HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use LUPRON DEPOT 11.25 mg safely and effectively. See full prescribing information for LUPRON DEPOT 11.25 mg.

LUPRON DEPOT 11.25 mg (leuprolide acetate for depot suspension), for intramuscular use
Initial U.S. Approval: 1997

----------INDICATIONS AND USAGE----------

- LUPRON DEPOT 11.25 mg for 3-month administration is a gonadotropin-releasing hormone (GnRH) agonist indicated for:
  - Management of endometriosis, including pain relief and reduction of endometriotic lesions. (1.1)
  - In combination with a norethindrone acetate 5 mg tablet taken once daily as add-back therapy: initial management of the painful symptoms of endometriosis and for management of recurrence of symptoms. (1.1)

  Limitation of use:

  Initial treatment course of LUPRON DEPOT (whether used alone or with add-back therapy) is limited to 6 months. A single retreatment course of not more than 6 months of LUPRON DEPOT plus add-back therapy may be given if symptoms recur. Do not use LUPRON DEPOT alone for retreatment. 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, 5.1)
- LUPRON DEPOT 11.25 mg is also indicated for concomitant use with iron therapy for preoperative hematologic improvement of patients with anemia caused by uterine leiomyomata (fibroids). (1.2)

  Limitation of use:
  The recommended treatment is limited to one injection. (1.2, 5.1)

----------DOSAGE AND ADMINISTRATION----------

Reconstitute leuprolide acetate prior to use. (2.3)

Endometriosis:

- LUPRON DEPOT 11.25 mg given by a healthcare provider 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)
- Assess bone density before retreatment begins. (2.1, 5.1)

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 or any of the excipients in LUPRON DEPOT 11.25 mg. (4, 5.3)
- Undiagnosed abnormal uterine bleeding. (4)
- Pregnancy or suspected pregnancy. (4, 8.1)
- Lactation. (4)

When add-back therapy with norethindrone acetate is considered, refer also to Contraindications in the norethindrone acetate package insert. (4)

----------WARNINGS AND PRECAUTIONS----------

- Loss of bone mineral density: Do not exceed the labeled duration of treatment for endometriosis. Do not use more than one injection for preoperative hematologic improvement in women with fibroids. (1.1, 1.2, 5.1)
- Exclude pregnancy before starting treatment and discontinue use if pregnancy occurs. Use non-hormonal methods of contraception only. (5.2)
- Serious allergic reactions have been reported with LUPRON DEPOT 11.25 mg. (5.3)
- When add-back therapy with norethindrone acetate is used, refer also to Warnings and Precautions in the norethindrone acetate package insert. (5)

----------ADVERSE REACTIONS----------

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

---------- USE IN SPECIFIC POPULATIONS----------

- Pediatric: Safety and effectiveness of LUPRON DEPOT for treatment of endometriosis or fibroids has not been established in females less than 18 years of age. (8.4)
- Geriatric: LUPRON DEPOT 11.25 mg has not been studied in women over 65 years of age and is not indicated in this population. (8.5)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 04/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Endometriosis

LUPRON DEPOT 11.25 mg for 3-month administration is indicated for management of endometriosis, including pain relief and reduction of endometriotic lesions. Laparoscopic staging of endometriosis does not necessarily correlate with the severity of symptoms.

LUPRON DEPOT 11.25 mg in combination with a norethindrone acetate 5 mg tablet taken once daily as add-back therapy is also 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 to reduce vasomotor symptoms associated with use of LUPRON DEPOT 11.25 mg. Decide between use of LUPRON DEPOT 11.25.mg alone or LUPRON DEPOT 11.25.mg plus norethindrone acetate add-back therapy for initial management of the symptoms and signs of endometriosis in consultation with the patient, considering the risks and benefits of adding norethindrone to LUPRON DEPOT 11.25 mg *[see Warnings and Precautions (5.6)]*. For the safe and effective use of norethindrone acetate, refer to the norethindrone acetate prescribing information.

Limitation of use:
Duration of use is limited due to concerns about adverse impact on bone mineral density *[see Warnings and Precautions (5.1)]*. The initial treatment course of LUPRON DEPOT 11.25 mg (whether used alone or with add-back therapy) is limited to six months. A single retreatment course of not more than six months of LUPRON DEPOT 11.25 mg plus norethindrone acetate add-back therapy may be administered after the initial course of treatment if symptoms recur. Do not use LUPRON DEPOT 11.25 mg alone for retreatment. The total duration of therapy with LUPRON DEPOT 11.25 mg plus add-back therapy should not exceed 12 months *[see Dosage and Administration (2.1)]*.

1.2 Uterine Leiomyomata (Fibroids)

LUPRON DEPOT 11.25 mg used concomitantly with iron therapy is indicated for the preoperative hematologic improvement of patients with anemia caused by fibroids. Consider a one-month trial period on iron alone, as some patients will respond to iron alone *[see Clinical*

Studies (14.3)]. LUPRON DEPOT 11.25 mg may be added if the response to iron alone is considered inadequate. Add-back therapy with norethindrone acetate is **not** warranted for this indication.

Limitation of use:
The recommended treatment is one injection of LUPRON DEPOT 11.25 mg. This dosage form is indicated only for women for whom three months of hormonal suppression is deemed necessary.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information

Endometriosis

Table 1. LUPRON DEPOT 11.25 mg Treatment of Endometriosis

Initial treatment (Initial treatment is limited to 6 months)	**Symptom recurrence (Retreatment is limited to 6 months)**
LUPRON DEPOT 11.25 mg IM every 3 months for 1 to 2 doses with or without concurrent oral norethindrone acetate 5 mg daily add-back therapy	**Do not use LUPRON DEPOT 11.25 mg without add-back therapy for symptom recurrence.** Assess BMD prior to retreatment. *[See Warnings and Precautions (5.1)]*. LUPRON DEPOT 11.25 mg IM every 3 months for 1 to 2 doses with concurrent oral norethindrone acetate 5 mg daily add-back therapy (for a maximum of 12 months total treatment).

Fibroids

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

2.2 Different Formulations of LUPRON DEPOT

Due to different release characteristics of the formulations, **Do not** give a fractional dose of the LUPRON DEPOT 11.25 mg given every 3 months, as it is not equivalent to the same dose of the LUPRON DEPOT 3.75 mg monthly formulation.

2.3 Reconstitution and Administration for Injection of LUPRON DEPOT

- Reconstitute and administer the lyophilized microspheres as a single intramuscular injection as directed below.

- 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:

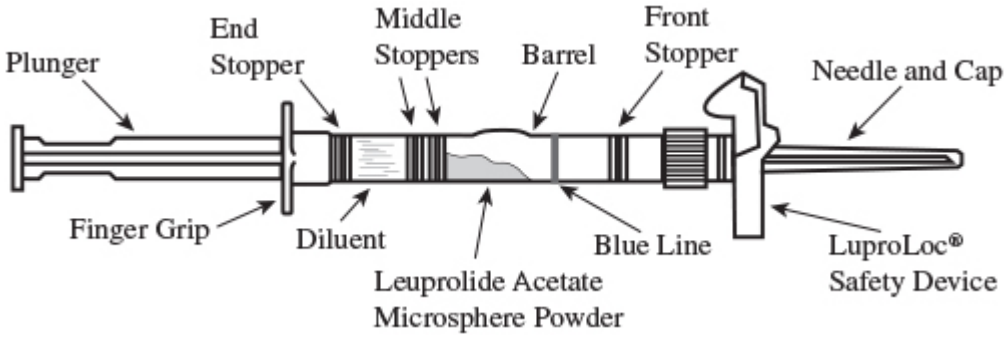
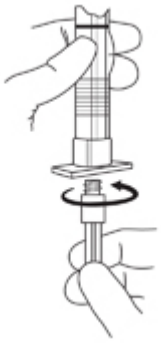
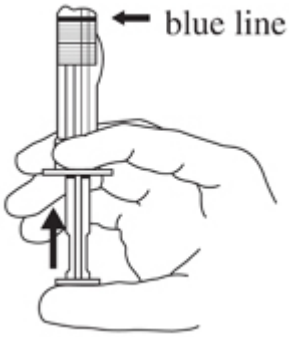


    Figure B:



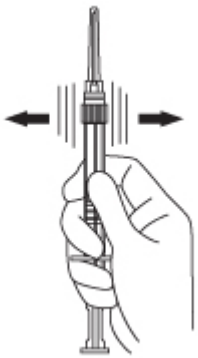
    3. Hold the syringe UPRIGHT. Release the diluent by SLOWLY PUSHING the plunger for 6 to 8 seconds until the first middle stopper is **at the blue line** in the middle of the barrel (see Figure C).

Figure C:



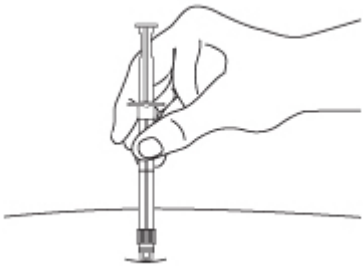
4. Keep the syringe **upright**. Mix the microspheres (powder) thoroughly by gently shaking the syringe until the powder forms a uniform suspension. The suspension will appear milky. If the powder adheres to the stopper or caking/clumping is present, tap the syringe with your finger to disperse. **Do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

   Figure D:



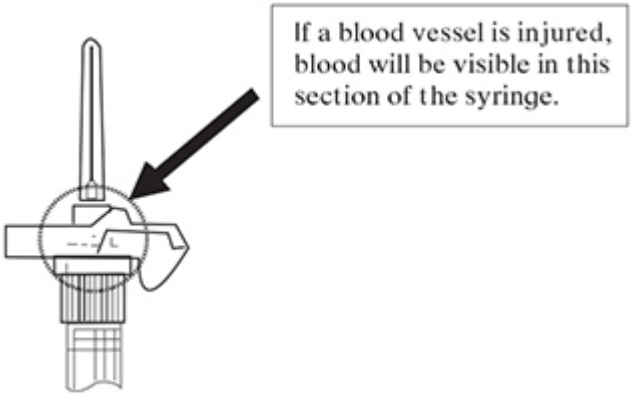
5. Keep the syringe **upright**. With the opposite hand pull the needle cap upward without twisting.
6. Keep the syringe **upright.** Advance the plunger to expel the air from the syringe. The syringe is now ready for injection.
7. After cleaning the injection site with an alcohol swab, administer the intramuscular 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

LUPRON DEPOT (leuprolide acetate for depot suspension) 11.25 mg for 3-month administration contains leuprolide acetate and is a lyophilized powder for reconstitution with supplied diluent in a prefilled dual chamber syringe.

4 CONTRAINDICATIONS

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

- Hypersensitivity to gonadotropin-releasing hormone (GnRH), GnRH agonist analogs, 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
- Known, suspected or planned pregnancy during the course of therapy *[see Warnings and Precautions (5.2) and Use in Specific Populations (8.1)]*
- Lactating women *[see Warnings and Precautions (5.2) and Use in Specific Populations (8.3)]*

When considering add-back therapy with norethindrone acetate, refer also to **Contraindications** in the norethindrone acetate package insert.

5 WARNINGS AND PRECAUTIONS

When considering add-back therapy with norethindrone acetate, refer also to **Warnings and Precautions** in the norethindrone acetate package insert.

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. Concurrent 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)]*. Nonetheless, duration of use of LUPRON DEPOT 11.25 mg plus add-back therapy for endometriosis is limited to two six-month courses of treatment due to concerns about the adverse impact on BMD. Assess BMD before retreatment. Do not retreat with LUPRON DEPOT 11.25 mg alone *[see Indications and Usage (1.1)]*.

Duration of use LUPRON DEPOT 11.25 mg for preoperative hematologic improvement in women with fibroids is limited to one three-month course of treatment *[see Indications and Usage (1.2)]*. The symptoms associated with fibroids will recur following discontinuation of therapy.

In women with major risk factors for decreased BMD such as chronic alcohol (> 3 units per day) or tobacco use, strong family history of osteoporosis, or chronic use of drugs that can decrease BMD, such as anticonvulsants or corticosteroids, use of LUPRON DEPOT 11.25 mg may pose an additional risk, and the risks and benefits should be weighed carefully.

5.2 Pregnancy Risk

LUPRON DEPOT 11.25 mg may cause fetal harm if administered to a pregnant woman. Exclude pregnancy before initiating treatment with LUPRON DEPOT 11.25 mg. 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. Therefore, patients should use non-hormonal methods of contraception. Advise patients to notify their healthcare provider if they believe they may be pregnant. Discontinue LUPRON DEPOT 11.25 mg if a patient becomes pregnant during treatment and inform the patient of potential risk to the fetus *[see Contraindications (4)* and *Use in Specific Populations (8.1)]*.

5.3 Serious Allergic Reactions

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 associated with endometriosis 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 patients on leuprolide acetate therapy. These included patients with and without concurrent medications and comorbid conditions.

5.6 Clinical Depression

Depression may occur or worsen during treatment with norethindrone acetate. Carefully observe women with a history of depression and consider discontinuing norethindrone acetate if depression recurs to a serious degree.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

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

LUPRON DEPOT (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 patients treated with LUPRON DEPOT 3.75 mg discontinued prematurely due to hot flashes.

Common Adverse Reactions

LUPRON DEPOT 3.75 mg was utilized in controlled clinical trials that studied the drug in 166 endometriosis and 166 uterine fibroids patients. Adverse reactions reported in ≥ 5% of patients in either of these populations are noted in the following tables.

Table 2. Adverse Reactions Reported in ≥ 5% of Patients Taking LUPRON DEPOT-Endometriosis (2 Studies)

	LUPRON DEPOT 3.75 mg N=166	**Danazol N=136**	**Placebo N=31**
	%	**%**	**%**
Hot flashes/sweats*	84	57	29
Headache*	32	22	6
Vaginitis*	28	17	0
Depression/emotional lability*	22	20	3
General pain	19	16	3
Weight gain/loss	13	26	0
Nausea/vomiting	13	13	3
Decreased libido*	11	4	0
Dizziness	11	3	0
Acne	10	20	0
Skin reactions	10	15	3
Joint disorder*	8	8	0
Edema	7	13	3
Paresthesias	7	8	0
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 patients 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; *Hemic and Lymphatic System* - Ecchymosis; *Nervous System* - Anxiety*, Insomnia/Sleep disorders*, Delusions, Memory disorder, Personality disorder; *Skin and Appendages* - Alopecia, Hair disorder; *Special Senses* - Ophthalmologic disorders*; *Urogenital System* - Dysuria*, Lactation.
* = Possible effect of decreased estrogen.

Table 3. Adverse Reactions Reported in ≥ 5% of Patients - Uterine Fibroids (4 Studies)

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

In these same studies, symptoms reported in < 5% of patients included: *Body as a Whole* - Body odor, Flu syndrome, Injection site reactions; *Cardiovascular System* - Tachycardia; *Digestive System* - Appetite changes, Dry mouth; *Endocrine System* - Androgen-like effects; *Nervous System* - Anxiety*, Insomnia/Sleep disorders*; *Respiratory System* - Rhinitis; *Skin and Appendages* - Nail disorder; *Special Senses* - Conjunctivitis, Taste perversion; *Urogenital System* - Menstrual disorders.
* = Possible effect of decreased estrogen.

In one controlled clinical trial utilizing the monthly formulation of LUPRON DEPOT, patients diagnosed with uterine fibroids received a higher dose (7.5 mg) of LUPRON DEPOT. Adverse reactions seen with this dose that were not seen at the lower dose included galactorrhea, pyelonephritis, and urinary incontinence. 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 endometriosis patients receiving LUPRON DEPOT 3.75 mg (N=20) or LUPRON DEPOT 11.25 mg (N=21), similar adverse reactions were reported by the two groups of patients. In general the safety profiles of the two formulations were comparable in this study.

LUPRON DEPOT with Norethindrone Acetate Add-back Therapy

The safety of co-administering LUPRON DEPOT 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 leuprolide acetate 3.75 mg (13 injections) alone or monthly IM injections of leuprolide acetate 3.75 mg (13 injections) plus

5 mg norethindrone acetate daily. The population age range was 17-43 years old. The majority of patients were Caucasian (87%).

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

In the open label study, 13% of patients treated monthly with LUPRON DEPOT 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 patients in any treatment group, during the first 6 months of treatment in the two add-back clinical studies, in which patients were treated with monthly LUPRON DEPOT 3.75 mg with or without norethindrone acetate co-treatment. The most frequently-occurring adverse reactions observed in these studies were hot flashes and headaches.

Table 4. Adverse Reactions Occurring in the First Six Months of Treatment in ≥ 5% of Patients with Endometriosis

	Controlled Study		Open Label Study
	LD-Only*	LD/N†	LD/N†
	N=51	N=55	N=136
Adverse Reactions	**%**	**%**	**%**
Any Adverse Reaction	98	96	93
Hot flashes/Sweats	98	87	57
Headache/Migraine	65	51	46
Depression/Emotional Lability	31	27	34
Insomnia/Sleep Disorder	31	13	15
Nausea/Vomiting	25	29	13
Pain	24	29	21
Vaginitis	20	15	8
Asthenia	18	18	11
Dizziness/Vertigo	16	11	7
Altered Bowel Function (constipation, diarrhea)	14	15	10
Weight Gain	12	13	4
Decreased Libido	10	4	7
Nervousness/Anxiety	8	4	11
Breast Changes/Pain/Tenderness	6	13	8
Memory Disorder	6	2	4
Skin/Mucous Membrane Reaction	4	9	11
GI Disturbance (dyspepsia, flatulence)	4	7	4
Androgen-Like Effects (acne, alopecia)	4	5	18
Changes in Appetite	4	0	6
Injection Site Reaction	2	9	3
Neuromuscular Disorder (leg cramps, paresthesia)	2	9	3
Menstrual Disorders	2	0	5
Edema	0	9	7

* LD-Only = LUPRON DEPOT 3.75 mg
† LD/N = LUPRON DEPOT 3.75 mg plus norethindrone acetate 5 mg

In the controlled clinical trial, 50 of 51 (98%) patients in the LUPRON DEPOT 3.75 mg arm and 48 of 55 (87%) patients 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)

Assessment Visit	Treatment Group	Number of Patients Reporting Hot Flashes		Number of Days with Hot Flashes		Maximum Number Hot Flashes in 24 Hours	
		N	(%)	N[2]	Mean	N[2]	Mean
Week 24	LD-Only*	32/37	86	37	19	36	5.8
	LD/N†	22/38	58[1]	38	7[1]	38	1.9[1]

* LD-Only = LUPRON DEPOT 3.75 mg
† LD/N = LUPRON DEPOT 3.75 mg plus norethindrone acetate 5 mg
[1]Statistically significantly less than the LD-Only group ($p<0.01$)
[2]Number of patients assessed.

Serious Adverse Reactions

Urinary tract infection, renal calculus, depression

Changes in Laboratory Values during Treatment

Liver Enzymes

Three percent of uterine fibroid patients 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. None of the laboratory increases were associated with clinical symptoms.

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

Lipids

Triglycerides were increased above the upper limit of normal in 12% of the endometriosis patients who received LUPRON DEPOT 3.75 mg and in 32% of the subjects receiving LUPRON DEPOT 11.25 mg.

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

Percent changes from baseline for serum lipids and percentages of patients with serum lipid values outside of the normal range in the two studies of leuprolide acetate and norethindrone acetate are summarized in the tables below. The major impact of adding norethindrone acetate to treatment with LUPRON DEPOT 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 24

	LUPRON DEPOT 3.75 mg		**LUPRON DEPOT 3.75 mg plus norethindrone acetate 5 mg daily**			
	Controlled Study (n=39)		**Controlled Study (n=41)**		**Open Label Study (n=117)**	
	Baseline Value*	Wk 24 % Change	Baseline Value*	Wk 24 % Change	Baseline Value*	Wk 24 % Change
Total Cholesterol	170.5	9.2%	179.3	0.2%	181.2	2.8%
HDL Cholesterol	52.4	7.4%	51.8	-18.8%	51.0	-14.6%
LDL Cholesterol	96.6	10.9%	101.5	14.1%	109.1	13.1%
LDL/HDL Ratio	2.0†	5.0%	2.1†	43.4%	2.3†	39.4%
Triglycerides	107.8	17.5%	130.2	9.5%	105.4	13.8%
* mg/dL † ratio						

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

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

	LUPRON DEPOT 3.75 mg		**LUPRON DEPOT 3.75 mg plus norethindrone acetate 5 mg daily**			
	Controlled Study (n=39)		**Controlled Study (n=41)**		**Open Label Study (n=117)**	
	Wk 0	Wk 24*	Wk 0	Wk 24*	Wk 0	Wk 24*
Total Cholesterol (>240 mg/dL)	15%	23%	15%	20%	6%	7%
HDL Cholesterol (<40 mg/dL)	15%	10%	15%	44%	15%	41%
LDL Cholesterol (>160 mg/dL)	0%	8%	5%	7%	9%	11%
LDL/HDL Ratio (>4.0)	0%	3%	2%	15%	7%	21%
Triglycerides (>200 mg/dL)	13%	13%	12%	10%	5%	9%
* Includes all patients regardless of baseline value.						

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

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

Other adverse reactions reported are:

- *Hepato-biliary disorder* - Serious liver injury
- *Injury, poisoning and procedural complications* - Spinal fracture
- *Investigations* - Decreased white blood count
- *Musculoskeletal and connective tissue disorder* - Tenosynovitis-like symptoms
- *Nervous System disorder* - Convulsion, peripheral neuropathy, paralysis
- *Vascular disorder* - Hypotension, Hypertension

Serious venous and arterial thrombotic and thromboembolic reactions have been reported, including deep vein thrombosis, pulmonary embolism, myocardial infarction, stroke, and transient ischemic attack

Pituitary apoplexy

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

7 DRUG INTERACTIONS

7.1 Drug-Drug Interactions

No pharmacokinetic-based drug-drug interaction studies have been conducted with LUPRON DEPOT 11.25 mg. However, drug interactions associated with cytochrome P-450 enzymes would not be expected to occur *[see Clinical Pharmacology (12.3)]*.

7.2 Drug/Laboratory Test Interactions

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 may be affected.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X *[see Contraindications (4)]*

Teratogenic Effects

LUPRON DEPOT 11.25 mg is contraindicated in women who are or may become pregnant while receiving the drug *[see Contraindications (4)]*. Before starting and during treatment with LUPRON DEPOT 11.25 mg, establish whether the patient is pregnant. LUPRON DEPOT 11.25 mg is not a contraceptive. Females of reproductive potential should use a non-hormonal method of contraception *[see Warnings and Precautions (5.2)]*.

LUPRON DEPOT 11.25 mg may cause fetal harm when administered to a pregnant woman.

When administered on day 6 of pregnancy at test dosages of 0.00024, 0.0024, and 0.024 mg/kg (1/300 to 1/3 of the human dose) to rabbits, leuprolide acetate 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 *[see Nonclinical Pharmacology (13.1)]*.

8.3 Nursing Mothers

Do not use LUPRON DEPOT 11.25 mg in nursing mothers because the effects of LUPRON DEPOT on lactation and/or the breast-fed child have not been determined.

It is not known whether LUPRON DEPOT 11.25 mg is excreted in human milk.

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

8.4 Pediatric Use

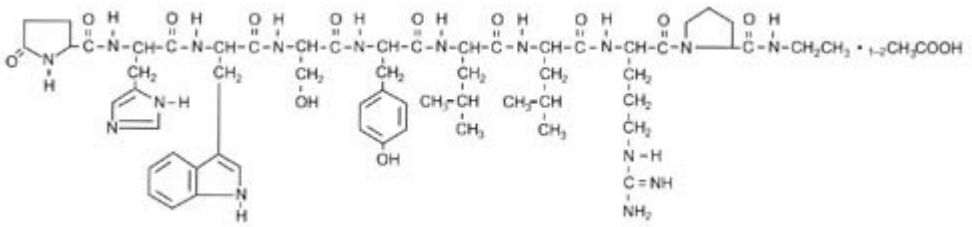
LUPRON DEPOT 11.25 mg is not indicated in premenarcheal adolescents. Safety and effectiveness of LUPRON DEPOT 11.25 mg for treatment of endometriosis or fibroids have not been established in females less than 18 years of age.

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 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:



LUPRON DEPOT 11.25 mg for 3-month administration is available in a prefilled dual-chamber syringe containing sterile lyophilized microspheres which, when mixed with diluent, become a suspension intended as an intramuscular injection.

The front chamber of LUPRON DEPOT 11.25 mg for 3-month administration prefilled dual-chamber syringe contains leuprolide acetate for depot suspension (11.25 mg), polylactic acid (99.3 mg) and D-mannitol (19.45 mg). The second chamber of diluent contains carboxymethylcellulose sodium (7.5 mg), D-mannitol (75.0 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 for 3-month administration, 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 results in an initial stimulation followed by a prolonged suppression of pituitary gonadotropins. Repeated dosing at quarterly (LUPRON DEPOT 11.25 mg) intervals results in decreased secretion of gonadal steroids. Consequently, tissues and functions that depend on gonadal steroids for their maintenance become quiescent. This effect is reversible on discontinuation of drug therapy.

Leuprolide acetate is not active when given orally.

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.

12.3 Pharmacokinetics

Absorption

Following a single injection of the three 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, intramuscular 11.25 mg LUPRON DEPOT (n=19) every 12 weeks or intramuscular 3.75 mg LUPRON DEPOT (n=15) every 4 weeks was administered for 24 weeks. There was no statistically significant difference in changes of serum estradiol concentration from baseline between the 2 treatment groups.

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.

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 drug-drug interaction studies have been conducted with LUPRON DEPOT 11.25 mg. However, because leuprolide acetate for depot suspension is a peptide that is primarily degraded by peptidase and not by cytochrome P-450 enzymes, drug interactions associated with cytochrome P-450 enzyme 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.

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 (pre-pubertal and adult rats and monkeys) with leuprolide acetate and other GnRH analogs have shown functional recovery.

14 CLINICAL STUDIES

The safety and efficacy of LUPRON DEPOT 11.25 mg for 3-month administration for the following indications has been established based on adequate and well-controlled adult studies (See Table 8) of LUPRON DEPOT 3.75 mg for 1-month administration and on a single trial of LUPRON DEPOT 11.25 mg for 3-month administration:

- The management of endometriosis, including pain relief and reduction of endometriotic lesions
- The initial management of endometriosis and for management of recurrence of symptoms (with norethindrone acetate add-back therapy)
- Preoperative hematologic improvement of patients with anemia caused by uterine leiomyomata (with iron therapy)

See *Clinical Studies (14.1, 14.2,* and *14.3)* for the results of the adequate and well-controlled studies in these conditions.

14.1 Endometriosis

LUPRON DEPOT Monotherapy

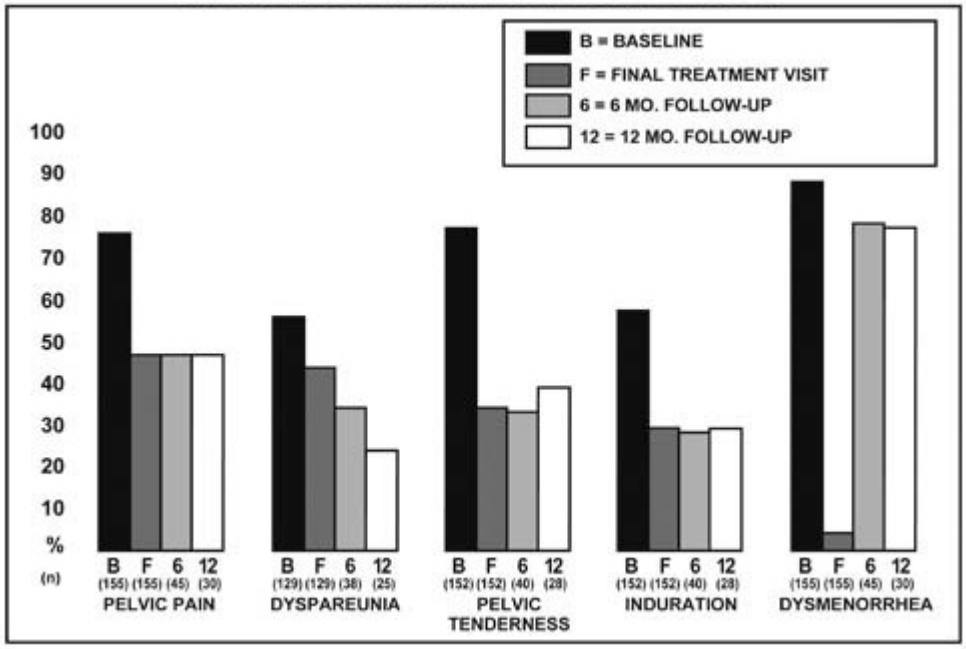
In controlled clinical studies, LUPRON DEPOT 3.75 mg monthly for six months was shown to be comparable to danazol 800 mg/day in relieving the clinical sign/symptoms of endometriosis (pelvic pain, dysmenorrhea, dyspareunia, pelvic tenderness, and induration) and in reducing the size of endometrial implants 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 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 8 illustrates the percent of patients with symptoms at baseline, final treatment visit and sustained relief at 6 and 12 months following discontinuation of treatment for the various symptoms evaluated during the two controlled clinical studies. A total of 166 patients received LUPRON DEPOT 3.75 mg. Seventy-five percent (N=125) of these elected to participate in the follow-up period. Of these patients, 36% and 24% are included in the 6 month and 12 month follow-up analysis, respectively. All the patients who had a pain evaluation at baseline and at a minimum of one treatment visit are included in the Baseline (B) and final treatment visit (F) analysis.

Figure 1. Percent of Patients with Signs/Symptoms of Endometriosis at Baseline, Final Treatment Visit, and After 6 and 12 Months of Follow-Up



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 also Clinical Pharmacology (12.2).*

A six-month pharmacokinetic/pharmacodynamic post-marketing study in 41 women that included both the 3.75 mg dose (N=20) administered once monthly and the 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 leuprolide acetate. In both treatment groups, suppression of menses (defined as no new menses for at least 60 consecutive days) was achieved in 100% of the patients 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 coadministration of LUPRON DEPOT and norethindrone acetate on the loss of bone mineral density (BMD) associated with LUPRON DEPOT and on the efficacy of LUPRON DEPOT in relieving symptoms of endometriosis. (All patients in these studies received calcium supplementation with 1000 mg elemental calcium). A total of 242 women were treated with monthly administration of leuprolide acetate 3.75 mg (13 injections) and 191 of them were co-administered 5 mg norethindrone acetate taken daily. The population age range was 17-43 years old. The majority of patients were Caucasian (87%).

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

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

Table 8 below provides detailed efficacy data regarding relief of symptoms of endometriosis based on the two studies of co-administration of leuprolide acetate and norethindrone acetate.

Table 8. Percentages of Patients with Symptoms of Endometriosis and Mean Clinical Severity Scores

			Percent of Patients with Symptoms			Clinical Pain Severity Score		
			Baseline		Final	Baseline		Final
Variable	**Study**	**Group**	**N[1]**	**(%)[2]**	**(%)**	**N[1]**	**Value[3]**	**Change**
Dysmenorrhea	Controlled Study	LD*[4]	51	(100)	(4)	50	3.2	-2.0
		LD/N†	55	(100)	(4)	54	3.1	-2.0
	Open Label Study	LD/N[5]	136	(99)	(9)	134	3.3	-2.1
Pelvic Pain	Controlled Study	LD[4]	51	(100)	(66)	50	2.9	-1.1
		LD/N	55	(96)	(56)	54	3.1	-1.1
	Open Label Study	LD/N[5]	136	(99)	(63)	134	3.2	-1.2
Deep Dyspareunia	Controlled Study	LD	42	(83)	(37)	25	2.4	-1.0
		LD/N	43	(84)	(45)	30	2.7	-0.8
	Open Label Study	LD/N	102	(91)	(53)	94	2.7	-1.0
Pelvic Tenderness	Controlled Study	LD[4]	51	(94)	(34)	50	2.5	-1.0
		LD/N	54	(91)	(34)	52	2.6	-0.9
	Open Label Study	LD/N[5]	136	(99)	(39)	134	2.9	-1.4
Pelvic Induration	Controlled Study	LD[4]	51	(51)	(12)	50	1.9	-0.4
		LD/N	54	(46)	(17)	52	1.6	-0.4
	Open Label Study	LD/N[5]	136	(75)	(21)	134	2.2	-0.9

* LD = LUPRON DEPOT 3.75 mg assessment
† LD/N = LUPRON DEPOT 3.75 mg plus norethindrone acetate 5 mg
[1] Number of patients that were included in the assessment
[2] Percentage of patients with the symptom/sign
[3] Value description: 1=none; 2= mild; 3= moderate; 4= severe
[4] 6-month study duration of treatment
[5] 12months study duration of treatment with 12 months follow up

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

Changes in Bone Density

The effect of LUPRON DEPOT 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

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

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

The change in BMD following discontinuation of treatment is shown in Table 10.

Table 10. Mean Percent Change from Baseline in BMD of Lumbar Spine in Post-Treatment Follow-up Period

Post Treatment Measurement	Controlled Study						Open Label Study		
	LD-Only			LD/N			LD/N		
	N	Mean % Change	95% CI (%)	N	Mean % Change	95% CI (%)	N	Mean % Change	95% CI (%)[2]
Month 8	19	-3.3	(-4.9, -1.8)	23	-0.9	(-2.1, 0.4)	89	-0.6	(-1.2, 0.0)
Month 12	16	-2.2	(-3.3, -1.1)	12	-0.7	(-2.1, 0.6)	65	0.1	(-0.6, 0.7)

[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 for a period of three to six months was studied in four controlled clinical trials.

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

Table 11. Percent of Patients Achieving Hematocrit ≥ 36% and Hemoglobin ≥ 12 GM/DL

Treatment Group	Week 4	Week 8	Week 12
LUPRON DEPOT 3.75 mg with Iron (N=104)	40*	71†	75*
Iron Alone (N=98)	17	39	49
* P-Value < 0.01 † P-Value < 0.001			

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

In this same study, a decrease of ≥25% was seen in uterine and myoma volumes in 60% and 54% of patients respectively. The mean fibroid diameter was 6.3 cm at pretreatment and decreased to 5.6 cm at the end of treatment. LUPRON DEPOT 3.75 mg was found to relieve symptoms of bloating, pelvic pain, and pressure.

In three other controlled clinical trials, enrollment was not based on hematologic status. Mean uterine volume decreased by 41% and myoma volume decreased by 37% at final visit as evidenced by ultrasound or MRI. The mean fibroid diameter was 5.6 cm at pretreatment and decreased to 4.7 cm at the end of treatment. These patients also experienced a decrease in symptoms including excessive vaginal bleeding and pelvic discomfort. Ninety-five percent of these patients became amenorrheic with 61%, 25%, and 4% experiencing amenorrhea during the first, second, and third treatment months respectively.

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

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 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.

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

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
- a complete prescribing information enclosure

Each syringe contains sterile lyophilized microspheres of leuprolide acetate incorporated in a biodegradable polymer of polylactic acid. When mixed with 1.5 mL of the diluent, LUPRON DEPOT 11.25 mg is administered as a single intramuscular 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

Advise patients about the Warnings and Precautions for LUPRON DEPOT 11.25 mg, including:

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) and Warnings and Precautions (5.1)]*:

- for endometriosis, to:
    - one six-month course of treatment if given without add-back therapy
    - two six-month courses of treatment, if given with add-back therapy in the second six-month course
- for preoperative hematologic improvement in women with fibroids, to:
    - one three-month course of treatment in combination with iron therapy

Pregnancy Warning

- Advise patients not to use this drug if they are pregnant or planning a pregnancy, suspect they may be pregnant, or are breastfeeding *[see Warnings and Precautions (5.2) and Use in Special Populations (8.1, 8.3)]*.
- Advise patients about the risk to an exposed fetus and need to use non-hormonal contraception *[see Warnings and Precautions (5.2) and Use in Special Populations (8.1)]*.

Allergic Reaction to GnRH agonists

Advise patients not to use this drug if they have experienced an allergic reaction to GnRH agonists *[see Warnings and Precautions (5.3) and Adverse Reactions (6.2)]*.

New or Worsened Symptoms

Advise patients to notify their healthcare provider if they develop new or worsened symptoms after beginning treatment *[see Warnings and Precautions (5.4)]*.

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

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