PRODUCT MONOGRAPH

Pr LUPRON DEPOT®

leuprolide acetate for depot suspension
pre-filled dual-chamber syringe containing sterile lyophilized microspheres
3.75 mg/syringe (1-Month slow release) and 11.25 mg/syringe (3-Month slow release)

Gonadotropin-releasing hormone analog

Date of Initial Approval:
March 11, 1999

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Submission Control No: 210906

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[Pr]LUPRON DEPOT

leuprolide acetate for depot suspension

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form/Strength	Clinically Relevant Non-medicinal Ingredients
intramuscular	pre-filled dual-chamber syringe containing sterile lyophilized microspheres / 3.75 mg (1-month slow release)	carboxymethylcellulose sodium, DL-lactic and glycolic acids copolymer, D-mannitol, gelatin, glacial acetic acid, polysorbate 80
	pre-filled dual-chamber syringe containing sterile lyophilized microspheres / 11.25 mg (3-month slow release)	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

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

Endometriosis

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

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

LUPRON DEPOT with norethindrone acetate 5 mg daily is indicated for the initial management of endometriosis and for management of recurrence of symptoms.

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.

Uterine Fibroids

LUPRON DEPOT 3.75 mg (1-Month SR) concomitantly with iron therapy is indicated for the preoperative hematologic improvement in women of reproductive age with anemia caused by uterine leiomyomata (uterine fibroids). Recommended duration of therapy with LUPRON DEPOT 3.75 mg (1-Month SR) is up to three months.

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.

Experience with LUPRON DEPOT 3.75 mg (1-Month SR) for the treatment of endometriosis or uterine fibroids has been limited to women 18 years of age and older.

CONTRAINDICATIONS

- LUPRON DEPOT (leuprolide acetate for depot suspension) is contraindicated in patients with hypersensitivity to the drug or its components or similar nonapeptides or components of the container. Isolated cases of anaphylaxis have been reported. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section 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 acetate is excreted in human milk; therefore, LUPRON DEPOT is contraindicated in patients who are breast-feeding.
- Refer to the norethindrone acetate 5 mg tablet Product Monograph for contraindications specific to norethindrone acetate.

WARNINGS AND PRECAUTIONS

General

Postmarketing reports of convulsions have been observed in patients on leuprolide acetate therapy. These included patients in the female and pediatric populations, patients with a history of seizures, epilepsy, cerebrovascular disorders, central nervous system anomalies or tumors, and in patients on concomitant medications that have been associated with convulsions such as bupropion and selective serotonin reuptake inhibitors (SSRIs). Convulsions have also been reported in patients in the absence of any of the conditions mentioned above.

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.

Refer to the norethindrone acetate 5 mg tablet Product Monograph for information on the WARNINGS and PRECAUTIONS related to norethindrone acetate.

Carcinogenesis and Mutagenesis

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

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

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

Dependence/Tolerance

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

Endocrine and Metabolism

Changes in Bone Density

Endometriosis

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. For a period of up to six months, this bone loss should not be important.

Clinical studies indicate that concurrent hormonal replacement therapy (add-back therapy) with norethindrone acetate 5 mg daily and calcium supplementation is effective in reducing the loss of bone mineral density which occurs with LUPRON DEPOT. See **CLINICAL TRIALS**, **Endometriosis**, **Study Results**, **LUPRON DEPOT 3.75 mg (1-Month SR)**, **Safety**, Bone Mineral Density in Studies M92-878 and M97-777.

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 retreatment begins to ensure that values are within normal limits. Retreatment with a six-month course of LUPRON DEPOT and norethindrone acetate 5 mg daily may be considered. Retreatment with LUPRON DEPOT alone is not recommended.

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, and concomitant treatment with norethindrone acetate 5 mg daily should be considered. Retreatment with gonadotropin-releasing hormone analogs, including LUPRON DEPOT, is not advisable in patients with major risk factors for loss in bone mineral content.

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 6 or 12 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 6 and 12 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.

Two clinical studies demonstrated that concurrent hormonal therapy with norethindrone acetate 5 mg daily and calcium supplementation significantly reduced the loss of bone mineral density that occurs with LUPRON DEPOT treatment, without compromising the efficacy of LUPRON DEPOT in relieving symptoms of endometriosis. The bone mineral density data from these two studies, evaluated after six months and one year of treatment at the lumbar spine, are presented in **Table 1**.

Table 1. Mean Percent Change from Baseline in Bone Mineral Density of Lumbar Spine in the Add-Back Studies

	LUPRON DEPOT 3.75 mg		**LUPRON DEPOT 3.75 mg + norethindrone acetate 5 mg daily**			
	Controlled Study (Study M92-878)		**Controlled Study (Study M92-878)**		**Open Label Study (Study M97-777)**	
	N	Change	N	Change	N	Change
Week 24*	41	-3.2%	42	-0.3%	115	-0.2%
Week 52**	29	-6.3%	32	-1.0%	84	-1.1%

* Includes on-treatment measurements that fell within 2 to 252 days after the first day of treatment.

** Includes on-treatment measurements >252 days after the first day of treatment.

The safety of retreatment as well as treatment beyond six 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.

Uterine Fibroids

It can be anticipated that the administration of LUPRON DEPOT 3.75 mg (1-Month SR) in women causes some reduction of BMD. However, the short treatment duration (up to three months) in women with uterine fibroids who plan to undergo uterine fibroid surgery and the fact that BMD will rise again post therapy when sex steroids return to normal levels will make an impact on clinical outcome, such as fractures, unlikely.

Hepatic/Biliary/Pancreatic

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

Renal

The pharmacokinetics of leuprolide acetate in patients with 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. Refer to the "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.

Experience with LUPRON DEPOT 3.75 mg (1-Month SR) for treatment of endometriosis or uterine fibroids has been limited to women 18 years of age and older.

Geriatrics (> 65 years of age)

LUPRON DEPOT 3.75 mg (1-Month SR) and 11.25 mg (3-Month SR) have not been studied in women over 65 years of age and are not indicated in this population.

Monitoring and Laboratory Tests

Changes in Laboratory Values During Treatment

Plasma Enzymes

Endometriosis

During clinical trials with LUPRON DEPOT alone, regular laboratory monitoring revealed that serum glutamic oxaloacetic transaminase (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.

In two other clinical trials, 6 of 191 patients receiving LUPRON DEPOT 3.75 mg (1-Month SR) plus norethindrone acetate 5 mg daily for up to 12 months developed an elevated (at least twice the upper limit of normal) serum glutamic pyruvic transaminase (SGPT) or γ-glutamyltransferase (GGT). Five of the six increases were observed beyond six months of treatment. None were associated with elevated bilirubin concentration.

Uterine Fibroids

In clinical trials with LUPRON DEPOT 3.75 mg (1-Month SR), five (3%) patients had a post-treatment transaminase value that was at least twice the baseline value and above the upper limit of the normal range. None of the laboratory increases were associated with clinical symptoms.

Hematology

Endometriosis

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.

Uterine Fibroids

In LUPRON DEPOT 3.75 mg (1-Month SR) treated patients, although there were statistically significant mean decreases in platelet counts from baseline to final visit, the last mean platelet counts were within the normal range. Decreases in total WBC count and neutrophils were observed, but were not clinically significant.

Lipids

Endometriosis

At enrolment, 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, high-density lipoprotein (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. Low-density lipoprotein (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 to 210 mg/dL) in 32% of the subjects who had demonstrated normal baseline values.

In two other clinical trials, LUPRON DEPOT 3.75 mg (1-Month SR) plus norethindrone acetate 5 mg daily were evaluated for 12 months of treatment. LUPRON DEPOT 3.75 mg (1-Month SR) was used as a control group in one study. Percent changes from baseline for serum lipids and percentages of patients with serum lipid values outside of the normal range in the two studies are summarized in **Table 2** and **Table 3,** below.

Table 2. Serum Lipids: Mean Percent Changes From Baseline Values at Treatment Week 24 in the Add-Back Studies

	Controlled Study (Study M92-878)				**Open Label Study (Study M97-777)**	
	LUPRON DEPOT 3.75 mg N=39		**LUPRON DEPOT 3.75 mg + norethindrone acetate 5 mg N=41**		**LUPRON DEPOT 3.75 mg + norethindrone acetate 5 mg N=117**	
	Baseline Value (mg/dL)	**Week 24 % Change**	**Baseline Value (mg/dL)**	**Week 24 % Change**	**Baseline Value (mg/dL)**	**Week 24 % Change**
Total Cholesterol	170.5	9.2%	179.3	0.2%	181.2	2.8%
HDL Cholesterol	52.4	7.4%	51.8	-18.8%	51.0	-14.6%
LDL Cholesterol	96.6	10.9%	101.5	14.1%	109.1	13.1%
LDL/HDL Ratio[1]	2.0	5.0%	2.1	43.4%	2.3	39.4%
Triglycerides	107.8	17.5%	130.2	9.5%	105.4	13.8%

1. Values expressed as ratio

Changes from baseline tended to be greater at Week 52. After treatment, mean serum lipid levels from patients with follow up data returned to pretreatment values.

Table 3. Percentage of Patients with Serum Lipid Values Outside of the Normal Range in the Add-Back Studies

	Controlled Study (Study M92-878)				Open Label Study (Study M97-777)	
	LUPRON DEPOT 3.75 mg N=39		LUPRON DEPOT 3.75 mg + norethindrone acetate 5 mg N=41		LUPRON DEPOT 3.75 mg + norethindrone acetate 5 mg N=117	
	Week 0	Week 24[1]	Week 0	Week 24[1]	Week 0	Week 24[1]
Total Cholesterol (>240 mg/dL)	15%	23%	15%	20%	6%	7%
HDL Cholesterol (<40 mg/dL)	15%	10%	15%	44%	15%	41%
LDL Cholesterol (>160 mg/dL)	0%	8%	5%	7%	9%	11%
LDL/HDL Ratio (>4.0)	0%	3%	2%	15%	7%	21%
Triglycerides (>200 mg/dL)	13%	13%	12%	10%	5%	9%

1. Includes all patients regardless of baseline values.

Low HDL-cholesterol (<40 mg/dL) and elevated LDL-cholesterol (>160 mg/dL) are recognized risk factors for cardiovascular disease. The long-term significance of the observed treatment-related changes in serum lipids in women with endometriosis is unknown. Therefore, assessment of cardiovascular risk factors should be considered prior to initiation of concurrent treatment with LUPRON DEPOT and norethindrone acetate.

Uterine Fibroids

In patients receiving LUPRON DEPOT 3.75 mg (1-Month SR), mean changes in cholesterol (+11 mg/dL to +29 mg/dL), LDL cholesterol (+8 mg/dL to +22 mg/dL), HDL cholesterol (0 to +6 mg/dL), and the LDL/HDL ratio (-0.1 to +0.5) were observed across studies. In the one study in which triglycerides were determined, the mean increase from baseline was 32 mg/dL.

Other Changes

Endometriosis

In comparative studies, the following changes were seen in approximately 5 to 8% of patients. LUPRON DEPOT was associated with elevations of lactate dehydrogenase (LDH) and phosphorus, and decreases in white blood cell (WBC) counts, and danazol therapy was associated with increases in hematocrit, platelet count, and LDH.

Uterine Fibroids

Slight to moderate mean increases were noted for glucose, uric acid, BUN, creatinine, total protein, albumin, bilirubin, alkaline phosphatase, LDH, calcium, and phosphorus. None of these increases were clinically significant.

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**.

Refer to the norethindrone acetate 5 mg tablet Product Monograph for information on the adverse reactions related to norethindrone acetate.

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

Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

Endometriosis

LUPRON DEPOT 3.75 mg (1-Month SR)

In two controlled clinical trials treating endometriosis, one comparing LUPRON DEPOT (leuprolide acetate for depot suspension) 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 (**Table 4**).

Table 4. 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

	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)
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)

	LUPRON DEPOT 3.75 mg (1-Month SR) N=166 (%)	Danazol 800 mg/day N=136 (%)	Placebo N=31 (%)
	Number of Reports (%)		
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.

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 5**.

Table 5. Adverse Events Reported by 20 Healthy Female Subjects Receiving LUPRON DEPOT 11.25 mg (3-Month SR) in a Pharmacokinetic Trial

	LUPRON DEPOT 11.25 mg (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)

	LUPRON DEPOT 11.25 mg (3-Month SR) N=20 (%)
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

Table 6 lists the potentially drug-related adverse events observed in at least 5% of patients in any treatment group, during the first six months of treatment in the add-back clinical studies, in which patients were treated with monthly LUPRON DEPOT 3.75 mg (1-Month SR) with or without norethindrone acetate co-treatment.

Table 6. Treatment-Related Adverse Events Occurring in ≥ 5% of Patients

	Controlled Study (Study M92-878)		Open Label (Study M97-777)
	LUPRON DEPOT 3.75 mg N=51 (%)	LUPRON DEPOT 3.75 mg + norethindrone acetate 5 mg N=55 (%)	LUPRON DEPOT 3.75 mg + norethindrone acetate 5 mg N=136 (%)
Any Adverse Event	50 (98)	53 (96)	126 (93)
Body as a Whole			
Asthenia	9 (18)	10 (18)	15 (11)
Headache/migraine	33 (65)	28 (51)	63 (46)
Injection site reaction	1 (2)	5 (9)	4 (3)
Pain	12 (24)	16 (29)	29 (21)
Cardiovascular System			
Hot flashes/sweats	50 (98)	48 (87)	78 (57)

	Controlled Study (Study M92-878)		Open Label (Study M97-777)
	LUPRON DEPOT 3.75 mg N=51 (%)	**LUPRON DEPOT 3.75 mg + norethindrone acetate 5 mg N=55 (%)**	**LUPRON DEPOT 3.75 mg + norethindrone acetate 5 mg N=136 (%)**
Digestive System			
Altered bowel function	7 (14)	8 (15)	14 (10)
Changes in appetite	2 (4)	0 (0)	8 (6)
GI disturbance	2 (4)	4 (7)	6 (4)
Nausea/vomiting	13 (25)	16 (29)	17 (13)
Metabolic and Nutritional Disorders			
Edema	0 (0)	5 (9)	9 (7)
Weight changes	6 (12)	7 (13)	6 (4)
Nervous System			
Anxiety	3 (6)	0 (0)	11 (8)
Depression/emotional lability	16 (31)	15 (27)	46 (34)
Dizziness/vertigo	8 (16)	6 (11)	10 (7)
Insomnia/sleep disorder	16 (31)	7 (13)	20 (15)
Libido changes	5 (10)	2 (4)	10 (7)
Memory disorder	3 (6)	1 (2)	6 (4)
Nervousness	4 (8)	2 (4)	15 (11)
Neuromuscular disorder	1 (2)	5 (9)	4 (3)
Skin and Appendages			
Alopecia	0 (0)	5 (9)	4 (3)
Androgen-like effects	2 (4)	3 (5)	24 (18)
Skin/mucous membrane reaction	2 (4)	5 (9)	15 (11)
Urogenital System			
Breast changes/pain/tenderness	3 (6)	7 (13)	11 (8)
Menstrual disorders	1 (2)	0 (0)	7 (5)
Vaginitis	10 (20)	8 (15)	11 (8)

In the controlled clinical trial, 50 of 51 (98%) patients in the LUPRON DEPOT 3.75 mg group and 48 of 55 (87%) patients in the LUPRON DEPOT 3.75 mg + norethindrone acetate 5 mg group reported experiencing hot flashes on one or more occasions during treatment. The median number of days on which hot flashes were reported during treatment was 25 and 5 ($P<0.05$) in the LUPRON DEPOT 3.75 mg and LUPRON DEPOT 3.75 mg + norethindrone acetate 5 mg treatment groups, respectively. The median maximum number of hot flashes in a day during treatment was 5 and 1 ($P<0.05$) in the LUPRON DEPOT 3.75 mg and LUPRON DEPOT 3.75 mg + norethindrone acetate 5 mg treatment groups, respectively.

Uterine Fibroids

Table 7 lists the adverse drug reactions observed in at least 5% of the LUPRON DEPOT treated patients in uterine fibroids clinical trials.

Table 7. Treatment-Related Adverse Events Occurring in ≥ 5% of Patients treated with LUPRON DEPOT for Uterine Fibroids Studies M86-034, M86-049, M86-062, and M90-411

System Organ Class (SOC)	N (%)	
	LUPRON DEPOT N = 167	**Placebo N = 163**
Infections and Infestations		
Vaginal infection	18 (10.8)	2 (1.2)
Psychiatric Disorders		
Depression	13 (7.8)	4 (2.5)
Affect lability	10 (6.0)	4 (2.5)
Nervousness	8 (4.8)	1 (0.6)
Insomnia	8 (4.8)	1 (0.6)
Nervous System Disorders		
Headache	44 (26.3)	31 (19.0)
Vascular Disorders		
Vasodilatation	122 (73.1)	28 (17.2)
Musculoskeletal and Connective Tissue Disorders		
Arthralgia	11 (6.6)	6 (3.7)
General Disorders and Administration site Conditions		
Asthenia	13 (7.8)	9 (5.5)
Oedema peripheral	8 (4.8)	2 (1.2)

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

LUPRON DEPOT 3.75 mg (1-Month SR)

The following were reported in less than 5% of patients treated with LUPRON DEPOT in endometriosis and uterine fibroids studies:

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

* Physiologic effect of decreased estrogen.

Abnormal Hematologic and Clinical Chemistry Findings

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

Post-Market Adverse Drug Reactions

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

Cases of serious venous and arterial thromboembolism have been reported, including deep vein thrombosis, pulmonary embolism, myocardial infarction, stroke, and transient ischemic attack. Although a temporal relationship was reported in some cases, most cases were confounded by risk factors or concomitant medication use. It is unknown if there is a causal association between the use of GnRH agonists and these events.

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

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 postmarketing surveillance:

Cardiovascular System:	hypotension
Central/Peripheral Nervous System:	convulsion, peripheral neuropathy and spinal fracture/paralysis
Hemic and Lymphatic Systems:	decreased WBC
Hepatobiliary Disorders:	hepatic dysfunction, serious liver injury
Integumentary System:	photosensitivity reactions, rash and urticaria
Miscellaneous:	hematoma, induration, inflammation, injection site reactions including pain, and sterile abscess
Musculoskeletal System:	tenosynovitis-like symptoms
Respiratory System:	dyspnea, interstitial lung disease, pulmonary fibrosis
Urogenital System:	menstrual disorders

Refer to the “Prostatic Cancer” and “Central Precocious Puberty” LUPRON and LUPRON DEPOT Product Monographs for other reported events.

DRUG INTERACTIONS

Overview

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

Refer to the norethindrone acetate 5 mg tablet Product Monograph for information on the drug interactions specific to norethindrone acetate.

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 Test Interactions

Administration of LUPRON DEPOT (leuprolide acetate for depot suspension) 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 (leuprolide acetate for depot suspension) must be administered under the supervision of a health professional.
- LUPRON DEPOT 3.75 and 11.25 mg administered intramuscularly is designed to provide continuous sustained release of leuprolide for one and three 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 Must Be Administered under the Supervision of a Health Professional.

Endometriosis

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 **DOSAGE AND ADMINISTRATION**, **Administration** and **CONSUMER INFORMATION**. The recommended duration of the initial treatment with LUPRON DEPOT 3.75 mg alone or in combination with norethindrone acetate 5 mg daily is 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 **DOSAGE AND ADMINISTRATION**, **Administration** and **CONSUMER INFORMATION**. The recommended duration of the initial treatment with LUPRON DEPOT 11.25 mg alone or in combination with norethindrone acetate 5 mg daily is six months.

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

Retreatment with LUPRON DEPOT alone cannot be recommended since safety data for retreatment are not available. If the symptoms of endometriosis recur after the course of initial 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, combination with norethindrone acetate 5 mg daily may be considered for an additional six-month course of treatment. Retreatment beyond this additional six-month course cannot be recommended. It is recommended that bone density be assessed before retreatment begins to ensure that values are within normal limits. If norethindrone acetate is contraindicated for the individual patient, then retreatment is not recommended.

An assessment of cardiovascular risk and management of risk factors such as cigarette smoking is recommended before beginning treatment with LUPRON DEPOT and LUPRON DEPOT with norethindrone acetate.

Uterine Fibroids

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** with concomitant daily oral iron therapy for the preoperative hematologic improvement of patients with leiomyomas and iron-deficiency anemia caused by excessive uterine bleeding. The recommended duration of the treatment with LUPRON DEPOT 3.75 mg is up to three months.

Daily oral iron supplementation should be taken. Instruct the patient on the daily dose.

The iron supplement can be chosen in accordance with what is locally available. Refer to the Iron Natural and Non-prescription Health Products Directorate (NNHPD) monograph and/or product packaging labels for information on iron dosage and administration.

Missed Dose

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

Administration

Reconstitution

Parenteral Products

The lyophilized microspheres contained in the front chamber of the pre-filled 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** (six to eight seconds) the plunger until the first stopper is at the blue line in the middle of the barrel.

5. Keep the syringe upright. Gently shake the syringe to thoroughly mix the microspheres (powder) to form a uniform suspension. The suspension will appear milky.

6. If the microspheres adhere to the stopper or caking/clumping is present, tap the syringe against your finger to disperse. DO NOT USE if any of the powder has not gone into suspension.

7. Keep the syringe upright. With the opposite hand, remove the needle cap without twisting and advance the plunger to expel the air from the syringe.

8. At the time of reconstitution, inject the entire contents of the syringe intramuscularly. The suspension settles very quickly following reconstitution; therefore, LUPRON DEPOT should be mixed and used immediately.

   Note: Aspirated blood would be visible just below the luer lock connection if a blood vessel is accidentally penetrated. If present, blood can be seen through the transparent LuproLoc® safety device. If blood is present remove the needle immediately. Do not inject the medication.

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

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

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

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

In rats, subcutaneous administration of leuprolide acetate as a single dose of approximately 133 times the recommended human dose, expressed on a per body weight basis, resulted in dyspnea, decreased activity, and excessive scratching. 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.

In cases of overdosage, the patients should be monitored closely and management should be symptomatic and supportive.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Leuprolide is a synthetic nonapeptide analog of naturally-occurring gonadotropin-releasing hormone (GnRH or LHRH). The analog possesses greater potency than the natural hormone. When administered as indicated, leuprolide acts as a potent inhibitor of gonadotropin production. It is chemically unrelated to steroids.

Unlike steroid hormones, leuprolide exerts specific action on the pituitary gonadotrophs and the human reproductive tract.

This specificity reduces the likelihood of secondary adverse effects such as gynecomastia, thromboembolism, edema, liver and gallbladder involvement.

Pharmacodynamics

General

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

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

In humans, subcutaneous administration of single daily doses of leuprolide acetate results in an initial increase in circulating levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), leading to a transient increase in the levels of the gonadal steroids (testosterone and dihydrotestosterone in males and estrone and estradiol in premenopausal females). However, continuous administration results in decreased levels of LH and FSH in all patients. In males, testosterone is reduced to castrate levels. In premenopausal females, estrogens are reduced to postmenopausal 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 (leuprolide acetate for depot suspension) 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) intramuscularly, 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 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 three months.

Pharmacokinetics

Intramuscular injections of LUPRON DEPOT 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 healthy females, a mean peak plasma leuprolide concentration of 36.3 ng/mL was observed at four 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 three 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 five prostate cancer patients reached mean maximum concentration two to six hours after dosing and were approximately 6% of the peak parent drug concentration. One week after dosing, mean plasma M-I concentrations were approximately 20% of leuprolide concentrations.

Excretion

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

Special Populations and Conditions

Pediatrics

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

Geriatrics

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

Hepatic Insufficiency

The pharmacokinetics of leuprolide acetate in patients with hepatic impairment have not been determined.

Renal Insufficiency

The pharmacokinetics of leuprolide acetate in patients with renal impairment have not been determined.

STORAGE AND STABILITY

Store LUPRON DEPOT (leuprolide acetate for depot suspension) between 15 and 25°C. Protect from freezing.

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

SPECIAL HANDLING INSTRUCTIONS

It is very important to activate the LuproLoc safety device immediately after injection. This is done by pushing the arrow forward with the thumb or finger until the device is fully extended and a CLICK is heard or felt. See **DOSAGE AND ADMINISTRATION**, **Administration**, **Reconstitution**.

DOSAGE FORMS, COMPOSITION AND PACKAGING

LUPRON DEPOT (leuprolide acetate for depot suspension) is available in two strengths: 3.75 mg (1-Month SR) and 11.25 mg (3-Month SR).

LUPRON DEPOT 3.75 mg (1-Month SR) and 11.25 mg (3-Month SR) are supplied in single dose kits containing one pre-filled dual-chamber syringe with 23 G needle, **Consumer Information** leaflet and a **Special Instructions for Use** leaflet.

Listing of Non-Medicinal Ingredients

LUPRON DEPOT 3.75 mg (1-Month SR)

The front chamber of the LUPRON DEPOT 3.75 mg (1-Month SR) pre-filled dual-chamber syringe contains 3.75 mg of leuprolide acetate with the following non-medicinal ingredients: DL-lactic and glycolic acids copolymer, D-mannitol and gelatin.

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

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

During the manufacturing process of LUPRON DEPOT 3.75 mg (1-Month SR), acetic acid is lost, leaving the leuprolide peptide.

LUPRON DEPOT 11.25 mg (3-Month SR)

The front chamber of the LUPRON DEPOT 11.25 mg (3-Month SR) pre-filled dual-chamber syringe contains 11.25 mg of leuprolide acetate with the following non-medicinal ingredients: D-mannitol and polylactic acid.

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

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

During the manufacturing process of LUPRON DEPOT 11.25 mg (3-Month SR), acetic acid is lost, leaving the leuprolide peptide.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Proper name: leuprolide acetate

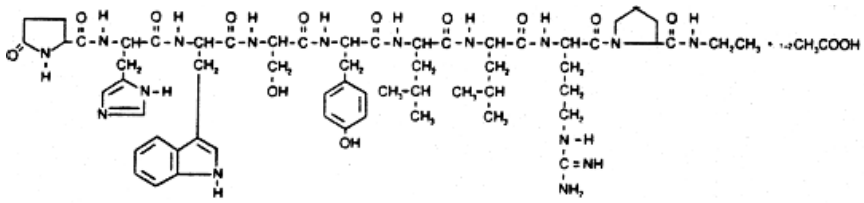
Chemical name: 5-oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-Leucyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide acetate.

or: des-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

Endometriosis

Study Demographics and Trial Design

LUPRON DEPOT 3.75 mg (1-Month SR)

The first two studies conducted were Phase III, randomized, double-blind, multi-centre studies of the effects of LUPRON DEPOT (leuprolide acetate for depot suspension) 3.75 mg (1-Month SR) in endometriosis. Study M86-031 was placebo-controlled, while Study M86-039 used danazol as an active control. The studies were conducted at a total of 23 investigative sites, with 11 investigators participating in both studies. Study M86-031 had a planned sample size of 60 (30 LUPRON DEPOT, 30 placebo), and Study M86-039 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 Study M86-031 and 270 patients entered Study M86-039.

The number of patients enrolled into each study and the number of evaluable (for efficacy) is summarized in **Table 8**.

Table 8. 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 (Studies M86-031 and M86-039)

Study	Number of Investigators	Number of Patients Entered			Number 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 Studies M86-031 and M86-039. Of the 166 patients, 153 were treated for the full six-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 9**.

Table 9. Summary of Patient Demographics for Clinical Trials in Endometriosis

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	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 to 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
M92-878	Phase III, 4-arm, parallel, randomized, double-blind, multicenter study	3.75 mg LUPRON DEPOT alone vs. LUPRON DEPOT plus norethindrone acetate 5 mg 52 weeks	106	28.6 (18 to 43)	Females only
M97-777	Phase IV, open-label, single-arm, multicenter extension of Study III	LUPRON DEPOT plus norethindrone acetate 5 mg 52 weeks	136	28.8 (17 to 41)	Females only

Definitions: b.i.d. = twice daily; n = number.

Two other clinical studies were conducted with LUPRON DEPOT 3.75 mg (1-Month SR) in patients with endometriosis. Study M92-878 was a double-blind, randomized, parallel-group, multi-center study, conducted at 26 investigative sites, with planned sample sizes of 200 (four groups of 50 patients; LUPRON DEPOT alone or in combination with estrogen and/or the progestin norethindrone acetate as add-back regimens). Study M97-777 was an open-label, single-arm, multi-center extension of Study M92-878, conducted at 24 investigative sites, with a planned sample size of 135. Both studies had a 52-week Treatment Period with either 24 months (Study M92-878) or 12 months (Study M97-777) of follow-up after the completion of treatment.

The primary efficacy objective of studies M92-878 and M97-777 was to compare the efficacy of continuous, combined administration of oral norethindrone acetate 5 mg and LUPRON DEPOT to the efficacy of administration of LUPRON DEPOT alone, in the management of endometriosis.

A total of 242 patients were enrolled in studies M92-878 and M97-777 to receive either LUPRON DEPOT alone (51 patients) or in combination with norethindrone acetate 5 mg (191 patients). The number of patients enrolled into each study and the number of evaluable (for efficacy) is summarized in **Table 10**.

Table 10. Number of Patients Enrolled in Studies M92-878 and M97-777

Study	Number of Investigators	Number of Patients Randomized		Number of Patients Completing Treatment	
		LUPRON DEPOT 3.75 mg	LUPRON DEPOT 3.75 mg + norethindrone acetate 5 mg	LUPRON DEPOT 3.75 mg	LUPRON DEPOT 3.75 mg + norethindrone acetate 5 mg
M92-878	26	51	55	32	31
M97-777	24	--	136	--	82
Total	44*	51	191	32	113

* Six investigators entered patients in both studies.

Of the 51 patients randomized to receive LUPRON DEPOT only, 32 completed the 52-week study period while 19 terminated prematurely. Of the 191 patients who received LUPRON DEPOT with norethindrone acetate, 113 completed the 52-week study period and 78 terminated prematurely.

A summary of the trial design and patient demographics is shown in **Table 9**.

Study Results

LUPRON DEPOT 3.75 mg (1-Month SR)

The results of the studies were as follows:

Clinical Evaluation in Studies M86-031 and M86-039

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 11** summarizes changes in clinical evaluation of dysmenorrhea at the Final Visit against baseline for patients included in the efficacy analysis.

Table 11. 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 12** summarizes the changes in clinical evaluation of pelvic pain at the Final Visit compared to baseline for patients included in the efficacy analysis.

Table 12. 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 13** summarizes the changes in clinical evaluation of dyspareunia at the Final Visit compared to baseline for patients included in the efficacy evaluation.

Table 13. 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 14**.

Table 14. 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 15**.

Table 15. 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 postmenopausal 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.

Clinical Evaluation in Studies M92-878 and M97-777

Clinical assessment of pain parameters (dysmenorrhea, pelvic pain, deep dyspareunia, pelvic tenderness, and pelvic induration) was evaluated on the four-point Biberoglu and Berhman scale completed by the study staff. Return to baseline pain levels during follow-up was also assessed using this scale. Improvement in pain was also evaluated via patient evaluations of

dysmenorrhea, pelvic pain and deep dyspareunia using analog scales (0 = none; 10 = intolerable). Pain evaluations were collected at each visit during treatment and the first year of follow-up. Improvement in ovarian enlargement was assessed by comparing ovarian size determined at each visit during treatment and the first year of the Follow-Up period to baseline measurements. Estradiol level was assessed at each Treatment period visit beginning with Day 0 (baseline) and once at the first Follow-Up period visit after resumption of menses. Menses frequency and duration were collected on patient diaries. Suppression of estradiol (E_2) and menses are used as efficacy markers.

Pain Parameters

Statistically significant mean decreases from baseline in all pain scores were seen in patients taking either LUPRON DEPOT alone or in combination with norethindrone acetate 5 mg ($p < 0.001$). The improvements were generally statistically significant by Week 4 and were maintained throughout the 52-week Treatment Period. **Table** 16 summarizes the prevalence in clinical pain variables at the Final Visits against baseline for patients included in the efficacy analysis.

Table 16. Prevalence of Clinical Pain Variables at Baseline and the Final Treatment Visit (Integrated Results from Study M92-878 and Study M97-777)

Variable	Treatment Group	Baseline n/N (%)	Final Treatment Visit n/N (%)
Dysmenorrhea	LUPRON DEPOT	51/51 (100)	2/50 (4)
	LUPRON DEPOT + norethindrone acetate	190/191 (99)	14/188 (7)
Pelvic Pain	LUPRON DEPOT	51/51 (100)	33/50 (66)
	LUPRON DEPOT + norethindrone acetate	188/191 (98)	115/188 (61)
Deep Dyspareunia	LUPRON DEPOT	35/42 (83)	17/46 (37)
	LUPRON DEPOT + norethindrone acetate	129/145 (89)	78/153 (51)
Pelvic Tenderness	LUPRON DEPOT	48/51 (94)	17/50 (34)
	LUPRON DEPOT + norethindrone acetate	184/190 (97)	70/187 (37)
Pelvic Induration	LUPRON DEPOT	26/51 (51)	6/50 (12)
	LUPRON DEPOT + norethindrone acetate	127/190 (67)	37/187 (20)

Serum Estradiol Levels

Statistically significant within-group mean decreases from baseline were noted for both groups at all visits starting at Week 4 ($p < 0.001$) and were generally constant throughout the Treatment Period. For the majority of visits, the mean decrease for the LUPRON DEPOT plus norethindrone acetate group was statistically significantly greater than that of the LUPRON DEPOT-Only group ($p < 0.01$). The mean of serum estradiol levels averaged over the Treatment Period was within or near the menopausal range (< 15 pg/mL) for both treatment groups: 8.40 pg/mL for Integrated LUPRON DEPOT plus norethindrone acetate and 15.59 pg/mL for LUPRON DEPOT-Only.

Menstrual Suppression

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). A summary of menstrual data for patients who were in the Treatment Period for at least 60 days is presented in **Table 17**.

Table 17. Menses Suppression During the Treatment Period

Parameter	LUPRON DEPOT	LUPRON DEPOT + norethindrone acetate 5 mg
Suppression n/N (%)	47/47 (100)	174/177 (98)*
Suppression Maintained to End of Treatment n/N (%)	41/47 (87)	132/174 (76)*

* Values are integrated from Studies M92-878 and M97-777.

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.

Based on results from studies M92-878 and M97-777, norethindrone acetate 5 mg daily is an effective add-back regimen combined with LUPRON DEPOT and does not have any relevant negative impact on endometriosis symptoms when compared with LUPRON DEPOT alone. Duration of initial treatment or retreatment should be limited to a period of six months.

Conclusion

LUPRON DEPOT, alone or in combination with norethindrone acetate 5 mg add-back, 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.

Safety

Adverse Events in Studies M86-031 and M86-039

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 postmenopausal 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 18**.

Table 18. 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

Adverse Events in Studies M92-878 and M97-777

Almost 100% of patients (190 of 191) in the Integrated LUPRON DEPOT plus norethindrone acetate group reported one or more adverse events during the Treatment Period. The most prevalent adverse events were vasodilatation (hot flashes) and headache, which were reported by 68% and 60% of patients, respectively.

When the Integrated LUPRON DEPOT plus norethindrone acetate group was compared with the LUPRON DEPOT-Only group from Study M92-878, statistically significant differences ($p < 0.05$) were noted between the groups in the prevalence of hot flashes and sweating. The prevalence of hot flashes was greater for the LUPRON DEPOT-Only group, while the prevalence of sweating was greater for the LUPRON DEPOT plus norethindrone acetate group. Potentially study drug-related adverse events for which there was a difference between the

Integrated LUPRON DEPOT plus norethindrone acetate and LUPRON DEPOT-Only groups of 10% or more are summarized in **Table 19**.

Table 19. Adverse Events Attributed to Study Drug with ≥ 10% Difference Between Groups in Prevalence During the Treatment Period

	Study M92-878 **LUPRON DEPOT** **N=51**		**Integrated Studies** **M92-878 and M97-777** **LUPRON DEPOT + norethindrone acetate 5 mg** **N=191**	
COSTART Term	**N**	**%**	**N**	**%**
Hot Flashes/ Sweats	50	98	136	71*
Headache/Migraine	34	67	98	51
Nausea/Vomiting	15	29	37	19
Edema	0	0	21	11+
Insomnia/Sleep Disorders	16	31	38	20
Androgen-Like Effects	2	4	29	15+
Vaginitis	12	24	24	13

* Statistically significantly less than the LUPRON DEPOT-Only group (p <0.05).

+ Statistically significantly greater than the LUPRON DEPOT-Only group (p <0.05).

There is minimal overall risk to treatment with the combination of LUPRON DEPOT and norethindrone acetate. The adverse event pattern characteristically seen in patients treated with LUPRON DEPOT or other GnRH agonists and norethindrone acetate largely reflects the menopausal symptom profile seen with GnRH agonist treatment. Although much reduced in incidence compared to the administration of LUPRON DEPOT alone, hot flashes remains the most prevalent of these events.

Bone Mineral Density in Studies M86-031 and M86-039

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.

Bone Mineral Density in Studies M92-878 and M97-777

The mean changes from baseline in BMD during the Treatment Period experienced by the Integrated LUPRON DEPOT plus norethindrone acetate group were compared to those of the Study M92-878 LUPRON DEPOT-Only group. There was no statistically significant difference in mean BMD between the two groups at baseline. Statistically significant ($p < 0.001$) mean decreases in BMD from baseline were noted for the Integrated LUPRON DEPOT plus norethindrone acetate group at Week 52, and at all evaluations for the LUPRON DEPOT-Only group.

Comparisons of the mean percent changes from baseline between the two groups showed that the LUPRON DEPOT plus norethindrone acetate group experienced a statistically significantly ($p < 0.001$) smaller decrease in BMD than the LUPRON DEPOT-Only group at all evaluations. The results of the analyses of percent change in BMD from baseline to the Week 24 and Week 52 visits for the comparison of the Integrated LUPRON DEPOT plus norethindrone acetate (with calcium supplementation) and Study M92-878 LUPRON DEPOT-Only treatment groups are presented in **Table 20**.

Table 20. Mean Percent Change from Baseline in Lumbar Spine Bone Mineral Density

Treatment Group	N	Week 24	N	Week 52
LUPRON DEPOT	41	-3.2%*	29	-6.3%*
LUPRON DEPOT + norethindrone acetate 5 mg daily	157	-0.2%+	116	-1.0%*+

* Statistically significant within-group change ($p < 0.001$).

+ Statistically significant difference between groups ($p < 0.001$), combined and in each study separately.

Overall, changes in safety parameters as a result of LUPRON DEPOT administration did not exceed expected limits. Adverse events experienced by patients in the four studies were primarily those symptoms characteristically experienced in the postmenopausal population and reflect the hormonal suppression which forms the basis of the therapeutic effect. In Studies M92-878 and M97-777, bone mineral density was minimally decreased from baseline after 12 months of treatment with LUPRON DEPOT when used in conjunction with norethindrone acetate and calcium supplementation. This decrease was considerably less than that seen with LUPRON DEPOT alone. The concurrent use of LUPRON DEPOT with norethindrone acetate 5 mg daily is effective in reducing loss of bone mineral density that occurs with LUPRON DEPOT alone.

Hot Flashes in Studies M92-878 and M97-777

The incidence of the menopausal symptoms of vasodilatation (hot flashes) and sweating was significantly less than that seen in patients who received treatment with leuprolide acetate alone.

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. Concomitant administration of norethindrone acetate 5 mg in combination with LUPRON DEPOT resulted in a decreased prevalence and severity of adverse events attributable to the chronic hypoestrogenic state induced by LUPRON DEPOT and greatly attenuated the loss of bone mineral density and the incidence of hot flashes.

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 to 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 three months.

Uterine Fibroids

Study Demographics and Trial Design

The safety and efficacy of leuprolide acetate were assessed in 309 adult women with uterine fibroids in one pivotal trial (Study M90-411) and additional 128 patients enrolled in three supportive trials (Studies M86-034, M86-049, and M86-062).

Study M90-411 was a Phase 3, stratified, randomized, double-blind, parallel-group, multicenter study, with a 12-week treatment period and a 6-month follow-up (**Table 21**). The study evaluated 2 doses of leuprolide acetate [7.5 mg (not approved for uterine fibroids indication), 3.75 mg] plus iron versus placebo plus iron for the preoperative treatment of anemia caused by uterine fibroids. Subjects were enrolled by stratifying hematologic status at baseline (hematocrit ≤ 28% and > 28%).

The supportive controlled trials had similar study designs, sample sizes, and treatment duration (24 weeks), and assessed the safety and efficacy of leuprolide acetate 3.75 mg versus placebo in women with uterine fibroids who were surgical candidates.

Table 21. Summary of Controlled Clinical Trials Supporting Safety and Efficacy in Patients with Uterine Fibroids

Study #	Trial Design	Dosage, Route of Administration and Duration	Study Subjects by Arm Entered/Completed (n)	Mean Age (Range)[a]
M90-411	Phase 3, stratified, randomized, double-blind, parallel-group multicenter study	LA 7.5 mg[c] + iron LA 3.75 mg + iron Placebo + iron LA and placebo given intramuscular at 4-week intervals, oral iron tablet given 2 or 3 times daily[b] 12-week treatment period and a 6-month follow-up	LA 7.5 mg[c] + iron: 107/104 LA 3.75 mg + iron: 104/93 Placebo + iron: 98/84	LA 7.5 mg[c] + iron: 39.1 (26–52) yrs LA 3.75 mg + iron: 39.4 (23–50) yrs Placebo: 39.2 (23–51) yrs
M86-034	Phase 3, randomized, double-blind, parallel-group single-center study	LA 3.75 mg Placebo Intramuscular monthly 24 weeks	LA: 20/17 Placebo: 20/17	LA: 41.1 (29–53) yrs Placebo: 39.3 (29–49) yrs

Study #	Trial Design	Dosage, Route of Administration and Duration	Study Subjects by Arm Entered/Completed (n)	Mean Age (Range)[a]
M86-049	Phase 3, randomized, double-blind, parallel-group multicenter study	LA 3.75 mg Placebo Intramuscular monthly 24 weeks	LA: 22/20 Placebo: 22/10	LA: 36.5 (25–47) yrs Placebo: 35.0 (28-45) yrs
M86-062	Phase 3, randomized, double-blind, parallel-group multicenter study	LA 3.75 mg Placebo Intramuscular monthly 24 weeks	LA: 21/20 Placebo: 23/10	LA: 34.5 (28–47) yrs Placebo: 33.0 (20–44) yrs

Definition(s): LA = leuprolide acetate

a. Age at study start for efficacy evaluable subjects.

b. Ferrous sulfate tablets, 525 mg twice daily, or if intolerance to ferrous sulfate developed, ferrous gluconate tablets, 324 mg 3 times daily.

c. 7.5 mg is not approved for uterine fibroids indication.

Description of Clinical Studies

In the controlled Phase 3 studies, 255 of 274 subjects (93.1%) randomized to leuprolide acetate completed the treatment period compared to 122 of 163 subjects (74.8%) randomized to placebo. A total of 248 leuprolide acetate subjects and 141 placebo subjects were included in efficacy evaluations.

The primary efficacy endpoint in Study M90-411 was the change in hematologic status from baseline to each monthly visit (Weeks 4, 8, and 12) and to the final visit. A response was defined as an increase of ≥ 2 g/dL in hemoglobin and/or ≥ 6% in hematocrit. Because subjects could meet these criteria and still be anemic, absolute cutoffs were also specified for a response. These were hemoglobin ≥ 12 g/dL and hematocrit ≥ 36%. Efficacy was additionally evaluated based on changes uterine and fibroid volume by pelvic ultrasound or MRI, uterine size (in gestational weeks) by pelvic examination, clinical signs and symptoms, estradiol levels, uterine bleeding, and quality of life.

The primary efficacy endpoints in the supportive studies were changes in uterine and fibroid volume. Uterine volume was measured by pelvic ultrasound in Study M86-034; uterine and fibroid volumes were measured by non-magnetic resonance (NMR) imaging in Study M86-049 or by ultrasound or NMR imaging in Study M86-062. Efficacy was additionally evaluated based on changes in gestational weeks, clinical signs and symptoms, hormone levels, hematocrit determinations, and the menstrual record.

Study Results

Results from the pivotal Study M90-411 for both the efficacy subset of subjects as well as for all subjects demonstrated a statistically significantly higher percentage of subjects in each of the leuprolide acetate dose groups and therefore, a hematologic response in both hemoglobin and hematocrit at Final Visit relative to placebo (**Table 22**).

Table 22. Study M90-411: Percentage of Subjects with Hematologic Response at Final Visit

	n/N (%) of Subjects with an Increase of ≥ 2 g/dL in Hemoglobin and an Increase of ≥ 6% in Hematocrit		
Evaluation	**Placebo**	**Leuprolide Acetate 7.5 mg[a]**	**Leuprolide Acetate 3.75 mg**
Evaluable Subjects, N = 253			
Stratum A (hematocrit ≤ 28%)	18/24 (75)	33/35 (94) P = 0.053	26/28 (93) P = 0.123
Stratum B (hematocrit > 28%)	20/48 (42)	43/62 (69) P = 0.006	42/56 (75) P < 0.001
Combined Strata	38/72 (53)	76/97 (78) P < 0.001	68/84 (81) P < 0.001
All Subjects, N = 296			
Stratum A (hematocrit ≤ 28%)	27/35 (77)	38/40 (95) P = 0.038	34/35 (97) P = 0.028
Stratum B (hematocrit > 28%)	29/60 (48)	46/66 (70) P = 0.018	44/60 (73) P = 0.009
Combined Strata	56/95 (59)	84/106 (79) P = 0.001	78/95 (82) P < 0.001
	n/N (%) of Subjects with Hemoglobin ≥ 12 g/dL *and* Hematocrit ≥ 36%		
Evaluable Subjects, N = 253			
Stratum A (hematocrit ≤ 28%)	9/24 (38)	24/35 (69) *P* = 0.032	19/28 (68) *P* = 0.050
Stratum B (hematocrit > 28%)	24/48 (50)	48/62 (77) *P* = 0.004	43/56 (77) *P* = 0.007
Combined Strata	33/72 (46)	72/97 (74) *P* < 0.001	62/84 (74) *P* < 0.001

	n/N (%) of Subjects with an Increase of ≥ 2 g/dL in Hemoglobin and an Increase of ≥ 6% in Hematocrit		
All Subjects, N = 296			
Stratum A (hematocrit ≤ 28%)	12/35 (34)	28/40 (70) P = 0.003	24/35 (69) P = 0.008
Stratum B (hematocrit > 28%)	32/60 (53)	51/66 (77) P = 0.005	45/60 (75) P = 0.022
Combined Strata	44/95 (46)	79/106 (75) P < 0.001	69/95 (73) P < 0.001

Note: For the comparisons within each stratum, the *P* value is from a pairwise Fisher's exact test. For the comparisons for the combined strata, the *P* value is from a CMH statistic with strata as the blocking factor.

a. 7.5 mg is not approved for uterine fibroids indication

In Study M90-411, at least 25% reduction from baseline to Final Visit in uterine and fibroid volume was reported in 36/60 (60%) and 22/41 (54%) of the efficacy evaluable patients treated with leuprolide acetate 3.75 mg (combined strata). For the efficacy evaluable subjects treated with leuprolide acetate 3.75 mg (combined strata), median reduction in uterine volume was 39%, and median reductions in fibroid volume was 27%. For the placebo-treated subjects there was a slight increase in median uterine volume (10%) and fibroid volume (8%). The differences were statistically significant between the leuprolide acetate 3.75 mg and placebo groups for all analyses for the reduction in uterine volume except for Stratum A (subjects with hematocrit ≤ 28%) for evaluable subjects.

Reductions in uterine volume were reflected in improvements in clinical symptoms. A smaller percentage of subjects who received leuprolide acetate 3.75 mg compared with those who received placebo experienced bloating [38/76 (50.0%) and 37/56 (66.1%), respectively], pelvic pain [32/76 (42.1%) and 35/56 (62.5%)], pressure [28/76 (36.8%) and 25/56 (44.6%)], and menorrhagia [3/76 (3.9%) and 31/56 (55.4%)] at Final Visit (no statistical test was performed for these analyses). There was no consistent treatment effect with leuprolide acetate against symptoms of constipation, dyspareunia, menometrorrhagia, and urinary disorder.

In the supportive controlled studies (M86-034, M86-049, and M86-062), leuprolide acetate 3.75 mg was shown to be statistically significantly superior to placebo in reducing uterine and fibroid volume (**Table 23**).

In an analysis combining the 3 supportive controlled studies, there was a statistically significantly (P = 0.004) greater increase in hematocrit at Final Visit with leuprolide acetate 3.75 mg (1.6%) compared to placebo (-1.1%) in subjects who had menorrhagia prior to treatment. Ninety-five percent of these patients became amenorrheic.

Table 23. Studies M86-034, M86-049, and M86-062: Percent of Evaluable Subjects with ≥ 25% Reduction in Uterine or Fibroid Volume at Final Visit

Endpoint	n/N (%) of Subjects with ≥ 25% Reduction in Uterine or Fibroid Volume		
	Placebo	Leuprolide Acetate 3.75 mg	P value versus Placebo
Uterine Volume			
M86-034	0/20 (0)	13/17 (76)	< 0.001
M86-049	3/19 (16)	16/21 (76)	< 0.001
M86-062	2/19 (11)	14/18 (78)	< 0.001
Fibroid Volume			
M86-049	1/18 (6)	15/19 (79)	< 0.001
M86-062	3/17 (18)	9/15 (60)	0.027

Notes: *P* value is from Fisher's exact test.

Fibroid volume was not measured in Study M86-034.

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

Pharmacodynamics

LUPRON

Several studies in rats were conducted to determine the effects of prolonged administration of leuprolide.

In two non-tumor studies, leuprolide showed in male rats a marked reduction of LH and FSH, accompanied by decreased plasma testosterone at 20 mcg/twice a day for 106 days in the first study and at 20 and 100 mcg/twice a day for 160 days in the second study.

In a tumor study, in male rats implanted with R3327-G prostatic carcinoma, a daily dose of leuprolide at 1, 50 or 1000 mcg/kg for 20 days showed a significant reduction in the tumor growth rate, and enhanced the survival of the animals.

Leuprolide has also been tested in female rats having mammary tumors induced by the administration of 7-12-dimethylbenz[α]-anthracene (DMBA). Doses of leuprolide used ranged from 0.01 mcg to 10 mcg twice a day, up to 31 days. Except for 0.01 mcg which was a "no-effect-dose", leuprolide produced regression of tumor growth similar to the effects seen in the castrate control.

Pharmacokinetics

LUPRON DEPOT

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

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

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

- In a series of experiments with multiple administration (once every four weeks), serum testosterone levels in rats at a dose of 3 mg/kg and those in dogs at 1.5 mg/kg did not show any flare-up at the second and third injection, and continued to be maintained at the suppressed levels. This study demonstrates that leuprolide acetate for depot suspension releases the drug at a constant rate for one month and has a long acting potency.

- In another study, the effects of leuprolide acetate for depot suspension on accessory sex organ weights and hormone levels in adult male rats were compared to those produced by leuprolide acetate solution with subcutaneous administration. One group of rats were given 0.2, 1.0 and 5.0 mg/kg/day leuprolide acetate solution for four weeks; the other group received 0.6, 3.0 and 15 mg/kg leuprolide acetate for depot suspension once a week for 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 three-month period when LUPRON DEPOT (3-Month SR) formulation was studied in rats and dogs.

Human Pharmacology

Pharmacodynamics

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

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

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

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

Pharmacokinetics

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

Absorption

LUPRON

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

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

LUPRON DEPOT

The pharmacokinetic profile of LUPRON DEPOT has been characterized in an open, single-dose study in 10 orchierectomized prostatic cancer patients given 7.5 mg (1-Month SR) intramuscularly. Blood plasma levels were measured over an 8-week period.

After an initial burst, mean plasma leuprolide acetate concentrations declined to approximately 0.8 ng/mL within four days after the injection and remained basically stable for 2.5 weeks. Prolonged plasma concentrations were achieved with all but one patient with detectable plasma levels up to 4 weeks. Approximately 85 to 100% of the observed 8-week AUC was obtained for each patient after the first four weeks. After 8 weeks, plasma levels were essentially undetectable in all patients.

An estimate of the absolute bioavailability from this dosage form was approximately 90% when compared to an equivalent intravenous solution dose used in another study.

TOXICOLOGY

Acute Toxicity

LUPRON

Acute studies were conducted in rats and mice at 100 mg/kg/day. Only signs of decreased motor activity, dyspnea, and excessive scratching were reported; the 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.

Long-Term Toxicity

LUPRON

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

Mouse

Maximum tolerated dose studies (prelude to carcinogenicity studies) were conducted in mice. The mice were dosed subcutaneously with 0, 20, 60, 200 and 600 mg/kg/day. Marked skin irritation at injection sites was observed in mice dosed with 200 and 600 mg/kg/day. Hypertrophy of anterior pituitary cells were observed in female mice dosed with 200 mg/kg/day but not at 600 mg/kg/day. Sex organ atrophy, secondary to the drug pharmacologic effects, were observed in all treated male and female mice. The maximum tolerated dose in mice was 60 mg/kg/day.

Rat

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

Maximum tolerated dose studies (prelude to carcinogenicity studies) were conducted in rats. Rats were dosed subcutaneously with 0, 10, 30, 100 and 300 mg/kg/day for 90 days. Drug related pituitary hyperplasia and hypertrophy, atrophy of sex organs (both sexes) and marked skin irritation at the injection sites were observed in rats. As a result, no maximum tolerated dose was established by the study.

Monkey

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

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

LUPRON DEPOT

Rat

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

In another toxicity study, male rats were given leuprolide acetate for depot suspension subcutaneously once a week for three weeks, at doses of 30 mg/kg/week (corresponding to 2.4 mg/kg/week of leuprolide acetate injection). Atrophy of the testes, and a slight induration were noted. The "no-toxic effect" dose was considered to be 30 mg/kg/week.

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

Dog

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

Special Studies

LUPRON DEPOT

Rabbit

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

Deposition of the test drug at site of injection was noted at 2 and 14 days after the injection, along with slight hemorrhage and dilatation of capillaries at 50 days after the injection.

Leuprolide acetate for depot suspension was reported not to produce significant subcutaneous irritation in rabbits in this study.

In a second irritation study, male rabbits were injected once or four successive times with leuprolide acetate for depot suspension (15% suspension) by intramuscular administration. Results were compared to those obtained with placebo-microcapsule or a 0.75% solution of acetic acid as the positive control. Deposition at injection sites, and slight irritation changes (hemorrhage, edema, inflammation) were noted: leuprolide acetate for depot suspension produced the same effects with same the degree as the placebo-microcapsule, but these are less than those of the positive control (0.75% acetic acid), and their severity were not potentiated by four repeated injections.

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

Guinea Pig

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

Preliminary antigenicity study. Leuprolide acetate for depot suspension was given to guinea pigs at a dose of 123 mg/kg every two weeks by intramuscular route four times, and once by subcutaneous route two weeks after the last intramuscular dose. Results were compared to controls treated with placebo-microcapsule 122 mg/kg intraperitoneally, or with ovalbumin 5 mg/animal intravenously. No systemic anaphylactic reactions were observed with animals treated with leuprolide acetate for depot suspension and placebo-microcapsule, but some induced equivocal weak antibody production was noted.

In a second study, the sensitization potential of leuprolide acetate for depot suspension at doses of 50 mg/animal/dosing by intramuscular (systemic anaphylaxis) or at doses of approximately 7.2 mg/animal/dosing (0.05 mL of a 144.23 mg/mL of suspension) intradermal (delayed hypersensitivity), were compared to those seen with gelatin, egg albumin or captan. No signs of anaphylactic reactions nor delayed hypersensitivity were observed for leuprolide acetate for depot suspension, while signs of anaphylactic reactions (such as nose scratching, sneezing, dyspnea or local irritation) were noted with other compounds.

Mutagenicity and Carcinogenicity

Mutagenicity

LUPRON

Leuprolide has been studied in vitro and in vivo, using bacterial and mammalian systems.

In vitro assays using *Salmonella* and *Saccharomyces* with and without the presence of liver microsomal enzyme from Aroclor-1254 induced rats, no signs of mutagenicity have been observed.

Leuprolide was non-mutagenic in vivo cytogenic assay in rats or in the Mouse Dominant Lethal assay at doses of 0, 1, 2 and 4 mg/kg administered subcutaneously.

Both in vitro and in vivo studies have provided no evidence of a mutagenic potential of leuprolide.

LUPRON DEPOT

In the Ames Test, using *S. typhimurium*, strains TA 98, TA 100, TA 1535 and TA 1537, and *E. coli* strain WP2hcr, leuprolide acetate for depot suspension was found not mutagenic at dosing ranging from 0.03 to 10 mg/plate, irrespective of treatment with mammalian metabolic activation system (S-9 mix).

Carcinogenicity

LUPRON DEPOT

Two rodent carcinogenicity studies were conducted for two years with daily doses of 0.6, 1.5, and 4 mg/kg/day in the rat, and with 0.6, 6, and 60 mg/kg/day in the mouse.

In rats, a dose-related incidence of pituitary hyperplasia, hypertrophy and benign pituitary adenomas were noted at 12-month necropsy, while a statistically significant dose-related incidence of benign pituitary adenomas was observed in both male and female rats after 24 months when the drug was administered subcutaneously at high daily doses (0.6 to 4 mg/kg).

In mice, no drug-induced neoplastic changes or pituitary abnormalities were observed at doses as high as 60 mg/kg for two years.

Patients have been treated with leuprolide for up to three years with doses as high as 10 mg/day, and for two years with doses as high as 20 mg/day. Clinical signs of pituitary abnormalities have not been observed in any of these patients.

Reproduction and Teratology

Fertility and Reproduction

LUPRON DEPOT

Fertility and reproductive performance studies cannot be conducted with leuprolide, because the compound affects the pituitary-gonadal axis and influences endocrine reproductive organs. As a result, there would be a decrease in fertility and reproduction.

Clinical and pharmacologic studies in females 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. There are no data in humans relating to male fertility following treatment with leuprolide acetate.

Although no clinical studies have been completed in children to assess the full reversibility of fertility suppression, animal studies (prepubertal and adult rats and monkeys) with leuprolide acetate and other GnRH analogs have shown functional recovery. However, following a study with leuprolide acetate, immature male rats demonstrated tubular degeneration in the testes even after a recovery period. In spite of the failure to recover histologically, the treated males proved to be as fertile as the controls. Also, no histologic changes were observed in the female rats following the same protocol. In both sexes, the offspring of the treated animals appeared normal. The effect of the treatment of the parents on the reproductive performance of the F1 generation was not tested. The clinical significance of these findings is unknown.

Teratology

LUPRON DEPOT

Leuprolide administered to pregnant rats at dosages of 0, 1, 3 and 10 mcg/kg/day from Gestational Day 6 to Gestational Day 15 (major period of organogenesis) was not teratogenic. At 10 mcg/kg/day, leuprolide increased the incidence of resorptions; surviving fetuses showed no abnormalities. The "no-toxic-effect" dosage was 3 mcg/kg/day.

Leuprolide increased the incidence of embryonic resorptions in pregnant rabbits when dosed with 0, 0.1, 0.3 or 1.0 mcg/kg/day during the period of major organogenesis, i.e., Gestational Day 6 through Gestational Day 18. Surviving fetuses showed no abnormalities (see **CONTRAINDICATIONS**).

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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:

Endometriosis:

Use LUPRON DEPOT 3.75 mg (1-Month slow release) and 11.25 mg (3-Month slow release) for up to 6 months:

- **as a sole treatment for:** endometriosis, including pain relief and reducing lesions
- **as a sole treatment for women close to menopause who do not want surgery:** may relieve symptoms
- **as a sole treatment for women close to menopause along with surgery:** may relieve symptoms
- **as a combination treatment with 5 mg norethindrone acetate:** for initial treatment or when symptoms return

Uterine Fibroids (before surgery)

Use LUPRON DEPOT 3.75 mg (1-Month slow release) for up to 3 months:

- **as a combination treatment with an iron supplement:** to improve anemia before surgery for uterine fibroids

What it does:

LUPRON DEPOT works to inhibit the production of gonadotropins from the pituitary gland, thereby decreasing estrogens to postmenopausal levels in premenopausal women.

When it should not be used:

Do not take LUPRON DEPOT if you:

- are allergic to leuprolide acetate, any similar nonapeptides (e.g., histrelin, desorelin), or any of the other ingredients in LUPRON DEPOT
- are pregnant or planning to get pregnant
- have abnormal vaginal bleeding of unknown cause
- are breast-feeding

You must use non-hormonal methods of birth control while receiving LUPRON DEPOT.

What the medicinal ingredient is:

leuprolide acetate

What the non-medicinal ingredients are:

LUPRON DEPOT 3.75 mg (1-Month slow release) also contains carboxymethylcellulose sodium, DL-lactic and glycolic acids copolymer, D-mannitol, gelatin, glacial acetic acid, polysorbate 80 and water for injection.

LUPRON DEPOT 11.25 mg (3-Month slow release) also contains carboxymethylcellulose sodium, D-mannitol, glacial acetic acid, polylactic acid, polysorbate 80 and water for injection.

What dosage forms it comes in:

Pre-filled syringes with two parts. The two parts must be mixed prior to giving the intramuscular injection.

- First part has leuprolide acetate.
- Second part has a special diluent.

LUPRON DEPOT comes in two strengths:

- 3.75 mg (1-Month slow release)
- 11.25 mg (3-Month slow release)

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.
- You have had or are suspected of having seizures, epilepsy, cerebrovascular disorder, central nervous system anomalies, or brain tumor.
- You are taking other medication(s) that have been associated with convulsions or seizures such as bupropion and any SSRI medication for depression.

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.

INTERACTIONS WITH THIS MEDICATION

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

PROPER USE OF THIS MEDICATION

LUPRON DEPOT is to be given to you:

- as an injection into the muscle (intramuscular injection).
- under the supervision of a health professional.

Usual Dose:

Endometriosis:

- 3.75 mg (1-Month slow release) once a month for 6 months,

OR

- 11.25 mg (3-Month slow release) once every 3 months for 6 months.

Uterine Fibroids (before surgery):

- 3.75 mg (1-Month slow release) once a month for up to 3 months.

For the 3 months you are on LUPRON DEPOT: take an oral iron supplement every day.
Your doctor or pharmacist will tell you how much iron to take every day.

Overdose:

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

Missed Dose:

If you miss an appointment by a few days, it should not disrupt the benefits of treatment, but keeping a consistent schedule of LUPRON DEPOT injections is an important part of treatment.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

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

Possible common side effects with the use of LUPRON DEPOT include:

- hot flashes, excessive sweats
- gastrointestinal problems, nausea, vomiting
- decreased libido
- muscle or joint pain
- weakness
- breast tenderness/pain and/or vaginitis (infection or inflammation of the vagina)
- emotional changes such as feeling depressed
- headache/migraine
- upset sleep
- nervousness/rapid heart beat
- edema (swelling, water retention)
- weight gain or loss
- skin reaction at the injection site such as itching, redness, burning, and/or swelling
- acne
- menstrual cramps (dysmenorrhea)

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

Side effects reported after the drug was available for sale (postmarketing) include:

- convulsion
- liver problems, including serious liver injury
- serious allergic reaction (anaphylaxis and anaphylactoid)
- inflammation of the lung (interstitial lung disease)
- pituitary apoplexy; symptoms include sudden headache, vomiting, visual changes, problem with eye muscle movement (ophthalmoplegia), altered mental status, and sometimes cardiovascular collapse

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom/effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common	Headache	✓		
	Hot flashes/sweats		✓	
	Skin reactions including reaction at site of injection		✓	
	Vomiting/nausea	✓		
Uncommon	Abnormal swelling or numbness of limbs		✓	
	Convulsion		✓	
	Severe bone pain		✓	
	Severe pain in chest or abdomen		✓	
	Vision changes		✓	
Reported from post-marketing with unknown frequency	New onset or worsening of shortness of breath or dry cough, often seen with exertion, as potential symptoms of pulmonary fibrosis or interstitial lung disease (inflammation of the lung)		✓	

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

HOW TO STORE IT

Store between 15 and 25°C. Protect from freezing.

REPORTING SIDE EFFECTS

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

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

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

MORE INFORMATION

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

www.abbvie.ca

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

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