This is combined labeling. Examples of different fonts and colors appear below.

- General information
- Information on endometriosis
- Information on uterine fibroids.

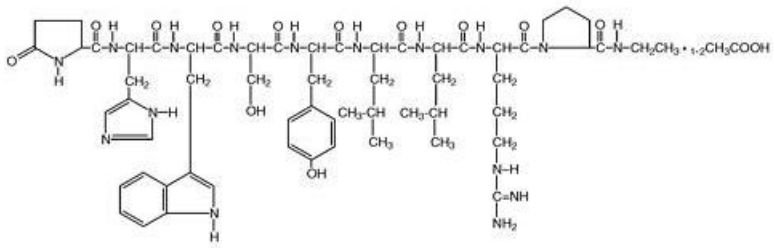
Lupron Depot® - 3 Month 11.25 mg

(leuprolide acetate for depot suspension)

3-MONTH FORMULATION

DESCRIPTION

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



LUPRON DEPOT-3 Month 11.25 mg is available in a prefilled dual-chamber syringe containing sterile lyophilized microspheres which, when mixed with diluent become a suspension intended as an intramuscular injection to be given **ONCE EVERY THREE MONTHS.**

The front chamber of LUPRON DEPOT-3 Month 11.25 mg prefilled dual-chamber syringe contains leuprolide acetate (11.25 mg), polylactic acid (99.3 mg) and D-mannitol (19.45 mg). The second chamber of diluent contains carboxymethylcellulose sodium (7.5 mg), D-mannitol (75.0 mg), polysorbate 80 (1.5 mg), water for injection, USP, and glacial acetic acid, USP to control pH.

During the manufacture of LUPRON DEPOT-3 Month 11.25 mg, acetic acid is lost, leaving the peptide.

CLINICAL PHARMACOLOGY

Leuprolide acetate is a long-acting GnRH analog. A single injection of LUPRON DEPOT-3 Month 11.25 mg will result in an initial stimulation followed by a prolonged suppression of pituitary gonadotropins. Repeated dosing at quarterly (LUPRON DEPOT-3 Month 11.25 mg) intervals results in decreased secretion of gonadal steroids; consequently, tissues and functions that depend on gonadal steroids for their maintenance become quiescent. This effect is reversible on discontinuation of drug therapy.

Leuprolide acetate is not active when given orally.

Pharmacokinetics

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

Distribution The mean steady-state volume of distribution of leuprolide following intravenous bolus administration to healthy male volunteers was 27 L. *In vitro* binding to human plasma proteins ranged from 43% to 49%.

Metabolism In healthy male volunteers, a 1 mg bolus of leuprolide administered intravenously revealed that the mean systemic clearance was 7.6 L/h, with a terminal elimination half-life of approximately 3 hours based on a two compartment model.
In rats and dogs, administration of ^{14}C-labeled leuprolide was shown to be metabolized to smaller inactive peptides, a pentapeptide (Metabolite I), tripeptides (Metabolites II and III) and a dipeptide (Metabolite IV). These fragments may be further catabolized.
In a pharmacokinetic/pharmacodynamic study of endometriosis patients, intramuscular 11.25 mg LUPRON DEPOT (n=19) every 12 weeks or intramuscular 3.75 mg LUPRON DEPOT (n=15) every 4 weeks was administered for 24 weeks. There was no statistically significant difference between the 2 treatment groups in trough plasma concentrations of leuprolide or M-I collected from weeks 4 through 24. No accumulation of plasma leuprolide or M-I concentrations was observed with multiple dosing of either treatment group. There was also no statistically significant difference in changes of serum estradiol concentration from baseline between the 2 treatment groups.
M-I Plasma concentrations measured in 5 prostate cancer patients reached maximum concentration 2 to 6 hours after dosing and were approximately 6% of the peak parent drug concentration. One week after dosing, mean plasma M-I concentrations were approximately 20% of mean leuprolide concentrations.

Excretion Following administration of LUPRON DEPOT 3.75 mg to 3 patients, less than 5% of the dose was recovered as parent and M-I metabolite in the urine.

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

Drug Interactions No pharmacokinetic-based drug-drug interaction studies have been conducted with LUPRON DEPOT. However, because leuprolide acetate is a peptide that is primarily degraded by peptidase and not by cytochrome P-450 enzymes as noted in specific studies, and the drug is only about 46% bound to plasma proteins, drug interactions would not be expected to occur.

CLINICAL STUDIES
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) was in the menopausal range. Throughout the remainder of the dosing period, mean serum estradiol levels ranged from the menopausal to the early follicular range.
Serum estradiol was suppressed to ≤ 20 pg/mL in all subjects within four weeks and remained suppressed (≤ 40 pg/mL) in 80% of subjects until the end of the 12-week dosing interval, at which time two of these subjects had a value between 40 and 50 pg/mL. Four additional subjects had at least two consecutive elevations of estradiol (range 43-240 pg/mL) levels during the 12-week dosing interval, but there was no indication of luteal function for any of the subjects during this period.
LUPRON DEPOT-3 Month 11.25 mg 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-3 Month 11.25 mg produced similar pharmacodynamic effects in terms of hormonal and menstrual suppression to those achieved with monthly injections of LUPRON DEPOT 3.75 mg during the controlled clinical trials for the management of endometriosis and the anemia caused by uterine fibroids.

Endometriosis: In a Phase IV pharmacokinetic/pharmacodynamic study of patients, LUPRON DEPOT-3 Month 11.25 mg (N=21) was shown to be comparable to monthly LUPRON DEPOT 3.75 mg (N=20) in relieving the

clinical signs/symptoms of endometriosis (dysmenorrhea, non-menstrual pelvic pain, pelvic tenderness and pelvic induration). In both treatment groups, suppression of menses was achieved in 100% of the patients who remained in the study for at least 60 days. Suppression is defined as no new menses for at least 60 consecutive days.

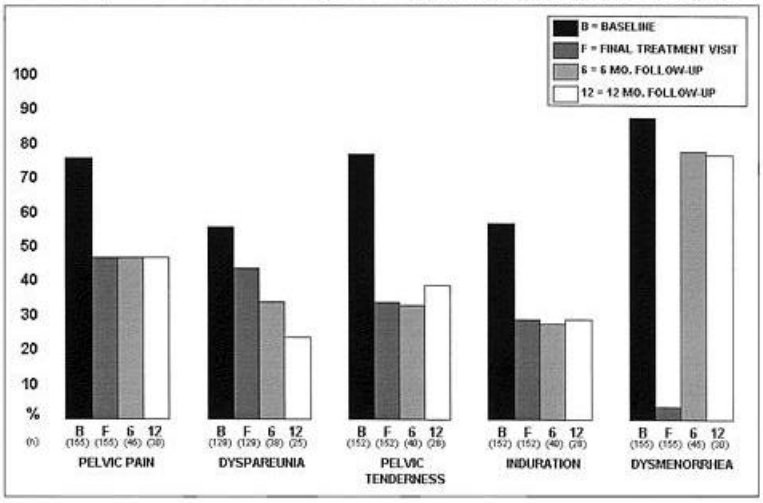
In controlled clinical studies, LUPRON DEPOT 3.75 mg monthly for six months was shown to be comparable to danazol 800 mg/day in relieving the clinical sign/symptoms of endometriosis (pelvic pain, dysmenorrhea, dyspareunia, pelvic tenderness, and induration) and in reducing the size of endometrial implants as evidenced by laparoscopy.

The clinical significance of a decrease in endometriotic lesions is not known at this time, and in addition laparoscopic staging of endometriosis does not necessarily correlate with the severity of symptoms.

LUPRON DEPOT 3.75 mg monthly induced amenorrhea in 74% and 98% of the patients after the first and second treatment months respectively. Most of the remaining patients reported episodes of only light bleeding or spotting. In the first, second and third post-treatment months, normal menstrual cycles resumed in 7%, 71% and 95% respectively, of those patients who did not become pregnant.

Figure 1 illustrates the percent of patients with symptoms at baseline, final treatment visit and sustained relief at 6 and 12 months following discontinuation of treatment for the various symptoms evaluated during the two controlled clinical studies. A total of 166 patients received LUPRON DEPOT 3.75 mg. Seventy-five percent (N=125) of these elected to participate in the follow-up periods. Of these patients, 36% and 24% are included in the 6 month and 12 month follow-up analysis, respectively. All the patients who had a pain evaluation at baseline and at a minimum of one treatment visit, are included in the Baseline (B) and final treatment visit (F) analysis.

FIGURE 1 - PERCENT OF PATIENTS WITH SIGN/SYMPTOMS OF ENDOMETRIOSIS AT BASELINE, FINAL TREATMENT VISIT, AND AFTER 6 AND 12 MONTHS OF FOLLOW-UP



Hormonal replacement therapy: Clinical studies suggest that the addition of hormonal replacement therapy (estrogen and/or progestin) to LUPRON is effective in reducing loss of bone mineral density which occurs with LUPRON, without compromising the efficacy of LUPRON in relieving symptoms of endometriosis. The optimal drug/dose is not established.

Uterine Leiomyomata (Fibroids): LUPRON DEPOT 3.75 mg for a period of three to six months was studied in four controlled clinical trials.

In one of these clinical studies, enrollment was based on hematocrit ≤ 30% and/or hemoglobin ≤ 10.2 g/dL. Administration of LUPRON DEPOT 3.75 mg, concomitantly with iron, produced an increase of ≥ 6% hematocrit and ≥ 2 g/dL hemoglobin in 77% of patients at three months of therapy. The mean change in hematocrit was 10.1% and the mean change in hemoglobin was 4.2 g/dL. Clinical response was judged to be a hematocrit of > 36% and hemoglobin of ≥ 12 g/dL, thus allowing for autologous blood donation prior to surgery. At two and three months respectively, 71% and 75% of patients met this criterion (Table 1). These data suggest however, that some patients may benefit from iron alone or 1 to 2 months of LUPRON DEPOT 3.75 mg.

Table 1:
PERCENT OF PATIENTS ACHIEVING
HEMATOCRIT ≥ 36% AND HEMOGLOBIN ≥ 12 GM/DL

Treatment Group	Week 4	Week 8	Week 12
LUPRON DEPOT 3.75 mg with Iron (N=104)	40 *	71 **	75 *
Iron Alone (N=98)	17	39	49

*P-Value <0.01
**P-Value <0.001

Excessive vaginal bleeding (menorrhagia or menometrorrhagia) decreased in 80% of patients at three months. Episodes of spotting and menstrual-like bleeding were noted in 16% of patients at final visit.
In this same study, a decrease of > 25% was seen in uterine and myoma volumes in 60% and 54% of patients respectively. The mean fibroid diameter was 6.3 cm at pretreatment and decreased to 5.6 cm at the end of treatment. LUPRON DEPOT 3.75 mg was found to relieve symptoms of bloating, pelvic pain, and pressure.
In three other controlled clinical trials, enrollment was not based on hematologic status. Mean uterine volume decreased by 41% and myoma volume decreased by 37% at final visit as evidenced by ultrasound or MRI. The mean fibroid diameter was 5.6 cm at pretreatment and decreased to 4.7 cm at the end of treatment. These patients also experienced a decrease in symptoms including excessive vaginal bleeding and pelvic discomfort. Ninety-five percent of these patients became amenorrheic with 61%, 25%, and 4% experiencing amenorrhea during the first, second, and third treatment months respectively.
In addition, posttreatment follow-up was carried out in one clinical trial for a small percentage of LUPRON DEPOT 3.75 mg patients (N=46) among the 77% who demonstrated a >/= 25% decrease in uterine volume while on therapy. Menses usually returned within two months of cessation of therapy. Mean time to return to pretreatment uterine size was 8.3 months. Regrowth did not appear to be related to pretreatment uterine volume.
There is no evidence that pregnancy rates are enhanced or adversely affected by the use of LUPRON DEPOT.

INDICATIONS AND USAGE

Endometriosis:
LUPRON DEPOT-3 Month 11.25 mg is indicated for management of endometriosis, including pain relief and reduction of endometriotic lesions.
Experience with LUPRON DEPOT in females has been limited to women 18 years of age and older treated for no more than 6 months.
Uterine Leiomyomata (Fibroids):
LUPRON DEPOT-3 Month 11.25 mg concomitantly with iron therapy is indicated for the preoperative hematologic improvement of patients with anemia caused by uterine leiomyomata. The clinician may wish to consider a one-month trial period on iron alone inasmuch as some of the patients will respond to iron alone. (See Table 1, CLINICAL STUDIES section.) LUPRON may be added if the response to iron alone is considered inadequate. Recommended therapy is a single injection of LUPRON DEPOT-3 Month 11.25 mg. This dosage form is indicated only for women for whom three months of hormonal suppression is deemed necessary.
Experience with LUPRON DEPOT in females has been limited to women 18 years of age and older treated for no more than 6 months.

CONTRAINDICATIONS

Hypersensitivity to GnRH, GnRH agonist analogs or any of the excipients in LUPRON DEPOT. A report of an anaphylactic reaction to synthetic GnRH (Factrel) has been reported in the medical literature. [1]
LUPRON DEPOT is contraindicated in women who are or may become pregnant while receiving the drug. LUPRON DEPOT may cause fetal harm when administered to a pregnant woman. Major fetal abnormalities were observed in rabbits but not in rats after administration of LUPRON DEPOT throughout gestation. There was increased fetal mortality and decreased fetal weights in rats and rabbits. (See **Pregnancy** section.) The effects on fetal mortality are expected consequences of the alterations in hormonal levels brought about by the drug. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Use in women who are breast-feeding. (See **Nursing Mothers** section.)
Undiagnosed abnormal vaginal bleeding.

WARNINGS
As the effects of LUPRON DEPOT-3 Month 11.25 mg are present throughout the course of therapy, the drug should only be used in patients who require hormonal suppression for at least three months.
Experience with LUPRON DEPOT in females has been limited to six months; therefore, exposure should be limited to six months of therapy.
When used at the recommended dose and dosing interval, LUPRON DEPOT usually inhibits ovulation and stops menstruation. Contraception is not insured, however, by taking LUPRON DEPOT. Therefore, patients should use non-hormonal methods of contraception. Patients should be advised to see their physician if they believe they may be pregnant. If a patient becomes pregnant during treatment, the drug must be discontinued and the patient must be apprised of the potential risk to the fetus. (See **CONTRAINDICATIONS** section.)
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.

PRECAUTIONS
Information for Patients An information pamphlet for patients is included with the product. Patients should be aware of the following information:
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.
Patients should not use LUPRON DEPOT if they are pregnant, breast feeding, have undiagnosed abnormal vaginal bleeding, or are allergic to any of the ingredients in LUPRON DEPOT.
LUPRON DEPOT is contraindicated for use during pregnancy. Therefore, a non-hormonal method of contraception should be used during treatment. Patients should be advised that if they miss successive doses of LUPRON DEPOT, breakthrough bleeding or ovulation may occur with the potential for conception. If a patient becomes pregnant during treatment, she should discontinue treatment and consult her physician.
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.
The induced hypoestrogenic state **also** results in a small loss in bone density over the course of treatment, which may not be fully reversible. In patients with major risk factors for decreased bone mineral content such as chronic alcohol and/or tobacco use, strong family history of osteoporosis, or chronic use of drugs that can reduce bone mass such as anticonvulsants or corticosteroids, LUPRON DEPOT therapy may pose an additional risk. In these patients, the risks and benefits must be weighed carefully before therapy with LUPRON DEPOT is instituted. Clinical studies suggest that the addition of hormonal replacement therapy (estrogen and/or progestin) to LUPRON is effective in reducing loss of bone mineral density which occurs with LUPRON, without compromising the efficacy of LUPRON in relieving symptoms of endometriosis. The optimal drug/dose is not established.
Treatment for more than six months cannot be recommended since safety data beyond six months are not available.

Laboratory Tests See **ADVERSE REACTIONS** section.
Drug/Laboratory Test Interactions See **ADVERSE REACTIONS** section. Administration of LUPRON DEPOT in therapeutic doses results in suppression of the pituitary-gonadal system. Normal function is usually restored within three months after treatment is discontinued. Due to the suppression of the pituitary-gonadal system by LUPRON DEPOT, diagnostic tests of pituitary gonadotropic and gonadal functions conducted during treatment and for up to three months after discontinuation of LUPRON DEPOT may be affected.

Carcinogenesis, Mutagenesis, Impairment of Fertility A two-year carcinogenicity study was conducted in rats and mice. In rats, a dose-related increase of benign pituitary hyperplasia and benign pituitary adenomas was noted at 24 months when the drug was administered subcutaneously at high daily doses (0.6 to 4 mg/kg). There was a significant but not dose-related increase of pancreatic islet-cell adenomas in females and of testicular interstitial cell adenomas in males (highest incidence in the low dose group). In mice, no leuprolide acetate-induced tumors or pituitary abnormalities were observed at a dose as high as 60 mg/kg for two years. Patients have been treated with leuprolide acetate for up to three years with doses as high as 10 mg/day and for two years with doses as high as 20 mg/day without demonstrable pituitary abnormalities.
Mutagenicity studies have been performed with leuprolide acetate using bacterial and mammalian systems. These studies provided no evidence of a mutagenic potential.
Clinical and pharmacologic studies in adults (> 18 years) with leuprolide acetate and similar analogs have shown reversibility of fertility suppression when the drug is discontinued after continuous administration for periods of up to 24 weeks.

Pregnancy, Teratogenic Effects Pregnancy Category X. (See **CONTRAINDICATIONS** section.) 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 of the human dose) to rabbits, LUPRON DEPOT produced a dose-related increase in major fetal abnormalities. Similar studies in rats failed to demonstrate an increase in fetal malformations. There was increased fetal mortality and decreased fetal weights with the two higher doses of LUPRON DEPOT in rabbits and with the highest dose (0.024 mg/kg) in rats.

Nursing Mothers It is not known whether LUPRON DEPOT is excreted in human milk. Because many drugs are excreted in human milk, and because the effects of LUPRON DEPOT on lactation and/or the breast-fed child have not been determined, LUPRON DEPOT should not be used by nursing mothers.

Pediatric Use Safety and effectiveness of LUPRON DEPOT-3 Month 11.25 mg have not been established in pediatric patients. See LUPRON DEPOT-PED ® (leuprolide acetate for depot suspension) labeling for the safety and effectiveness in children with central precocious puberty.

ADVERSE REACTIONS

Clinical Trials

The **monthly formulation of LUPRON DEPOT 3.75 mg** was utilized in controlled clinical trials that studied the drug in 166 endometriosis and 166 uterine fibroids patients. Adverse events reported in >/= 5% of patients in either of these populations and thought to be potentially related to drug are noted in Table 2.

Table 2:
Adverse Events Reported to be Causally Related to Drug in ³ 5% of Patients

	Endometriosis (2 Studies)			Uterine Fibroids (4 Studies)	
	LUPRON DEPOT 3.75 mg	Danazol	Placebo	LUPRON DEPOT 3.75 mg	Placebo
	N=166	N=136	N=31	N=166	N=163
	N (%)	N (%)	N (%)	N (%)	N (%)
Body as a Whole					
Asthenia	5 (3)	9 (7)	0 (0)	14 (8.4)	8 (4.9)
General pain	31 (19)	22 (16)	1 (3)	14 (8.4)	10 (6.1)
Headache*	53 (32)	30 (22)	2 (6)	43 (25.9)	29 (17.8)
Cardiovascular System					
Hot flashes/sweats*	139 (84)	77 (57)	9 (29)	121 (72.9)	29 (17.8)
Gastrointestinal System					
Nausea/vomiting	21 (13)	17 (13)	1 (3)	8 (4.8)	6 (3.7)
GI disturbances*	11 (7)	8 (6)	1 (3)	5 (3.0)	2 (1.2)
Metabolic and Nutritional Disorders					
Edema	12 (7)	17 (13)	1 (3)	9 (5.4)	2 (1.2)

Weight gain/loss	22 (13)	36 (26)	0 (0)	5 (3.0)	2 (1.2)
Endocrine System					
Acne	17 (10)	27 (20)	0 (0)	0 (0)	0 (0)
Hirsutism	2 (1)	9 (7)	1 (3)	1 (0.6)	0 (0)
Musculoskeletal System					
Joint disorder*	14 (8)	11 (8)	0 (0)	13 (7.8)	5 (3.1)
Myalgia*	1 (1)	7 (5)	0 (0)	1 (0.6)	0 (0)
Nervous System					
Decreased libido*	19 (11)	6 (4)	0 (0)	3 (1.8)	0 (0)
Depression/emotional lability*	36 (22)	27 (20)	1 (3)	18 (10.8)	7 (4.3)
Dizziness	19 (11)	4 (3)	0 (0)	3 (1.8)	6 (3.7)
Nervousness*	8 (5)	11 (8)	0 (0)	8 (4.8)	1 (0.6)
Neuromuscular disorders*	11 (7)	17 (13)	0 (0)	3 (1.8)	0 (0)
Paresthesias	12 (7)	11 (8)	0 (0)	2 (1.2)	1 (0.6)
Skin and Appendages					
Skin reactions	17 (10)	20 (15)	1 (3)	5 (3.0)	2 (1.2)
Urogenital System					
Breast changes/ tenderness/pain*	10 (6)	12 (9)	0 (0)	3 (1.8)	7 (4.3)
Vaginitis*	46 (28)	23 (17)	0 (0)	19 (11.4)	3 (1.8)

In these same studies, symptoms reported in < 5% of patients included: *Body as a Whole* --Body odor, Flu syndrome, Injection site reactions; *Cardiovascular System* --Palpitations, Syncope, Tachycardia; *Digestive System* --Appetite changes, Dry mouth, Thirst; *Endocrine System* --Androgen-like effects; *Hemic and Lymphatic System* --Ecchymosis, Lymphadenopathy; *Nervous System* --Anxiety,* Insomnia/Sleep disorders,* Delusions, Memory disorder, Personality disorder; *Respiratory System* --Rhinitis; *Skin and Appendages* --Alopecia, Hair disorder, Nail disorder; *Special Senses* --Conjunctivitis, Ophthalmologic disorders,* Taste perversion; *Urogenital System* --Dysuria,* Lactation, Menstrual disorders.

* = Physiologic effect of the drug.

In one controlled clinical trial utilizing the monthly formulation of LUPRON DEPOT, patients diagnosed with uterine fibroids received a higher dose (7.5 mg) of LUPRON DEPOT. Events seen with this dose that were thought to be potentially related to drug and were not seen at the lower dose included glossitis, hypesthesia, lactation, pyelonephritis, and urinary disorders. Generally, a higher incidence of hypoestrogenic effects was observed at the higher dose.

In a pharmacokinetic trial involving 20 healthy female subjects receiving LUPRON DEPOT-3 Month 11.25 mg, a few adverse events were reported with this formulation that were not reported previously. These included face edema, agitation, laryngitis, and ear pain.

In a Phase IV study involving endometriosis patients receiving LUPRON DEPOT 3.75 mg (N=20) or LUPRON DEPOT-3 Month 11.25 mg (N=21), similar adverse events were reported by the two groups of patients. In general the safety profiles of the two formulations were comparable in this study.

Changes in Bone Density

In controlled clinical studies, patients with endometriosis (six months of therapy) or uterine fibroids (three months of therapy) were treated with LUPRON DEPOT 3.75 mg. In endometriosis patients, vertebral bone density as measured by dual energy x-ray absorptiometry (DEXA) decreased by an average of 3.2% at six months compared with the pretreatment value. In this same study, LUPRON DEPOT 3.75 mg alone and LUPRON DEPOT 3.75 mg plus three different hormonal add-back regimens were compared for one year. All add-back groups demonstrated mean changes in bone mineral density of </=1% from baseline and showed statistically significantly (P-value <0.001) less loss of bone density than the group treated with LUPRON DEPOT 3.75 mg alone, at all time points. Clinical studies suggest that the addition of hormonal replacement therapy (estrogen and/or progestin) to LUPRON is effective in reducing loss of bone mineral density which occurs with LUPRON, without compromising the efficacy of LUPRON in relieving symptoms of endometriosis. The optimal drug/dose is not established. In the Phase IV, six-month pharmacokinetic/pharmacodynamic study in endometriosis patients who were treated with LUPRON DEPOT 3.75 mg or LUPRON DEPOT-3 Month 11.25 mg, vertebral bone density measured by

DEXA decreased compared with baseline by an average of 3.0% and 2.8% at six months for the two groups, respectively.
When LUPRON DEPOT 3.75 mg was administered for three months in uterine fibroid patients, vertebral trabecular bone mineral density as assessed by quantitative digital radiography (QDR) revealed a mean decrease of 2.7% compared with baseline. Six months after discontinuation of therapy, a trend toward recovery was observed. Use of LUPRON DEPOT for longer than three months (uterine fibroids) or six months (endometriosis) or in the presence of other known risk factors for decreased bone mineral content may cause additional bone loss **and is not recommended.**

Changes in Laboratory Values During Treatment
Liver Enzymes
Three percent of uterine fibroid patients treated with LUPRON DEPOT 3.75 mg, manifested posttreatment transaminase values that were 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.

Lipids
Triglycerides were increased above the upper limit of normal in 12% of the endometriosis patients who received LUPRON DEPOT 3.75 mg and in 32% of the subjects receiving LUPRON DEPOT-3 Month 11.25 mg.
Of those endometriosis and uterine fibroid patients whose pretreatment cholesterol values were in the normal range, mean change following therapy was +16 mg/dL to +17 mg/dL in endometriosis patients and +11 mg/dL to +29 mg/dL in uterine fibroid patients. In the endometriosis treated patients, increases from the pretreatment values were statistically significant ($p<0.03$). There was essentially no increase in the LDL/HDL ratio in patients from either population receiving LUPRON DEPOT 3.75 mg.

Chemistry
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.

Postmarketing
During postmarketing surveillance with other dosage forms and in the same and/or different populations, the following adverse events were reported. Like other drugs in this class, mood swings, including depression, have been reported as a physiologic effect of decreased sex steroids. There have been very rare reports of suicidal ideation and attempt. Many, but not all, of these patients had a history of depression or other psychiatric illness. Patients should be counseled on the possibility of worsening of depression.
Symptoms consistent with an anaphylactoid or asthmatic process have been reported. Rash, urticaria, and photosensitivity reactions have also been reported.
Localized reactions including induration and abscess have been reported at the site of injection.
Symptoms consistent with fibromyalgia (eg: joint and muscle pain, headaches, sleep disorders, gastrointestinal distress, and shortness of breath) have been reported individually and collectively.
Cardiovascular System --Hypotension, Pulmonary embolism; *Hemic and Lymphatic System* --Decreased WBC; *Central/Peripheral Nervous System* --Peripheral neuropathy, Spinal fracture/paralysis; *Musculoskeletal System* --Tenosynovitis-like symptoms; *Urogenital System* --Prostate pain.
See other LUPRON DEPOT and LUPRON Injection package inserts for other events reported in the same and different patient populations.

OVERDOSAGE
In 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.

DOSAGE AND ADMINISTRATION
LUPRON DEPOT Must Be Administered Under the Supervision of a Physician.

Endometriosis: The recommended dose of LUPRON DEPOT-3 Month 11.25 mg is one injection every three months, for a maximum recommended duration of six months. Retreatment cannot be recommended since safety data for retreatment are not available. If the symptoms of endometriosis recur after a course of therapy, and further treatment with LUPRON DEPOT-3 Month 11.25 mg is contemplated, it is recommended that bone density be assessed before retreatment begins to ensure that values are within normal limits.

Uterine Leiomyomata (Fibroids): The recommended dose of LUPRON DEPOT-3 Month 11.25 mg is one injection. The symptoms associated with uterine leiomyomata will recur following discontinuation of therapy. If additional treatment with LUPRON DEPOT-3 Month 11.25 mg is contemplated, bone density should be assessed prior to initiation of therapy to ensure that values are within normal limits.

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.

Incorporated in a depot formulation, the lyophilized microspheres are to be reconstituted and administered as a single intramuscular injection, in accord with the following directions:

1. To prepare for injection, screw the white plunger into the end stopper until the stopper begins to turn.
2. Remove and discard the tab around the base of the needle.
3. Holding the syringe upright, release the diluent by SLOWLY PUSHING the plunger until the first stopper is at the blue line in the middle of the barrel.
4. Gently shake the syringe to thoroughly mix the particles to form a uniform suspension. The suspension will appear milky.
5. If the microspheres (particles) adhere to the stopper, tap the syringe against your finger.
6. Then remove the needle guard and advance the plunger to expel the air from the syringe.
7. At the time of reconstitution, inject the entire contents of the syringe intramuscularly as you would for a normal injection. The suspension settles very quickly following reconstitution; therefore, it is preferable that LUPRON DEPOT-3 Month 11.25 mg be mixed and used immediately. Reshake suspension if settling occurs.

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.

HOW SUPPLIED

LUPRON DEPOT-3 Month 11.25 mg is packaged as follows:

Kit with prefilled

dual-chamber syringe NDC 0300-3663-01

Each syringe contains sterile lyophilized microspheres which are leuprolide acetate incorporated in a biodegradable polymer of polylactic acid. When mixed with 1.5 mL of diluent, LUPRON DEPOT-3 Month 11.25 mg is administered as a single IM injection **EVERY THREE MONTHS.**

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [See USP Controlled Room Temperature]

Rx only

REFERENCE

MacLeod TL, *et al* . Anaphylactic reaction to synthetic luteinizing hormone-releasing hormone. *Fertil Steril* 1987 Sept;48(3):500-502.

U.S. Patent Nos. 4,652,441; 4,728,721; 4,849,228; 4,917,893; 4,954,298; 5,330,767; 5,476,663; 5,480,656; 5,575,987; 5,631,020; 5,631,021; 5,643,607; and 5,716,640.

Manufactured for
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by Takeda Chemical Industries, Ltd. Osaka, JAPAN 541
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(No. 3663)
03-5052-R7; Revised: May 2000