LUPRON DEPOT® 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-arginyln-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 $^{14}$C-labeled leuprolide was shown to be metabolized to smaller inactive peptides, a pentapeptide (Metabolite I), tripeptides (Metabolites II and III) and a dipeptide (Metabolite IV). These fragments may be further catabolized.

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.

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.

**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 amenorrhic 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 ≥ 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 ≤ 30% and/or hemoglobin ≤ 10.2 g/dL. Administration of LUPRON DEPOT 3.75 mg, concomitantly with iron, produced an increase of ≥ 6% hematocrit and ≥ 2 g/dL hemoglobin in 77% of patients at three months of therapy. The mean change in hematocrit was 10.1% and the mean change in hemoglobin was 4.2 g/dL. Clinical response was judged to be a hematocrit of ≥ 36% and hemoglobin of ≥ 12 g/dL, thus allowing for autologous blood donation prior to surgery. At 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 ≥ 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 ≥ 12 GM/DL**

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Week 4</th>
<th>Week 8</th>
<th>Week 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>LUPRON DEPOT 3.75 mg with Iron</td>
<td>41*</td>
<td>71†</td>
<td>79*</td>
</tr>
<tr>
<td>Iron Alone</td>
<td>17</td>
<td>40</td>
<td>56</td>
</tr>
</tbody>
</table>

* 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 gonadotropin 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® (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 ≥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 ≥ 5% OF PATIENTS

<table>
<thead>
<tr>
<th></th>
<th>Endometriosis (2 Studies)</th>
<th>Uterine Fibroids (4 Studies)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LUPRON DEPOT 3.75 mg N=166</td>
<td>Danazol N=136 Placebo N=31</td>
</tr>
<tr>
<td>Body as a Whole</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthenia</td>
<td>5 (3)</td>
<td>9 (7)</td>
</tr>
<tr>
<td>General pain</td>
<td>31 (19)</td>
<td>22 (16)</td>
</tr>
<tr>
<td>Headache*</td>
<td>53 (32)</td>
<td>30 (22)</td>
</tr>
<tr>
<td>Cardiovascular System</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hot flashes/sweats*</td>
<td>139 (84)</td>
<td>77 (57)</td>
</tr>
<tr>
<td>Gastrointestinal System</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>21 (13)</td>
<td>17 (13)</td>
</tr>
<tr>
<td>GI disturbances*</td>
<td>11 (7)</td>
<td>8 (6)</td>
</tr>
<tr>
<td>Metabolic and Nutritional Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Edema</td>
<td>12 (7)</td>
<td>17 (13)</td>
</tr>
<tr>
<td>Weight gain/loss</td>
<td>22 (13)</td>
<td>36 (26)</td>
</tr>
<tr>
<td>Endocrine System</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acne</td>
<td>17 (10)</td>
<td>27 (20)</td>
</tr>
<tr>
<td>Hirsutism</td>
<td>2 (1)</td>
<td>9 (7)</td>
</tr>
<tr>
<td>Musculoskeletal System</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Joint disorder*</td>
<td>14 (8)</td>
<td>11 (8)</td>
</tr>
<tr>
<td>Myalgia*</td>
<td>1 (1)</td>
<td>7 (5)</td>
</tr>
<tr>
<td>Nervous System</td>
<td></td>
<td></td>
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<tr>
<td>------------------------</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td>Decreased libido*</td>
<td>19</td>
<td>11</td>
</tr>
<tr>
<td>Depression/emotional</td>
<td>36</td>
<td>22</td>
</tr>
<tr>
<td>lability*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>19</td>
<td>11</td>
</tr>
<tr>
<td>Nervousness*</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>Neuromuscular disorders*</td>
<td>11</td>
<td>7</td>
</tr>
<tr>
<td>Paresthesias</td>
<td>12</td>
<td>7</td>
</tr>
<tr>
<td>Skin and Appendages</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin reactions</td>
<td>17</td>
<td>10</td>
</tr>
<tr>
<td>Breast changes/tenderness/pain*</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>Vaginitis*</td>
<td>46</td>
<td>28</td>
</tr>
</tbody>
</table>

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 LUPRÓN DEPOT, patients diagnosed with uterine fibroids received a higher dose (7.5 mg) of LUPRÓN 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>
<thead>
<tr>
<th>Table 3 TREATMENT-RELATED ADVERSE EVENTS OCCURRING IN ≥5% OF PATIENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controlled Study</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Controlled Study</th>
<th>Open Label Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervous System</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased libido*</td>
<td>19</td>
<td>11</td>
</tr>
<tr>
<td>Depression/emotional lability*</td>
<td>36</td>
<td>22</td>
</tr>
<tr>
<td>Dizziness</td>
<td>19</td>
<td>11</td>
</tr>
<tr>
<td>Nervousness*</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>Neuromuscular disorders*</td>
<td>11</td>
<td>7</td>
</tr>
<tr>
<td>Paresthesias</td>
<td>12</td>
<td>7</td>
</tr>
<tr>
<td>Skin and Appendages</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin reactions</td>
<td>17</td>
<td>10</td>
</tr>
</tbody>
</table>

<p>| Urogenital System | | | | | | | | | | |
| Breast changes/tenderness/pain* | 10 | 6 | 12 | 9 | 0 | 0 | 3 | 1.8 | 7 | 4.3 |
| Vaginitis* | 46 | 28 | 23 | 17 | 0 | 19 | 11.4 | 3 | 1.8 |</p>
<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>LD - Only* N=51</th>
<th>LD/N† N=55</th>
<th>LD/N† N=136</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Any Adverse Event</strong></td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td>Body as a Whole</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthenia</td>
<td>9 (18)</td>
<td>10 (18)</td>
<td>15 (11)</td>
</tr>
<tr>
<td>Headache/Migraine</td>
<td>33 (65)</td>
<td>28 (51)</td>
<td>63 (46)</td>
</tr>
<tr>
<td>Injection Site Reaction</td>
<td>1 (2)</td>
<td>5 (9)</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Pain</td>
<td>12 (24)</td>
<td>16 (29)</td>
<td>29 (21)</td>
</tr>
<tr>
<td>Cardiovascular System</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hot flashes/sweats</td>
<td>50 (98)</td>
<td>48 (87)</td>
<td>78 (57)</td>
</tr>
<tr>
<td>Digestive System</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Altered Bowel Function</td>
<td>7 (14)</td>
<td>8 (15)</td>
<td>14 (10)</td>
</tr>
<tr>
<td>Changes in Appetite</td>
<td>2 (4)</td>
<td>0 (0)</td>
<td>8 (6)</td>
</tr>
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<td>GI Disturbance</td>
<td>2 (4)</td>
<td>4 (7)</td>
<td>6 (4)</td>
</tr>
<tr>
<td>Nausea/Vomiting</td>
<td>13 (25)</td>
<td>16 (29)</td>
<td>17 (13)</td>
</tr>
<tr>
<td>Metabolic and Nutritional Disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Edema</td>
<td>0 (0)</td>
<td>5 (9)</td>
<td>9 (7)</td>
</tr>
<tr>
<td>Weight Changes</td>
<td>6 (12)</td>
<td>7 (13)</td>
<td>6 (4)</td>
</tr>
<tr>
<td>Nervous System</td>
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<tr>
<td>Anxiety</td>
<td>3 (6)</td>
<td>0 (0)</td>
<td>11 (8)</td>
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<tr>
<td>Depression/Emotional Lability</td>
<td>16 (31)</td>
<td>15 (27)</td>
<td>46 (34)</td>
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<tr>
<td>Dizziness/Vertigo</td>
<td>8 (16)</td>
<td>6 (11)</td>
<td>10 (7)</td>
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<td>Insomnia/Vertigo</td>
<td>16 (31)</td>
<td>7 (13)</td>
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<td>Libido Changes</td>
<td>5 (10)</td>
<td>2 (4)</td>
<td>10 (7)</td>
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<td>Memory Disorder</td>
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<td>1 (2)</td>
<td>6 (4)</td>
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<tr>
<td>Nervousness</td>
<td>4 (8)</td>
<td>2 (4)</td>
<td>15 (11)</td>
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<tr>
<td>Neuromuscular Disorder</td>
<td>1 (2)</td>
<td>5 (9)</td>
<td>4 (3)</td>
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<td>Skin and Appendages</td>
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<td>Alopecia</td>
<td>0 (0)</td>
<td>5 (9)</td>
<td>4 (3)</td>
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<td>Androgen-Like Effects</td>
<td>2 (4)</td>
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<td>24 (18)</td>
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<tr>
<td>Skin/Mucous Membrane Reaction</td>
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<td>5 (9)</td>
<td>15 (11)</td>
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<td>Urogenital System</td>
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<td>Breast Changes/Pain/Tenderness</td>
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<td>7 (13)</td>
<td>11 (8)</td>
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<tr>
<td>Menstrual Disorders</td>
<td>1 (2)</td>
<td>0 (0)</td>
<td>7 (5)</td>
</tr>
<tr>
<td>Vaginitis</td>
<td>10 (20)</td>
<td>8 (15)</td>
<td>11 (8)</td>
</tr>
</tbody>
</table>

* 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>
<thead>
<tr>
<th>Week</th>
<th>Controlled Study</th>
<th>Open Label Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>24*</td>
<td>41 -3.2% (-3.8, -2.6)</td>
<td>115 -0.2% (-0.6, 0.2)</td>
</tr>
<tr>
<td>52†</td>
<td>29 -6.3% (-7.1, -5.4)</td>
<td>84 -1.1% (-1.6, -0.5)</td>
</tr>
</tbody>
</table>

* 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.

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 (±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

<table>
<thead>
<tr>
<th></th>
<th>LUPRON Controlled Study (n=39)</th>
<th>LUPRON plus norethindrone acetate 5 mg daily Controlled Study (n=41)</th>
<th>Open Label Study (n=117)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline Value*</td>
<td>Wk 24 % Change</td>
<td>Baseline Value*</td>
</tr>
<tr>
<td>Total Cholesterol</td>
<td>170.5</td>
<td>9.2%</td>
<td>179.3</td>
</tr>
<tr>
<td>HDL Cholesterol</td>
<td>52.4</td>
<td>7.4%</td>
<td>51.8</td>
</tr>
<tr>
<td>LDL Cholesterol</td>
<td>96.6</td>
<td>10.9%</td>
<td>101.5</td>
</tr>
<tr>
<td>LDL/HDL Ratio</td>
<td>2.0†</td>
<td>5.0%</td>
<td>2.1†</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>107.8</td>
<td>17.5%</td>
<td>130.2</td>
</tr>
</tbody>
</table>

* 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

<table>
<thead>
<tr>
<th></th>
<th>LUPRON Controlled Study (n=39)</th>
<th>LUPRON plus norethindrone acetate 5 mg daily Controlled Study (n=41)</th>
<th>Open Label Study (n=117)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Wk 0 Wk 24*</td>
<td>Wk 0 Wk 24*</td>
<td>Wk 0 Wk 24*</td>
</tr>
<tr>
<td>Total Cholesterol (&gt;240 mg/dL)</td>
<td>15% 23%</td>
<td>15% 20%</td>
<td>6% 7%</td>
</tr>
<tr>
<td>HDL Cholesterol (&lt;40 mg/dL)</td>
<td>15% 10%</td>
<td>15% 44%</td>
<td>15% 41%</td>
</tr>
<tr>
<td>LDL Cholesterol (&gt;160 mg/dL)</td>
<td>0% 8%</td>
<td>5% 7%</td>
<td>9% 11%</td>
</tr>
<tr>
<td>LDL/HDL Ratio (&gt;4.0)</td>
<td>0% 3%</td>
<td>2% 15%</td>
<td>7% 21%</td>
</tr>
<tr>
<td>Triglycerides (&gt;200 mg/dL)</td>
<td>13% 13%</td>
<td>12% 10%</td>
<td>5% 9%</td>
</tr>
</tbody>
</table>
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 (e.g., 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® 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® 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

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

03-A891 October, 2013
LUPRON DEPOT 11.25 mg (leuprolide acetate for depot suspension) for injection, for intramuscular use

Indications and Usage (1.1, 1.2) 03/2020
Dosage and Administration (2.1) 03/2020
Warnings and Precautions, Risks Associated with Norethindrone Combination Treatment (5.7) 03/2020

INDICATIONS AND USAGE

LUPRON DEPOT 11.25 mg is a gonadotropin-releasing hormone (GnRH) agonist indicated for:

Endometriosis:
- Management of endometriosis, including pain relief and reduction of endometriotic lesions. (1.1)
- In combination with a norethindrone acetate for initial management of the painful symptoms of endometriosis and for management of recurrence of symptoms. (1.1)

Limitations of Use:
- The total duration of therapy with LUPRON DEPOT 11.25 mg plus add-back therapy should not exceed 12 months due to concerns about adverse impact on bone mineral density. (1.1, 2.1, 5.1)
- Uterine Leiomyomata (Fibroids): Concomitant use with iron therapy for preoperative hematologic improvement of women with anemia caused by fibroids for whom three months of hormonal suppression is deemed necessary. (1.2)

Limitations of Use:
- LUPRON DEPOT 11.25 mg is not indicated for combination use with norethindrone acetate add-back therapy for the preoperative hematologic improvement of women with anemia caused by heavy menstrual bleeding due to fibroids. (1.2)

DOSAGE AND ADMINISTRATION

LUPRON DEPOT 11.25 mg for 3-month administration, given as a single intramuscular injection.
LUPRON DEPOT 11.25 mg has different release characteristics than LUPRON 3.75 mg and is dosed differently. (2.1)
- Do not substitute LUPRON DEPOT 11.25 mg for LUPRON DEPOT 3.75 mg.
- Do not administer LUPRON DEPOT 11.25 mg more frequently than every 3 months.
- Do not give a fractional dose of the LUPRON DEPOT 11.25 mg, as it is not equivalent to the same dose of the LUPRON DEPOT 3.75 mg monthly formulation.

Reconstitute LUPRON DEPOT 11.25 mg prior to use. (2.2)

Endometriosis:
- LUPRON DEPOT 11.25 mg administered as a single intramuscular (IM) injection once every three months for up to two injections (6 months of therapy). LUPRON DEPOT may be administered alone or in combination with daily 5 mg tablet of norethindrone acetate (add-back). (2.1)

If endometriosis symptoms recur after initial course of therapy, retreatment for no more than six months may be considered but only with the addition of norethindrone acetate add-back therapy. Do not re-treat with LUPRON DEPOT 11.25 mg alone. (2.1)

Fibroids:
- Recommended dose of LUPRON DEPOT 11.25 mg is one IM injection. (2.1)

Dosage Forms and Strengths
- Depot suspension for injection: 11.25 mg lyophilized powder for reconstitution in a dual-chamber syringe. (3)

CONTRAINDICATIONS
- Hypersensitivity to GnRH, GnRH agonist analogs, including leuprolide acetate, or any of the excipients in LUPRON DEPOT 11.25 mg. (4, 5.3)
- Undiagnosed abnormal uterine bleeding. (4)
- Pregnancy. (4, 8.1)

If LUPRON DEPOT 11.25 mg is administered with norethindrone acetate, the contraindications for norethindrone acetate also apply. (4)

WARNINGS AND PRECAUTIONS
- Loss of bone mineral density (BMD): Duration of treatment is limited by risk of bone mineral density. When using for management of endometriosis: combination use with norethindrone acetate is effective in reducing loss of BMD; do not retreat without combination norethindrone acetate. Assess BMD before retreatment. (1.1, 1.2, 5.1)
- Embryo-Fetal Toxicity: May cause fetal harm. Exclude pregnancy before initiating treatment if clinically indicated and discontinue use if pregnancy occurs. Use non-hormonal methods of contraception only. (5.2)
- Hypersensitivity reactions, including anaphylaxis, have been reported with LUPRON DEPOT 11.25 mg. (5.3)
- If LUPRON is administered with norethindrone acetate, the warnings and precautions for norethindrone acetate apply to the combination regimen. (5.7)

ADVERSE REACTIONS
Most common adverse reactions (>10%) in clinical trials were hot flashes/sweats, headache/migraine, vaginitis, depression/emotional lability, general pain, weight gain/loss, nausea/vomiting, decreased libido, and dizziness. (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

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 3/2020

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Endometriosis

Monotherapy

LUPRON DEPOT 11.25 mg is indicated for management of endometriosis, including pain relief and reduction of endometriotic lesions.

In Combination with Norethindrone Acetate

LUPRON DEPOT 11.25 mg in combination with norethindrone acetate is indicated for initial management of the painful symptoms of endometriosis and for management of recurrence of symptoms.

Use of norethindrone acetate in combination with LUPRON DEPOT 11.25 mg is referred to as add-back therapy, and is intended to reduce the loss of bone mineral density (BMD) and reduce vasomotor symptoms associated with use of LUPRON DEPOT 11.25 mg.

Limitations of Use:

The total duration of therapy with LUPRON DEPOT 11.25 mg plus add-back therapy should not exceed 12 months due to concerns about adverse impact on bone mineral density [see Dosage and Administration (2.1) and Warnings and Precautions (5.1)].

1.2 Uterine Leiomyomata (Fibroids)

LUPRON DEPOT 11.25 mg, used concomitantly with iron therapy, is indicated for the preoperative hematologic improvement of women with anemia caused by fibroids for whom three months of hormonal suppression is deemed necessary.

Consider a one-month trial period on iron alone, as some women will respond to iron alone [see Clinical Studies (14.2)]. LUPRON DEPOT 11.25 mg may be added if the response to iron alone is considered inadequate.

Limitations of Use:

LUPRON DEPOT 11.25 mg is not indicated for combination use with norethindrone acetate add-back therapy for the preoperative hematologic improvement of women with anemia caused by heavy menstrual bleeding due to fibroids [see Dosage and Administration (2.1)].

2 DOSAGE AND ADMINISTRATION

2.1 Important Use Information

LUPRON DEPOT 11.25 mg for 3-month administration has different release characteristics than LUPRON 3.75 mg for 1-month administration and is dosed differently.

- Do not substitute LUPRON DEPOT 11.25 mg for LUPRON DEPOT 3.75 mg.
• Do not administer LUPRON DEPOT 11.25 mg more frequently than every 3 months.
• Do not give a fractional dose of the LUPRON DEPOT 11.25 mg, as it is not equivalent to the same dose of the LUPRON DEPOT 3.75 mg monthly formulation.

Endometriosis

The initial and retreatment dosage regimens for LUPRON DEPOT 11.25 mg for the management of women with endometriosis are outlined in Table 1.

Table 1. LUPRON DEPOT 11.25 mg, Management of Endometriosis

<table>
<thead>
<tr>
<th>Treatment Phase</th>
<th>LUPRON DEPOT 11.25 mg Dosing</th>
<th>Maximum Treatment Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial Treatment</td>
<td>11.25 mg IM every 3 months for 1 to 2 doses</td>
<td>6 months</td>
</tr>
<tr>
<td>Retreatment</td>
<td>11.25 mg IM every 3 months for 1 to 2 doses</td>
<td>6 months</td>
</tr>
<tr>
<td></td>
<td>TOTAL TREATMENT DURATION</td>
<td>12 MONTHS³</td>
</tr>
</tbody>
</table>

¹May use LUPRON DEPOT 11.25 mg with or without norethindrone acetate 5 mg tablet taken daily.

²Use LUPRON DEPOT 11.25 mg with norethindrone acetate for retreatment 5 mg tablet taken daily [see Warnings and Precautions (5.1)] and assess bone mineral density (BMD) prior to retreatment.

³Treatment should not exceed 12 months due to concerns about adverse impact on bone mineral density.

Fibroids

The recommended dosage of LUPRON DEPOT 11.25 mg is one IM injection of 11.25 mg which provides a three-month treatment course.

2.2 Reconstitution and Administration for Injection of LUPRON DEPOT

• Reconstitute and administer the lyophilized microsphere as a single IM injection as directed below. Visually inspect the drug product for particulate matter and discoloration prior to administration, whenever solution and container permit.
• Inject the LUPRON DEPOT 11.25 mg suspension immediately or discard if not used within two hours as the suspension does not contain a preservative.
  1. Visually inspect the LUPRON DEPOT 11.25 mg 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 A and Figure B).

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

Figure C:
4. Keep the syringe **upright**. Mix the microsphere 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 D).

Figure D:

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. The syringe is now ready for injection.

7. After cleaning the injection site with an alcohol swab, administer the IM injection by inserting the needle at a 90-degree angle into the gluteal area, anterior thigh, or deltoid. Injection sites should be alternated (see Figure E).

Figure E:

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

Figure F:

8. Inject the entire contents of the syringe intramuscularly.
9. Withdraw the needle. Once the syringe has been withdrawn, immediately activate the LuproLoc® 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 G).

Figure G:

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

3 DOSAGE FORMS AND STRENGTHS

For Injection: 11.25 mg of leuprolide acetate as a white lyophilized microsphere powder for reconstitution in a single dose prefilled dual chamber syringe; with one chamber containing the lyophilized powder and the other chamber containing the clear diluent.
4 CONTRAINDICATIONS

LUPRON DEPOT 11.25 mg is contraindicated in women with the following:

- Hypersensitivity to gonadotropin-releasing hormone (GnRH), GnRH agonist analogs, including leuprolide acetate, or any of the excipients in LUPRON DEPOT 11.25 mg [see Warnings and Precautions (5.3) and Adverse Reactions (6.2)]
- Undiagnosed abnormal uterine bleeding
- Pregnancy [see Warnings and Precautions (5.2) and Use in Specific Populations (8.1)]

When norethindrone acetate is administered with LUPRON DEPOT 11.25 mg, the contraindications to the use of norethindrone acetate also apply to this combination regimen. Refer to the norethindrone acetate prescribing information for a list of contraindications for norethindrone acetate.

5 WARNINGS AND PRECAUTIONS

5.1 Loss of Bone Mineral Density

LUPRON DEPOT 11.25 mg induces a hypoestrogenic state that results in loss of bone mineral density (BMD), some of which may not be reversible after stopping treatment. In women with major risk factors for decreased BMD such as chronic alcohol use (> 3 units per day), tobacco use, strong family history of osteoporosis, or chronic use of drugs that can decrease BMD, such as anticonvulsants or corticosteroids, use of LUPRON DEPOT 11.25 mg may pose an additional risk. Carefully weigh the risks and benefits of LUPRON DEPOT 11.25 mg use in these populations.

The duration of LUPRON DEPOT 11.25 mg treatment is limited by the risk of loss of bone mineral density [see Dosage and Administration (2.1)].

When using LUPRON DEPOT 11.25 mg for the management of endometriosis, combination use of norethindrone acetate (add-back therapy) is effective in reducing the loss of BMD that occurs with leuprolide acetate [see Clinical Studies (14.2)]. Do not retreat with LUPRON DEPOT 11.25 mg without combination norethindrone acetate. Assess BMD before retreatment.

5.2 Embryo-Fetal Toxicity

Based on animal reproduction studies and the drug’s mechanism of action, LUPRON DEPOT 11.25 mg may cause fetal harm if administered to a pregnant woman and is contraindicated in pregnant women. Exclude pregnancy prior to initiating treatment with LUPRON DEPOT 11.25 mg if clinically indicated. Discontinue LUPRON DEPOT 11.25 mg if the woman becomes pregnant during treatment and inform the woman of potential risk to the fetus [see Contraindications (4) and Use in Specific Populations (8.1)]. Advise women to notify their healthcare provider if they believe they may be pregnant.

When used at the recommended dose and dosing interval, LUPRON DEPOT 11.25 mg usually inhibits ovulation and stops menstruation. Contraception, however, is not ensured by taking LUPRON DEPOT 11.25 mg. If contraception is indicated, advise women to use non-hormonal methods of contraception while on treatment with LUPRON DEPOT 11.25 mg.
5.3 Hypersensitivity Reactions

Hypersensitivity reactions, including anaphylaxis, have been reported with LUPRON DEPOT use. LUPRON DEPOT 11.25 mg is contraindicated in women with a history of hypersensitivity to gonadotropin-releasing hormone (GnRH) or GnRH agonist analogs [see Adverse Reactions (6.2)].

In clinical trials of LUPRON DEPOT 11.25 mg, 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.

5.4 Initial Flare of Symptoms

Following the first dose of LUPRON DEPOT 11.25 mg, sex steroids temporarily rise above baseline because of the physiologic effect of the drug. Therefore, an increase in symptoms may be observed during the initial days of therapy, but these should dissipate with continued therapy.

5.5 Convulsions

There have been postmarketing reports of convulsions in women on GnRH agonists, including leuprolide acetate. These included women with and without concurrent medications and comorbid conditions.

5.6 Clinical Depression

Depression may occur or worsen during treatment with GnRH agonists including LUPRON DEPOT 11.25 mg [see Adverse Reactions (6.1)]. Carefully observe women for depression, especially those with a history of depression and consider whether the risks of continuing LUPRON DEPOT 11.25 mg outweigh the benefits. Women with new or worsening depression should be referred to a mental health professional, as appropriate.

5.7 Risks Associated with Norethindrone Combination Treatment

If LUPRON DEPOT 11.25 mg is administered with norethindrone acetate, the warnings and precautions for norethindrone acetate apply to this regimen. Refer to the norethindrone acetate prescribing information for a full list of the warnings and precautions for norethindrone acetate.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Loss of Bone Mineral Density [see Warnings and Precautions (5.1)]
- Hypersensitivity Reactions [see Warnings and Precautions (5.3)]
- Initial Flare of Symptoms with Management of Endometriosis [see Warnings and Precautions (5.4)]
- Convulsions [see Warnings and Precautions (5.5)]
- Clinical Depression [see Warnings and Precautions (5.6)]
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.

LUPRON DEPOT 11.25 mg (Monotherapy)

The safety of LUPRON DEPOT 11.25 mg for the endometriosis and fibroids indications was established based on adequate and well-controlled adult studies of LUPRON DEPOT 3.75 mg for 1-month administration and on a single trial of LUPRON DEPOT 11.25 mg. The safety of LUPRON DEPOT 3.75 mg was evaluated in six clinical studies in which a total of 332 women were treated for up to six months. Women were treated with monthly IM injections of LUPRON DEPOT 3.75 mg. The population age range was 18 to 53 years old.

Adverse Reactions (>1%) Leading to Study Discontinuation

In the six studies 1.8% of women treated with LUPRON DEPOT 3.75 mg discontinued prematurely due to hot flashes.

Common Adverse Reactions

The safety of LUPRON DEPOT 3.75 mg was evaluated in controlled clinical trials in 166 women with endometriosis and 166 women with uterine fibroids. Adverse reactions reported in ≥ 5% of women in either of these populations are noted in Tables 2 and 3, below.

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>LUPRON DEPOT 3.75 mg (N=166)</th>
<th>Danazol (N=136)</th>
<th>Placebo (N=31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hot flashes/sweats*</td>
<td>84%</td>
<td>57%</td>
<td>29%</td>
</tr>
<tr>
<td>Headache*</td>
<td>32%</td>
<td>22%</td>
<td>6%</td>
</tr>
<tr>
<td>Vaginitis*</td>
<td>28%</td>
<td>17%</td>
<td>0%</td>
</tr>
<tr>
<td>Depression/emotional lability*</td>
<td>22%</td>
<td>20%</td>
<td>3%</td>
</tr>
<tr>
<td>General pain</td>
<td>19%</td>
<td>16%</td>
<td>3%</td>
</tr>
<tr>
<td>Weight gain/loss</td>
<td>13%</td>
<td>26%</td>
<td>0%</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>13%</td>
<td>13%</td>
<td>3%</td>
</tr>
<tr>
<td>Decreased libido*</td>
<td>11%</td>
<td>4%</td>
<td>0%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>11%</td>
<td>3%</td>
<td>0%</td>
</tr>
<tr>
<td>Acne</td>
<td>10%</td>
<td>20%</td>
<td>0%</td>
</tr>
<tr>
<td>Skin reactions</td>
<td>10%</td>
<td>15%</td>
<td>3%</td>
</tr>
<tr>
<td>Joint disorder*</td>
<td>8%</td>
<td>8%</td>
<td>0%</td>
</tr>
<tr>
<td>Edema</td>
<td>7%</td>
<td>13%</td>
<td>3%</td>
</tr>
<tr>
<td>Paresthesias</td>
<td>7%</td>
<td>8%</td>
<td>0%</td>
</tr>
</tbody>
</table>
GI disturbances* | 7 | 6 | 3
Neuromuscular disorders* | 7 | 13 | 0
Breast changes/tenderness/pain* | 6 | 9 | 0
Nervousness* | 5 | 8 | 0

In these same studies, symptoms reported in < 5% of women included:
- **Body as a Whole** - Injection site reactions
- **Cardiovascular System** - Palpitations, syncope, tachycardia
- **Digestive System** - Appetite changes, dry mouth, thirst
- **Endocrine System** - Androgen-like effects, lactation
- **Blood and Lymphatic System** - Ecchymosis
- **Nervous/Psychiatric System** - Anxiety*, insomnia/sleep disorders*, delusions, memory disorder, personality disorder
- **Dermal System** - Alopecia, hair disorder
- **Ocular system** - Ophthalmologic disorders*
- **Urogenital System** - Dysuria*.

* = Possible effect of decreased estrogen.

### Table 3. Adverse Reactions Reported in ≥ 5% of Women with Uterine Fibroids (4 Studies) Taking LUPRON DEPOT 3.75 mg

<table>
<thead>
<tr>
<th></th>
<th>LUPRON DEPOT 3.75 mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=166</td>
<td>N=163</td>
</tr>
<tr>
<td>Hot flashes/sweats*</td>
<td>73</td>
<td>18</td>
</tr>
<tr>
<td>Headache*</td>
<td>26</td>
<td>18</td>
</tr>
<tr>
<td>Vaginitis*</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>Depression/emotional lability*</td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td>Asthenia</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>General pain</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Joint disorder*</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>Edema</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Nervousness*</td>
<td>5</td>
<td>1</td>
</tr>
</tbody>
</table>

In these same studies, symptoms reported in < 5% of women included:
- **Body as a Whole** - Body odor, flu syndrome, injection site reactions
- **Cardiovascular System** - Tachycardia
- **Digestive System** - Appetite changes, dry mouth, taste perversion
- **Endocrine System** - Androgen-like effects, menstrual disorders
- **Nervous/Psychiatric System** - Anxiety*, insomnia/sleep disorders*
- **Respiratory System** - Rhinitis
- **Dermal System** - Nail disorder
- **Ocular system** - Conjunctivitis

* = Possible effect of decreased estrogen.
In one controlled clinical trial utilizing the monthly formulation of LUPRON DEPOT 3.75 mg and LUPRON DEPOT 7.5 mg in women diagnosed with uterine fibroids received one injection every 4 weeks for a duration of 12 weeks. Adverse reactions of galactorrhea, pyelonephritis, and urinary incontinence were reported in the 7.5 mg dose group but not in the 3.75 mg dose group. 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 11.25 mg, a few adverse reactions were reported with this formulation that were not reported previously, including face edema.

In a phase 4 study involving women with endometriosis who received LUPRON DEPOT 3.75 mg (N=20) administered monthly or LUPRON DEPOT 11.25 mg (N=21) administered every 3 months, similar adverse reactions were reported by the two groups of women. In general, the safety profiles of the two formulations were comparable in this study.

LUPRON DEPOT 3.75 mg in combination with Norethindrone Acetate 5 mg

The safety of co-administering LUPRON DEPOT 3.75 mg and norethindrone acetate was evaluated in two clinical studies in which a total of 242 women with endometriosis were treated for up to one year. Women were treated with monthly IM injections of LUPRON DEPOT 3.75 mg (13 injections) alone or monthly IM injections of LUPRON DEPOT 3.75 mg (13 injections) plus norethindrone acetate 5 mg daily. The population age range was 17 to 43 years old. The majority of women were Caucasian (87%).

In one study, 106 women were randomized to one year of treatment with LUPRON DEPOT 3.75 mg alone or with LUPRON DEPOT 3.75 mg and norethindrone acetate. The other study was an open-label, single arm clinical study in 136 women on one year of treatment with LUPRON DEPOT 3.75 mg plus 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 women treated monthly with LUPRON DEPOT 3.75 mg and 18% of women treated monthly with LUPRON DEPOT 3.75 mg plus norethindrone acetate discontinued therapy due to adverse reactions, most commonly hot flashes (6%) and insomnia (4%) in the LUPRON DEPOT 3.75 mg alone group and hot flashes and emotional lability (4% each) in the LUPRON DEPOT 3.75 mg plus norethindrone group.

In the open-label study, 13% of women treated monthly with LUPRON DEPOT 3.75 mg plus norethindrone acetate discontinued therapy due to adverse reactions, most commonly depression (4%) and acne (2%).

Common Adverse Reactions

Table 4 lists the adverse reactions observed in at least 5% of women in any treatment group, during the first 6 months of treatment in the two add-back clinical studies, in which women were treated with monthly LUPRON DEPOT 3.75 mg with or without norethindrone acetate 5mg daily co-treatment. The most frequently-occurring adverse reactions observed in these studies were hot flashes and headaches.
Table 4. Adverse Reactions Occurring in the First Six Months of Treatment in ≥ 5% of Women with Endometriosis

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>Controlled Study</th>
<th>Open Label Study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LD-Only* N=51</td>
<td>LD/N† N=55</td>
</tr>
<tr>
<td>Any Adverse Reaction</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Hot flashes/Sweats</td>
<td>98</td>
<td>96</td>
</tr>
<tr>
<td>Headache/Migraine</td>
<td>65</td>
<td>51</td>
</tr>
<tr>
<td>Depression/Emotional Lability</td>
<td>31</td>
<td>27</td>
</tr>
<tr>
<td>Insomnia/Sleep Disorder</td>
<td>31</td>
<td>13</td>
</tr>
<tr>
<td>Nausea/Vomiting</td>
<td>25</td>
<td>29</td>
</tr>
<tr>
<td>Pain</td>
<td>24</td>
<td>29</td>
</tr>
<tr>
<td>Vaginitis</td>
<td>20</td>
<td>15</td>
</tr>
<tr>
<td>Asthenia</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>Dizziness/Vertigo</td>
<td>16</td>
<td>11</td>
</tr>
<tr>
<td>Altered Bowel Function (constipation, diarrhea)</td>
<td>14</td>
<td>15</td>
</tr>
<tr>
<td>Weight Gain</td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td>Decreased Libido</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>Nervousness/Anxiety</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Breast Changes/Pain/Tenderness</td>
<td>6</td>
<td>13</td>
</tr>
<tr>
<td>Memory Disorder</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Skin/Mucous Membrane Reaction</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>GI Disturbance (dyspepsia, flatulence)</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Androgen-Like Effects (acne, alopecia)</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Changes in Appetite</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Injection Site Reaction</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>Neuromuscular Disorder (leg cramps, paresthesia)</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>Menstrual Disorders</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Edema</td>
<td>0</td>
<td>9</td>
</tr>
</tbody>
</table>

* 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%) women in the LUPRON DEPOT 3.75 mg arm and 48 of 55 (87%) women in the LUPRON DEPOT 3.75 mg plus norethindrone acetate arm reported experiencing hot flashes on one or more occasions during treatment.

Table 5 presents hot flash data in the last month of treatment.

Table 5. Hot Flashes in the Month Prior to the Assessment Visit (Controlled Study)
### Serious Adverse Reactions

Urinary tract infection (1.9%), renal calculus (0.7%), depression (0.7%)

### Changes in Laboratory Values during Treatment

#### Liver Enzymes

Three percent of women with uterine fibroids treated with LUPRON DEPOT 3.75 mg for 1-month administration, manifested post-treatment transaminase values that were at least twice the baseline value and above the upper limit of the normal range.

In the two clinical trials of women with endometriosis, 2% (4 of 191) women receiving leuprolide acetate plus norethindrone acetate for up to 12 months developed an elevated (at least twice the upper limit of normal) SGPT and 1% (2 of 136) developed an elevated GGT. Among these six women with increased liver tests, the increases in five 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 women with endometriosis who received LUPRON DEPOT 3.75 mg and in 32% of the women receiving LUPRON DEPOT 11.25 mg.

Of those endometriosis and women with uterine fibroid whose pretreatment cholesterol values were in the normal range, mean change following therapy was +16 mg/dL to +17 mg/dL in women with endometriosis and +11 mg/dL to +29 mg/dL in women with uterine fibroids. In the women with endometriosis, increases from the pretreatment values were statistically significant (p<0.03). There was essentially no increase in the LDL/HDL ratio in women from either population receiving LUPRON DEPOT 3.75 mg.

Percent changes from baseline for serum lipids and percentages of women with serum lipid values outside of the normal range in the two studies of LUPRON DEPOT 3.75 mg and norethindrone acetate are summarized in Table 6 and Table 7 below. The major impact of adding norethindrone acetate to treatment with LUPRON DEPOT 3.75 mg was a decrease in serum HDL cholesterol and an increase in the LDL/HDL ratio.

#### Table 6. Serum Lipids: Mean Percent Changes from Baseline Values at Treatment Week

<table>
<thead>
<tr>
<th>Assessment Visit</th>
<th>Treatment Group</th>
<th>Number of Women Reporting Hot Flashes</th>
<th>Number of Days with Hot Flashes</th>
<th>Maximum Number of Hot Flashes in 24 Hours</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>N (%)</td>
<td>N² Mean</td>
<td>N² Mean</td>
</tr>
<tr>
<td>Week 24</td>
<td>LD-Only*</td>
<td>32/37</td>
<td>86</td>
<td>37</td>
</tr>
<tr>
<td></td>
<td>LD/N†</td>
<td>22/38</td>
<td>58¹</td>
<td>38</td>
</tr>
</tbody>
</table>

* LD-Only = LUPRON DEPOT 3.75 mg.
† LD/N = LUPRON DEPOT 3.75 mg plus norethindrone acetate 5 mg.
¹Statistically significantly less than the LD-Only group (p<0.01).
²Number of women assessed.
Changes from baseline tended to be greater at Week 52. After treatment, mean serum lipid levels from women with follow-up data returned to pretreatment values.

### Table 7. Percentage of Women with Serum Lipids Values Outside of the Normal Range

<table>
<thead>
<tr>
<th></th>
<th>LUPRON DEPOT 3.75 mg</th>
<th>LUPRON DEPOT 3.75 mg plus norethindrone acetate 5 mg daily</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Controlled Study (n=39)</td>
<td>Controlled Study (n=41)</td>
</tr>
<tr>
<td>Total Cholesterol (&gt;240 mg/dL)</td>
<td>15%</td>
<td>15%</td>
</tr>
<tr>
<td>HDL Cholesterol (&lt;40 mg/dL)</td>
<td>15%</td>
<td>15%</td>
</tr>
<tr>
<td>LDL Cholesterol (&gt;160 mg/dL)</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>LDL/HDL Ratio (&gt;4.0)</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Triglycerides (&gt;200 mg/dL)</td>
<td>13%</td>
<td>13%</td>
</tr>
</tbody>
</table>

* Includes all women regardless of baseline value.

### 6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of LUPRON DEPOT monotherapy or LUPRON DEPOT with norethindrone acetate add-back therapy. 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 which includes other dosage forms and other populations, the following adverse reactions were reported:

- **Body as a whole:** Hypersensitivity reactions including anaphylaxis, localized reactions including induration and abscess at the site of injection
- **Nervous/Psychiatric System:** Mood swings, including depression; suicidal ideation and attempt; convulsion, peripheral neuropathy, paralysis
- **Hepato-biliary system**: Serious liver injury
- **Injury, poisoning and procedural complications**: Spinal fracture
- **Investigations**: Decreased white blood count
- **Musculoskeletal and connective tissue system**: Tenosynovitis-like symptoms
- **Vascular system**: Hypotension, hypertension, deep vein thrombosis, pulmonary embolism, myocardial infarction, stroke, transient ischemic attack
- **Respiratory system**: Symptoms consistent with an asthmatic process
- **Multi-system disorders**: Symptoms consistent with fibromyalgia (e.g., joint and muscle pain, headaches, sleep disorders, gastrointestinal distress, and shortness of breath), individually and collectively.

**Pituitary apoplexy**

During postmarketing 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**

No drug-drug interaction studies have been conducted with LUPRON DEPOT 11.25 mg.

**8 USE IN SPECIFIC POPULATIONS**

**8.1 Pregnancy**

**Risk Summary**

LUPRON DEPOT 11.25 mg is contraindicated in pregnancy [see Contraindications (4)].

LUPRON DEPOT 11.25 mg may cause fetal harm based on findings from animal studies and the drug’s mechanism of action [see Clinical Pharmacology (12.1)]. There are limited human data on the use of LUPRON DEPOT in pregnant women. Based on animal reproduction studies, LUPRON DEPOT 11.25 mg may be associated with an increased risk of pregnancy complications, including early pregnancy loss and fetal harm. In animal reproduction studies, subcutaneous administration of leuprolide acetate to rabbits during the period of organogenesis caused embryo-fetal toxicity, decreased fetal weights and a dose-dependent increase in major fetal abnormalities in animals at doses less than the recommended human dose based on body surface area using an estimated daily dose. A similar rat study also showed increased fetal mortality and decreased fetal weights but no major fetal abnormalities at doses less than the recommended human dose based on body surface area using an estimated daily dose [see Data].

**Data**

**Animal Data**
When administered on day 6 of pregnancy at test dosages of 0.00024 mg/kg, 0.0024 mg/kg, and 0.024 mg/kg (1/300 to 1/3 of the human dose) to rabbits, leuprolide acetate 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.

**8.2 Lactation**

*Risk Summary*

There are no data on the presence of leuprolide acetate in either animal or human milk, the effects on the breastfed infants, or the effects on milk production.

The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for LUPRON DEPOT 11.25 mg and any potential adverse effects on the breastfed infant from LUPRON DEPOT 11.25 mg or from the underlying maternal condition.

**8.3 Females and Males of Reproductive Potential**

*Pregnancy Testing*

Exclude pregnancy in women of reproductive potential prior to initiating LUPRON DEPOT 11.25 mg if clinically indicated [see Warnings and Precautions (5.2)].

*Contraception*

*Females*

LUPRON DEPOT 11.25 mg may cause embryo-fetal harm when administered during pregnancy. LUPRON DEPOT 11.25 mg is not a contraceptive. If contraception is indicated, advise females of reproductive potential to use a non-hormonal method of contraception during treatment with LUPRON DEPOT 11.25 mg [see Warnings and Precautions (5.2)].

*Infertility*

Based on its pharmacodynamic effects of decreasing secretion of gonadal steroids, fertility is expected to be decreased while on treatment with LUPRON DEPOT 11.25 mg. 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 [see Clinical Pharmacology (12.1)].

There is no evidence that pregnancy rates are affected following discontinuation of LUPRON DEPOT 11.25 mg.

Animal studies (prepubertal and adult rats and monkeys) with leuprolide acetate and other GnRH analogs have shown functional recovery of fertility suppression.

**8.4 Pediatric Use**

Safety and effectiveness of LUPRON DEPOT 11.25 mg for management of endometriosis and the preoperative hematologic improvement of women with anemia caused by fibroids have been established in females of reproductive age. Efficacy is expected to be the same for postpubertal
adolescents under the age of 18 as for users 18 years and older. The safety and effectiveness of LUPRON DEPOT 11.25 mg for these indications have not been established in premenarcheal pediatric patients.

8.5 Geriatric Use

LUPRON DEPOT 11.25 mg is not indicated in postmenopausal women and has not been studied in this population.

11 DESCRIPTION

Leuprolide acetate is a synthetic nonapeptide analog of gonadotropin-releasing hormone [GnRH or luteinizing hormone releasing hormone (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:

![Chemical Structure of Leuprolide Acetate](image)

LUPRON DEPOT 11.25 mg (leuprolide acetate for depot suspension for injection) is available in a prefilled dual-chamber syringe containing sterile lyophilized microspheres powder which, when mixed with diluent, become a suspension intended as an IM injection.

The front chamber of LUPRON DEPOT 11.25 mg 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 (75.0 mg), polysorbate 80 (1.5 mg), water for injection, USP, and glacial acetic acid, USP to control pH.

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Leuprolide acetate is a long-acting GnRH analog. A single injection of LUPRON DEPOT 11.25 mg results in an initial stimulation followed by a prolonged suppression of pituitary gonadotropins. Repeated dosing of LUPRON DEPOT 11.25 mg 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.

12.2 Pharmacodynamics

In a pharmacokinetic/pharmacodynamic study of LUPRON DEPOT 11.25 mg 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 ≤20 pg/mL in all subjects within four weeks and remained suppressed (≤40 pg/mL) in 80% of subjects until the end of the 12-week dosing interval, at which time two of these subjects had a value between 40 and 50 pg/mL. Four additional subjects had at least two consecutive elevations of estradiol (range 43-240 pg/mL) levels during the 12-week dosing interval, but there was no indication of luteal function for any of the subjects during this period.

Administration of LUPRON DEPOT 11.25 mg 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 11.25 mg may be affected.

12.3 Pharmacokinetics

Absorption

Following a single injection of the 3-month formulation of LUPRON DEPOT 11.25 mg in female subjects, a mean plasma leuprolide concentration of 36.3 ng/mL was observed at 4 hours. Leuprolide appeared to be released at a constant rate following the onset of steady-state levels during the third week after dosing and mean levels then declined gradually to near the lower limit of detection by 12 weeks. The mean (± standard deviation) leuprolide concentration from 3 to 12 weeks was 0.23 ± 0.09 ng/mL. However, intact leuprolide and an inactive major metabolite could not be distinguished by the assay which was employed in the study. The initial burst, followed by the rapid decline to a steady-state level, was similar to the release pattern seen with the monthly formulation.

In a pharmacokinetic/pharmacodynamic study of endometriosis patients, IM LUPRON DEPOT 11.25 mg (n=19) every 12 weeks or IM LUPRON DEPOT 3.75 mg (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.

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

Leuprolide acetate is a peptide that is primarily degraded by peptidase. 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.

Metabolite I, a smaller inactive peptide, 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.

Use in Specific Populations

The pharmacokinetics of LUPRON DEPOT have not been evaluated in patients with hepatic and renal impairment.

Drug Interactions

No pharmacokinetic drug-drug interaction studies have been conducted with LUPRON DEPOT 11.25 mg. However, leuprolide acetate is a peptide that is not degraded by cytochrome P-450 enzymes; hence, drug interactions associated with cytochrome P-450 enzymes would not be expected to occur.

13 NONCLINICAL TOXICOLOGY

13.1 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.
14 CLINICAL STUDIES

The safety and efficacy of LUPRON DEPOT 11.25 mg for the indicated populations has been established based on adequate and well-controlled studies in adults (See Table 8) of LUPRON DEPOT 3.75 mg and on a single trial of LUPRON DEPOT 11.25 mg [see Indications and Usage (1)].

14.1 Endometriosis

LUPRON DEPOT 11.25 mg Monotherapy

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, and 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 women after the first and second month of treatment, respectively. Most of the remaining women 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 women, respectively, excluding those who became pregnant.

Figure 1 illustrates the percent of women 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 women received LUPRON DEPOT 3.75 mg. Seventy-five percent (N=125) of these elected to participate in the follow-up period. Of these women, 36% and 24% are included in the 6-month and 12-month follow-up analysis, respectively. All the women who had a pain evaluation at baseline and at least of one treatment visit are included in the Baseline (B) and final treatment visit (F) analysis.

Figure 1. Percent of Women with Signs/Symptoms of Endometriosis at Baseline, Final Treatment Visit, and After 6 and 12 Months of Follow-Up, LUPRON DEPOT 3.75 mg Monthly for Six Months
In a pharmacokinetic/pharmacodynamic study of healthy female subjects (N=20) LUPRON DEPOT 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 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 [see Clinical Pharmacology (12.2)].

A six-month pharmacokinetic/pharmacodynamic post-marketing study in 41 women that included both the LUPRON DEPOT 3.75 mg dose (N=20) administered once monthly and the LUPRON DEPOT 11.25 mg dose (N=21) 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 LUPRON DEPOT 3.75 mg and LUPRON DEPOT 11.25 mg. In both treatment groups, suppression of menses (defined as no new menses for at least 60 consecutive days) was achieved in 100% of the women who remained in the study for at least 60 days. Vertebral bone density
measured by dual energy x-ray absorptiometry (DEXA) decreased compared with baseline by an average of 3.0% and 2.8% at six months for the two groups, respectively.

**LUPRON DEPOT with Norethindrone Acetate Add-Back Therapy**

Two clinical studies with treatment duration of 12 months were conducted to evaluate the effect of co-administration of LUPRON DEPOT 3.75 mg and norethindrone acetate on the loss of bone mineral density (BMD) associated with LUPRON DEPOT 3.75 mg and on the efficacy of LUPRON DEPOT in relieving symptoms of endometriosis. All women in these studies received calcium supplementation with 1000 mg elemental calcium. A total of 242 women were treated with monthly administration of LUPRON DEPOT 3.75 mg (13 injections) and 191 of them were co-administered 5 mg norethindrone acetate taken daily. The population age range was 17-43 years old. The majority of women were Caucasian (87%).

One co-administration study was a controlled, randomized and double-blind study included 51 women treated monthly with LUPRON DEPOT 3.75 mg alone and 55 women treated monthly with LUPRON DEPOT 3.75 mg 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 LUPRON DEPOT 3.75 mg monthly and daily norethindrone acetate 5 mg, with follow-up for up to 12 months after completing treatment. See Table 8.

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

Table 8 below provides detailed efficacy data regarding relief of symptoms of endometriosis based on the two studies of co-administration of LUPRON DEPOT 3.75 mg monthly and norethindrone acetate 5 mg daily.

**Table 8. Effect of LUPRON DEPOT and Norethindrone Acetate on the Symptoms of Endometriosis and Mean Clinical Severity Scores**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Study</th>
<th>Group</th>
<th>N1 (%)</th>
<th>Final (%)</th>
<th>N1 Value3 Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysmenorrhea</td>
<td>Controlled Study</td>
<td>LD</td>
<td>51 (100)</td>
<td>50 (4)</td>
<td>3.2 -2.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LD/N†</td>
<td>55 (100)</td>
<td>54 (4)</td>
<td>3.1 -2.0</td>
</tr>
<tr>
<td></td>
<td>Open Label Study</td>
<td>LD/N</td>
<td>136 (99)</td>
<td>134 (9)</td>
<td>3.3 -2.1</td>
</tr>
<tr>
<td>Pelvic Pain</td>
<td>Controlled Study</td>
<td>LD</td>
<td>51 (100)</td>
<td>50 (66)</td>
<td>2.9 -1.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LD/N</td>
<td>55 (96)</td>
<td>54 (56)</td>
<td>3.1 -1.1</td>
</tr>
<tr>
<td></td>
<td>Open Label Study</td>
<td>LD/N</td>
<td>136 (99)</td>
<td>134 (63)</td>
<td>3.2 -1.2</td>
</tr>
<tr>
<td>Deep Dyspareunia</td>
<td>Controlled Study</td>
<td>LD</td>
<td>42 (83)</td>
<td>25 (37)</td>
<td>2.4 -1.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LD/N</td>
<td>43 (84)</td>
<td>30 (45)</td>
<td>2.7 -0.8</td>
</tr>
<tr>
<td></td>
<td>Open Label Study</td>
<td>LD/N</td>
<td>102 (91)</td>
<td>94 (53)</td>
<td>2.7 -1.0</td>
</tr>
<tr>
<td>Pelvic Tenderness</td>
<td>Controlled Study</td>
<td>LD</td>
<td>51 (94)</td>
<td>50 (34)</td>
<td>2.5 -1.0</td>
</tr>
</tbody>
</table>
Suppression of menses (menses was defined as three or more consecutive days of menstrual bleeding) was maintained throughout treatment in 84% and 73% of women 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 LUPRON DEPOT 3.75 mg and norethindrone acetate on bone mineral density was evaluated by dual energy x-ray absorptiometry (DEXA) 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 9.

### Table 9. Mean Percent Change from Baseline in Bone Mineral Density of Lumbar Spine

<table>
<thead>
<tr>
<th></th>
<th>LUPRON DEPOT 3.75 mg (LD only)</th>
<th>LUPRON DEPOT 3.75 mg plus norethindrone acetate 5 mg daily (LD/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Controlled Study</td>
<td>Controlled Study</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>Change Mean (95% CI)#</td>
</tr>
<tr>
<td>Week 24*</td>
<td>41</td>
<td>-3.2% (-3.8, -2.6)</td>
</tr>
<tr>
<td>Week 52†</td>
<td>29</td>
<td>-6.3% (-7.1, -5.4)</td>
</tr>
</tbody>
</table>

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

The change in BMD following discontinuation of treatment is shown in Table 10.
Table 10. Mean Percent Change from Baseline in BMD of Lumbar Spine in Post-Treatment Follow-up Period

<table>
<thead>
<tr>
<th>Post Treatment Measurement</th>
<th>Controlled Study</th>
<th></th>
<th></th>
<th></th>
<th>Open Label Study</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LD-Only</td>
<td>LD/N</td>
<td></td>
<td></td>
<td>LD/N</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Mean % Change</td>
<td>95% CI (%)</td>
<td>N</td>
<td>Mean % Change</td>
<td>95% CI (%)</td>
<td>N</td>
<td>Mean % Change</td>
<td>95% CI (%)</td>
</tr>
<tr>
<td>Month 8</td>
<td>19 -3.3 (-4.9, -1.8)</td>
<td>23 -0.9 (-2.1, 0.4)</td>
<td>89 -0.6 (-1.2, 0.0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Month 12</td>
<td>16 -2.2 (-3.3, -1.1)</td>
<td>12 -0.7 (-2.1, 0.6)</td>
<td>65 0.1 (-0.6, 0.7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

These clinical studies demonstrated that co-administration of leuprolide acetate and norethindrone acetate 5 mg daily is effective in significantly reducing the loss of bone mineral density that occurs with both LUPRON DEPOT 3.75 mg and 11.25 mg treatments, and in relieving symptoms of endometriosis.

14.2 Fibroids

LUPRON DEPOT 3.75 mg monthly for a period of three to six months was studied in four controlled clinical trials.

In one of these clinical studies, enrollment was based on hematocrit ≤ 30% and/or hemoglobin ≤ 10.2 g/dL. Administration of LUPRON DEPOT 3.75 mg monthly, concomitantly with iron, produced an increase of ≥ 6% hematocrit and ≥ 2 g/dL hemoglobin in 77% of women at three months of therapy. The mean change in hematocrit was 10.1% and the mean change in hemoglobin was 4.2 g/dL. Clinical response was judged to be a hematocrit of ≥ 36% and hemoglobin of ≥ 12 g/dL, thus allowing for autologous blood donation prior to surgery. At two and three months, respectively, 71% and 75% of women met this criterion (Table 11). These data suggest however, that some women may benefit from iron alone or 1 to 2 months of LUPRON DEPOT 3.75 mg.

Table 11. Percent of Women Achieving Hematocrit ≥ 36% and Hemoglobin ≥ 12 g/dL

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Week 4</th>
<th>Week 8</th>
<th>Week 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>LUPRON DEPOT 3.75 mg with Iron (N=104)</td>
<td>40*</td>
<td>71†</td>
<td>75*</td>
</tr>
<tr>
<td>Iron Alone (N=98)</td>
<td>17</td>
<td>39</td>
<td>49</td>
</tr>
</tbody>
</table>

* P-Value < 0.01
† P-Value < 0.001

Excessive vaginal bleeding (menorrhagia or menometrorrhagia) decreased in 80% of women at three months. Episodes of spotting and menstrual-like bleeding were noted in 16% of women at final visit.

In this same study, a decrease in uterine volume and myoma volume of ≥25% was seen in 60% and 54% of women, 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 women also experienced a decrease in symptoms including excessive vaginal bleeding and pelvic discomfort. Ninety-five percent of these women became amenorrheic with 61%, 25%, and 4% experiencing amenorrhea during the first, second, and third treatment months respectively.

In addition, post-treatment follow-up was carried out in one clinical trial for a small percentage of women on LUPRON DEPOT 3.75 mg (N=46) among the 77% who demonstrated a ≥ 25% decrease in uterine volume while on therapy. Menses usually returned within two months of cessation of therapy. Mean time to return to pretreatment uterine size was 8.3 months. Regrowth did not appear to be related to pretreatment uterine volume.

Changes in Bone Density

In one of the studies for fibroids described above, when LUPRON DEPOT 3.75 mg was administered for three months in uterine fibroid women, 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.

16 HOW SUPPLIED/STORAGE AND HANDLING

Each LUPRON DEPOT 11.25 mg kit (NDC 0074-3663-03) contains:
- one prefilled dual-chamber syringe
- one plunger
- two alcohol swabs

Each single-dose dual chamber syringe contains sterile white lyophilized microsphere powder of 11.25 mg of leuprolide acetate incorporated in a biodegradable polymer in one chamber and a colorless diluent (1.5 mL) in the other chamber. When mixed with the diluent, LUPRON DEPOT 11.25 mg for injection, is administered as a single IM injection.

Store between 20° to 25°C (68° to 77°F). Excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Loss of Bone Density

Advise patients about the risk of loss of bone mineral density and that treatment is limited [see Dosage and Administration (2.1)]. Advise patients about other factors that can increase and decrease their risk of bone mineral density loss [see Warnings and Precautions (5.1)].

Embryo-Fetal Toxicity
• Advise females of reproductive potential of the possible risk to a fetus. Advise patients to inform healthcare provider of a known or suspected pregnancy [see Warnings and Precautions (5.2) and Use in Special Populations (8.1)].

• If contraception is indicated, advise females of reproductive potential to use non-hormonal contraception during treatment with LUPRON DEPOT 11.25 mg [see Use in Special Populations (8.3)].

Hypersensitivity Reactions
Inform patients that hypersensitivity reactions, including anaphylaxis, have been reported with LUPRON DEPOT. Advise patients to seek appropriate medical care if symptoms of hypersensitivity reactions occur [see Warnings and Precautions (5.3) and Adverse Reactions (6.2)].

Initial Flare of Symptoms
Advise patients that they may experience an increase in symptoms during the initial days of therapy. Advise patients that these symptoms should dissipate with continued therapy [see Warnings and Precautions (5.4)].

Convulsions
Inform patients that convulsions have been reported in patients who have received LUPRON DEPOT. Advise patients to seek medical attention in the event of a convulsion [see Warnings and Precautions (5.5)].

Clinical Depression
Inform patients that depression may occur or worsen during treatment with GnRH agonists, including LUPRON DEPOT 11.25 mg, especially in patients with a history of depression. Advise patients to immediately report thoughts and behaviors of concern to healthcare providers [see Warnings and Precautions (5.6)].