

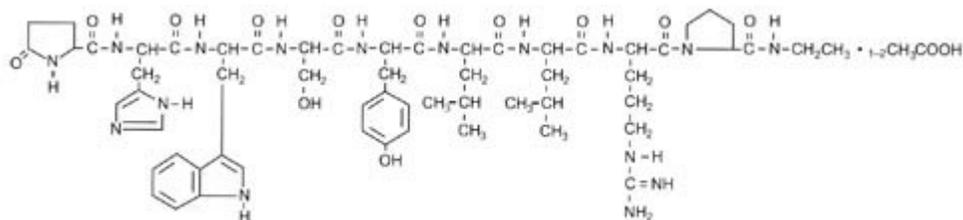
## LUPRON DEPOT<sup>®</sup> -3 Month 11.25 mg

### (leuprolide acetate for depot suspension) 3-MONTH FORMULATION

Rx only

#### 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 ( $\pm$  standard deviation) leuprolide concentration from 3 to 12 weeks was  $0.23 \pm 0.09$  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  $^{14}\text{C}$ -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 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  $\leq 20$  pg/mL in all subjects within four weeks and remained suppressed ( $\leq 40$  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.

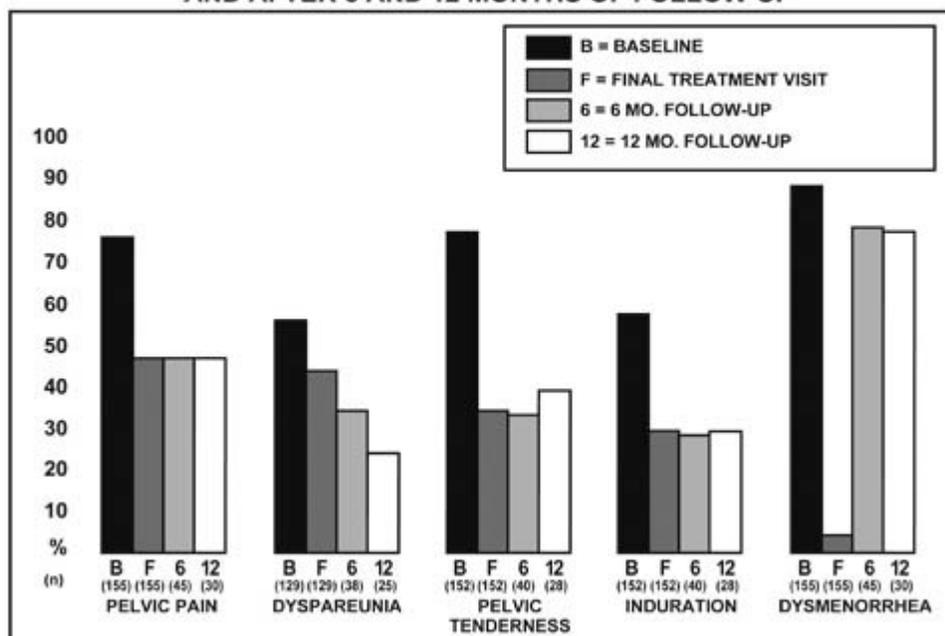
In controlled clinical studies, LUPRON DEPOT 3.75 mg monthly for six months was shown to be comparable to danazol 800 mg/day in relieving the clinical sign/symptoms of endometriosis (pelvic pain, dysmenorrhea, dyspareunia, pelvic tenderness, and induration) and in reducing the size of endometrial implants 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% of patients, respectively, excluding those who became 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 period. 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**

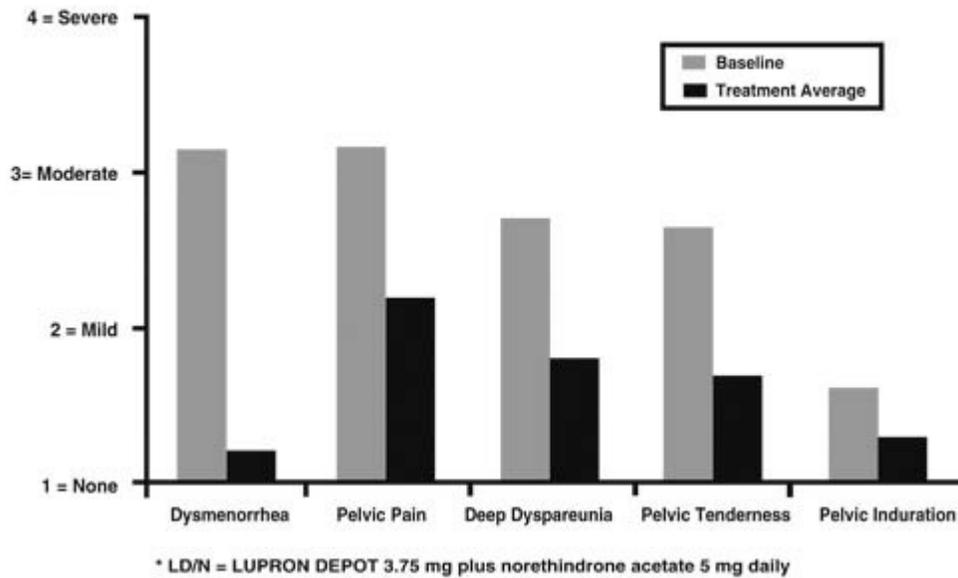


### Hormonal add-back therapy

Two clinical studies with a treatment duration of 12 months indicate that concurrent hormonal therapy (norethindrone acetate 5 mg daily) is effective in significantly reducing the loss of bone mineral density associated with LUPRON, without compromising the efficacy of LUPRON in relieving symptoms of endometriosis. (All patients in these studies received calcium supplementation with 1000 mg elemental calcium). One controlled, randomized and double-blind study included 51 women treated with LUPRON DEPOT 3.75 mg alone and 55 women treated with LUPRON DEPOT 3.75 mg plus norethindrone acetate 5 mg (LD/N) daily. The second study was an open label study in which 136 women were treated with monthly LUPRON DEPOT 3.75 mg plus norethindrone acetate 5 mg daily. This study confirmed the reduction in loss of bone mineral density that was observed in the controlled study. Suppression of menses was maintained throughout treatment in 84% and 73% of patients receiving LD/N, in the controlled study and open label study, respectively. The median time for menses resumption after treatment with LD/N was 8 weeks.

Figure 2 Illustrates the mean pain scores for the LD/N group from the controlled study.

**Figure 2**  
**Treatment Period Mean Pain Scores For LD/N\* Patients**



### 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  $\leq 30\%$  and/or hemoglobin  $\leq 10.2$  g/dL. Administration of LUPRON DEPOT 3.75 mg, concomitantly with iron, produced an increase of  $\geq 6\%$  hematocrit and  $\geq 2$  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  $\geq 36\%$  and hemoglobin of  $\geq 12$  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  $\geq 36\%$  AND HEMOGLOBIN  $\geq 12$  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  $\geq 25\%$  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  $\geq 25\%$  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. LUPRON DEPOT with norethindrone acetate 5 mg daily is also indicated for initial management of endometriosis and for management of recurrence of symptoms. (Refer also to norethindrone acetate prescribing information for [WARNINGS, PRECAUTIONS, CONTRAINDICATIONS](#) and [ADVERSE REACTIONS](#) associated with norethindrone acetate). Duration of initial treatment or retreatment should be limited to 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–3 Month 11.25 mg in females has been limited to women 18 years of age and older treated for no more than 6 months.

## **CONTRAINDICATIONS**

1. Hypersensitivity to GnRH, GnRH agonist analogs or any of the excipients in LUPRON DEPOT.
2. Undiagnosed abnormal vaginal bleeding.
3. 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.
4. Use in women who are breast-feeding. (See **Nursing Mothers** section.)
5. Norethindrone acetate is contraindicated in women with the following conditions:
  - Thrombophlebitis, thromboembolic disorders, cerebral apoplexy, or a past history of these conditions
  - Markedly impaired liver function or liver disease
  - Known or suspected carcinoma of the breast

## WARNINGS

1. 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.
2. Experience with LUPRON DEPOT–3 Month 11.25 mg in females has been limited to six months; therefore, exposure should be limited to six months of therapy.
3. Safe use of leuprolide acetate or norethindrone acetate in pregnancy has not been established clinically. Before starting treatment with LUPRON DEPOT pregnancy must be excluded.
4. 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.)
5. 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.
6. Symptoms consistent with an anaphylactoid or asthmatic process have been rarely reported post-marketing.
7. The following applies to co-treatment with LUPRON and norethindrone acetate:

Norethindrone acetate treatment should be discontinued if there is a sudden partial or complete loss of vision or if there is sudden onset of proptosis, diplopia, or migraine. If examination reveals papilledema or retinal vascular lesions, medication should be withdrawn.

Because of the occasional occurrence of thrombophlebitis and pulmonary embolism in patients taking progestogens, the physician should be alert to the earliest manifestations of the disease in women taking norethindrone acetate.

Assessment and management of risk factors for cardiovascular disease is recommended prior to initiation of add-back therapy with norethindrone acetate. Norethindrone acetate should be used with caution in women with risk factors, including lipid abnormalities or cigarette smoking.

## PRECAUTIONS

### Information for Patients

Patients should be aware of the following information:

1. Since menstruation usually stops 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.
2. 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.
3. 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.
4. 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.
5. Patients should be counseled on the possibility of the development or worsening of depression and the occurrence of memory disorders.
6. The induced hypoestrogenic state **also** results in a loss in bone density over the course of treatment, some of which may not be reversible. Clinical studies show that concurrent hormonal therapy with norethindrone acetate 5 mg daily is effective in reducing loss of bone mineral density that occurs with LUPRON. (All patients received calcium supplementation with 1000 mg elemental calcium.) (See *Changes in Bone Density* section).
7. If the symptoms of endometriosis recur after a course of therapy, retreatment with a six-month course of LUPRON DEPOT and norethindrone acetate 5 mg daily may be considered. Retreatment beyond this one 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. Retreatment with LUPRON DEPOT alone is not recommended.
8. 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 alone is instituted, and concomitant treatment with norethindrone acetate 5 mg daily should be considered. Retreatment with gonadotropin-releasing hormone analogs, including LUPRON is not advisable in patients with major risk factors for loss of bone mineral content.

9. Because norethindrone acetate may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, cardiac or renal dysfunctions require careful observation during norethindrone acetate add-back therapy.
10. Patients who have a history of depression should be carefully observed during treatment with norethindrone acetate and norethindrone acetate should be discontinued if severe depression occurs.

### **Convulsions**

There have been postmarketing reports of convulsions in patients on leuprolide acetate therapy. These included patients with and without concurrent medications and comorbid conditions.

### **Laboratory Tests**

See [ADVERSE REACTIONS](#) section.

### **Drug Interactions**

See [CLINICAL PHARMACOLOGY, Pharmacokinetics](#).

### **Drug/Laboratory Test Interactions**

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

### **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. 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.

## **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. Experience with LUPRON DEPOT for treatment of endometriosis has been limited to women 18 years of age and older. See LUPRON DEPOT-PED<sup>®</sup> (leuprolide acetate for depot suspension) labeling for the safety and effectiveness in children with central precocious puberty.

## Geriatric Use

This product has not been studied in women over 65 years of age and is not indicated in this population.

## 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  $\geq 5\%$  of patients in either of these populations and thought to be potentially related to drug are noted in the following table.

**Table 2 ADVERSE EVENTS REPORTED TO BE CAUSALLY RELATED TO DRUG IN  $\geq 5\%$  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: <i>Body as a Whole</i> - Body odor, Flu syndrome, Injection site reactions; <i>Cardiovascular System</i> - Palpitations, Syncope, Tachycardia; <i>Digestive System</i> - Appetite changes, Dry mouth, Thirst; <i>Endocrine System</i> - Androgen-like effects; <i>Hemic and Lymphatic System</i> - Ecchymosis, Lymphadenopathy; <i>Nervous System</i> - Anxiety*, Insomnia/Sleep disorders*, Delusions, Memory disorder, Personality disorder; <i>Respiratory System</i> - Rhinitis; <i>Skin and Appendages</i> - Alopecia, Hair disorder, Nail disorder; <i>Special Senses</i> - Conjunctivitis, Ophthalmologic disorders*, Taste perversion; <i>Urogenital System</i> - Dysuria*, Lactation, Menstrual disorders.										
* = Possible effect of decreased estrogen.										

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.

Table 3 lists the potentially drug-related adverse events observed in at least 5% of patients in any treatment group, during the first 6 months of treatment in the add-back clinical studies, in which patients were treated with monthly LUPRON DEPOT 3.75 mg with or without norethindrone acetate co-treatment.

**Table 3 TREATMENT-RELATED ADVERSE EVENTS OCCURRING IN ≥ 5% OF PATIENTS**

	Controlled Study				Open Label Study	
	LD - Only* N=51		LD/N† N=55		LD/N† N=136	
Adverse Events	N	(%)	N	(%)	N	(%)
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)
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)
* LD-Only = LUPRON DEPOT 3.75 mg						
† LD/N = LUPRON DEPOT 3.75 mg plus norethindrone acetate 5 mg						

In the controlled clinical trial, 50 of 51 (98%) patients in the LD group (LUPRON DEPOT 3.75 mg) and 48 of 55 (87%) patients in the LD/N group (LUPRON DEPOT 3.75 mg plus norethindrone acetate 5 mg daily) reported experiencing hot flashes on one or more occasions during treatment. During Month 6 of treatment, 32 of 37 (86%) patients in the LD group and 22 of 38 (58%) patients in the LD/N group reported having experienced hot flashes. The mean number of days on which hot flashes were reported during this month of treatment was 19 and 7 in the LD and LD/N treatment groups, respectively. The mean maximum number of hot flashes in a day during this month of treatment was 5.8 and 1.9 in the LD and LD/N treatment groups, respectively.

## 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. Clinical studies demonstrate that concurrent hormonal therapy (norethindrone acetate 5 mg daily) and calcium supplementation is effective in significantly reducing the loss of bone mineral density that occurs with LUPRON treatment, without compromising the efficacy of LUPRON in relieving symptoms of endometriosis. LUPRON DEPOT 3.75 mg plus norethindrone acetate 5 mg daily was evaluated in two clinical trials. The results from this regimen were similar in both studies. LUPRON DEPOT 3.75 mg was used as a control group in one study. The bone mineral density data of the lumbar spine from these two studies are presented in Table 4.

**Table 4 MEAN PERCENT CHANGE FROM BASELINE IN BONE MINERAL DENSITY OF LUMBAR SPINE**

	LUPRON DEPOT 3.75 mg		LUPRON DEPOT 3.75 mg plus norethindrone acetate 5 mg daily			
	Controlled Study		Controlled Study		Open Label Study	
	N	Change (Mean, 95% CI) <sup>#</sup>	N	Change (Mean, 95% CI) <sup>#</sup>	N	Change (Mean, 95% CI) <sup>#</sup>
Week 24*	41	-3.2% (-3.8, -2.6)	42	-0.3% (-0.8, 0.3)	115	-0.2% (-0.6, 0.2)
Week 52 <sup>†</sup>	29	-6.3% (-7.1, -5.4)	32	-1.0% (-1.9, -0.1)	84	-1.1% (-1.6, -0.5)
* Includes on-treatment measurements that fell within 2-252 days after the first day of treatment.						
<sup>†</sup> Includes on-treatment measurements >252 days after the first day of treatment.						
<sup>#</sup> 95% CI: 95% Confidence Interval						

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.

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

### 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.

In two other clinical trials, LUPRON DEPOT 3.75 mg plus norethindrone acetate 5 mg daily were evaluated for 12 months of treatment. LUPRON DEPOT 3.75 mg 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 the tables below.

**Table 5 SERUM LIPIDS: MEAN PERCENT CHANGES FROM BASELINE VALUES AT TREATMENT WEEK 24**

	LUPRON DEPOT 3.75 mg		LUPRON DEPOT 3.75 mg plus norethindrone acetate 5 mg daily			
	Controlled Study (n=39)		Controlled Study (n=41)		Open Label Study (n=117)	
	Baseline Value*	Wk 24 % Change	Baseline Value*	Wk 24 % Change	Baseline Value*	Wk 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	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%
* mg/dL						
† 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 6 PERCENTAGE OF PATIENTS WITH SERUM LIPID VALUES OUTSIDE OF THE NORMAL RANGE**

	LUPRON DEPOT 3.75 mg		LUPRON DEPOT 3.75 mg plus norethindrone acetate 5 mg daily			
	Controlled Study (n=39)		Controlled Study (n=41)		Open Label Study (n=117)	
	Wk 0	Wk 24*	Wk 0	Wk 24*	Wk 0	Wk 24*
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%

\* Includes all patients regardless of baseline value.

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 and norethindrone acetate.

## 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. In the hormonal add-back studies LUPRON DEPOT in combination with norethindrone acetate was associated with elevations of GGT and SGPT in 6% to 7% of patients.

## **Postmarketing**

The following adverse reactions have been identified during postapproval use of LUPRON DEPOT. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

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. There have been 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 development or worsening of depression during treatment with LUPRON.

Symptoms consistent with an anaphylactoid or asthmatic process have been rarely 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.

### **Other events reported are:**

*Hepato-biliary disorder:* Rarely reported serious liver injury

*Injury, poisoning and procedural complications:* Spinal fracture

*Investigations:* Decreased WBC

*Musculoskeletal and Connective tissue disorder:* Tenosynovitis-like symptoms

*Nervous System Disorder:* Convulsion, peripheral neuropathy, paralysis

*Vascular Disorder:* Hypotension

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 analogs and these events.

## **Pituitary apoplexy**

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

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 duration of treatment with LUPRON DEPOT–3 Month 11.25 mg alone or in combination with norethindrone acetate is six months. The choice of LUPRON DEPOT alone or LUPRON DEPOT plus norethindrone acetate therapy for initial management of the symptoms and signs of endometriosis should be made by the health care professional in consultation with the patient and should take into consideration the risks and benefits of the addition of norethindrone to LUPRON DEPOT alone.

If the symptoms of endometriosis recur after a course of therapy, retreatment with a six-month course of LUPRON DEPOT-3 Month 11.25 mg administered every three months and norethindrone acetate 5 mg daily may be considered. Retreatment beyond this one 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. LUPRON DEPOT alone is not recommended for retreatment. 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 norethindrone acetate.

### **Uterine Leiomyomata (Fibroids)**

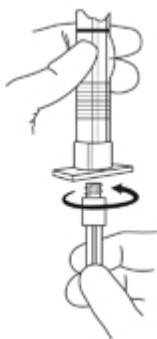
The recommended dose of LUPRON DEPOT–3 Month 11.25 mg is one injection. The symptoms associated with uterine leiomyomata will recur following discontinuation of therapy. If additional treatment with LUPRON DEPOT–3 Month 11.25 mg is contemplated, bone density should be assessed prior to initiation of 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.**

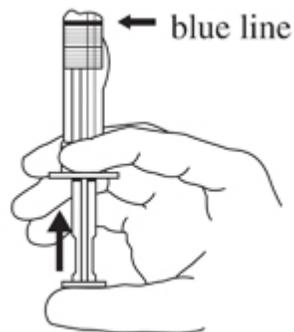
*For optimal performance of the prefilled dual chamber syringe (PDS), read and follow the following instructions:*

#### Reconstitution and Administration Instructions

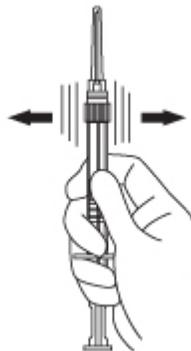
- The lyophilized microspheres are to be reconstituted and administered as a single intramuscular injection.
  - Since LUPRON DEPOT does not contain a preservative, the suspension should be injected immediately or discarded if not used within two hours.
  - As with other drugs administered by injection, the injection site should be varied periodically.
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 prior to mixing with the diluent. The diluent should appear clear.
  2. To prepare for injection, screw the white plunger into the end stopper until the stopper begins to turn.



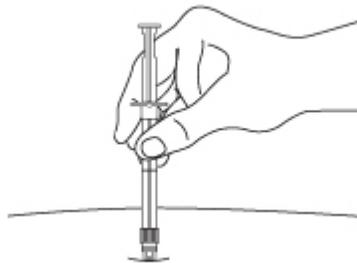
3. Hold the syringe UPRIGHT. Release the diluent by SLOWLY PUSHING (6 to 8 seconds) the plunger until the first stopper is at the blue line in the middle of the barrel.



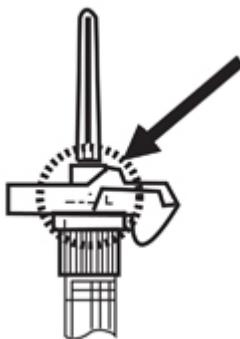
4. Keep the syringe UPRIGHT. Mix the microspheres (powder) thoroughly by gently shaking the syringe until the powder forms a uniform suspension. The suspension will appear milky. If the powder adheres to the stopper or caking/clumping is present, tap the syringe with your finger to disperse. DO NOT USE if any of the powder has not gone into suspension.



5. Hold the syringe UPRIGHT. With the opposite hand pull the needle cap upward without twisting.
6. Keep the syringe UPRIGHT. Advance the plunger to expel the air from the syringe. Now the syringe is ready for injection.
7. After cleaning the injection site with an alcohol swab, the intramuscular injection should be performed by inserting the needle at a 90 degree angle into the gluteal area, anterior thigh, or deltoid; injection sites should be alternated.



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<sup>®</sup> safety device. If blood is present remove the needle immediately. Do not inject the medication.



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

#### **AFTER INJECTION**

9. Withdraw the needle. Once the syringe has been withdrawn, activate immediately the LuproLoc<sup>®</sup> safety device by pushing the arrow on the lock upward towards the needle tip with the thumb or finger, as illustrated, until the needle cover of the safety device over the needle is fully extended and a **CLICK** is heard or felt.



## ADDITIONAL INFORMATION

- Dispose of the syringe according to local regulations/procedures.

## HOW SUPPLIED

Each LUPRON DEPOT – 3 Month 11.25 mg kit (NDC 0074-3663-03) contains:

- one prefilled dual-chamber syringe
- one plunger
- two alcohol swabs
- a complete prescribing information enclosure

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 the 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]

## REFERENCES

1. NIOSH Alert: Preventing occupational exposures to antineoplastic and other hazardous drugs in healthcare settings. 2004. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 2004-165.
2. OSHA Technical Manual, TED 1-0.15A, Section VI: Chapter 2. Controlling Occupational Exposure to Hazardous Drugs. OSHA, 1999.  
[http://www.osha.gov/dts/osta/otm/otm\\_vi/otm\\_vi\\_2.html](http://www.osha.gov/dts/osta/otm/otm_vi/otm_vi_2.html)

3. American Society of Health-System Pharmacists. ASHP guidelines on handling hazardous drugs. *Am J Health-Syst Pharm.* 2006; 63; 1172-1193.
4. Polovich, M., White, J.M., & Kelleher, L.O. (eds.) 2005. Chemotherapy and biotherapy guidelines and recommendations for practice (2nd. Ed.) Pittsburgh, PA: Oncology Nursing Society.

Manufactured for  
AbbVie Inc.  
North Chicago, IL 60064  
by Takeda Pharmaceutical Company Limited  
Osaka, Japan 540-8645

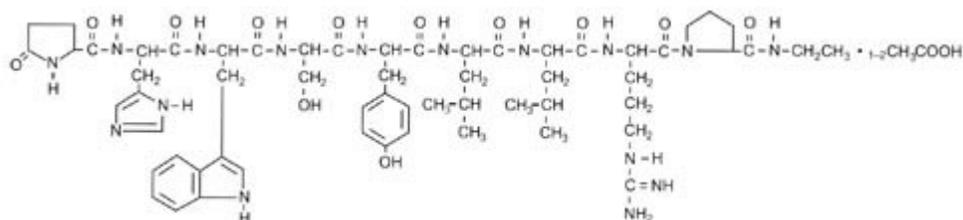
October, 2013

## LUPRON DEPOT<sup>®</sup> 3.75 mg (leuprolide acetate for depot suspension)

### Rx only

### DESCRIPTION

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



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

The front chamber of LUPRON DEPOT 3.75 mg prefilled dual-chamber syringe contains leuprolide acetate (3.75 mg), purified gelatin (0.65 mg), DL-lactic and glycolic acids copolymer (33.1 mg), and D-mannitol (6.6 mg). The second chamber of diluent contains carboxymethylcellulose sodium (5 mg), D-mannitol (50 mg), polysorbate 80 (1 mg), water for injection, USP, and glacial acetic acid, USP to control pH.

During the manufacture of LUPRON DEPOT 3.75 mg, acetic acid is lost, leaving the peptide.

### CLINICAL PHARMACOLOGY

Leuprolide acetate is a long-acting GnRH analog. A single monthly injection of LUPRON DEPOT 3.75 mg results in an initial stimulation followed by a prolonged suppression of pituitary gonadotropins.

Repeated dosing at monthly 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. Intramuscular injection of the depot formulation provides plasma concentrations of leuprolide over a period of one month.

## **Pharmacokinetics**

### **Absorption**

A single dose of LUPRON DEPOT 3.75 mg 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 postdosing. 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.

### **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 <sup>14</sup>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.

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

## **Excretion**

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

## **Special Populations**

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

## **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**

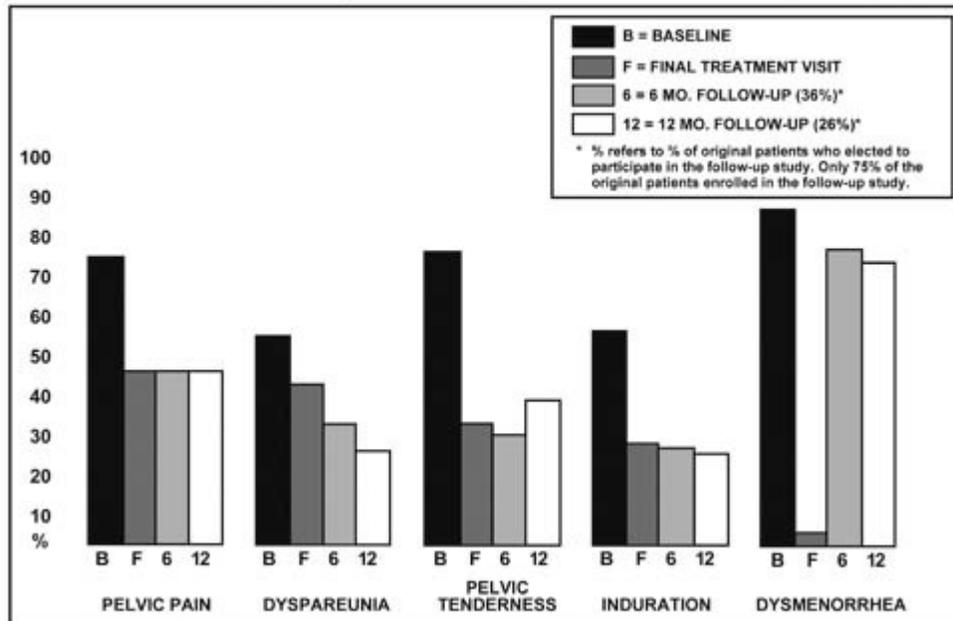
### **Endometriosis**

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% of patients, respectively, excluding those who became 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 two controlled clinical studies. This included all patients at end of treatment and those who elected to participate in the follow-up period. This might provide a slight bias in the results at follow-up as 75% of the original patients entered the follow-up study, and 36% were evaluated at 6 months and 26% at 12 months.

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

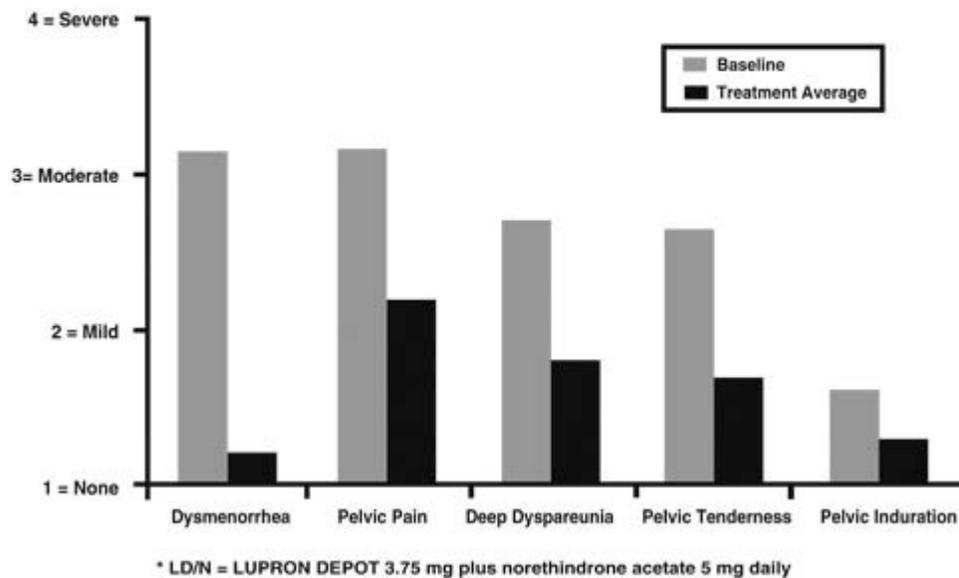


### **Hormonal replacement therapy**

Two clinical studies with a treatment duration of 12 months indicate that concurrent hormonal therapy (norethindrone acetate 5 mg daily) is effective in significantly reducing the loss of bone mineral density associated with LUPRON, without compromising the efficacy of LUPRON in relieving symptoms of endometriosis. (All patients in these studies received calcium supplementation with 1000 mg elemental calcium). One controlled, randomized and double-blind study included 51 women treated with LUPRON DEPOT alone and 55 women treated with LUPRON plus norethindrone acetate 5 mg daily. The second study was an open label study in which 136 women were treated with LUPRON plus norethindrone acetate 5 mg daily. This study confirmed the reduction in loss of bone mineral density that was observed in the controlled study. Suppression of menses was maintained throughout treatment in 84% and 73% of patients receiving LD/N in the controlled study and open label study, respectively. The median time for menses resumption after treatment with LD/N was 8 weeks.

Figure 2 illustrates the mean pain scores for the LD/N group from the controlled study.

**Figure 2**  
**Treatment Period Mean Pain Scores For LD/N\* Patients**



### **Uterine Leiomyomata (Fibroids)**

In controlled clinical trials, administration of LUPRON DEPOT 3.75 mg for a period of three or six months was shown to decrease uterine and fibroid volume, thus allowing for relief of clinical symptoms (abdominal bloating, pelvic pain, and pressure). Excessive vaginal bleeding (menorrhagia and menometrorrhagia) decreased, resulting in improvement in hematologic parameters.

In three 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. These patients also experienced a decrease in symptoms including excessive vaginal bleeding and pelvic discomfort. Benefit occurred by three months of therapy, but additional gain was observed with an additional three months of LUPRON DEPOT 3.75 mg. Ninety-five percent of these patients became amenorrheic with 61%, 25%, and 4% experiencing amenorrhea during the first, second, and third treatment months respectively.

Post-treatment follow-up was carried out for a small percentage of LUPRON DEPOT 3.75 mg patients among the 77% who demonstrated a  $\geq 25\%$  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.

In another controlled clinical study, enrollment was based on hematocrit  $\leq 30\%$  and/or hemoglobin  $\leq 10.2$  g/dL. Administration of LUPRON DEPOT 3.75 mg, concomitantly with iron, produced an increase of  $\geq 6\%$  hematocrit and  $\geq 2$  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  $\geq 36\%$  and hemoglobin of  $\geq 12$  g/dL, thus allowing for autologous blood donation prior to surgery. At three months, 75% of patients met this criterion.

At three months, 80% of patients experienced relief from either menorrhagia or menometrorrhagia. As with the previous studies, episodes of spotting and menstrual-like bleeding were noted in some patients.

In this same study, a decrease of  $\geq 25\%$  was seen in uterine and myoma volumes in 60% and 54% of patients respectively. LUPRON DEPOT 3.75 mg was found to relieve symptoms of bloating, pelvic pain, and pressure.

There is no evidence that pregnancy rates are enhanced or adversely affected by the use of LUPRON DEPOT 3.75 mg.

## **INDICATIONS AND USAGE**

### **Endometriosis**

LUPRON DEPOT 3.75 mg is indicated for management of endometriosis, including pain relief and reduction of endometriotic lesions. LUPRON DEPOT monthly with norethindrone acetate 5 mg daily is also indicated for initial management of endometriosis and for management of recurrence of symptoms. (Refer also to norethindrone acetate prescribing information for [WARNINGS, PRECAUTIONS, CONTRAINDICATIONS](#) and [ADVERSE REACTIONS](#) associated with norethindrone acetate). Duration of initial treatment or retreatment should be limited to 6 months.

### **Uterine Leiomyomata (Fibroids)**

LUPRON DEPOT 3.75 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](#).) LUPRON may be added if the response to iron alone is considered inadequate. Recommended duration of therapy with LUPRON DEPOT 3.75 mg is **up to** three months.

Experience with LUPRON DEPOT in females has been limited to women 18 years of age and older.

**Table 1 PERCENT OF PATIENTS ACHIEVING HEMOGLOBIN  $\geq$  12 GM/DL**

<b>Treatment Group</b>	<b>Week 4</b>	<b>Week 8</b>	<b>Week 12</b>
LUPRON DEPOT 3.75 mg with Iron	41*	71†	79*
Iron Alone	17	40	56
* P-Value < 0.01			
† P-Value < 0.001			

## CONTRAINDICATIONS

1. Hypersensitivity to GnRH, GnRH agonist analogs or any of the excipients in LUPRON DEPOT.
2. Undiagnosed abnormal vaginal bleeding.
3. 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.
4. Use in women who are breast-feeding. (See [Nursing Mothers](#) section.)
5. Norethindrone acetate is contraindicated in women with the following conditions:
  - Thrombophlebitis, thromboembolic disorders, cerebral apoplexy, or a past history of these conditions
  - Markedly impaired liver function or liver disease
  - Known or suspected carcinoma of the breast

## WARNINGS

Safe use of leuprolide acetate or norethindrone acetate in pregnancy has not been established clinically. Before starting treatment with LUPRON DEPOT, pregnancy must be excluded.

When used monthly at the recommended dose, 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.

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.

Symptoms consistent with an anaphylactoid or asthmatic process have been rarely reported post-marketing.

The following applies to co-treatment with LUPRON and norethindrone acetate:

Norethindrone acetate treatment should be discontinued if there is a sudden partial or complete loss of vision or if there is sudden onset of proptosis, diplopia, or migraine. If examination reveals papilledema or retinal vascular lesions, medication should be withdrawn.

Because of the occasional occurrence of thrombophlebitis and pulmonary embolism in patients taking progestogens, the physician should be alert to the earliest manifestations of the disease in women taking norethindrone acetate.

Assessment and management of risk factors for cardiovascular disease is recommended prior to initiation of add-back therapy with norethindrone acetate. Norethindrone acetate should be used with caution in women with risk factors, including lipid abnormalities or cigarette smoking.

## **PRECAUTIONS**

### **Information for Patients**

Patients should be aware of the following information:

1. Since menstruation usually stops 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.
2. 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.

3. Safe use of the drug in pregnancy has not been established clinically. 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.
4. 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.
5. Patients should be counseled on the possibility of the development or worsening of depression and the occurrence of memory disorders.
6. The induced hypoestrogenic state **also** results in a loss in bone density over the course of treatment, some of which may not be reversible. Clinical studies show that concurrent hormonal therapy with norethindrone acetate 5 mg daily is effective in reducing loss of bone mineral density that occurs with LUPRON. (All patients received calcium supplementation with 1000 mg elemental calcium.) (See *Changes in Bone Density* section).
7. If the symptoms of endometriosis recur after a course of therapy, retreatment with a six-month course of LUPRON DEPOT and norethindrone acetate 5 mg daily may be considered. Retreatment beyond this one 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. Retreatment with LUPRON DEPOT alone is not recommended.
8. 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 alone is instituted, and concomitant treatment with norethindrone acetate 5 mg daily should be considered. Retreatment with gonadotropin-releasing hormone analogs, including LUPRON is not advisable in patients with major risk factors for loss of bone mineral content.
9. Because norethindrone acetate may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, cardiac or renal dysfunctions require careful observation during norethindrone acetate add-back therapy.
10. Patients who have a history of depression should be carefully observed during treatment with norethindrone acetate and norethindrone acetate should be discontinued if severe depression occurs.

## **Convulsions**

There have been postmarketing reports of convulsions in patients on leuprolide acetate therapy. These included patients with and without concurrent medications and comorbid conditions.

## **Laboratory Tests**

See [ADVERSE REACTIONS](#) section.

## **Drug Interactions**

See [CLINICAL PHARMACOLOGY, Pharmacokinetics](#).

## **Drug/Laboratory Test Interactions**

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

## **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. 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.

### **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**

Experience with LUPRON DEPOT 3.75 mg for treatment of endometriosis has been limited to women 18 years of age and older. See LUPRON DEPOT-PED<sup>®</sup> (leuprolide acetate for depot suspension) labeling for the safety and effectiveness in children with central precocious puberty.

#### **Geriatric Use**

This product has not been studied in women over 65 years of age and is not indicated in this population.

## **ADVERSE REACTIONS**

### **Clinical Trials**

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

As would be expected with a drug that lowers serum estradiol levels, the most frequently reported adverse reactions were those related to hypoestrogenism.

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  $\geq 5\%$  of patients in either of these populations and thought to be potentially related to drug are noted in the following table.

**Table 2 ADVERSE EVENTS REPORTED TO BE CAUSALLY RELATED TO DRUG IN  $\geq 5\%$  OF PATIENTS**

	Endometriosis (2 Studies)						Uterine Fibroids (4 Studies)			
	LUPRON DEPOT 3.75 mg N=166		Danazol N=136		Placebo N=31		LUPRON DEPOT 3.75 mg N=166		Placebo 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.

\* = Possible effect of decreased estrogen.

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.

Table 3 lists the potentially drug-related adverse events observed in at least 5% of patients in any treatment group during the first 6 months of treatment in the add-back clinical studies.

In the controlled clinical trial, 50 of 51 (98%) patients in the LD group and 48 of 55 (87%) patients in the LD/N group reported experiencing hot flashes on one or more occasions during treatment. During Month 6 of treatment, 32 of 37 (86%) patients in the LD group and 22 of 38 (58%) patients in the LD/N group reported having experienced hot flashes. The mean number of days on which hot flashes were reported during this month of treatment was 19 and 7 in the LD and LD/N treatment groups, respectively. The mean maximum number of hot flashes in a day during this month of treatment was 5.8 and 1.9 in the LD and LD/N treatment groups, respectively.

**Table 3 TREATMENT-RELATED ADVERSE EVENTS OCCURRING IN ≥5% OF PATIENTS**

	Controlled Study				Open Label Study	
	LD - Only* N=51		LD/N† N=55		LD/N† N=136	
Adverse Events	N	(%)	N	(%)	N	(%)
<i>Any Adverse Event</i>	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)
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)
* LD-Only = LUPRON DEPOT 3.75 mg						
† LD/N = LUPRON DEPOT 3.75 mg plus norethindrone acetate 5 mg						

### 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. Clinical studies demonstrate that concurrent hormonal therapy (norethindrone acetate 5 mg daily) and calcium supplementation is effective in significantly reducing the loss of bone mineral density that occurs with LUPRON treatment, without compromising the efficacy of LUPRON in relieving symptoms of endometriosis.

LUPRON DEPOT 3.75 mg plus norethindrone acetate 5 mg daily was evaluated in two clinical trials. The results from this regimen were similar in both studies. LUPRON DEPOT 3.75 mg was used as a control group in one study. The bone mineral density data of the lumbar spine from these two studies are presented in Table 4.

**Table 4 MEAN PERCENT CHANGE FROM BASELINE IN BONE MINERAL DENSITY OF LUMBAR SPINE**

	LUPRON DEPOT 3.75mg		LUPRON DEPOT 3.75 mg plus norethindrone acetate 5 mg daily			
	Controlled Study		Controlled Study		Open Label Study	
	N	Change (Mean, 95% CI) <sup>#</sup>	N	Change (Mean, 95% CI) <sup>#</sup>	N	Change (Mean, 95% CI) <sup>#</sup>
Week 24*	41	-3.2% (-3.8, -2.6)	42	-0.3% (-0.8, 0.3)	115	-0.2% (-0.6, 0.2)
Week 52 <sup>†</sup>	29	-6.3% (-7.1, -5.4)	32	-1.0% (-1.9, -0.1)	84	-1.1% (-1.6, -0.5)

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

† Includes on-treatment measurements >252 days after the first day of treatment.
# 95% CI: 95% Confidence Interval

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

### Plasma Enzymes

#### Endometriosis

During early clinical trials with LUPRON DEPOT 3.75 mg, regular laboratory monitoring revealed that AST levels were more than twice the upper limit of normal in only one patient. There was no clinical or other laboratory evidence of abnormal liver function.

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

#### Uterine Leiomyomata (Fibroids)

In clinical trials with LUPRON DEPOT 3.75 mg, 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.

### Lipids

#### Endometriosis

In earlier clinical studies, 4% of the LUPRON DEPOT 3.75 mg patients and 1% of the danazol patients had total cholesterol values above the normal range at enrollment. 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 3.75 mg patients and 9% of the danazol patients had post-treatment values above the normal range.

The mean ( $\pm$ SEM) pretreatment values for total cholesterol from all patients were 178.8 (2.9) mg/dL in the LUPRON DEPOT 3.75 mg groups and 175.3 (3.0) mg/dL in the danazol group. At the end of treatment, the mean values for total cholesterol from all patients were 193.3 mg/dL in the LUPRON DEPOT 3.75 mg group and 194.4 mg/dL 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 and in 6% of the patients who received danazol.

At the end of treatment, HDL cholesterol fractions decreased below the lower limit of the normal range in 2% of the LUPRON DEPOT 3.75 mg patients compared with 54% of those receiving danazol. LDL cholesterol fractions increased above the upper limit of the normal range in 6% of the patients receiving LUPRON DEPOT 3.75 mg compared with 23% of those receiving danazol. There was no increase in the LDL/HDL ratio in patients receiving LUPRON DEPOT 3.75 mg but there was approximately a two-fold increase in the LDL/HDL ratio in patients receiving danazol.

In two other clinical trials, LUPRON DEPOT 3.75 mg plus norethindrone acetate 5 mg daily was evaluated for 12 months of treatment. LUPRON DEPOT 3.75 mg 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 the tables below.

**Table 5 SERUM LIPIDS: MEAN PERCENT CHANGES FROM BASELINE VALUES AT TREATMENT WEEK 24**

	LUPRON		LUPRON plus norethindrone acetate 5 mg daily			
	Controlled Study (n=39)		Controlled Study (n=41)		Open Label Study (n=117)	
	Baseline Value*	Wk 24 % Change	Baseline Value*	Wk 24 % Change	Baseline Value*	Wk 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	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%
* mg/dL						
† 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 6 PERCENTAGE OF PATIENTS WITH SERUM LIPID VALUES OUTSIDE OF THE NORMAL RANGE**

	LUPRON	LUPRON plus norethindrone acetate 5 mg daily

	Controlled Study (n=39)		Controlled Study (n=41)		Open Label Study (n=117)	
	Wk 0	Wk 24*	Wk 0	Wk 24*	Wk 0	Wk 24*
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%

\* Includes all patients regardless of baseline value.

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 and norethindrone acetate.

#### **Uterine Leiomyomata (Fibroids)**

In patients receiving LUPRON DEPOT 3.75 mg, 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**

The following changes were seen in approximately 5% to 8% of patients. In the earlier comparative studies, LUPRON DEPOT 3.75 mg was associated with elevations of LDH and phosphorus, and decreases in WBC counts. Danazol therapy was associated with increases in hematocrit, platelet count, and LDH. In the hormonal add-back studies LUPRON DEPOT in combination with norethindrone acetate was associated with elevations of GGT and SGPT.

##### **Uterine Leiomyomata (Fibroids)**

Hematology: (see [CLINICAL STUDIES](#) section) In LUPRON DEPOT 3.75 mg 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.

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**

The following adverse reactions have been identified during postapproval use of LUPRON DEPOT. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

During postmarketing surveillance, the following adverse events were reported. Like other drugs in this class, mood swings, including depression, have been reported. There have been 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 development or worsening of depression during treatment with LUPRON.

Symptoms consistent with an anaphylactoid or asthmatic process have been rarely 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 disorder, gastrointestinal distress, and shortness of breath) have been reported individually and collectively.

Other events reported are:

*Hepato-biliary disorder:* Rarely reported serious liver injury

*Injury, poisoning and procedural complications:* Spinal fracture

*Investigations:* Decreased WBC

*Musculoskeletal and Connective tissue disorder:* Tenosynovitis-like symptoms

*Nervous System Disorder:* Convulsion, peripheral neuropathy, paralysis

*Vascular Disorder:* Hypotension

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 analogs and these events.

### **Pituitary apoplexy**

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

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

### **OVERDOSAGE**

In rats subcutaneous administration of 250 to 500 times the recommended human dose, expressed on a per body weight basis, resulted in dyspnea, decreased activity, and local irritation at the injection site. There is no evidence that there is a clinical counterpart of this phenomenon. In early clinical trials 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 duration of treatment with LUPRON DEPOT 3.75 mg alone or in combination with norethindrone acetate is six months. The choice of LUPRON DEPOT alone or LUPRON DEPOT plus norethindrone acetate therapy for initial management of the symptoms and signs of endometriosis should be made by the health care professional in consultation with the patient and should take into consideration the risks and benefits of the addition of norethindrone to LUPRON DEPOT alone.

If the symptoms of endometriosis recur after a course of therapy, retreatment with a six-month course of LUPRON DEPOT administered monthly and norethindrone acetate 5 mg daily may be

considered. Retreatment beyond this one 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. LUPRON DEPOT alone is not recommended for retreatment. 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 norethindrone acetate.

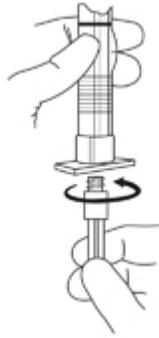
### **Uterine Leiomyomata (Fibroids)**

*Recommended duration of therapy with LUPRON DEPOT 3.75 mg is **up to 3 months**. The symptoms associated with uterine leiomyomata will recur following discontinuation of therapy. If additional treatment with LUPRON DEPOT 3.75 mg is contemplated, bone density should be assessed prior to initiation of therapy to ensure that values are within normal limits.*

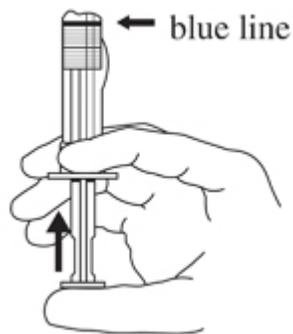
The recommended dose of LUPRON DEPOT is 3.75 mg, incorporated in a depot formulation. *For optimal performance of the prefilled dual chamber syringe (PDS), read and follow the following instructions:*

#### Reconstitution and Administration Instructions

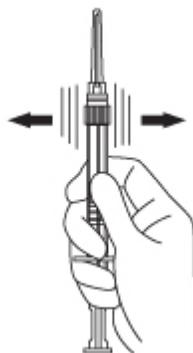
- The lyophilized microspheres are to be reconstituted and administered as a single intramuscular injection.
  - Since LUPRON DEPOT does not contain a preservative, the suspension should be injected immediately or discarded if not used within two hours.
  - As with other drugs administered by injection, the injection site should be varied periodically.
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 prior to mixing with the diluent. 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. Hold the syringe UPRIGHT. Release the diluent by SLOWLY PUSHING (6 to 8 seconds) the plunger until the first stopper is at the blue line in the middle of the barrel.

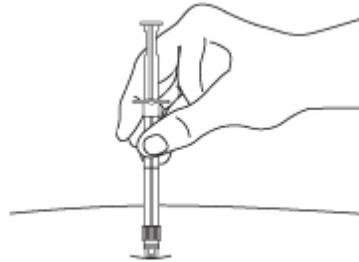


4. Keep the syringe UPRIGHT. Mix the microspheres (powder) thoroughly by gently shaking the syringe until the powder forms a uniform suspension. The suspension will appear milky. If the powder adheres to the stopper or caking/clumping is present, tap the syringe with your finger to disperse. DO NOT USE if any of the powder has not gone into suspension.

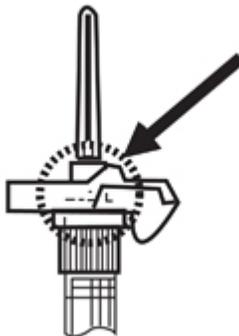


5. Hold the syringe UPRIGHT. With the opposite hand pull the needle cap upward without twisting.

6. Keep the syringe UPRIGHT. Advance the plunger to expel the air from the syringe. Now the syringe is ready for injection.
7. After cleaning the injection site with an alcohol swab, the intramuscular injection should be performed by inserting the needle at a 90 degree angle into the gluteal area, anterior thigh, or deltoid; injection sites should be alternated.



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<sup>®</sup> safety device. If blood is present remove the needle immediately. Do not inject the medication.

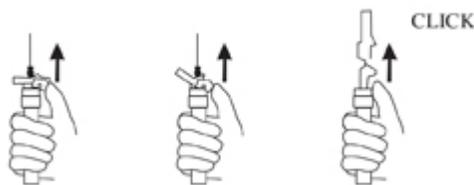


8. Inject the entire contents of the syringe intramuscularly at the time of reconstitution. The suspension settles very quickly following reconstitution; therefore, LUPRON DEPOT should be mixed and used immediately.

#### **AFTER INJECTION**

9. Withdraw the needle. Once the syringe has been withdrawn, activate immediately the LuproLoc<sup>®</sup> safety device by pushing the arrow on the lock upward towards the needle tip

with the thumb or finger, as illustrated, until the needle cover of the safety device over the needle is fully extended and a **CLICK** is heard or felt.



### **ADDITIONAL INFORMATION**

- Dispose of the syringe according to local regulations/procedures.

### **HOW SUPPLIED**

Each LUPRON DEPOT 3.75 mg kit (NDC 0074-3641-03) contains:

- one prefilled dual-chamber syringe
- one plunger
- two alcohol swabs
- a complete prescribing information enclosure

Each syringe contains sterile lyophilized microspheres, which is leuprolide incorporated in a biodegradable copolymer of lactic and glycolic acids. When mixed with diluent, LUPRON DEPOT 3.75 mg is administered as a single monthly IM injection.

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

### **REFERENCES**

1. NIOSH Alert: Preventing occupational exposures to antineoplastic and other hazardous drugs in healthcare settings. 2004. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 2004-165.
2. OSHA Technical Manual, TED 1-0.15A, Section VI: Chapter 2. Controlling Occupational Exposure to Hazardous Drugs. OSHA, 1999.  
[http://www.osha.gov/dts/osta/otm/otm\\_vi/otm\\_vi\\_2.html](http://www.osha.gov/dts/osta/otm/otm_vi/otm_vi_2.html)

3. American Society of Health-System Pharmacists. ASHP guidelines on handling hazardous drugs. *Am J Health-Syst Pharm.* 2006; 63; 1172-1193.
4. Polovich, M., White, J.M., & Kelleher, L.O. (eds.) 2005. Chemotherapy and biotherapy guidelines and recommendations for practice (2nd. Ed.) Pittsburgh, PA: Oncology Nursing Society.

Manufactured for  
AbbVie Inc.  
North Chicago, IL 60064  
by Takeda Pharmaceutical Company Limited  
Osaka, Japan 540-8645

October, 2013

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use LUPANETA PACK safely and effectively. See full prescribing information for LUPANETA PACK.

LUPANETA PACK (leuprolide acetate for depot suspension; norethindrone acetate tablets), co-packaged for intramuscular use and for oral use, respectively  
Initial U.S. Approval: 2012

### RECENT MAJOR CHANGES

Warnings and Precautions, Convulsions (5.9) 10/2013

### INDICATIONS AND USAGE

LUPANETA PACK contains leuprolide acetate, a gonadotropin-releasing hormone (GnRH) agonist and norethindrone acetate, a progestin, indicated for

- Initial management of the painful symptoms of endometriosis (1)
- Management of recurrence of symptoms (1)

Limitations of Use: Initial treatment course is limited to 6 months and use is not recommended longer than a total of 12 months due to concerns about adverse impact on bone mineral density. (1, 2.1, 5.1)

### DOSAGE AND ADMINISTRATION

- Leuprolide acetate for depot suspension 3.75 mg given by a healthcare provider as a single intramuscular injection every month for up to six injections (6 months of therapy) (2.1)
- Norethindrone acetate 5 mg tablets taken orally by the patient once per day for up to 6 months (2.1)
- If endometriosis symptoms recur after initial course of therapy, consider retreatment for up to another six months (2.1)
- Assess bone density before retreatment begins (2.1, 5.1)
- Reconstitute leuprolide acetate prior to use, see important administration instructions (2.3)

### DOSAGE FORMS AND STRENGTHS

- Leuprolide acetate for depot suspension 3.75 mg syringe (3)
- Norethindrone acetate 5 mg tablets; 30 count bottle (3)

### CONTRAINDICATIONS

- Hypersensitivity to GnRH, GnRH agonist or any of the excipients in leuprolide acetate for depot suspension or norethindrone acetate (4)

- Undiagnosed abnormal uterine bleeding (4)
- Pregnancy or suspected pregnancy (4, 8.1)
- Women who are breast-feeding (4)
- Known, suspected or history of breast or other hormone-sensitive cancer (4)
- Thrombotic or thromboembolic disorders (4)
- Liver tumors or liver disease (4)

### WARNINGS AND PRECAUTIONS

- Loss of bone mineral density: do not use for more than two six-month treatment courses. (1, 2.1, 5.1)
- Exclude pregnancy before starting treatment and discontinue use if pregnancy occurs; use non-hormonal methods of contraception only. (5.2)
- Discontinue in case of sudden loss of vision or onset of proptosis, diplopia or migraine. (5.3)
- Carefully observe patients with history of depression and discontinue the drug if the depression recurs to a serious degree. (5.4)
- Assess and manage risk factors for cardiovascular disease before starting LUPANETA PACK. (5.6)

### ADVERSE REACTIONS

Leuprolide acetate for depot suspension: Most common related adverse reactions (>10%) were hot flashes/sweats, headache/migraine, depression/emotional lability, nausea/vomiting, nervousness/anxiety, insomnia, pain, acne, asthenia, vaginitis, weight gain, constipation/diarrhea (6.1)

Progestins: breakthrough bleeding, spotting (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact AbbVie Inc. at 1-800-633-9110 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch)

### USE IN SPECIFIC POPULATIONS

Pediatric: Safety and effectiveness of LUPANETA PACK has not been established in pediatric patients. (8.4)

Geriatric: LUPANETA PACK has not been studied in women over 65 years of age and is not indicated in this population. (8.5)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 10/2013

## FULL PRESCRIBING INFORMATION: CONTENTS\*

### 1 INDICATIONS AND USAGE

### 2 DOSAGE AND ADMINISTRATION

- 2.1 Dosing Information
- 2.2 Different Formulations of Leuprolide Acetate
- 2.3 Reconstitution and Administration for Injection of Leuprolide Acetate

### 3 DOSAGE FORMS AND STRENGTHS

### 4 CONTRAINDICATIONS

### 5 WARNINGS AND PRECAUTIONS

- 5.1 Loss of Bone Mineral Density
- 5.2 Pregnancy Risk
- 5.3 Visual Abnormalities
- 5.4 Clinical Depression
- 5.5 Serious Allergic Reactions
- 5.6 Cardiovascular and Metabolic Disorders
- 5.7 Initial Flare of Symptoms
- 5.8 Fluid Retention
- 5.9 Convulsions

### 6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience
- 6.2 Postmarketing Experience

### 7 DRUG INTERACTIONS

- 7.1 Drug-Drug Interactions

### 7.2 Drug/Laboratory Test Interactions

### 8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use

### 11 DESCRIPTION

### 12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

### 13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

### 14 CLINICAL STUDIES

### 15 REFERENCES

### 16 HOW SUPPLIED/STORAGE AND HANDLING

### 17 PATIENT COUNSELING INFORMATION

\* Sections or subsections omitted from the full prescribing information are not listed

# FULL PRESCRIBING INFORMATION

## 1 INDICATIONS AND USAGE

LUPANETA PACK (leuprolide acetate for depot suspension and norethindrone acetate tablets) is indicated for initial management of the painful symptoms of endometriosis and for management of recurrence of symptoms.

Limitation of Use: Duration of use is limited due to concerns about adverse impact on bone mineral density [see *Warnings and Precautions (5.1)*]. The initial treatment course of LUPANETA PACK is limited to six months. A single retreatment course of not more than six months may be administered after the initial course of treatment if symptoms recur. Use of LUPANETA PACK for longer than a total of 12 months is not recommended.

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Dosing Information

LUPANETA PACK is a co-packaging of leuprolide acetate for depot suspension for intramuscular use and norethindrone acetate tablets for oral use. Administer as follows:

- 3.75 mg of leuprolide acetate by intramuscular injection once a month for up to six injections (6 months of therapy); to be administered by a healthcare provider
- 5 mg of norethindrone acetate orally once daily for up to 6 months of therapy

The initial course of treatment with leuprolide acetate for depot suspension 3.75 mg in combination with norethindrone acetate 5 mg daily is not to exceed six months.

If the symptoms of endometriosis recur after the initial course of therapy, consider retreatment with LUPANETA PACK for up to another six months. It is recommended that bone density be assessed before retreatment begins [see *Warnings and Precautions (5.1)*].

Treatment beyond two six-month courses has not been studied and is not recommended due to concerns about adverse impact on bone mineral density.

### 2.2 Different Formulations of Leuprolide Acetate

Due to the specific release characteristics of the 1-month depot formulation, HCPs should not administer 3 doses of the 3.75 mg 1-month formulation simultaneously to mimic the pharmacological profile of the 11.25 mg 3-month formulation.

### 2.3 Reconstitution and Administration for Injection of Leuprolide Acetate

- Reconstitute and administer the lyophilized microspheres as a single intramuscular injection.
  - Inject the suspension immediately or discard if not used within two hours, because leuprolide acetate for depot suspension does not contain a preservative.
1. Visually inspect the leuprolide acetate for depot suspension powder. **DO NOT USE** the syringe if clumping or caking is evident. A thin layer of powder on the wall of the syringe is considered normal prior to mixing with the diluent. The diluent should appear clear.
  2. To prepare for injection, screw the white plunger into the end stopper until the stopper begins to turn (see Figure 1 and Figure 2).

Figure 1:

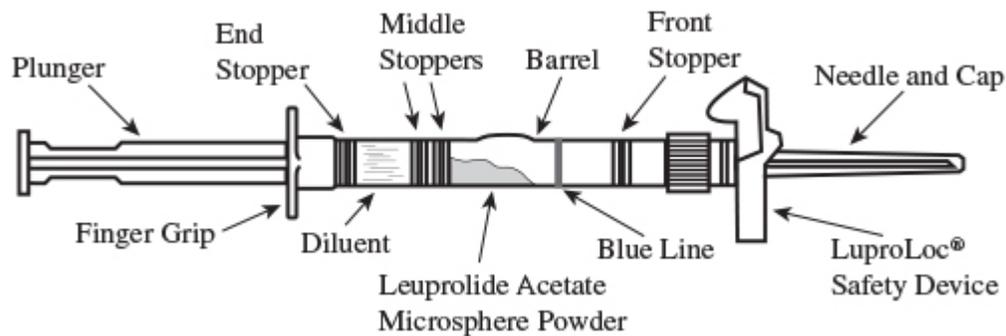
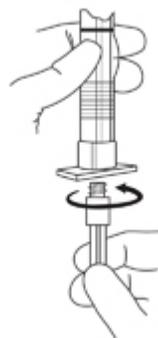
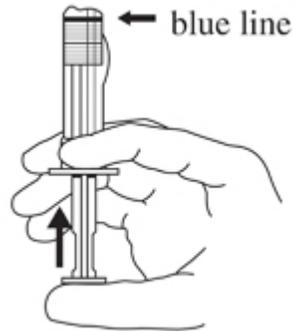


Figure 2:



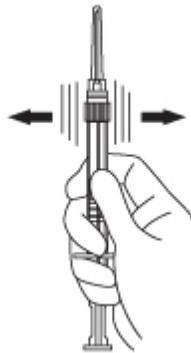
3. Hold the syringe UPRIGHT. Release the diluent by SLOWLY PUSHING (6 to 8 seconds) the plunger until the first middle stopper is at the blue line in the middle of the barrel (see Figure 3).

Figure 3:



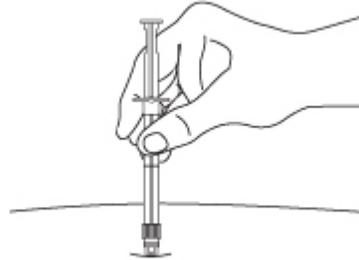
4. Keep the syringe UPRIGHT. Mix the microspheres (powder) thoroughly by gently shaking the syringe until the powder forms a uniform suspension. The suspension will appear milky. If the powder adheres to the stopper or caking/clumping is present, tap the syringe with your finger to disperse. DO NOT USE if any of the powder has not gone into suspension (see Figure 4).

Figure 4:



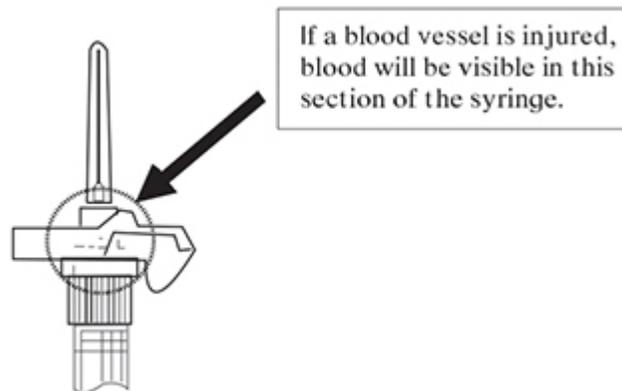
5. Keep the syringe UPRIGHT. With the opposite hand pull the needle cap upward without twisting.
6. Keep the syringe UPRIGHT. Advance the plunger to expel the air from the syringe. Now the syringe is ready for injection.
7. After cleaning the injection site with an alcohol swab, administer the intramuscular injection by inserting the needle at a 90 degree angle into the gluteal area, anterior thigh, or deltoid (see Figure 5). Alternate injection sites.

Figure 5:



NOTE: If a blood vessel is accidentally penetrated, aspirated blood will be visible just below the luer lock (see Figure 6) and can be seen through the transparent LuproLoc safety device. If blood is present, remove the needle immediately. Do not inject the medication.

Figure 6:



8. Inject the entire contents of the syringe intramuscularly.
9. Withdraw the needle. Once the syringe has been withdrawn, immediately activate the LuproLoc<sup>®</sup> safety device by pushing the arrow on the lock upward towards the needle tip with the thumb or finger, as illustrated, until the needle cover of the safety device over the needle is fully extended and a CLICK is heard or felt (see Figure 7).

Figure 7:



10. Dispose of the syringe according to local regulations/procedures [see References (15)].

### 3 DOSAGE FORMS AND STRENGTHS

LUPANETA PACK 1-month copackaged kit contains two separate components:

- Leuprolide acetate for depot suspension 3.75 mg for 1-month administration: Leuprolide acetate lyophilized powder for reconstitution with supplied diluent in a prefilled dual chamber syringe
- Norethindrone acetate 5 mg tablets: White to off-white oval, flat-faced beveled edged, uncoated debossed with 'G with breakline' on one side and 304 on other side

### 4 CONTRAINDICATIONS

LUPANETA PACK is contraindicated in women with the following:

- Hypersensitivity to gonadotropin-releasing hormone (GnRH), GnRH agonist analogs, any of the excipients in leuprolide acetate for depot suspension, or norethindrone acetate
- Undiagnosed abnormal uterine bleeding
- Known, suspected or planned pregnancy during the course of therapy [see Use in Specific Populations (8.1)]
- Lactating women [see Use in Specific Populations (8.3)]
- Known, suspected or history of breast cancer or other hormone-sensitive cancer
- Current or history of thrombotic or thromboembolic disorder
- Liver tumors or liver disease

## **5 WARNINGS AND PRECAUTIONS**

### **5.1 Loss of Bone Mineral Density**

Leuprolide acetate for depot suspension induces a hypoestrogenic state that results in loss of bone mineral density (BMD), some of which may not be reversible. Concurrent use of norethindrone acetate is effective in reducing the loss of BMD that occurs with leuprolide acetate [see *Clinical Studies (14)*]. Nonetheless, duration of use of LUPANETA PACK is limited to two six-month courses of treatment due to concerns about the adverse impact on BMD. It is recommended that BMD be assessed before retreatment. Retreatment with leuprolide acetate for depot suspension alone is not recommended.

In women with major risk factors for decreased BMD such as chronic alcohol (> 3 units per day) or tobacco use, strong family history of osteoporosis, or chronic use of drugs that can decrease BMD, such as anticonvulsants or corticosteroids, use of LUPANETA PACK may pose an additional risk, and the risks and benefits should be weighed carefully.

### **5.2 Pregnancy Risk**

Leuprolide acetate for depot suspension may cause fetal harm if administered to a pregnant woman. Exclude pregnancy before initiating treatment with LUPANETA PACK. When used at the recommended dose and dosing interval, leuprolide acetate for depot suspension usually inhibits ovulation and stops menstruation. Contraception, however, is not ensured by taking leuprolide acetate for depot suspension. Therefore, patients should use nonhormonal methods of contraception. Advise patients to notify their healthcare provider if they believe they may be pregnant. Discontinue LUPANETA PACK if a patient becomes pregnant during treatment and inform the patient of potential risk to the fetus [see *Contraindications (4)* and *Use in Specific Populations (8.1)*].

### **5.3 Visual Abnormalities**

Discontinue norethindrone acetate tablets in the LUPANETA PACK pending examination if there is a sudden partial or complete loss of vision or if there is sudden onset of proptosis, diplopia, or migraine. Discontinue LUPANETA PACK if examination reveals papilledema or retinal vascular lesions.

### **5.4 Clinical Depression**

Depression may occur or worsen during treatment with LUPANETA PACK. Carefully observe patients with a history of clinical depression and discontinue LUPANETA PACK if the depression recurs to a serious degree.

## **5.5 Serious Allergic Reactions**

In clinical trials of LUPANETA PACK, adverse events of asthma were reported in women with pre-existing histories of asthma, sinusitis and environmental or drug allergies. Symptoms consistent with an anaphylactoid or asthmatic process have been reported postmarketing.

## **5.6 Cardiovascular and Metabolic Disorders**

Assess and manage risk factors for cardiovascular disease before starting LUPANETA PACK. Closely monitor women on norethindrone acetate who have risk factors for arterial vascular disease (e.g., hypertension, diabetes mellitus, tobacco use, hypercholesterolemia, and obesity) and/or venous thromboembolism (e.g., family history of VTE, obesity, and smoking) when using LUPANETA PACK. [*see Contraindications (4)*].

## **5.7 Initial Flare of Symptoms**

Following the first dose of leuprolide acetate, sex steroids temporarily rise above baseline because of the physiologic effect of the drug. Therefore, an increase in symptoms associated with endometriosis may be observed during the initial days of therapy, but these should dissipate with continued therapy.

## **5.8 Fluid Retention**

Because norethindrone acetate may cause some degree of fluid retention, carefully observe women with conditions that might be influenced by this effect, such as epilepsy, migraine, cardiac or renal dysfunctions.

## **5.9 Convulsions**

There have been postmarketing reports of convulsions in patients on leuprolide acetate therapy. These included patients with and without concurrent medications and comorbid conditions.

# **6 ADVERSE REACTIONS**

## **6.1 Clinical Trials Experience**

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The safety of co-administering leuprolide acetate for depot suspension and norethindrone acetate was evaluated in two clinical studies in which a total of 242 women were treated for up to one

year. Women were treated with monthly IM injections of leuprolide acetate 3.75 mg (13 injections) alone or monthly IM injections of leuprolide acetate 3.75 mg (13 injections) and 5 mg norethindrone acetate daily. The population age range was 17-43 years old. The majority of patients were Caucasian (87%).

One study was a controlled clinical trial in which 106 women were randomized to one year of treatment with leuprolide acetate for depot suspension alone or with leuprolide acetate for depot suspension and norethindrone acetate. The other study was an open-label single arm clinical study in 136 women of one year of treatment with leuprolide acetate for depot suspension and norethindrone acetate, with follow-up for up to 12 months after completing treatment.

Adverse Reactions (>1%) Leading to Study Discontinuation:

In the controlled study, 18% of patients treated monthly with leuprolide acetate and 18% of patients treated monthly with leuprolide acetate plus norethindrone acetate discontinued therapy due to adverse reactions, most commonly hot flashes (6%) and insomnia (4%) in the leuprolide acetate alone group and hot flashes and emotional lability (4% each) in the leuprolide acetate and norethindrone group.

In the open label study, 13% of patients treated monthly with leuprolide acetate plus norethindrone acetate discontinued therapy due to adverse reactions, most commonly depression (4%) and acne (2%).

Common Adverse Reactions:

Table 1 lists the adverse reactions observed in at least 5% of patients in any treatment group, during the first 6 months of treatment in the add-back clinical studies, in which patients were treated with monthly leuprolide acetate for depot suspension 3.75 mg with or without norethindrone acetate co-treatment. The most frequently-occurring adverse reactions observed in these studies were hot flashes and headaches.

<b>Table 1. Adverse Reactions Occurring in the First Six Months of Treatment in ≥ 5% of Patients with Endometriosis</b>						
	<b>Controlled Study</b>				<b>Open Label Study</b>	
	<b>LA-Only*</b>		<b>LA/N†</b>		<b>LA/N†</b>	
	<b>N=51</b>		<b>N=55</b>		<b>N=136</b>	
<b>Adverse Reactions</b>	<b>N</b>	<b>%</b>	<b>N</b>	<b>%</b>	<b>N</b>	<b>%</b>
<b>Any Adverse Reaction</b>	50	98	53	96	126	93
<b>Body as a Whole</b>						
Asthenia		18		18		11
Headache/Migraine		65		51		46
Injection Site Reaction		2		9		3
Pain		24		29		21
<b>Cardiovascular System</b>						
Hot flashes/Sweats		98		87		57
<b>Digestive System</b>						
Altered Bowel Function (constipation, diarrhea)		14		15		10
Changes in Appetite		4		0		6
GI Disturbance (dyspepsia, flatulence)		4		7		4
Nausea/Vomiting		25		29		13
<b>Metabolic and Nutritional Disorders</b>						
Edema		0		9		7
Weight Gain		12		13		4
<b>Nervous System</b>						
Depression/Emotional Lability		31		27		34
Dizziness/Vertigo		16		11		7
Insomnia/Sleep Disorder		31		13		15
Decreased Libido		10		4		7
Memory Disorder		6		2		4
Nervousness/Anxiety		8		4		11
Neuromuscular Disorder (leg cramps, paresthesia)		2		9		3
<b>Skin and Appendages</b>						
Androgen-Like Effects (acne, alopecia)		4		5		18
Skin/Mucous Membrane Reaction		4		9		11
<b>Urogenital System</b>						
Breast Changes/Pain/Tenderness		6		13		8
Menstrual Disorders		2		0		5
Vaginitis		20		15		8
* LA-Only = leuprolide acetate 3.75 mg						
† LA/N = leuprolide acetate 3.75 mg plus norethindrone acetate 5 mg						

In the controlled clinical trial, 50 of 51 (98%) patients in the leuprolide acetate alone group and 48 of 55 (87%) patients in the leuprolide acetate and norethindrone group reported experiencing hot flashes on one or more occasions during treatment. Table 2 presents hot flash data in the sixth month of treatment.

Table 2. Hot Flashes in the Month Prior to the Assessment Visit (Controlled Study)							
Assessment Visit	Treatment Group	Number of Patients Reporting Hot Flashes		Number of Days with Hot Flashes		Maximum Number of Hot Flashes in 24 Hours	
		N	(%)	N <sup>2</sup>	Mean	N <sup>2</sup>	Mean
Week 24	LA-Only*	32/37	86	37	19	36	5.8
	LA/N†	22/38	58 <sup>1</sup>	38	7 <sup>1</sup>	38	1.9 <sup>1</sup>

\* LA-Only = leuprolide acetate 3.75 mg  
† LA/N = leuprolide acetate 3.75 mg plus norethindrone acetate 5 mg  
<sup>1</sup>Statistically significantly less than the LA-Only group (p<0.01)  
<sup>2</sup>Number of patients assessed.

### Serious Adverse Reactions:

Urinary tract infection, renal calculus, depression

### Changes in Laboratory Values during Treatment:

#### **Liver Enzymes**

In the two clinical trials of women with endometriosis, 4 of 191 patients receiving leuprolide acetate and norethindrone acetate for up to 12 months developed an elevated (at least twice the upper limit of normal) SGPT and 2 of 136 developed an elevated GGT. Five of the 6 increases were observed beyond 6 months of treatment. None was associated with an elevated bilirubin concentration.

#### **Lipids**

Percent changes from baseline for serum lipids and percentages of patients with serum lipid values outside of the normal range in the two studies of leuprolide acetate and norethindrone acetate are summarized in the tables below. The major impact of adding norethindrone acetate to treatment with leuprolide acetate for depot suspension was a decrease in serum HDL cholesterol and an increase in the LDL/HDL ratio.

<b>Table 3. Serum Lipids: Mean Percent Changes from Baseline Values at Treatment Week 24</b>						
	leuprolide acetate 3.75 mg		leuprolide acetate for depot suspension 3.75 mg plus norethindrone acetate 5 mg daily			
	Controlled Study (n=39)		Controlled Study (n=41)		Open Label Study (n=117)	
	Baseline Value*	Wk 24% Change	Baseline Value*	Wk 24% Change	Baseline Value*	Wk 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	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%
* mg/dL † ratio						

Changes from baseline tended to be greater at Week 52. After treatment, mean serum lipid levels from patients with follow up data (105 of 158 patients) returned to pretreatment values.

<b>Table 4. Percent of Patients with Serum Lipid Values Outside of the Normal Range</b>				
	leuprolide acetate for depot suspension 3.75 mg plus norethindrone acetate 5 mg daily			
	Controlled Study (n=41)		Open Label Study (n=117)	
	Baseline	Wk 24*	Baseline	Wk 24*
Total Cholesterol (>240 mg/dL)	15%	20%	6%	7%
HDL Cholesterol (<40 mg/dL)	15%	44%	15%	41%
LDL Cholesterol (>160 mg/dL)	5%	7%	9%	11%
LDL/HDL Ratio (>4.0)	2%	15%	7%	21%
Triglycerides (>200 mg/dL)	12%	10%	5%	9%
* Includes all patients regardless of baseline value.				

## 6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of leuprolide acetate for depot suspension or norethindrone acetate. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

### Leuprolide Acetate for Depot Suspension

During postmarketing surveillance with other dosage forms and in the same or different populations, the following adverse reactions were reported:

- Allergic reactions (anaphylactic, rash, urticaria, and photosensitivity reactions)
- Mood swings, including depression
- Suicidal ideation and attempt
- Symptoms consistent with an anaphylactoid or asthmatic process
- Localized reactions including induration and abscess at the site of injection
- Symptoms consistent with fibromyalgia (e.g., joint and muscle pain, headaches, sleep disorders, gastrointestinal distress, and shortness of breath), individually and collectively

**Other adverse reactions reported are:**

*Hepato-biliary disorder* - Serious liver injury

*Injury, poisoning and procedural complications* - Spinal fracture

*Investigations* - Decreased white blood count

*Musculoskeletal and connective tissue disorder* - Tenosynovitis-like symptoms

*Nervous System disorder* - Convulsion, peripheral neuropathy, paralysis

*Vascular disorder* - Hypotension, Hypertension

Serious venous and arterial thrombotic and thromboembolic events, including deep vein thrombosis, pulmonary embolism, myocardial infarction, stroke, and transient ischemic attack

**Pituitary apoplexy**

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

## **7 DRUG INTERACTIONS**

### **7.1 Drug-Drug Interactions**

#### **Leuprolide Acetate for Depot Suspension**

No pharmacokinetic-based drug-drug interaction studies have been conducted with leuprolide acetate for depot suspension. However, drug interactions associated with cytochrome P-450 enzymes or protein binding would not be expected to occur [*see Clinical Pharmacology (12.3)*].

#### **Norethindrone Acetate**

No pharmacokinetic drug interaction studies investigating any drug-drug interactions with norethindrone acetate have been conducted. Drugs or herbal products that induce or inhibit certain enzymes, including CYP3A4, may decrease or increase the serum concentrations of norethindrone.

### **7.2 Drug/Laboratory Test Interactions**

#### **Leuprolide Acetate for Depot Suspension**

Administration of leuprolide acetate for depot suspension in therapeutic doses results in suppression of the pituitary-gonadal system. Normal function is usually restored within three months after treatment is discontinued. Therefore, diagnostic tests of pituitary gonadotropic and gonadal functions conducted during treatment and for up to three months after discontinuation of leuprolide acetate for depot suspension may be affected.

## **8 USE IN SPECIFIC POPULATIONS**

### **8.1 Pregnancy**

Pregnancy Category X – [*See Contraindications (4)*]

#### **Teratogenic Effects**

LUPANETA PACK is contraindicated in women who are or may become pregnant while receiving the drug [*see Contraindications (4)*]. Before starting and during treatment with leuprolide acetate for depot suspension, establish whether the patient is pregnant. Leuprolide acetate for depot suspension is not a contraceptive. In reproductively capable women, a non-hormonal method of contraception should be used [*see Warnings and Precautions (5.4)*].

Leuprolide acetate for depot suspension may cause fetal harm when administered to a pregnant woman.

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, leuprolide acetate for depot suspension 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 leuprolide acetate for depot suspension in rabbits and with the highest dose (0.024 mg/kg) in rats.

### **8.3 Nursing Mothers**

Do not use LUPANETA PACK in nursing mothers because the effects of leuprolide acetate for depot suspension on lactation and/or the breast-fed child have not been determined.

It is not known whether leuprolide acetate for depot suspension is excreted in human milk.

Detectable amounts of progestins have been identified in the milk of mothers receiving them [*see Contraindications (4)*].

### **8.4 Pediatric Use**

LUPANETA PACK is not indicated in premenarcheal adolescents. Safety and effectiveness of LUPANETA PACK have not been established in pediatric patients. Experience with LUPANETA PACK for treatment of endometriosis has been limited to women 18 years of age and older.

### **8.5 Geriatric Use**

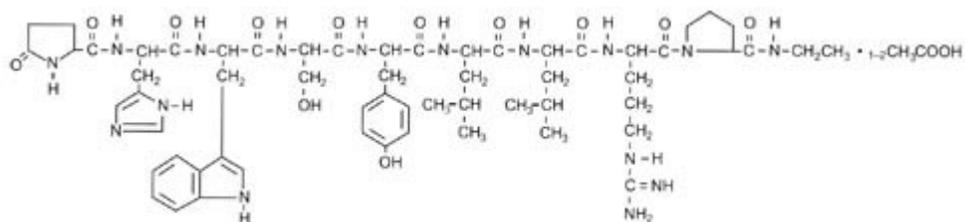
LUPANETA PACK is not indicated in postmenopausal women and has not been studied in women over 65 years of age.

## **11 DESCRIPTION**

LUPANETA PACK (leuprolide acetate for depot suspension; norethindrone acetate tablets) 1-month contains one dual chamber syringe with leuprolide acetate for depot suspension 3.75 mg and norethindrone acetate tablets USP: 5 mg (bottle of 30 tablets).

### **Leuprolide Acetate for Depot Suspension**

Leuprolide acetate for depot suspension is a synthetic nonapeptide analog of gonadotropin-releasing hormone (GnRH or LH-RH), a GnRH agonist. 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:



Leuprolide acetate for depot suspension 3.75 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.

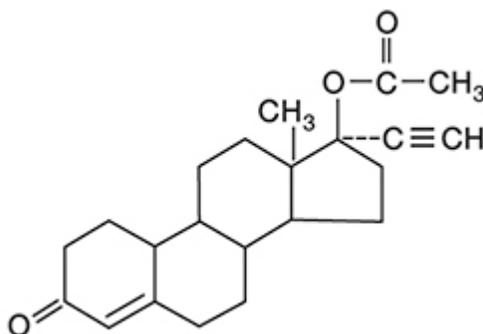
The front chamber of leuprolide acetate for depot suspension 3.75 mg prefilled dual-chamber syringe contains leuprolide acetate for depot suspension (3.75 mg), purified gelatin (0.65 mg), DL-lactic and glycolic acids copolymer (33.1 mg), and D-mannitol (6.6 mg). The second chamber of diluent contains carboxymethylcellulose sodium (5 mg), D-mannitol (50 mg), polysorbate 80 (1 mg), water for injection, USP, and glacial acetic acid, USP to control pH.

During the manufacture of leuprolide acetate for depot suspension, acetic acid is lost, leaving the peptide.

### Norethindrone Acetate

Norethindrone acetate tablets USP - 5 mg oral tablets.

Norethindrone acetate USP, (17-hydroxy-19-nor-17 $\alpha$ -pregn-4-en-20-yn-3-one acetate), a synthetic, orally active progestin, is the acetic acid ester of norethindrone. It is a white, or creamy white, crystalline powder.



Norethindrone acetate tablets USP, 5 mg contain the following inactive ingredients: colloidal silicon dioxide, lactose monohydrate, magnesium stearate, microcrystalline cellulose and talc.

## **12 CLINICAL PHARMACOLOGY**

### **12.1 Mechanism of Action**

#### **Leuprolide Acetate for Depot Suspension**

Leuprolide acetate for depot suspension is a long-acting GnRH analog. A single injection of leuprolide acetate for depot suspension results in an initial elevation followed by a prolonged suppression of pituitary gonadotropins. Repeated dosing at quarterly 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.

#### **Norethindrone Acetate**

Norethindrone acetate induces secretory changes in an estrogen-primed endometrium.

### **12.2 Pharmacodynamics**

In a pharmacokinetic/pharmacodynamic study of leuprolide acetate 11.25 mg for 3-month administration in 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  $\leq 20$  pg/mL in all subjects within four weeks and remained suppressed ( $\leq 40$  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.

## 12.3 Pharmacokinetics

### Absorption

#### Leuprolide Acetate for Depot Suspension

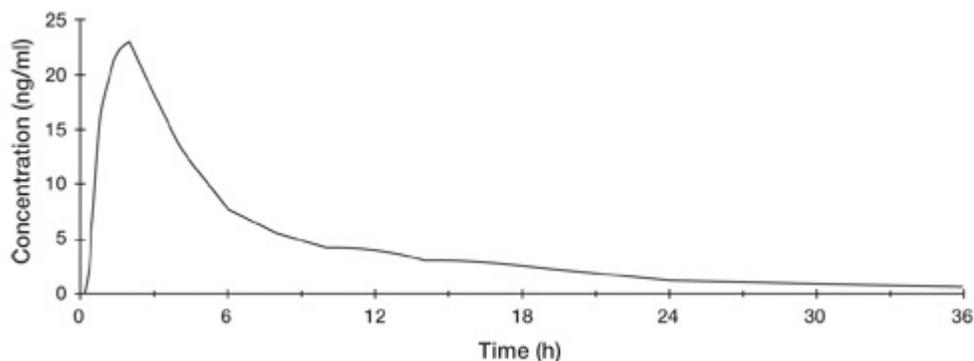
Following a single injection of the three month formulation of leuprolide acetate for depot suspension (11.25 mg) in female subjects, a mean plasma leuprolide concentration of 36.3 ng/mL was observed at 4 hours. Leuprolide appeared to be released at a constant rate following the onset of steady-state 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 ( $\pm$  standard deviation) leuprolide concentration from 3 to 12 weeks was  $0.23 \pm 0.09$  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.

#### Norethindrone Acetate

Norethindrone acetate is deacetylated to norethindrone after oral administration, and the disposition of norethindrone acetate is indistinguishable from that of orally administered norethindrone. Norethindrone acetate is absorbed from norethindrone acetate tablets, with maximum plasma concentration of norethindrone generally occurring at about 2 hours post-dose (see Figure 8). The pharmacokinetic parameters of norethindrone following single oral administration of 5 mg norethindrone acetate under fasting conditions in 29 healthy female volunteers are summarized in Table 5.

<b>Table 5. Pharmacokinetic Parameters after a Single Dose of Norethindrone Acetate in Healthy Women</b>	
Norethindrone Acetate (n=29) Arithmetic Mean $\pm$ SD	
Norethindrone	
AUC (0-inf) (ng/ml*h)	166.90 $\pm$ 56.28
C <sub>max</sub> (ng/ml)	26.19 $\pm$ 6.19
t <sub>max</sub> (h)	1.83 $\pm$ 0.58
t <sub>1/2</sub> (h)	8.51 $\pm$ 2.19
AUC = area under the curve, C <sub>max</sub> = maximum plasma concentration, t <sub>max</sub> = time at maximum plasma concentration, t <sub>1/2</sub> = half-life, SD = standard deviation	

**Figure 8. Mean Norethindrone Plasma Concentration Profile after a Single Dose of 5 mg Norethindrone Acetate Administered to 29 Healthy Female Volunteers under Fasting Conditions**



#### *Effect of Food:*

The effect of food administration on the pharmacokinetics of norethindrone acetate has not been studied.

#### **Distribution**

##### **Leuprolide Acetate for Depot Suspension**

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%.

##### **Norethindrone Acetate**

Norethindrone is 36% bound to sex hormone-binding globulin (SHBG) and 61% bound to albumin. Volume of distribution of norethindrone is about 4 L/kg.

#### **Metabolism**

##### **Leuprolide Acetate for Depot Suspension**

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 <sup>14</sup>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 leuprolide acetate for depot suspension (n=19) every 12 weeks or intramuscular 3.75 mg leuprolide acetate for depot suspension (n=15) every 4 weeks was administered for 24 weeks. There was 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.

### **Norethindrone Acetate**

Norethindrone undergoes extensive biotransformation, primarily via reduction, followed by sulfate and glucuronide conjugation. The majority of metabolites in the circulation are sulfates, with glucuronides accounting for most of the urinary metabolites.

### **Excretion**

#### **Leuprolide Acetate for Depot Suspension**

Following administration of leuprolide acetate for depot suspension 3.75 mg for 1-month administration to 3 patients, less than 5% of the dose was recovered as parent and M-I metabolite in the urine.

### **Norethindrone Acetate**

Plasma clearance value for norethindrone is approximately 0.4 L/hr/kg. Norethindrone is excreted in both urine and feces, primarily as metabolites. The mean terminal elimination half-life of norethindrone following a single dose administration of norethindrone acetate is approximately 9 hours.

## **Specific Populations**

### **Hepatic Impairment**

The effect of hepatic disease on the disposition of norethindrone after norethindrone acetate administration has not been evaluated. However, norethindrone acetate is contraindicated in markedly impaired liver function or liver disease [*see Contraindications (4)*].

The pharmacokinetics of the leuprolide acetate for depot suspension in hepatically impaired patients has not been determined.

### **Renal Impairment**

The effect of renal disease on the disposition of norethindrone after norethindrone acetate administration has not been evaluated. In pre-menopausal women with chronic renal failure undergoing peritoneal dialysis who received multiple doses of an oral contraceptive containing ethinyl estradiol and norethindrone, plasma norethindrone concentration was unchanged compared to concentrations in pre-menopausal women with normal renal function.

The pharmacokinetics of the leuprolide acetate for depot suspension in renally impaired patients has not been determined.

### **Race**

The effect of race on the disposition of norethindrone after norethindrone acetate administration has not been evaluated.

## **Drug Interactions**

### **Leuprolide Acetate for Depot Suspension**

Leuprolide acetate for depot suspension 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.

## **13 NONCLINICAL TOXICOLOGY**

### **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

#### **Leuprolide Acetate for Depot Suspension**

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. 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.

## **14 CLINICAL STUDIES**

#### **Leuprolide Acetate for Depot Suspension**

Initial endometriosis efficacy data for leuprolide acetate for depot suspension were based on the 3.75 mg dose administered once monthly.

A pharmacokinetic/pharmacodynamic study in 41 women that included both the 3.75 mg dose administered once monthly and the 11.25 mg dose administered once every three months did not reveal clinically significant differences in terms of efficacy in reducing painful symptoms of endometriosis or magnitude of the decrease in bone mineral density (BMD) associated with use of leuprolide acetate.

## **Leuprolide Acetate for Depot Suspension Plus Norethindrone Acetate**

Two clinical studies with treatment duration of 12 months were conducted to evaluate the effect of coadministration of leuprolide acetate for depot suspension and norethindrone acetate on the loss of bone mineral density (BMD) associated with leuprolide acetate for depot suspension and on the efficacy of leuprolide acetate for depot suspension in relieving symptoms of endometriosis. (All patients in these studies received calcium supplementation with 1000 mg elemental calcium). A total of 242 women were treated with monthly administration of leuprolide acetate 3.75 mg (13 injections) and with 5 mg norethindrone acetate taken daily. The population age range was 17-43 years old. The majority of patients were Caucasian (87%).

One coadministration study was a controlled, randomized and double-blind study included 51 women treated monthly with leuprolide acetate for depot suspension alone and 55 women treated monthly with leuprolide acetate for depot suspension plus norethindrone acetate daily. Women in this trial were followed for up to 24 months after completing one year of treatment. The other study was an open-label single arm clinical study in 136 women of one year of treatment with leuprolide acetate for depot suspension and norethindrone acetate, with follow-up for up to 12 months after completing treatment.

The second study was an open label, single arm study in which 136 women were treated monthly with leuprolide acetate for depot suspension plus norethindrone acetate daily, with follow-up for up to 12 months after completing treatment.

The assessment of efficacy was based on the investigator's or the patient's monthly assessment of five signs or symptoms of endometriosis (dysmenorrhea, pelvic pain, deep dyspareunia, pelvic tenderness and pelvic induration).

Table 6 below provides detailed efficacy data regarding relief of symptoms of endometriosis based on the two studies of coadministration of leuprolide acetate and norethindrone acetate.

			Percent of Patients with Symptom			Clinical Pain Severity Score		
			Baseline		Final	Baseline		Final
Variable	Study	Group	N <sup>1</sup>	(%) <sup>2</sup>	(%)	N <sup>1</sup>	Value <sup>3</sup>	Change
Dysmenorrhea	Controlled Study	LA*	51	(100)	(4)	50	3.2	-2.0
		LA/N†	55	(100)	(4)	54	3.1	-2.0
	Open Label Study	LA/N	136	(99)	(9)	134	3.3	-2.1
Pelvic Pain	Controlled Study	LA	51	(100)	(66)	50	2.9	-1.1
		LA/N	55	(96)	(56)	54	3.1	-1.1
	Open Label Study	LA/N	136	(99)	(63)	134	3.2	-1.2
Deep Dyspareunia	Controlled Study	LA	42	(83)	(37)	25	2.4	-1.0
		LA/N	43	(84)	(45)	30	2.7	-0.8
	Open Label Study	LA/N	102	(91)	(53)	94	2.7	-1.0
Pelvic Tenderness	Controlled Study	LA	51	(94)	(34)	50	2.5	-1.0
		LA/N	54	(91)	(34)	52	2.6	-0.9
	Open Label Study	LA/N	136	(99)	(39)	134	2.9	-1.4
Pelvic Induration	Controlled Study	LA	51	(51)	(12)	50	1.9	-0.4
		LA/N	54	(46)	(17)	52	1.6	-0.4
	Open Label Study	LA/N	136	(75)	(21)	134	2.2	-0.9

\* LA = leuprolide acetate 3.75 mg  
† LA/N = leuprolide acetate 3.75 mg plus norethindrone acetate 5 mg  
<sup>1</sup> Number of patients that were included in the assessment  
<sup>2</sup> Percentage of patients with the symptom/sign  
<sup>3</sup> Value description: 1=none; 2= mild; 3= moderate; 4= severe

Suppression of menses (menses was defined as three or more consecutive days of menstrual bleeding) was maintained throughout treatment in 84% and 73% of patients receiving leuprolide acetate and norethindrone acetate, in the controlled study and open label study, respectively. The median time for menses resumption after treatment with leuprolide acetate and norethindrone acetate was 8 weeks.

### Changes in Bone Density

The effect of leuprolide acetate for depot suspension and norethindrone acetate on bone mineral density was evaluated by dual energy x-ray absorptiometry (DXA) scan in the two clinical trials. For the open-label study, success in mitigating BMD loss was defined as the lower bound of the 95% confidence interval around the change from baseline at one year of treatment not to exceed -2.2%. The bone mineral density data of the lumbar spine from these two studies are presented in Table 7.

<b>Table 7. Mean Percent Change from Baseline in BMD of Lumbar Spine</b>						
	<b>leuprolide acetate for depot suspension 3.75 mg</b>		<b>leuprolide acetate for depot suspension 3.75 mg plus norethindrone acetate 5 mg daily</b>			
	<b>Controlled Study</b>		<b>Controlled Study</b>		<b>Open Label Study</b>	
	<b>N</b>	<b>Change (Mean, 95% CI)#</b>	<b>N</b>	<b>Change (Mean, 95% CI)#</b>	<b>N</b>	<b>Change (Mean, 95% CI)#</b>
Week 24*	41	-3.2% (-3.8, -2.6)	42	-0.3% (-0.8, 0.3)	115	-0.2% (-0.6, 0.2)
Week 52†	29	-6.3% (-7.1, -5.4)	32	-1.0% (-1.9, -0.1)	84	-1.1% (-1.6, -0.5)

\* Includes on-treatment measurements that fell within 2-252 days after the first day of treatment.  
† Includes on-treatment measurements >252 days after the first day of treatment.  
# 95% CI: 95% Confidence Interval

The change in BMD following discontinuation of treatment is shown in Table 8.

<b>Table 8. Mean Percent Change from Baseline in BMD of Lumbar Spine in Post-Treatment Follow-up Period</b>									
<b>Post Treatment Measurement</b>	<b>Controlled Study</b>						<b>Open Label Study</b>		
	<b>LA-Only</b>			<b>LA/N</b>			<b>LA/N</b>		
	<b>N</b>	<b>Mean % Change</b>	<b>95% CI (%)</b>	<b>N</b>	<b>Mean % Change</b>	<b>95% CI (%)</b>	<b>N</b>	<b>Mean % Change</b>	<b>95% CI (%)<sup>2</sup></b>
Month 8	19	-3.3	(-4.9, -1.8)	23	-0.9	(-2.1, 0.4)	89	-0.6	(-1.2, 0.0)
Month 12	16	-2.2	(-3.3, -1.1)	12	-0.7	(-2.1, 0.6)	65	0.1	(-0.6, 0.7)

<sup>1</sup> Patients with post treatment measurements  
<sup>2</sup> 95% CI (2-sided) of percent change in BMD values from baseline

These clinical studies demonstrated that coadministration of leuprolide acetate and norethindrone acetate 5 mg daily is effective in significantly reducing the loss of bone mineral density that occurs with leuprolide acetate for depot suspension treatment, and in relieving symptoms of endometriosis.

## 15 REFERENCES

### Leuprolide Acetate for Depot Suspension

1. NIOSH Alert: Preventing occupational exposures to antineoplastic and other hazardous drugs in healthcare settings. 2004. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 2004-165.

2. OSHA Technical Manual, TED 1-0.15A, Section VI: Chapter 2. Controlling Occupational Exposure to Hazardous Drugs. OSHA, 1999.  
[http://www.osha.gov/dts/osta/otm/otm\\_vi/otm\\_vi\\_2.html](http://www.osha.gov/dts/osta/otm/otm_vi/otm_vi_2.html)
3. American Society of Health-System Pharmacists. ASHP guidelines on handling hazardous drugs. *Am J Health-Syst Pharm.* 2006; 63; 1172-1193.
4. Polovich, M., White, J.M., & Kelleher, L.O. (eds.) 2005. Chemotherapy and biotherapy guidelines and recommendations for practice (2nd. Ed.) Pittsburgh, PA: Oncology Nursing Society.

## **16 HOW SUPPLIED/STORAGE AND HANDLING**

LUPANETA PACK for 1-month copackaged kit (NDC 0074-1052-05) is available in cartons containing: leuprolide acetate for depot suspension 3.75 mg for 1-month administration Kit (NDC 0074-3641-04)

norethindrone acetate 5 mg tablets; 30 count bottle (NDC 0074-1049-02)

1. Leuprolide acetate for depot suspension 3.75 mg for 1-month administration kit contains:
  - one prefilled dual-chamber syringe
  - one plunger
  - two alcohol swab

Each syringe contains sterile lyophilized microspheres of leuprolide acetate incorporated in a biodegradable copolymer of lactic and glycolic acids. When mixed with diluent, leuprolide acetate for depot suspension 3.75 mg for 1-month administration is administered as a single intramuscular injection.

2. Norethindrone acetate 5 mg 30 count bottle

White to off-white oval, flat faced beveled edged, uncoated tablets debossed with 'G with breakline' on one side and 304 on other side.

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

## **17 PATIENT COUNSELING INFORMATION**

### **See FDA-approved patient labeling (Patient Information)**

Counsel patients about the Warnings and Precautions for LUPANETA PACK, including:

- Do not use this drug if they have experienced an allergic reaction to GnRH agonists or progestins
- Do not use this drug if they are pregnant or planning a pregnancy, suspect they may be pregnant, or are breastfeeding
- Risk of loss of bone mineral density and limitation of treatment to two six-month courses of treatment
- Risk to an exposed fetus and need to use nonhormonal contraception
- Discontinue norethindrone if they develop sudden loss of vision, double vision or sudden migraine
- The possibility of development or worsening of depression during treatment with leuprolide acetate for depot suspension
- Need for close monitoring if they have cardiovascular risk factors, or conditions like epilepsy, migraine or renal dysfunction
- Notify their healthcare provider if they develop new or worsened symptoms after beginning treatment

### **Leuprolide Acetate for Depot Suspension 3.75 mg:**

Manufactured for

AbbVie Inc. North Chicago, IL 60064

by Takeda Pharmaceutical Company Limited

Osaka, Japan 540-8645

**Norethindrone acetate**

Manufactured for

AbbVie Inc.

North Chicago, IL 60064

Manufactured by

Glenmark Generics Ltd.

Colvale-Bardez, Goa

403 513, India

**LUPANETA PACK**

Packaged by:

AbbVie Inc.

North Chicago, IL 60064

Revised 10/2013

## PATIENT INFORMATION

### **LUPANETA PACK<sup>®</sup> (loo-pan-e-tə pæk) (leuprolide acetate for depot suspension and norethindrone acetate tablets)**

Read this Patient Information before you start taking LUPANETA PACK and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment.

#### **What is LUPANETA PACK?**

LUPANETA PACK contains 2 different prescription medicines:

- **leuprolide acetate for depot suspension** is a medicine injected into your muscle and used to treat pain due to endometriosis.
- **norethindrone acetate tablets** is a medicine taken by mouth and used to help lower the side effect of bone thinning that is caused by leuprolide acetate for depot suspension.

LUPANETA PACK should not be used longer than 6 months at a time after you first start treatment for your endometriosis symptoms. LUPANETA PACK should not be used for more than a total of 12 months during your treatment.

It is not known if LUPANETA PACK is safe and effective in children under 18 years of age.

#### **Who should not take LUPANETA PACK?**

##### **Do not take LUPANETA PACK if you:**

- have had an allergic reaction to medicines like leuprolide acetate for depot suspension or norethindrone acetate tablets. See the end of this leaflet for a complete list of ingredients in LUPANETA PACK.
- have uterine bleeding for which a cause has not been found.
- are pregnant or may be pregnant. LUPANETA PACK may harm your unborn baby.
- are breast-feeding or plan to breast-feed. It is not known if LUPANETA PACK passes into your breast milk.
- had or have breast cancer or other cancers that are sensitive to hormones.
- have problems with blood clots, a stroke or a heart attack.

- have liver problems.

### What should I tell my doctor before taking LUPANETA PACK?

#### Before you take LUPANETA PACK, tell your doctor if you:

• drink alcohol	• smoke
• have a family history of bone loss (osteoporosis)	• have depression
• have high cholesterol	• have had blood clots, a stroke or a heart attack
• have migraine headaches	• have diabetes
• have epilepsy	• have kidney problems

**Tell your doctor about all the medicines you take**, including prescription and non-prescription medicines, vitamins, and herbal supplements.

Especially tell your doctor if you take anticonvulsant (seizure) or corticosteroid medicines.

Ask your doctor for a list of these medicines if you are not sure.

Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

### How should I take LUPANETA PACK?

- **Leuprolide acetate for depot suspension** for 1 month administration is injected into your muscle 1 time every month by a healthcare professional in your doctor’s office.
- **Take norethindrone acetate tablets** exactly as your doctor tells you to take them. Take 1 norethindrone acetate tablet by mouth every day for 1 month after you receive your injection.
- Talk to your doctor about the birth control method that is right for you before you start taking LUPANETA PACK. You will need to use a form of birth control that does not contain hormones, such as:
  - a diaphragm with spermicide
  - condoms with spermicide
  - a copper IUD
- If you become pregnant while taking LUPANETA PACK, stop taking the norethindrone acetate tablets and call your doctor right away.

### How well does LUPANETA PACK work?

LUPANETA PACK is used to treat pain due to endometriosis. The pain from endometriosis can happen when you have your period, during other times of the month, or during intercourse (sex). Most women feel some relief from their endometriosis pain after taking both drugs in LUPANETA PACK.

The tablets in LUPANETA PACK help lower the side effect of bone thinning that is caused by leuprolide acetate for depot suspension. Women taking both drugs in LUPANETA PACK lost an average of 1% of their bone density after about 1 year of treatment. Women regained some of their bone density about 1 year after they stopped treatment with LUPANETA PACK.

### **What are the possible side effects of LUPANETA PACK?**

**LUPANETA PACK may cause serious side effects, including:**

- **bone thinning (decreased bone mineral density)**
- **harm to your unborn baby**
- **vision problems.** Call your doctor right away if you have sudden loss of vision, double vision, bulging eyes, or migraine headaches.
- **depression or worsening depression**
- **allergic reactions.** Get medical help right away if you have any of these symptoms of a serious allergic reaction:
  - swelling of your face, lips, mouth, or tongue
  - trouble breathing
  - wheezing
  - severe itching
  - skin rash, redness, or swelling
  - dizziness or fainting
  - fast heartbeat or pounding in your chest (tachycardia)
  - sweating
- **worsening endometriosis symptoms when you start taking LUPANETA PACK**
- **swelling (fluid retention)**

The most common side effects of LUPANETA PACK include:

- hot flashes and sweats
- headaches or migraine headaches
- depression and mood swings
- nausea and vomiting
- problems sleeping
- nervousness or feeling anxious
- pain
- acne
- weakness
- vaginal infection or inflammation
- weight gain
- constipation or diarrhea

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of LUPANETA PACK. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

#### **How should I store norethindrone acetate tablets in the LUPANETA PACK?**

- Store norethindrone acetate tablets at room temperature between 68°F to 77°F (20°C to 25°C).

**Keep LUPANETA PACK and all medicines out of the reach of children.**

#### **General information about the safe and effective use of LUPANETA PACK.**

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use LUPANETA PACK for a condition for which it was not prescribed. Do not give LUPANETA PACK to other people, even if they have the same symptoms that you have. It may harm them.

This Patient Information leaflet summarizes the most important information about LUPANETA PACK. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about LUPANETA PACK that is written for health professionals.

For more information, go to [www.lupanetapack.com](http://www.lupanetapack.com) or call 1-800-633-9110.

### **What are the ingredients in LUPANETA PACK?**

#### **leuprolide acetate for depot suspension:**

Active Ingredients: leuprolide acetate for depot suspension

Inactive Ingredients: glycolic acids copolymer, D-mannitol, carboxymethylcellulose sodium, polysorbate 80, water for injection, USP, and glacial acetic acid, USP

#### **norethindrone acetate tablets:**

Active Ingredients: norethindrone acetate USP

Inactive Ingredients: colloidal silicon dioxide, lactose monohydrate, magnesium stearate, microcrystalline cellulose and talc.

This Patient Information has been approved by the U.S. Food and Drug Administration.

#### **Leuprolide Acetate for Depot Suspension:**

Manufactured for

AbbVie Inc.

North Chicago, IL 60064

By Takeda Pharmaceutical Company Limited

Osaka, Japan 540-8645

#### **Norethindrone acetate:**

Manufactured for

AbbVie Inc.

North Chicago, IL 60064

By Glenmark Generics Ltd.

Colvale-Bardez, Goa

403 513, India

October, 2013

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use LUPANETA PACK safely and effectively. See full prescribing information for LUPANETA PACK.

**LUPANETA PACK (leuprolide acetate for depot suspension; norethindrone acetate tablets), co-packaged for intramuscular use and for oral use, respectively**  
Initial U.S. Approval: 2012

### RECENT MAJOR CHANGES

Warnings and Precautions, Convulsions (5.9) 10/2013

### INDICATIONS AND USAGE

LUPANETA PACK contains leuprolide acetate, a gonadotropin-releasing hormone (GnRH) agonist and norethindrone acetate, a progestin, indicated for

- Initial management of the painful symptoms of endometriosis (1)
- Management of recurrence of symptoms (1)

**Limitations of Use:** Initial treatment course is limited to 6 months and use is not recommended longer than a total of 12 months due to concerns about adverse impact on bone mineral density. (1, 2.1, 5.1)

### DOSAGE AND ADMINISTRATION

- Leuprolide acetate for depot suspension 11.25 mg given by a healthcare provider as a single intramuscular injection every 3 months for up to two injections (6 months of therapy) (2.1)
- Norethindrone acetate 5 mg tablets taken orally by the patient once per day for up to 6 months (2.1)
- If endometriosis symptoms recur after initial course of therapy, consider retreatment for up to another six months (2.1)
- Assess bone density before retreatment begins (2.1, 5.1)
- Reconstitute leuprolide acetate prior to use, see important administration instructions (2.3)

### DOSAGE FORMS AND STRENGTHS

- Leuprolide acetate for depot suspension 11.25 mg syringe (3)
- Norethindrone acetate 5 mg tablets; 90 count bottle (3)

### CONTRAINDICATIONS

- Hypersensitivity to GnRH, GnRH agonist or any of the excipients in leuprolide acetate for depot suspension or norethindrone acetate (4)

- Undiagnosed abnormal uterine bleeding (4)
- Pregnancy or suspected pregnancy (4, 8.1)
- Women who are breast-feeding (4)
- Known, suspected or history of breast or other hormone-sensitive cancer (4)
- Thrombotic or thromboembolic disorders (4)
- Liver tumors or liver disease (4)

### WARNINGS AND PRECAUTIONS

- Loss of bone mineral density: do not use for more than two six-month treatment courses. (1, 2.1, 5.1)
- Exclude pregnancy before starting treatment and discontinue use if pregnancy occurs; use non-hormonal methods of contraception only. (5.2)
- Discontinue in case of sudden loss of vision or onset of proptosis, diplopia or migraine. (5.3)
- Carefully observe patients with history of depression and discontinue the drug if the depression recurs to a serious degree. (5.4)
- Assess and manage risk factors for cardiovascular disease before starting LUPANETA PACK. (5.6)

### ADVERSE REACTIONS

**Leuprolide acetate for depot suspension:** Most common related adverse reactions (>10%) were hot flashes/sweats, headache/migraine, depression/emotional lability, nausea/vomiting, nervousness/anxiety, insomnia, pain, acne, asthenia, vaginitis, weight gain, constipation/diarrhea (6.1)

**Progestins:** breakthrough bleeding, spotting (6.1)

**To report SUSPECTED ADVERSE REACTIONS, contact AbbVie Inc. at 1-800-633-9110 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch)**

### USE IN SPECIFIC POPULATIONS

**Pediatric:** Safety and effectiveness of LUPANETA PACK has not been established in pediatric patients. (8.4)

**Geriatric:** LUPANETA PACK has not been studied in women over 65 years of age and is not indicated in this population. (8.5)

**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**

Revised: 10/2013

## FULL PRESCRIBING INFORMATION: CONTENTS\*

### 1 INDICATIONS AND USAGE

### 2 DOSAGE AND ADMINISTRATION

- 2.1 Dosing Information
- 2.2 Different Formulations of Leuprolide Acetate
- 2.3 Reconstitution and Administration for Injection of Leuprolide Acetate

### 3 DOSAGE FORMS AND STRENGTHS

### 4 CONTRAINDICATIONS

### 5 WARNINGS AND PRECAUTIONS

- 5.1 Loss of Bone Mineral Density
- 5.2 Pregnancy Risk
- 5.3 Visual Abnormalities
- 5.4 Clinical Depression
- 5.5 Serious Allergic Reactions
- 5.6 Cardiovascular and Metabolic Disorders
- 5.7 Initial Flare of Symptoms
- 5.8 Fluid Retention
- 5.9 Convulsions

### 6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience
- 6.2 Postmarketing Experience

### 7 DRUG INTERACTIONS

- 7.1 Drug-Drug Interactions

### 7.2 Drug/Laboratory Test Interactions

### 8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use

### 11 DESCRIPTION

### 12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

### 13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

### 14 CLINICAL STUDIES

### 15 REFERENCES

### 16 HOW SUPPLIED/STORAGE AND HANDLING

### 17 PATIENT COUNSELING INFORMATION

\* Sections or subsections omitted from the full prescribing information are not listed

# FULL PRESCRIBING INFORMATION

## 1 INDICATIONS AND USAGE

LUPANETA PACK (leuprolide acetate for depot suspension and norethindrone acetate tablets) is indicated for initial management of the painful symptoms of endometriosis and for management of recurrence of symptoms.

Limitation of Use: Duration of use is limited due to concerns about adverse impact on bone mineral density [see *Warnings and Precautions (5.1)*]. The initial treatment course of LUPANETA PACK is limited to six months. A single retreatment course of not more than six months may be administered after the initial course of treatment if symptoms recur. Use of LUPANETA PACK for longer than a total of 12 months is not recommended.

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Dosing Information

LUPANETA PACK is a co-packaging of leuprolide acetate for depot suspension for intramuscular use and norethindrone acetate tablets for oral use. Administer as follows:

- 11.25 mg of leuprolide acetate by intramuscular injection once every three months for up to two injections (6 months of therapy); to be administered by a healthcare provider
- 5 mg of norethindrone acetate orally once daily for up to 6 months of therapy

The initial course of treatment with leuprolide acetate for depot suspension 11.25 mg in combination with norethindrone acetate 5 mg daily is not to exceed six months.

If the symptoms of endometriosis recur after the initial course of therapy, consider retreatment with LUPANETA PACK for up to another six months. It is recommended that bone density be assessed before retreatment begins [see *Warnings and Precautions (5.1)*].

Treatment beyond two six-month courses has not been studied and is not recommended due to concerns about adverse impact on bone mineral density.

### 2.2 Different Formulations of Leuprolide Acetate

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

### 2.3 Reconstitution and Administration for Injection of Leuprolide Acetate

- Reconstitute and administer the lyophilized microspheres as a single intramuscular injection.
  - Inject the suspension immediately or discard if not used within two hours, because leuprolide acetate for depot suspension does not contain a preservative.
1. Visually inspect the leuprolide acetate for depot suspension powder. **DO NOT USE** the syringe if clumping or caking is evident. A thin layer of powder on the wall of the syringe is considered normal prior to mixing with the diluent. The diluent should appear clear.
  2. To prepare for injection, screw the white plunger into the end stopper until the stopper begins to turn (see Figure 1 and Figure 2).

Figure 1:

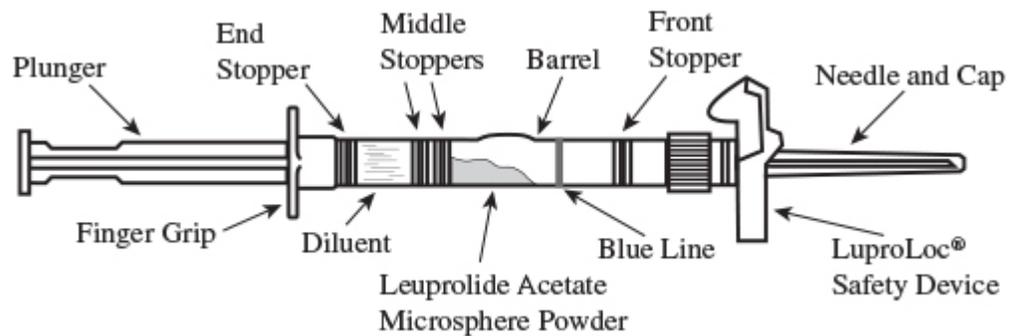
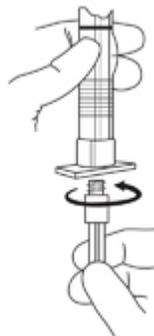
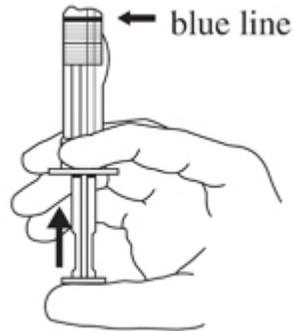


Figure 2:



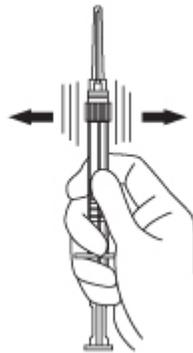
3. Hold the syringe UPRIGHT. Release the diluent by **SLOWLY PUSHING** (6 to 8 seconds) the plunger until the first middle stopper is at the blue line in the middle of the barrel (see Figure 3).

Figure 3:



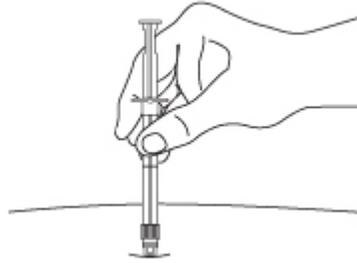
4. Keep the syringe UPRIGHT. Mix the microspheres (powder) thoroughly by gently shaking the syringe until the powder forms a uniform suspension. The suspension will appear milky. If the powder adheres to the stopper or caking/clumping is present, tap the syringe with your finger to disperse. DO NOT USE if any of the powder has not gone into suspension (see Figure 4).

Figure 4:



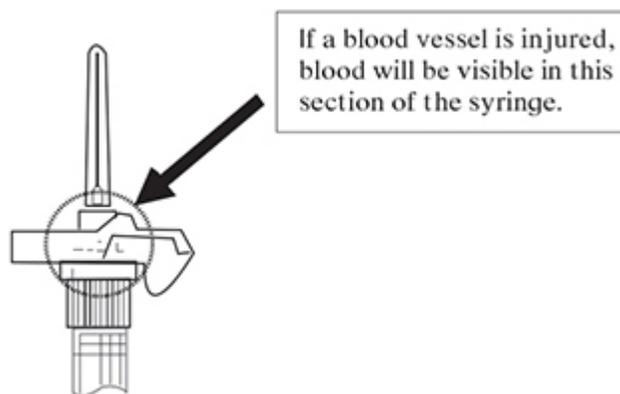
5. Keep the syringe UPRIGHT. With the opposite hand pull the needle cap upward without twisting.
6. Keep the syringe UPRIGHT. Advance the plunger to expel the air from the syringe. Now the syringe is ready for injection.
7. After cleaning the injection site with an alcohol swab, administer the intramuscular injection by inserting the needle at a 90 degree angle into the gluteal area, anterior thigh, or deltoid (see Figure 5).

Figure 5:



NOTE: If a blood vessel is accidentally penetrated, aspirated blood will be visible just below the luer lock (see Figure 6) and can be seen through the transparent LuproLoc safety device. If blood is present, remove the needle immediately. Do not inject the medication.

Figure 6:



8. Inject the entire contents of the syringe intramuscularly.
9. Withdraw the needle. Once the syringe has been withdrawn, immediately activate the LuproLoc<sup>®</sup> safety device by pushing the arrow on the lock upward towards the needle tip with the thumb or finger, as illustrated, until the needle cover of the safety device over the needle is fully extended and a **CLICK** is heard or felt (see Figure 7).

Figure 7:



10. Dispose of the syringe according to local regulations/procedures [*see References (15)*].

### 3 DOSAGE FORMS AND STRENGTHS

LUPANETA PACK 3-month copackaged kit contains two separate components:

- Leuprolide acetate for depot suspension 11.25 mg for 3-month administration: Leuprolide acetate lyophilized powder for reconstitution with supplied diluent in a prefilled dual chamber syringe
- Norethindrone acetate 5 mg tablets: White to off-white oval, flat-faced beveled edged, uncoated debossed with ‘G with breakline’ on one side and 304 on other side

### 4 CONTRAINDICATIONS

LUPANETA PACK is contraindicated in women with the following:

- Hypersensitivity to gonadotropin-releasing hormone (GnRH), GnRH agonist analogs, any of the excipients in leuprolide acetate for depot suspension, or norethindrone acetate
- Undiagnosed abnormal uterine bleeding
- Known, suspected or planned pregnancy during the course of therapy [*see Use in Specific Populations (8.1)*]
- Lactating women [*see Use in Specific Populations (8.3)*]
- Known, suspected or history of breast cancer or other hormone-sensitive cancer
- Current or history of thrombotic or thromboembolic disorder
- Liver tumors or liver disease

## **5 WARNINGS AND PRECAUTIONS**

### **5.1 Loss of Bone Mineral Density**

Leuprolide acetate for depot suspension induces a hypoestrogenic state that results in loss of bone mineral density (BMD), some of which may not be reversible. Concurrent use of norethindrone acetate is effective in reducing the loss of BMD that occurs with leuprolide acetate [see *Clinical Studies (14)*]. Nonetheless, duration of use of LUPANETA PACK is limited to two six-month courses of treatment due to concerns about the adverse impact on BMD. It is recommended that BMD be assessed before retreatment. Retreatment with leuprolide acetate for depot suspension alone is not recommended.

In women with major risk factors for decreased BMD such as chronic alcohol (> 3 units per day) or tobacco use, strong family history of osteoporosis, or chronic use of drugs that can decrease BMD, such as anticonvulsants or corticosteroids, use of LUPANETA PACK may pose an additional risk, and the risks and benefits should be weighed carefully.

### **5.2 Pregnancy Risk**

Leuprolide acetate for depot suspension may cause fetal harm if administered to a pregnant woman. Exclude pregnancy before initiating treatment with LUPANETA PACK. When used at the recommended dose and dosing interval, leuprolide acetate for depot suspension usually inhibits ovulation and stops menstruation. Contraception, however, is not ensured by taking leuprolide acetate for depot suspension. Therefore, patients should use nonhormonal methods of contraception. Advise patients to notify their healthcare provider if they believe they may be pregnant. Discontinue LUPANETA PACK if a patient becomes pregnant during treatment and inform the patient of potential risk to the fetus [see *Contraindications (4)* and *Use in Specific Populations (8.1)*].

### **5.3 Visual Abnormalities**

Discontinue norethindrone acetate tablets in the LUPANETA PACK pending examination if there is a sudden partial or complete loss of vision or if there is sudden onset of proptosis, diplopia, or migraine. Discontinue LUPANETA PACK if examination reveals papilledema or retinal vascular lesions.

### **5.4 Clinical Depression**

Depression may occur or worsen during treatment with LUPANETA PACK. Carefully observe patients with a history of clinical depression and discontinue LUPANETA PACK if the depression recurs to a serious degree.

### **5.5 Serious Allergic Reactions**

In clinical trials of LUPANETA PACK, adverse events of asthma were reported in women with pre-existing histories of asthma, sinusitis and environmental or drug allergies. Symptoms consistent with an anaphylactoid or asthmatic process have been reported postmarketing.

### **5.6 Cardiovascular and Metabolic Disorders**

Assess and manage risk factors for cardiovascular disease before starting LUPANETA PACK. Closely monitor women on norethindrone acetate who have risk factors for arterial vascular disease (e.g., hypertension, diabetes mellitus, tobacco use, hypercholesterolemia, and obesity) and/or venous thromboembolism (e.g., family history of VTE, obesity, and smoking) when using LUPANETA PACK [see *Contraindications (4)*].

### **5.7 Initial Flare of Symptoms**

Following the first dose of leuprolide acetate, sex steroids temporarily rise above baseline because of the physiologic effect of the drug. Therefore, an increase in symptoms associated with endometriosis may be observed during the initial days of therapy, but these should dissipate with continued therapy.

### **5.8 Fluid Retention**

Because norethindrone acetate may cause some degree of fluid retention, carefully observe women with conditions that might be influenced by this effect, such as epilepsy, migraine, cardiac or renal dysfunctions.

### **5.9 Convulsions**

There have been postmarketing reports of convulsions in patients on leuprolide acetate therapy. These included patients with and without concurrent medications and comorbid conditions.

## **6 ADVERSE REACTIONS**

### **6.1 Clinical Trials Experience**

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The safety of co-administering leuprolide acetate for depot suspension and norethindrone acetate was evaluated in two clinical studies in which a total of 242 women were treated for up to one

year. Women were treated with monthly IM injections of leuprolide acetate 3.75 mg (13 injections) alone or monthly IM injections of leuprolide acetate 3.75 mg (13 injections) and 5 mg norethindrone acetate daily. The population age range was 17-43 years old. The majority of patients were Caucasian (87%).

One study was a controlled clinical trial in which 106 women were randomized to one year of treatment with leuprolide acetate for depot suspension alone or with leuprolide acetate for depot suspension and norethindrone acetate. The other study was an open-label single arm clinical study in 136 women of one year of treatment with leuprolide acetate for depot suspension and norethindrone acetate, with follow-up for up to 12 months after completing treatment.

Adverse Reactions (>1%) Leading to Study Discontinuation:

In the controlled study, 18% of patients treated monthly with leuprolide acetate and 18% of patients treated monthly with leuprolide acetate plus norethindrone acetate discontinued therapy due to adverse reactions, most commonly hot flashes (6%) and insomnia (4%) in the leuprolide acetate alone group and hot flashes and emotional lability (4% each) in the leuprolide acetate and norethindrone group.

In the open label study, 13% of patients treated monthly with leuprolide acetate plus norethindrone acetate discontinued therapy due to adverse reactions, most commonly depression (4%) and acne (2%).

Common Adverse Reactions:

Table 1 lists the adverse reactions observed in at least 5% of patients in any treatment group, during the first 6 months of treatment in the add-back clinical studies, in which patients were treated with monthly leuprolide acetate for depot suspension 3.75 mg with or without norethindrone acetate co-treatment. The most frequently-occurring adverse reactions observed in these studies were hot flashes and headaches.

<b>Table 1. Adverse Reactions Occurring in the First Six Months of Treatment in ≥ 5% of Patients with Endometriosis</b>						
	<b>Controlled Study</b>				<b>Open Label Study</b>	
	<b>LA-Only*</b>		<b>LA/N†</b>		<b>LA/N†</b>	
	<b>N=51</b>		<b>N=55</b>		<b>N=136</b>	
<b>Adverse Reactions</b>	<b>N</b>	<b>%</b>	<b>N</b>	<b>%</b>	<b>N</b>	<b>%</b>
<b>Any Adverse Reaction</b>	50	98	53	96	126	93
<b>Body as a Whole</b>						
Asthenia		18		18		11
Headache/Migraine		65		51		46
Injection Site Reaction		2		9		3

Pain		24		29		21
<b>Cardiovascular System</b>						
Hot flashes/Sweats		98		87		57
<b>Digestive System</b>						
Altered Bowel Function (constipation, diarrhea)		14		15		10
Changes in Appetite		4		0		6
GI Disturbance (dyspepsia, flatulence)		4		7		4
Nausea/Vomiting		25		29		13
<b>Metabolic and Nutritional Disorders</b>						
Edema		0		9		7
Weight Gain		12		13		4
<b>Nervous System</b>						
Depression/Emotional Lability		31		27		34
Dizziness/Vertigo		16		11		7
Insomnia/Sleep Disorder		31		13		15
Decreased Libido		10		4		7
Memory Disorder		6		2		4
Nervousness/Anxiety		8		4		11
Neuromuscular Disorder (leg cramps, paresthesia)		2		9		3
<b>Skin and Appendages</b>						
Androgen-Like Effects (acne, alopecia)		4		5		18
Skin/Mucous Membrane Reaction		4		9		11
<b>Urogenital System</b>						
Breast Changes/Pain/Tenderness		6		13		8
Menstrual Disorders		2		0		5
Vaginitis		20		15		8
* LA-Only = leuprolide acetate 3.75 mg						
† LA/N = leuprolide acetate 3.75 mg plus norethindrone acetate 5 mg						

In the controlled clinical trial, 50 of 51 (98%) patients in the leuprolide acetate alone group and 48 of 55 (87%) patients in the leuprolide acetate and norethindrone group reported experiencing hot flashes on one or more occasions during treatment. Table 2 presents hot flash data in the sixth month of treatment.

Table 2. Hot Flashes in the Month Prior to the Assessment Visit (Controlled Study)							
Assessment Visit	Treatment Group	Number of Patients Reporting Hot Flashes		Number of Days with Hot Flashes		Maximum Number Hot Flashes in 24 Hours	
		N	(%)	N <sup>2</sup>	Mean	N <sup>2</sup>	Mean
Week 24	LA-Only*	32/37	86	37	19	36	5.8
	LA/N†	22/38	58 <sup>1</sup>	38	7 <sup>1</sup>	38	1.9 <sup>1</sup>
* LA-Only = leuprolide acetate 3.75 mg							
† LA/N = leuprolide acetate 3.75 mg plus norethindrone acetate 5 mg							
<sup>1</sup> Statistically significantly less than the LA-Only group (p<0.01)							
<sup>2</sup> Number of patients assessed.							

### Serious Adverse Reactions:

Urinary tract infection, renal calculus, depression

Changes in Laboratory Values during Treatment:

**Liver Enzymes**

In the two clinical trials of women with endometriosis, 4 of 191 patients receiving leuprolide acetate and norethindrone acetate for up to 12 months developed an elevated (at least twice the upper limit of normal) SGPT and 2 of 136 developed an elevated GGT. Five of the 6 increases were observed beyond 6 months of treatment. None was associated with an elevated bilirubin concentration.

**Lipids**

Percent changes from baseline for serum lipids and percentages of patients with serum lipid values outside of the normal range in the two studies of leuprolide acetate and norethindrone acetate are summarized in the tables below. The major impact of adding norethindrone acetate to treatment with leuprolide acetate for depot suspension was a decrease in serum HDL cholesterol and an increase in the LDL/HDL ratio.

<b>Table 3. Serum Lipids: Mean Percent Changes from Baseline Values at Treatment Week 24</b>						
	leuprolide acetate 3.75 mg		leuprolide acetate for depot suspension 3.75 mg plus norethindrone acetate 5 mg daily			
	Controlled Study (n=39)		Controlled Study (n=41)		Open Label Study (n=117)	
	Baseline Value*	Wk 24 % Change	Baseline Value*	Wk 24 % Change	Baseline Value*	Wk 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	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%

\* mg/dL  
† ratio

Changes from baseline tended to be greater at Week 52. After treatment, mean serum lipid levels from patients with follow up data (105 of 158 patients) returned to pretreatment values.

<b>Table 4. Percent of Patients with Serum Lipid Values Outside of the Normal Range</b>				
	leuprolide acetate for depot suspension 3.75 mg plus norethindrone acetate 5 mg daily			
	Controlled Study (n=41)		Open Label Study (n=117)	
	Baseline	Wk 24*	Baseline	Wk 24*

Total Cholesterol (>240 mg/dL)	15%	20%	6%	7%
HDL Cholesterol (<40 mg/dL)	15%	44%	15%	41%
LDL Cholesterol (>160 mg/dL)	5%	7%	9%	11%
LDL/HDL Ratio (>4.0)	2%	15%	7%	21%
Triglycerides (>200 mg/dL)	12%	10%	5%	9%
* Includes all patients regardless of baseline value.				

## 6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of leuprolide acetate for depot suspension or norethindrone acetate. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

### Leuprolide Acetate for Depot Suspension

During postmarketing surveillance with other dosage forms and in the same or different populations, the following adverse reactions were reported:

- Allergic reactions (anaphylactic, rash, urticaria, and photosensitivity reactions)
- Mood swings, including depression
- Suicidal ideation and attempt
- Symptoms consistent with an anaphylactoid or asthmatic process
- Localized reactions including induration and abscess at the site of injection
- Symptoms consistent with fibromyalgia (e.g., joint and muscle pain, headaches, sleep disorders, gastrointestinal distress, and shortness of breath), individually and collectively

### Other adverse reactions reported are:

*Hepato-biliary disorder* - Serious liver injury

*Injury, poisoning and procedural complications* - Spinal fracture

*Investigations* - Decreased white blood count

*Musculoskeletal and connective tissue disorder* - Tenosynovitis-like symptoms

*Nervous System disorder* - Convulsion, peripheral neuropathy, paralysis

*Vascular disorder* - Hypotension, Hypertension

Serious venous and arterial thrombotic and thromboembolic events, including deep vein thrombosis, pulmonary embolism, myocardial infarction, stroke, and transient ischemic attack

### **Pituitary apoplexy**

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

## **7 DRUG INTERACTIONS**

### **7.1 Drug-Drug Interactions**

#### **Leuprolide Acetate for Depot Suspension**

No pharmacokinetic-based drug-drug interaction studies have been conducted with leuprolide acetate for depot suspension. However, drug interactions associated with cytochrome P-450 enzymes or protein binding would not be expected to occur [*see Clinical Pharmacology (12.3)*].

#### **Norethindrone Acetate**

No pharmacokinetic drug interaction studies investigating any drug-drug interactions with norethindrone acetate have been conducted. Drugs or herbal products that induce or inhibit certain enzymes, including CYP3A4, may decrease or increase the serum concentrations of norethindrone.

### **7.2 Drug/Laboratory Test Interactions**

#### **Leuprolide Acetate for Depot Suspension**

Administration of leuprolide acetate for depot suspension in therapeutic doses results in suppression of the pituitary-gonadal system. Normal function is usually restored within three months after treatment is discontinued. Therefore, diagnostic tests of pituitary gonadotropic and gonadal functions conducted during treatment and for up to three months after discontinuation of leuprolide acetate for depot suspension may be affected.

## **8 USE IN SPECIFIC POPULATIONS**

### **8.1 Pregnancy**

Pregnancy Category X – [See *Contraindications (4)*]

#### **Teratogenic Effects**

LUPANETA PACK is contraindicated in women who are or may become pregnant while receiving the drug [see *Contraindications (4)*]. Before starting and during treatment with leuprolide acetate for depot suspension, establish whether the patient is pregnant. Leuprolide acetate for depot suspension is not a contraceptive. In reproductively capable women, a non-hormonal method of contraception should be used [see *Warnings and Precautions (5.4)*].

Leuprolide acetate for depot suspension may cause fetal harm when administered to a pregnant woman.

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, leuprolide acetate for depot suspension 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 leuprolide acetate for depot suspension in rabbits and with the highest dose (0.024 mg/kg) in rats.

### **8.3 Nursing Mothers**

Do not use LUPANETA PACK in nursing mothers because the effects of leuprolide acetate for depot suspension on lactation and/or the breast-fed child have not been determined.

It is not known whether leuprolide acetate for depot suspension is excreted in human milk.

Detectable amounts of progestins have been identified in the milk of mothers receiving them [see *Contraindications (4)*].

### **8.4 Pediatric Use**

LUPANETA PACK is not indicated in premenarcheal adolescents. Safety and effectiveness of LUPANETA PACK have not been established in pediatric patients. Experience with LUPANETA PACK for treatment of endometriosis has been limited to women 18 years of age and older.

## 8.5 Geriatric Use

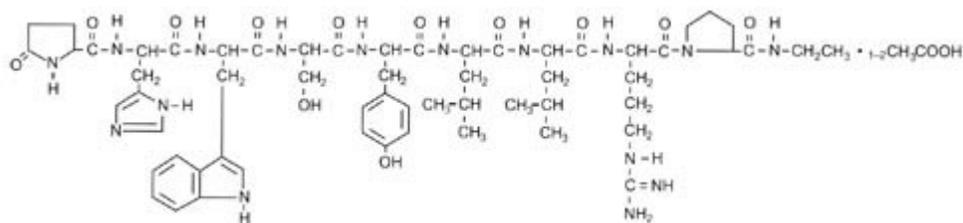
LUPANETA PACK is not indicated in postmenopausal women and has not been studied in women over 65 years of age.

## 11 DESCRIPTION

LUPANETA PACK (leuprolide acetate for depot suspension; norethindrone acetate tablets) 3-month contains one dual chamber syringe with leuprolide acetate for depot suspension 11.25 mg and norethindrone acetate tablets USP: 5 mg (bottle of 90 tablets).

### Leuprolide Acetate for Depot Suspension

Leuprolide acetate for depot suspension is a synthetic nonapeptide analog of gonadotropin-releasing hormone (GnRH or LH-RH), a GnRH agonist. 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:



Leuprolide acetate for depot suspension 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.

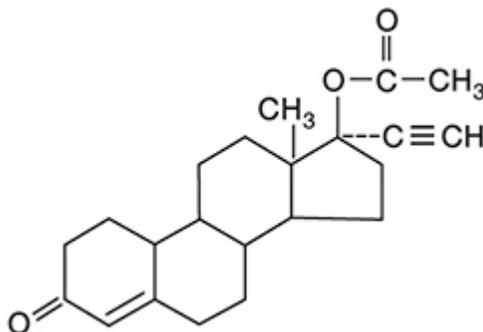
The front chamber of leuprolide acetate for depot suspension 11.25 mg for 3-month administration prefilled dual-chamber syringe contains leuprolide acetate for depot suspension (11.25 mg), polylactic acid (99.3 mg) and D-mannitol (19.45 mg). The second chamber of diluent contains carboxymethylcellulose sodium (7.5 mg), D-mannitol (75 mg), polysorbate 80 (1.5 mg), water for injection, USP, and glacial acetic acid, USP to control pH.

During the manufacture of leuprolide acetate for depot suspension, acetic acid is lost, leaving the peptide.

### Norethindrone Acetate

Norethindrone acetate tablets USP - 5 mg oral tablets.

Norethindrone acetate USP, (17-hydroxy-19-nor-17 $\alpha$ -pregn-4-en-20-yn-3-one acetate), a synthetic, orally active progestin, is the acetic acid ester of norethindrone. It is a white, or creamy white, crystalline powder.



Norethindrone acetate tablets USP, 5 mg contain the following inactive ingredients: colloidal silicon dioxide, lactose monohydrate, magnesium stearate, microcrystalline cellulose and talc.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

#### Leuprolide Acetate for Depot Suspension

Leuprolide acetate for depot suspension is a long-acting GnRH analog. A single injection of leuprolide acetate for depot suspension results in an initial elevation followed by a prolonged suppression of pituitary gonadotropins. Repeated dosing at quarterly 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.

#### Norethindrone Acetate

Norethindrone acetate induces secretory changes in an estrogen-primed endometrium.

### 12.2 Pharmacodynamics

In a pharmacokinetic/pharmacodynamic study of leuprolide acetate 11.25 mg for 3-month administration in 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  $\leq 20$  pg/mL in all subjects within four weeks and remained suppressed ( $\leq 40$  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.

### 12.3 Pharmacokinetics

#### Absorption

##### Leuprolide Acetate for Depot Suspension

Following a single injection of the three month formulation of leuprolide acetate for depot suspension (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 ( $\pm$  standard deviation) leuprolide concentration from 3 to 12 weeks was  $0.23 \pm 0.09$  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.

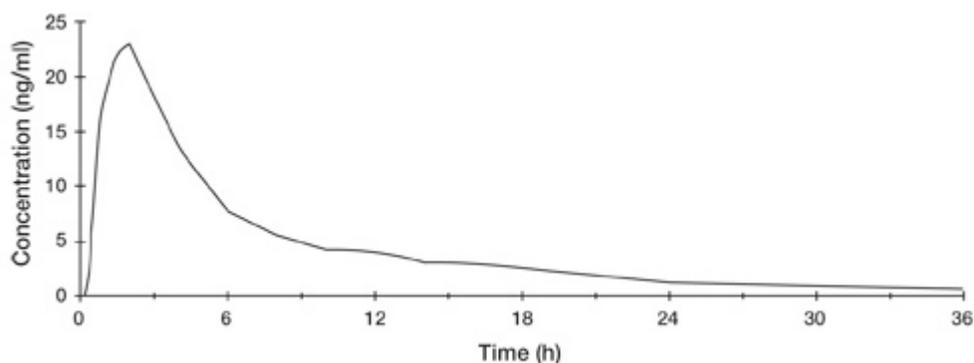
##### Norethindrone Acetate

Norethindrone acetate is deacetylated to norethindrone after oral administration, and the disposition of norethindrone acetate is indistinguishable from that of orally administered norethindrone. Norethindrone acetate is absorbed from norethindrone acetate tablets, with maximum plasma concentration of norethindrone generally occurring at about 2 hours post-dose (see Figure 8). The pharmacokinetic parameters of norethindrone following single oral administration of 5 mg norethindrone acetate under fasting conditions in 29 healthy female volunteers are summarized in Table 5.

<b>Table 5. Pharmacokinetic Parameters after a Single Dose of Norethindrone Acetate in Healthy Women</b>	
<b>Norethindrone Acetate (n=29)</b>	<b>Arithmetic Mean <math>\pm</math> SD</b>
Norethindrone	

AUC (0-inf) (ng/ml*h)	166.90 ± 56.28
C <sub>max</sub> (ng/ml)	26.19 ± 6.19
t <sub>max</sub> (h)	1.83 ± 0.58
t <sub>1/2</sub> (h)	8.51 ± 2.19
AUC = area under the curve, C <sub>max</sub> = maximum plasma concentration, t <sub>max</sub> = time at maximum plasma concentration, t <sub>1/2</sub> = half-life, SD = standard deviation	

**Figure 8. Mean Norethindrone Plasma Concentration Profile after a Single Dose of 5 mg Norethindrone Acetate Administered to 29 Healthy Female Volunteers under Fasting Conditions**



#### *Effect of Food:*

The effect of food administration on the pharmacokinetics of norethindrone acetate has not been studied.

#### **Distribution**

##### **Leuprolide Acetate for Depot Suspension**

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%.

##### **Norethindrone Acetate**

Norethindrone is 36% bound to sex hormone-binding globulin (SHBG) and 61% bound to albumin. Volume of distribution of norethindrone is about 4 L/kg.

## **Metabolism**

### **Leuprolide Acetate for Depot Suspension**

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 <sup>14</sup>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 leuprolide acetate for depot suspension (n=19) every 12 weeks or intramuscular 3.75 mg leuprolide acetate for depot suspension (n=15) every 4 weeks was administered for 24 weeks. There was 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.

### **Norethindrone Acetate**

Norethindrone undergoes extensive biotransformation, primarily via reduction, followed by sulfate and glucuronide conjugation. The majority of metabolites in the circulation are sulfates, with glucuronides accounting for most of the urinary metabolites.

## **Excretion**

### **Leuprolide Acetate for Depot Suspension**

Following administration of leuprolide acetate for depot suspension 3.75 mg for 1-month administration to 3 patients, less than 5% of the dose was recovered as parent and M-I metabolite in the urine.

### **Norethindrone Acetate**

Plasma clearance value for norethindrone is approximately 0.4 L/hr/kg. Norethindrone is excreted in both urine and feces, primarily as metabolites. The mean terminal elimination half-

life of norethindrone following a single dose administration of norethindrone acetate is approximately 9 hours.

### **Specific Populations**

#### **Hepatic Impairment**

The effect of hepatic disease on the disposition of norethindrone after norethindrone acetate administration has not been evaluated. However, norethindrone acetate is contraindicated in markedly impaired liver function or liver disease [*see Contraindications (4)*].

The pharmacokinetics of the leuprolide acetate for depot suspension in hepatically impaired patients has not been determined.

#### **Renal Impairment**

The effect of renal disease on the disposition of norethindrone after norethindrone acetate administration has not been evaluated. In pre-menopausal women with chronic renal failure undergoing peritoneal dialysis who received multiple doses of an oral contraceptive containing ethinyl estradiol and norethindrone, plasma norethindrone concentration was unchanged compared to concentrations in pre-menopausal women with normal renal function.

The pharmacokinetics of the leuprolide acetate for depot suspension in renally impaired patients has not been determined.

#### **Race**

The effect of race on the disposition of norethindrone after norethindrone acetate administration has not been evaluated.

### **Drug Interactions**

#### **Leuprolide Acetate for Depot Suspension**

Leuprolide acetate for depot suspension 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.

## **13 NONCLINICAL TOXICOLOGY**

### **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

#### **Leuprolide Acetate for Depot Suspension**

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. 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.

## **14 CLINICAL STUDIES**

#### **Leuprolide Acetate for Depot Suspension**

Initial endometriosis efficacy data for leuprolide acetate for depot suspension were based on the 3.75 mg dose administered once monthly.

A pharmacokinetic/pharmacodynamic study in 41 women that included both the 3.75 mg dose administered once monthly and the 11.25 mg dose administered once every three months did not reveal clinically significant differences in terms of efficacy in reducing painful symptoms of endometriosis or magnitude of the decrease in bone mineral density (BMD) associated with use of leuprolide acetate.

#### **Leuprolide Acetate for Depot Suspension Plus Norethindrone Acetate**

Two clinical studies with treatment duration of 12 months were conducted to evaluate the effect of coadministration of leuprolide acetate for depot suspension and norethindrone acetate on the loss of bone mineral density (BMD) associated with leuprolide acetate for depot suspension and on the efficacy of leuprolide acetate for depot suspension in relieving symptoms of endometriosis. (All patients in these studies received calcium supplementation with 1000 mg elemental calcium). A total of 242 women were treated with monthly administration of leuprolide acetate 3.75 mg (13 injections) and with 5 mg norethindrone acetate taken daily. The population age range was 17-43 years old. The majority of patients were Caucasian (87%).

One coadministration study was a controlled, randomized and double-blind study included 51 women treated monthly with leuprolide acetate for depot suspension alone and 55 women treated monthly with leuprolide acetate for depot suspension plus norethindrone acetate daily. Women in this trial were followed for up to 24 months after completing one year of treatment. The other study was an open-label single arm clinical study in 136 women of one year of treatment with leuprolide acetate for depot suspension and norethindrone acetate, with follow-up for up to 12 months after completing treatment.

The second study was an open label, single arm study in which 136 women were treated monthly with leuprolide acetate for depot suspension plus norethindrone acetate daily, with follow-up for up to 12 months after completing treatment.

The assessment of efficacy was based on the investigator's or the patient's monthly assessment of five signs or symptoms of endometriosis (dysmenorrhea, pelvic pain, deep dyspareunia, pelvic tenderness and pelvic induration).

Table 6 below provides detailed efficacy data regarding relief of symptoms of endometriosis based on the two studies of coadministration of leuprolide acetate and norethindrone acetate.

			Percent of Patients with Symptom			Clinical Pain Severity Score		
			Baseline		Final	Baseline		Final
Variable	Study	Group	N <sup>1</sup>	(%) <sup>2</sup>	(%)	N <sup>1</sup>	Value <sup>3</sup>	Change
Dysmenorrhea	Controlled Study	LA*	51	(100)	(4)	50	3.2	-2.0
		LA/N†	55	(100)	(4)	54	3.1	-2.0
	Open Label Study	LA/N	136	(99)	(9)	134	3.3	-2.1
Pelvic Pain	Controlled Study	LA	51	(100)	(66)	50	2.9	-1.1
		LA/N	55	(96)	(56)	54	3.1	-1.1
	Open Label Study	LA/N	136	(99)	(63)	134	3.2	-1.2
Deep Dyspareunia	Controlled Study	LA	42	(83)	(37)	25	2.4	-1.0
		LA/N	43	(84)	(45)	30	2.7	-0.8
	Open Label Study	LA/N	102	(91)	(53)	94	2.7	-1.0

Pelvic Tenderness	Controlled Study	LA	51	(94)	(34)	50	2.5	-1.0
		LA/N	54	(91)	(34)	52	2.6	-0.9
	Open Label Study	LA/N	136	(99)	(39)	134	2.9	-1.4
Pelvic Induration	Controlled Study	LA	51	(51)	(12)	50	1.9	-0.4
		LA/N	54	(46)	(17)	52	1.6	-0.4
	Open Label Study	LA/N	136	(75)	(21)	134	2.2	-0.9
* LA = leuprolide acetate 3.75 mg assessment								
† LA/N = leuprolide acetate 3.75 mg plus norethindrone acetate 5 mg								
<sup>1</sup> Number of patients that were included in the assessment								
<sup>2</sup> Percentage of patients with the symptom/sign								
<sup>3</sup> Value description: 1=none; 2= mild; 3= moderate; 4= severe								

Suppression of menses (menses was defined as three or more consecutive days of menstrual bleeding) was maintained throughout treatment in 84% and 73% of patients receiving leuprolide acetate and norethindrone acetate, in the controlled study and open label study, respectively. The median time for menses resumption after treatment with leuprolide acetate and norethindrone acetate was 8 weeks.

### Changes in Bone Density

The effect of leuprolide acetate for depot suspension and norethindrone acetate on bone mineral density was evaluated by dual energy x-ray absorptiometry (DXA) scan in the two clinical trials. For the open-label study, success in mitigating BMD loss was defined as the lower bound of the 95% confidence interval around the change from baseline at one year of treatment not to exceed -2.2%. The bone mineral density data of the lumbar spine from these two studies are presented in Table 7.

	leuprolide acetate for depot suspension 3.75 mg				leuprolide acetate for depot suspension 3.75 mg plus norethindrone acetate 5 mg daily		
	Controlled Study			Controlled Study		Open Label Study	
	N	Change (Mean, 95% CI)#		N	Change (Mean, 95% CI)#	N	Change (Mean, 95% CI)#
Week 24*	41	-3.2% (-3.8, -2.6)		42	-0.3% (-0.8, 0.3)	115	-0.2% (-0.6, 0.2)
Week 52†	29	-6.3% (-7.1, -5.4)		32	-1.0% (-1.9, -0.1)	84	-1.1% (-1.6, -0.5)

\* Includes on-treatment measurements that fell within 2-252 days after the first day of treatment.  
† Includes on-treatment measurements >252 days after the first day of treatment.  
# 95% CI: 95% Confidence Interval

The change in BMD following discontinuation of treatment is shown in Table 8.

Post Treatment Measurement	Controlled Study						Open Label Study			
	LA-Only			LA/N			LA/N			
	N	Mean %	95% CI	N	Mean %	95% CI	N	Mean %	95% CI	

		<b>Change</b>	<b>(%)</b>		<b>Change</b>	<b>(%)</b>		<b>Change</b>	<b>(%)<sup>2</sup></b>
Month 8	19	-3.3	(-4.9, -1.8)	23	-0.9	(-2.1, 0.4)	89	-0.6	(-1.2, 0.0)
Month 12	16	-2.2	(-3.3, -1.1)	12	-0.7	(-2.1, 0.6)	65	0.1	(-0.6, 0.7)

<sup>1</sup> Patients with post treatment measurements  
<sup>2</sup> 95% CI (2-sided) of percent change in BMD values from baseline

These clinical studies demonstrated that coadministration of leuprolide acetate and norethindrone acetate 5 mg daily is effective in significantly reducing the loss of bone mineral density that occurs with leuprolide acetate for depot suspension treatment, and in relieving symptoms of endometriosis.

## 15 REFERENCES

### Leuprolide Acetate for Depot Suspension

1. NIOSH Alert: Preventing occupational exposures to antineoplastic and other hazardous drugs in healthcare settings. 2004. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 2004-165.
2. OSHA Technical Manual, TED 1-0.15A, Section VI: Chapter 2. Controlling Occupational Exposure to Hazardous Drugs. OSHA, 1999.  
[http://www.osha.gov/dts/osta/otm/otm\\_vi/otm\\_vi\\_2.html](http://www.osha.gov/dts/osta/otm/otm_vi/otm_vi_2.html)
3. American Society of Health-System Pharmacists. ASHP guidelines on handling hazardous drugs. *Am J Health-Syst Pharm.* 2006; 63; 1172-1193.
4. Polovich, M., White, J.M., & Kelleher, L.O. (eds.) 2005. Chemotherapy and biotherapy guidelines and recommendations for practice (2nd. Ed.) Pittsburgh, PA: Oncology Nursing Society.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

LUPANETA PACK for 3-month copackaged kit (NDC 0074-1053-05) is available in cartons containing:

leuprolide acetate for depot suspension 11.25 mg for 3-month administration Kit (NDC 0074-3663-04)

norethindrone acetate 5 mg tablets; 90 count bottle (NDC 0074-1049-03)

1. Leuprolide acetate for depot suspension 11.25 mg for 3-month administration kit contains:
  - one prefilled dual-chamber syringe

- one plunger
- two alcohol swabs

Each syringe contains sterile lyophilized microspheres of leuprolide acetate incorporated in a biodegradable polymer of polylactic acid. When mixed with 1.5 mL of the diluent, leuprolide acetate for depot suspension 11.25 mg for 3-month administration is administered as a single intramuscular injection.

## 2. Norethindrone acetate 5 mg 90 count bottle

White to off-white oval, flat faced beveled edged, uncoated tablets debossed with 'G with breakline' on one side and 304 on other side.

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

## 17 PATIENT COUNSELING INFORMATION

### See FDA-approved patient labeling (Patient Information)

Counsel patients about the Warnings and Precautions for LUPANETA PACK, including:

- Do not use this drug if they have experienced an allergic reaction to GnRH agonists or progestins
- Do not use this drug if they are pregnant or planning a pregnancy, suspect they may be pregnant, or are breastfeeding
- Risk of loss of bone mineral density and limitation of treatment to two six-month courses of treatment
- Risk to an exposed fetus and need to use nonhormonal contraception
- Discontinue norethindrone if they develop sudden loss of vision, double vision or sudden migraine
- The possibility of development or worsening of depression during treatment with leuprolide acetate for depot suspension
- Need for close monitoring if they have cardiovascular risk factors, or conditions like epilepsy, migraine or renal dysfunction
- Notify their healthcare provider if they develop new or worsened symptoms after beginning treatment

**Leuprolide Acetate for Depot Suspension 11.25 mg:**

Manufactured for

AbbVie Inc.

North Chicago, IL 60064

by Takeda Pharmaceutical Company Limited

Osaka, Japan 540-8645

**Norethindrone acetate**

Manufactured for

AbbVie Inc.

North Chicago, IL 60064

Manufactured by

Glenmark Generics Ltd.

Colvale-Bardez, Goa

403 513, India

**LUPANETA PACK**

Packaged by:

AbbVie Inc.

North Chicago, IL 60064

Revised 10/2013

## PATIENT INFORMATION

### **LUPANETA PACK<sup>®</sup> (loo-pan-e-tə pæk) (leuprolide acetate for depot suspension and norethindrone acetate tablets)**

Read this Patient Information before you start taking LUPANETA PACK and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment.

#### **What is LUPANETA PACK?**

LUPANETA PACK contains 2 different prescription medicines:

- **leuprolide acetate for depot suspension** is a medicine injected into your muscle and used to treat pain due to endometriosis.
- **norethindrone acetate tablets** is a medicine taken by mouth and used to help lower the side effect of bone thinning that is caused by leuprolide acetate for depot suspension.

LUPANETA PACK should not be used longer than 6 months at a time after you first start treatment for your endometriosis symptoms. LUPANETA PACK should not be used for more than a total of 12 months during your treatment.

It is not known if LUPANETA PACK is safe and effective in children under 18 years of age.

#### **Who should not take LUPANETA PACK?**

##### **Do not take LUPANETA PACK if you:**

- have had an allergic reaction to medicines like leuprolide acetate for depot suspension or norethindrone acetate tablets. See the end of this leaflet for a complete list of ingredients in LUPANETA PACK.
- have uterine bleeding for which a cause has not been found
- are pregnant or may be pregnant. LUPANETA PACK may harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if LUPANETA PACK passes into your breast milk.
- had or have breast cancer or other cancers that are sensitive to hormones
- have problems with blood clots, a stroke or a heart attack.

- have liver problems

### What should I tell my doctor before taking LUPANETA PACK?

#### Before you take LUPANETA PACK, tell your doctor if you:

• drink alcohol	• smoke
• have a family history of bone loss (osteoporosis)	• have depression
• have high cholesterol	• have had blood clots, a stroke or a heart attack
• have migraine headaches	• have diabetes
• have epilepsy	• have kidney problems

**Tell your doctor about all the medicines you take**, including prescription and non-prescription medicines, vitamins, and herbal supplements.

Especially tell your doctor if you take anticonvulsant (seizure) or corticosteroid medicines.

Ask your doctor for a list of these medicines if you are not sure.

Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

### How should I take LUPANETA PACK?

- **Leuprolide acetate for depot suspension** for 3-month administration is injected into your muscle 1 time every 3 months by a healthcare professional in your doctor's office.
- **Take norethindrone acetate tablets** exactly as your doctor tells you to take them. Take 1 norethindrone acetate tablet by mouth every day for 3 months after you receive your injection.
- Talk to your doctor about the birth control method that is right for you before you start taking LUPANETA PACK. You will need to use a form of birth control that does not contain hormones, such as:
  - a diaphragm with spermicide
  - condoms with spermicide
  - a copper IUD
- If you become pregnant while taking LUPANETA PACK, stop taking the norethindrone acetate tablets and call your doctor right away.

### How well does LUPANETA PACK work?

LUPANETA PACK is used to treat pain due to endometriosis. The pain from endometriosis can happen when you have your period, during other times of the month, or during intercourse (sex). Most women feel some relief from their endometriosis pain after taking both drugs in LUPANETA PACK.

The tablets in LUPANETA PACK help lower the side effect of bone thinning that is caused by leuprolide acetate for depot suspension. Women taking both drugs in LUPANETA PACK lost an average of 1% of their bone density after about 1 year of treatment. Women regained some of their bone density about 1 year after they stopped treatment with LUPANETA PACK.

### **What are the possible side effects of LUPANETA PACK?**

**LUPANETA PACK may cause serious side effects, including:**

- **bone thinning (decreased bone mineral density)**
- **harm to your unborn baby**
- **vision problems.** Call your doctor right away if you have sudden loss of vision, double vision, bulging eyes, or migraine headaches.
- **depression or worsening depression**
- **allergic reactions.** Get medical help right away if you have any of these symptoms of a serious allergic reaction:
  - swelling of your face, lips, mouth, or tongue
  - trouble breathing
  - wheezing
  - severe itching
  - skin rash, redness, or swelling
  - dizziness or fainting
  - fast heartbeat or pounding in your chest (tachycardia)
  - sweating
- **worsening endometriosis symptoms when you start taking LUPANETA PACK**
- **swelling (fluid retention)**

The most common side effects of LUPANETA PACK include:

- hot flashes and sweats
- headaches or migraine headaches
- depression and mood swings
- nausea and vomiting
- problems sleeping
- nervousness or feeling anxious
- pain
- acne
- weakness
- vaginal infection or inflammation
- weight gain
- constipation or diarrhea

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of LUPANETA PACK. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

#### **How should I store norethindrone acetate tablets in the LUPANETA PACK?**

- Store norethindrone acetate tablets at room temperature between 68°F to 77°F (20°C to 25°C).

**Keep LUPANETA PACK and all medicines out of the reach of children.**

#### **General information about the safe and effective use of LUPANETA PACK.**

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use LUPANETA PACK for a condition for which it was not prescribed. Do not give LUPANETA PACK to other people, even if they have the same symptoms that you have. It may harm them.

This Patient Information leaflet summarizes the most important information about LUPANETA PACK. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about LUPANETA PACK that is written for health professionals.

For more information, go to [www.lupanetapack.com](http://www.lupanetapack.com) or call 1-800-633-9110.

### **What are the ingredients in LUPANETA PACK?**

#### **leuprolide acetate for depot suspension:**

Active Ingredients: leuprolide acetate for depot suspension

Inactive Ingredients: polylactic acid, D-mannitol, carboxymethylcellulose sodium, polysorbate 80, water for injection, USP, and glacial acetic acid, USP

#### **norethindrone acetate tablets:**

Active Ingredients: norethindrone acetate USP

Inactive Ingredients: colloidal silicon dioxide, lactose monohydrate, magnesium stearate, microcrystalline cellulose and talc.

This Patient Information has been approved by the U.S. Food and Drug Administration.

#### **Leuprolide Acetate for Depot Suspension:**

Manufactured for

AbbVie Inc.

North Chicago, IL 60064

By Takeda Pharmaceutical Company Limited

Osaka, Japan 540-8645

#### **Norethindrone acetate:**

Manufactured for

AbbVie Inc.

North Chicago, IL 60064

By Glenmark Generics Ltd.

Colvale-Bardez, Goa

403 513, India

October, 2013