOSAGE AND ADMINISTRATION

Dosing Considerations

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

LUPRON DEPOT® 3.75 and 11.25 mg administered intramuscularly is designed to provide continuous sustained release of leuprolide for 1, and 3 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 DEPOT® (leuprolide acetate for depot suspension) Must Be Administered under the Supervision of a Physician.

LUPRON DEPOT® 3.75 mg (1-Month SR)	LUPRON DEPOT® 11.25 mg (3-Month SR)
3.75 mg for 6 months (6 monthly injections)	11.25 mg for 6 months (1 injection every 3 months)

LUPRON DEPOT® 3.75 mg (1-Month SR)

The recommended dose of LUPRON DEPOT® (1-Month SR) is 3.75 mg administered **monthly** as a **single intramuscular injection**, after reconstitution with the special diluent. (See **Administration** and **CONSUMER INFORMATION**). The treatment course is for six months.

LUPRON DEPOT® 11.25 mg (3-Month SR)

The recommended dose of LUPRON DEPOT® (3-Month SR) is 11.25 mg administered as a **single intramuscular injection once every three months**, after reconstitution with the special diluent. (See **Administration** and **CONSUMER INFORMATION**).

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

Retreatment cannot be recommended since safety data for re-treatment are not available. If the symptoms of endometriosis recur after a course of therapy, and further treatment with either LUPRON DEPOT® 3.75 mg (1-Month SR) or LUPRON DEPOT® 11.25 mg (3-Month SR) is contemplated, it is recommended that bone density be assessed before re-treatment begins to ensure that values are within normal limits.

Missed Dose

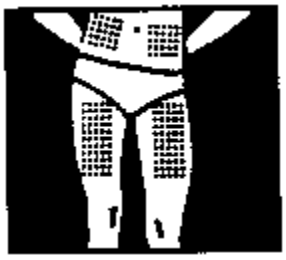
Missing an appointment by a few days should not disrupt the benefits of treatment, but keeping a consistent schedule of LUPRON DEPOT® injection is an important part of treatment.

Administration

As with 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

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

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

For LUPRON DEPOT® 3.75 mg (1-Month SR) and 11.25 mg (3-Month SR)

1. The LUPRON DEPOT® powder should be visually inspected and the syringe should **NOT BE USED** if clumping or caking is evident. A thin layer of powder on the wall of the syringe is considered normal. The diluent should appear clear.

2. To prepare for injection, screw the white plunger into the end stopper until the stopper begins to turn.

3. Remember to tighten the needle by twisting the needle cap clockwise. Do not overtighten.

4. Holding the syringe upright, release the diluent by **SLOWLY PUSHING** (6 - 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

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 at present that there is a clinical counterpart of this phenomenon.

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

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 down-regulation 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 pre-menopausal females). However, continuous administration results in decreased levels of LH and FSH in all patients. In males, testosterone is reduced to castrate levels. In pre-menopausal 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.

Endometriosis

Endometriosis is a gynecologic disorder wherein endometrial tissue is found to be established in sites outside the endometrial cavity. As definitive diagnosis can only be made during surgery, the true incidence of the disease is unknown.

The etiology of the disease is unclear. An accepted theory of the etiology of endometriosis is the retrograde flow of menstrual fluid with subsequent implantation of viable fragments of endometrium within the pelvic cavity (Sampson's theory). However, this theory does not explain the extra-pelvic sites of endometriosis such as the limbs, thoracic cavity and elsewhere. It has also been suggested that chronic irritation of the peritoneum by menstrual blood may be

causative. Another theory is that endometrial tissues are displaced into an implant in new sites during surgery. Genetic and immunologic factors may account for spontaneous endometriosis in a small segment of the population. It is also believed that endometriosis may be caused by lymphatic and hematogenous spread of normal endometrium to distant sites.

Endometriosis may be treated both surgically and medically. Since endometriosis resolves after oophorectomy and menopause, surgical castration may be used to treat the disease. A menopausal state may also be achieved medically. The resultant hypoestrogenic environment results in atrophic changes in both the uterine and ectopic endometrial tissue.

LUPRON DEPOT® achieves a menopausal state by suppression of the pituitary-ovarian axis by inhibiting the output of gonadotropins (FSH and LH) from the pituitary gland.

In female volunteers receiving a single dose of LUPRON DEPOT® 3.75 mg (1-Month SR) i.m., an initial burst of leuprolide in plasma was observed. Mean plasma leuprolide levels of approximately 0.23 to 0.34 ng/mL were maintained over a period of four to five weeks, and then slowly tapered off, becoming undetectable eight weeks after injection.

In a pharmacokinetic/pharmacodynamic study of healthy female subjects (N=20), the onset of estradiol suppression was observed for individual subjects between day 4 and week 4 after dosing. By the third week following the injection, the mean estradiol concentration (8 pg/mL) reached the menopausal range. Throughout the remainder of the dosing period, mean serum estradiol levels ranged from the menopausal to the early follicular range.

LUPRON DEPOT® 11.25 mg (3-Month SR) induced amenorrhea in 85% (N=17) of subjects during the initial month and 100% during the second month following the injection. All subjects remained amenorrheic through the remainder of the 12-week dosing interval. Episodes of light bleeding and spotting were reported by a majority of subjects during the first month after the injection and in a few subjects at a later time-points. Menses resumed on average 12 weeks (range 2.9 to 20.4 weeks) following the end of the 12-week dosing interval.

LUPRON DEPOT® 11.25 mg (3-Month SR) produced similar pharmacodynamic effects in terms of hormonal and menstrual suppression to those achieved with monthly injections of LUPRON DEPOT® 3.75 mg (1-Month SR) during the controlled clinical trials for the management of endometriosis. Similar clinical outcome to that with LUPRON DEPOT® 3.75 mg (1-Month SR) administered monthly is predicted with LUPRON DEPOT 11.25 mg (3-Month SR) administered every 3 months.

Pharmacokinetics

Intramuscular injections of LUPRON DEPOT® (leuprolide acetate for depot suspension) 3.75 mg (1-Month SR) and 11.25 mg (3-Month SR) provide effective plasma concentrations of leuprolide acetate over a period of one and three months, respectively (see **DETAILED PHARMACOLOGY**).

Leuprolide acetate is not active when given orally.

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

Following a single injection of the three month formulation of LUPRON DEPOT® 11.25 mg (3-Month SR) in female subjects, a mean peak plasma leuprolide concentration of 36.3 ng/mL was observed at 4 hours. Leuprolide appeared to be released at a constant rate following the onset of steady-state levels during the third week after dosing and mean levels then declined gradually to near the lower limit of detection by 12 weeks. The mean (± standard deviation) leuprolide acetate concentration from 3 to 12 weeks was 0.23 ± 0.09 ng/mL. 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 monthly formulation.

In adults, bioavailability by subcutaneous administration is comparable to that by intravenous administration. Leuprolide 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 ^{14}C-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

LUPRON DEPOT® (leuprolide acetate for depot suspension) 3.75 mg/syringe (1-Month SR): Store between 15 and 25°C (59-77°F). Protect from freezing.

LUPRON DEPOT® (leuprolide acetate for depot suspension) 11.25 mg/syringe (3-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 DEPOT®

LUPRON DEPOT® 3.75 mg (1-Month SR)

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

The front chamber of the prefilled dual-chamber syringe contains: leuprolide acetate (3.75 mg), purified gelatin (0.65 mg), DL-lactic and glycolic acids copolymer (33.1 mg), and D-mannitol (6.6 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® 11.25 mg (3-Month SR)

LUPRON DEPOT® 11.25 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 (11.25 mg), polylactic acid (99.3 mg), and D-mannitol (19.45 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**.

During the manufacturing process of LUPRON DEPOT® (1-Month SR and 3-Month SR), acetic acid is lost, leaving the peptide.

Availability of Dosage Forms

LUPRON DEPOT®

LUPRON DEPOT® 3.75 mg (1-Month SR), and LUPRON DEPOT® 11.25 mg (3-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.

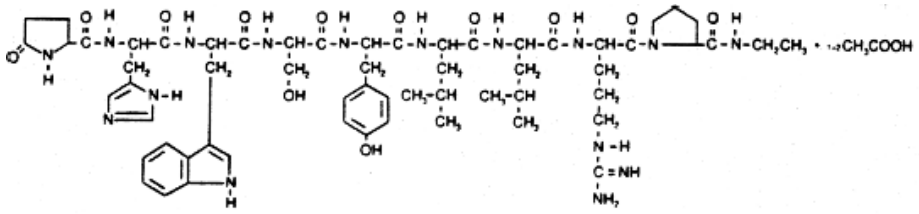
or: des-Glycine^{10}, [D-Leucine^{6}) LH-RH ethylamide acetate.

or: [D-Leu^{6}, des-Gly-$NH_2{}^{10}$, Proethylamide^{9}] GnRH.

Molecular formula and molecular mass:

$C_{59}H_{84}N_{16}O_{12} \cdot C_2H_4O_2$ 1209.41 as free base

Structural formula:



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

CLINICAL TRIALS

Study Demographics and Trial Design

LUPRON DEPOT® 3.75 mg (1-Month SR)

The two studies conducted are Phase III, randomized, double-blind, multi-centre studies of the effects of LUPRON DEPOT® 3.75 mg (1-Month SR) in endometriosis. The first, was placebo-controlled, while the second, used danazol as an active control. The studies were conducted at a total of 23 investigative sites, with 11 investigators participating in both studies. First study had a planned sample size of 60 (30 LUPRON DEPOT®, 30 placebo), and second study had a planned sample size of 250 (125 LUPRON DEPOT®, 125 danazol).

A total of 333 patients for the two studies were enrolled at 23 investigative centres.

Sixty-three patients entered the first study and 270 patients entered the second study.

The number of patients enrolled into each study and the number of evaluable (for efficacy) is summarized in **Table 3**.

Table 3
Number of Patients Enrolled in Two Phase III, Randomized, Double-Blind, Multicentre Studies Evaluating the Effects of LUPRON DEPOT® 3.75 mg (1-Month SR) in Endometriosis

Study	No. of Invest.	No. of Patients Entered			No. of Evaluable Patients		
		LUPRON DEPOT®	Placebo	Danazol	LUPRON DEPOT®	Placebo	Danazol
M86-031	12	32	31	--	28	24	--
M86-039	22	134	--	136	128	--	125
Total	23*	166	31	136	156	24	125

* Eleven investigators entered patients in both studies.

A total of 166 patients were exposed to LUPRON DEPOT® in the studies. Of the 166 patients, 153 were treated for the full 6-month study period and 13 prematurely terminated from the study and were treated for periods ranging from one to six months. The patients were treated with LUPRON DEPOT® for a total of 79 accumulated patient-years experience in these two studies (assuming each injection is equivalent to four weeks treatment).

A summary of the trial design and patient demographics is shown in **Table 4**.

Table 4 Summary of patient demographics for clinical trials in Endometriosis					
Study #	**Trial design**	**Dosage, route of administration and duration**	**Study subjects (n=number)**	**Mean age (Range)**	**Gender**
M86-031	Phase III, parallel randomized, double-blind, multicenter study	3.75 mg LUPRON DEPOT® *vs.* placebo Intramuscular 24 weeks	63	30 (19-44)	Females only
M86-039	Phase III, parallel randomized, double-blind, multicenter study	3.75 mg LUPRON DEPOT® plus danazol placebo *vs.* LUPRON DEPOT® placebo plus 200 mg danazol b.i.d. Intramuscular 24 weeks	270	Not available	Females only

Study Results

LUPRON DEPOT® 3.75 mg (1-Month SR)

The results of the studies were as follows:

1. Clinical Evaluation

At each study visit, an assessment was made of dysmenorrhea, non-menstrual pelvic pain, and dyspareunia (by patient interview). Symptoms were graded as absent, mild, moderate, or severe. Degree of analgesic use was utilized by the investigators to help assess pelvic pain. Pelvic tenderness, induration, and ovarian enlargement (by pelvic examination) were evaluated at every monthly visit for patients in the placebo-controlled pain study and every 12 weeks for patients in the active-controlled study. Pelvic tenderness and induration were also graded as absent, mild, moderate, or severe; ovarian size was assessed to be normal, two times normal, or greater than or equal to three times normal.

At each visit, a patient was considered improved if her evaluation at that visit had a less severe classification than did her baseline evaluation. A change to a more severe classification was counted as worse. Patients with a baseline classification of absent could not improve and patients with a baseline classification of severe could not get worse. Therefore, the percentages of patients with treatment changes of "worse", "no change", and "improved" do not add to 100%.

Forty-nine patients (28 LUPRON DEPOT®, 21 placebo) in the placebo-controlled study and 251 patients (127 LUPRON DEPOT®, 124 danazol) in the active-controlled study were evaluable for one or more of the clinical valuation variables.

Dysmenorrhea: LUPRON DEPOT® patients showed reductions in dysmenorrhea compared to baseline at every visit in both studies. **Table 5** summarizes changes in clinical evaluation of dysmenorrhea at the Final Visit against baseline for patients included in the efficacy analysis.

Table 5
Summary of Changes in Clinical Evaluation of Dysmenorrhea at the Final Visit Against Baseline for Patients Included in the Efficacy Analysis

	LUPRON DEPOT®	**Danazol**	**Placebo**
Worse	1/121 = 1%	3/11 = 3%	7/12 = 58%
No change	20/155 = 13%	14/124 = 11%	6/21 = 29%
Improved	134/136 = 99%	107/112 = 96%	8/21 = 30%

Pelvic pain: LUPRON DEPOT® patients showed decreases in pelvic pain severity levels at each visit. **Table 6** summarizes the changes in clinical evaluation of pelvic pain at the Final Visit compared to baseline for patients included in the efficacy analysis.

Table 6
Summary Changes in Clinical Evaluation of Pelvic Pain at the Final Visit Compared to Baseline for Patients Included in the Efficacy Analysis

	LUPRON DEPOT®	**Danazol**	**Placebo**
Worse	13/145 = 9%	5/116 = 4%	2/13 = 15%
No change	56/155 = 36%	56/124 = 45%	10/21 = 48%
Improved	86/118 = 73%	63/86 = 73%	9/21 = 43%

Dyspareunia: LUPRON DEPOT® patients in both studies showed slight decreases or no change when compared to baseline at all visits. **Table 7** summarizes the changes in clinical evaluation of dyspareunia at the Final Visit compared to baseline for patients included in the efficacy evaluation.

Table 7
Summary of the Changes in Clinical Evaluation of Dyspareunia at the Final Visit Compared to Baseline for Patients Included in the Efficacy Analysis

	LUPRON DEPOT®	**Danazol**	**Placebo**
Worse	22/126 = 17%	7/105 = 7%	4/13 = 31%
No change	65/139 = 47%	62/110 = 56%	6/13 = 46%
Improved	42/72 = 58%	41/58 = 71%	3/10 = 30%

Pelvic Tenderness: Decreases in severity levels of pelvic tenderness occurred at every visit for the combined LUPRON DEPOT® group. Pelvic tenderness changes from baseline to the Final Visit for both studies are summarized in **Table 8**.

Table 8 Pelvic Tenderness Changes from Baseline to the Final Visit for the Placebo- and Active-Controlled Studies			
	LUPRON DEPOT®	**Danazol**	**Placebo**
Worse	8/150 = 5%	6/120 = 5%	3/20 = 15%
No change	55/152 = 36%	61/122 = 50%	11/21 = 52%
Improved	89/117 = 76%	55/70 = 79%	7/21 = 33%

Induration: At baseline in each study, treatment groups were similar. In the placebo-controlled study, LUPRON DEPOT® patients showed similar or better results (less induration) than the placebo group at all visits. At the Final Visit, induration was significantly less for the LUPRON DEPOT® group (p=0.023). In active-controlled study, LUPRON DEPOT® patients showed similar results compared to the danazol group at all visits. No significant differences were seen between groups.

Ovarian Enlargement: For both studies, ovarian enlargement had a relatively low prevalence rate at baseline. Ovarian enlargement for most LUPRON DEPOT® patients and danazol patients either improved over time or did not change. Only two placebo patients had ovarian enlargement at baseline.

Menses: Menses were considered suppressed if no menstrual-like bleeding occurred for more than 60 days (day of first injection or first day of one episode of menstrual-like bleeding to the first day of the subsequent episode of menstrual-like bleeding or end-of-study).

In the placebo-controlled study menses were suppressed in all of the LUPRON DEPOT® patients (100%) and one of the placebo patients (4%). Once suppressed, menses remained suppressed through the study for all except three LUPRON DEPOT® patients.

In the active-controlled study menses were suppressed in 99% of the LUPRON DEPOT® patients and 96% of the danazol patients. However, suppression did not occur in one LUPRON DEPOT® and five danazol patients. Menses were completely suppressed from the initiation of treatment for 77% of the LUPRON DEPOT® and 63% of the danazol patients. The number of episodes of menstrual-like bleeding before suppression are presented in **Table 9**.

Table 9 Number of Episodes of Menstrual-Like Bleeding Before Suppression in the Active-Controlled Study		
Number of Episodes	**Number of Patients LUPRON DEPOT®**	**Number of Patients Danazol**
0	98	79
1	29	26
2	0	10
3	0	4

Once suppressed, menses remained suppressed through the study for all except eight LUPRON DEPOT® and 23 danazol patients.

Hormone Determinations

In each study, mean estradiol decreases were significantly greater for LUPRON DEPOT® patients compared to each of the control groups ($p<0.05$). Most estradiol values for LUPRON DEPOT® patients were at or near the post-menopausal range (<1.5 ng/dL). Progesterone decreased significantly within each treatment group in each study at every visit where hormonal determinations were made ($p<0.05$); however, between group significance was seen only in the placebo-controlled study.

Analgesic Usage

Analgesic usage for each patient was surveyed at each visit to assist the investigator in the evaluation of pain. In the placebo-controlled pain study, 98% of the patients took analgesics for pain; in the active-controlled study, 78% of the patients took analgesics for pain. The most common pain medications used were mild analgesics or non-narcotic analgesics.

2. Efficacy

The placebo- and active-controlled studies have proven that LUPRON DEPOT® is safe and effective in reducing not only the symptoms of endometriosis but also the extent of disease. It is at least as effective in this regard as is danazol and shows less of the androgenic adverse events which commonly accompany danazol treatments.

Conclusion: LUPRON DEPOT® was effective in producing a transient, therapeutic menopausal state in patients with endometriosis facilitating statistically and medically significant improvement in disease signs and symptoms, and reduction in the extent of disease.

3. Safety

Adverse Events

All 333 patients enrolled in the two studies were included in the adverse event analysis.

Adverse events reported by 95% (n=158) of the 166 LUPRON DEPOT® patients, by 93% (n=127) of the 136 danazol patients, and by 45% (n=14) of the 31 placebo patients. The most frequently reported adverse event in all treatment groups was vasodilatation (hot flashes) with 83% (n=138) of the LUPRON DEPOT® patients, 54% (n=74) of the danazol patients, and 29% (n=9) of the placebo patients reporting it.

Eighty-seven percent of those reporting vasodilatation rated it mild or moderate with 32 LUPRON DEPOT®, 9 danazol, and 1 placebo patient reporting it as severe. The mean onset of vasodilatation was 29 days after the initiation of treatment for the LUPRON DEPOT® group

and 35 days for the danazol group. Generally, vasodilatation continued intermittently throughout the study. The difference between treatment groups in the proportion of patients reporting it was statistically significant ($p<0.05$) in each study.

Other than vasodilatation, the adverse events having the highest prevalence (>10%) among LUPRON DEPOT® patients were headache (35%), vaginitis (27%), insomnia (17%), emotional lability (15%), nausea (13%), nervousness (12%), weight gain (11%), dizziness (11%), decreased libido (11%), and depression (11%). The severity of these events was predominantly mild or moderate.

The most prevalent events in the danazol group were vasodilatation (54%), weight gain (27%), headache (26%), acne (20%), vaginitis (19%), edema (18%), nervousness (16%), nausea (13%), depression (12%), and emotional lability (11%). In the placebo group, the most prevalent event was vasodilatation (29%). The only other adverse events to occur in more than 5% of the placebo patients were headache (10%) and insomnia (7%).

In the placebo-controlled study, the difference in prevalence between the treatment groups was significant for vasodilatation and headache. In the active-controlled study, the LUPRON DEPOT® group had significantly higher prevalence of vasodilatation, pelvic pain, insomnia, and decreased libido than did the danazol patients. Danazol patients had significantly more edema and weight gain than did the LUPRON DEPOT® patients.

Many of the adverse events occurring in more than 5% of the LUPRON DEPOT® group had onset within the first two months of treatment. Forty-nine percent (n=262) of the 530 total initial occurrences of these events had onset within the first month of treatment and 72% within the first two months.

Most of the events occurring in at least 5% of the LUPRON DEPOT® group are symptoms that occur frequently in the post-menopausal population and are generally considered to be related to the hypoestrogenic state. Other symptoms such as weight gain, acne, and hypertonia occurred with much greater frequency in the active-controlled study where LUPRON DEPOT® was compared with danazol which is known to have androgenic effects.

Other symptoms, such as pain, have no apparent explanation. Most of the adverse events reported in the studies were considered by the investigator to be probably or possibly related to treatment.

Eight patients in the LUPRON DEPOT® group terminated prematurely from the studies due to adverse events. Overall, 19 patients (8 LUPRON DEPOT®, 10 danazol, and 1 placebo) prematurely terminated the studies due to adverse events.

The length of treatment received by these patients who terminated prematurely is summarized in **Table 10**.

Table 10 Treatment Length for Patients Who Prematurely Terminated in the Placebo- and Active-Controlled Studies			
Treatment (months)	**LUPRON DEPOT®**	**Danazol**	**Placebo**
1	1	5	0
2	3	1	1
3	0	2	0
4	3	0	0
5	0	1	0
6	1	1	0
Total	8	10	1

Bone Mineral Density

Bone density measurements were performed pre-study and at the end of the treatment period.

An analysis of percent changes in bone mineral density from baseline to the end of treatment for the combined LUPRON DEPOT® patients from both studies shows that one hundred fifteen patients had a mean decrease of 4.2% in bone mineral density. This decrease was significant within the LUPRON DEPOT® treatment group ($p<0.001$) and is consistent with data published on the effect of other GnRH agonists on bone mineral density.

When LUPRON DEPOT® was compared to danazol, moderate mean decreases were observed in the LUPRON DEPOT® group, and slight to moderate mean increases were observed in the danazol group. Treatment with LUPRON DEPOT® produces a hypoestrogenic environment which can result in increased bone turnover, and treatment with danazol can result in androgenic effects such as increased bone mass.

Overall, changes in safety parameters as a result of LUPRON DEPOT® administration did not exceed expected limits. Adverse events experienced by patients in the studies were primarily those symptoms characteristically experienced in the post-menopausal population and reflect the hormonal suppression which forms the basis of the therapeutic effect.

Conclusion: The primary consequence of treatment with LUPRON DEPOT® is the predictable, yet substantially reversible, bone turnover consequent to hypoestrogenism. After six months of treatment, the risks attending this decrease in bone mineral density are minimal in women who began treatment with normal bone density.

LUPRON DEPOT® 11.25 mg (3-Month SR)

In a pharmacokinetic/pharmacodynamic study of healthy female subjects (N=20), the onset of estradiol suppression was observed for individual subjects between day 4 and week 4 after dosing. By the third week following the injection, the mean estradiol concentration (8 pg/mL)

reached the menopausal range. Throughout the remainder of the dosing period, mean serum estradiol levels ranged from the menopausal to the early follicular range.

Serum estradiol was suppressed to ≤ 20 pg/mL in all subjects within four weeks and remained suppressed (≤ 40 pg/mL) in 80% of subjects until the end of the 12-week dosing interval, at which time two of these subjects had a value between 40 and 50 pg/mL. Four additional subjects had at least two consecutive elevations of estradiol (range 43-240 pg/mL) levels during the 12-week dosing interval, but there was no indication of luteal function for any of the subjects during this period.

LUPRON DEPOT® 11.25 mg (3-Month SR) induced amenorrhea in 85% (N=17) of subjects during the initial month and 100% during the second month following the injection. All subjects remained amenorrheic through the remainder of the 12-week dosing interval. Episodes of light bleeding and spotting were reported by a majority of subjects during the first month after the injection and in a few subjects at a later time-points. Menses resumed on average 12 weeks (range 2.9 to 20.4 weeks) following the end of the 12-week dosing interval.

LUPRON DEPOT® 11.25 mg (3-Month SR) produced similar pharmacodynamic effects in terms of hormonal and menstrual suppression to those achieved with monthly injections of LUPRON DEPOT® 3.75 mg (1-Month SR) during the controlled clinical trials for the management of endometriosis. Similar clinical outcome to that with LUPRON DEPOT® 3.75 mg (1-Month SR) administered monthly is predicted with LUPRON DEPOT® 11.25 mg (3-Month SR) administered every 3 months.

DETAILED PHARMACOLOGY

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

Animal Pharmacology

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 had demonstrated a reduction in gonadotropins and sex steroids.

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

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

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

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 pharmacokinetics 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.) route in healthy male volunteers. Mean leuprolide plasma level curves were characteristic for each route. Mean levels during earlier sampling times were generally higher after the intravenous regimen, while levels during the later sampling times were generally higher after the subcutaneous regimen. The absolute bioavailability based on the ratio of the mean area under the curve (AUC) for S.C./I.V. was 0.94 with a range of 0.70 to 1.24.

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

LUPRON DEPOT®

The pharmacokinetic profile of LUPRON DEPOT® has been characterized in an open, single-dose study in 10 orchierectomized 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.

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 LD_{50} is greater than 100 mg/kg/day in rats and mice.

LUPRON DEPOT®

Mice and rats were given leuprolide acetate for depot suspension with different routes of administration: oral, intraperitoneal and subcutaneous (doses of 5 g/kg) and intramuscular (doses of 2 g/kg). No death occurred. The LD_{50} 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 same the degree as the placebo-microcapsule, but these are less than those of the positive control (0.75% acetic acid), and their severity were not potentiated by 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 include inflammatory lesions at the injection sites, and atrophic changes of the primary and accessory sex glands. The injection site change, seen in both control and test groups, was induced by the microcapsule, not leuprolide, and was reversible.

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 ranging from 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 DEPOT®
leuprolide acetate for depot suspension

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

ABOUT THIS MEDICATION

What the medication is used for:
Both LUPRON DEPOT® (leuprolide acetate for depot suspension) 3.75 mg (1-Month SR) and 11.25 mg (3-Month SR) are indicated in the treatment of endometriosis, including pain relief and reduction of endometriosis lesions, for a period of six months.

What it does:
Endometriosis is a gynecologic disorder wherein endometrial tissue is found to be established in sites outside the endometrial cavity. LUPRON DEPOT® achieves a menopausal state by inhibiting the output of gonadotropins (FSH and LH) from the pituitary gland and decreasing estrogen levels.

When it should not be used:
LUPRON DEPOT® should not be used if:

- You are allergic to leuprolide acetate, any similar nonapeptides (e.g., histrelin, desorelin), or any of the nonmedicinal ingredients in LUPRON DEPOT®.
- You are pregnant or planning to get pregnant.
  Note: You should use non-hormonal methods of contraception while receiving treatment with LUPRON DEPOT®.
- You have abnormal vaginal bleeding of unknown cause.
- You are breast-feeding.

Your doctor is in the best position to decide whether or not any conditions are present that pose a risk to you. Carefully follow the instructions given by your doctor, and always contact him/her if you experience any difficulties.

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
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® 3.75 mg (1-Month SR) is available in a prefilled dual-chamber syringe that contains 3.75 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® 11.25 mg (3-Month SR) is available in a prefilled dual-chamber syringe that contains 11.25 mg of leuprolide acetate as sustained-release microspheres and must be reconstituted with a special diluent prior to intramuscular administration once every three 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 suspect that you are pregnant.
- You are planning to become pregnant.
- You take hormonal methods of contraception
- You are breast-feeding
- 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.

Signs and symptoms of endometriosis can worsen at the beginning of therapy with LUPRON DEPOT®.

LUPRON DEPOT® is not recommended for use in children younger than 18 years of age or women over 65 years of age for the treatment of endometriosis.

LUPRON DEPOT® is not recommended for use beyond 6 months.

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® 3.75 mg (1-Month SR), report to your doctor **once every month** for your injection. If you are taking LUPRON DEPOT® 11.25 mg (3-Month SR), report to your doctor **once every three 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

After taking LUPRON DEPOT®, your estrogen levels will initially increase and then decrease over several weeks.

The following side effects are commonly experienced after the first few weeks and occur due to decreased levels of estrogen in the body:

- hot flashes / sweats
- gastrointestinal disturbances
- decreased libido
- muscle or joint pain
- breast tenderness/ pain and/or vaginitis (inflammation of the vagina)
- emotional changes such as feeling depressed
- headache / migraine
- nervousness / rapid heart beat

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	**Headache**	✓		
	Hot flashes / sweats		✓	
	Skin reactions including reaction at site of injection		✓	
	Vomiting / nausea	✓		

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

HOW TO STORE IT

Store between 15 and 25°C (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: cadrmp@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.

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