

Important Update to the Prescribing Information for LUPRON DEPOT® (leuprolide acetate for depot suspension) 11.25 mg.

In March 2020, the LUPRON DEPOT Prescribing Information (PI) was updated to reflect the Pregnancy and Lactation Labeling Rule (PLLR) to assist healthcare providers in assessing benefit versus risk and in subsequent counseling of pregnant women and nursing mothers. The following describes several of the changes in the LUPRON DEPOT Prescribing Information. Please refer to the complete PI to review additional changes.

The following items have been removed in the Prescribing Information (PI):

- **Section 4 Contraindications**
 - Lactating women

- **Section 8.2 Lactation**
 - 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.

The following items have been added in the PI:

- **Section 17 Patient Counseling Information**
 - 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)].

The following items have been updated in the PI to read:

- **Section 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)].

· Section 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.

· Section 4 Contraindications

- Pregnancy [see Warnings and Precautions (5.2) and Use in Specific Populations (8.1)]

· Section 5 Warnings and Precautions**- 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)].

- 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.

- **Section 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.

- **Sections 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.

- **Section 17 Patient Counseling Information**

- **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)].

This is not a complete list of all the changes made to the Prescribing Information for LUPRON DEPOT (11.25 mg). Please refer to the full Prescribing Information for more details.

INDICATIONS

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.

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.

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. 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.

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. 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.

IMPORTANT SAFETY INFORMATION

General Information

- LUPRON DEPOT 3.75 mg for 1-month administration and 11.25 mg are contraindicated in:
 - Patients who are hypersensitive to gonadotropin-releasing hormone (GnRH), GnRH agonist analogs or any of the excipients in LUPRON DEPOT.

- Undiagnosed abnormal uterine bleeding.
- Known or suspected pregnancy during the course of therapy.
- LUPRON DEPOT 3.75 mg for 1-month administration is also contraindicated in:
 - Lactating women.
- Bone loss may occur over the course of treatment, some of which may not be reversible. Please see indication-specific information below.
- LUPRON DEPOT may cause fetal harm when administered to a pregnant woman. Exclude pregnancy before initiating treatment and advise patients to notify their healthcare provider if they believe they may be pregnant. Used at the recommended dose, LUPRON DEPOT usually inhibits ovulation and stops menstruation. However, contraception is not ensured. Patients should use non-hormonal methods of contraception.
- Hypersensitivity reactions, including anaphylaxis, have been reported with LUPRON DEPOT use. In clinical trials, serious adverse events of asthma were reported in women with pre-existing histories of asthma, sinusitis, and environmental or drug allergies. Symptoms consistent with an anaphylactic or asthmatic process have been reported postmarketing.
- An increase in clinical signs and symptoms may be observed during the initial days of therapy due to a temporary rise in sex steroids, but will dissipate with continued therapy.
- Postmarketing reports of convulsions have been observed in patients on leuprolide acetate therapy, including patients with and without concurrent medications and comorbid conditions.
- 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. Add-back therapy with norethindrone acetate is **not** warranted for anemia associated with uterine fibroids.
- In clinical trials, adverse events occurring in >10% of patients were hot flashes/sweats, headache/migraine, decreased libido, depression/emotional lability, dizziness, nausea/vomiting, pain, vaginitis, and weight gain.
- Due to suppression of the pituitary-gonadal system by LUPRON DEPOT, diagnostic tests of pituitary gonadotropic and gonadal functions conducted during treatment, and for up to 3 months after discontinuation of LUPRON DEPOT, may be affected.
- LUPRON DEPOT is not indicated in premenarcheal adolescents. Experience with LUPRON DEPOT for endometriosis or anemia associated with uterine fibroids has been limited to women 18 years of age and older. LUPRON DEPOT is not indicated in postmenopausal women and has not been studied in this population.

Endometriosis

- When considering add-back therapy in combination with LUPRON DEPOT 11.25 mg, refer also to Contraindications, Warnings, and Precautions in the norethindrone acetate package insert.
- Norethindrone acetate as add-back therapy with LUPRON 3.75 mg in endometriosis is contraindicated in women with thrombophlebitis, thromboembolic disorders, cerebral apoplexy, or a past history of these conditions; markedly impaired liver function or liver disease; and known or suspected carcinoma of the breast.
- Assessment and management of risk factors for cardiovascular disease is recommended prior to initiation of add-back therapy with norethindrone acetate and LUPRON DEPOT 3.75 mg. Norethindrone acetate should be used with caution in women with risk factors, including lipid abnormalities or cigarette smoking.
- LUPRON DEPOT 3.75 mg plus 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.
- Induced hypoestrogenic state results in bone loss over the course of treatment, 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. In controlled clinical trials in patients with

endometriosis, at the end of 6 months of therapy with LUPRON DEPOT, lumbar spine bone density decreased by an average of 3.2% compared with the pretreatment values.

- In patients with major risk factors for loss of bone mineral content, risks and benefits of LUPRON DEPOT alone must be weighed carefully before therapy is instituted. Treatment with LUPRON DEPOT beyond an initial 6-month course is not advisable in these patients. In patients that are candidates for retreatment, it is recommended that bone density be assessed before retreatment. Retreatment with LUPRON DEPOT alone is not recommended.
- LUPRON DEPOT plus norethindrone acetate-treated patients had significantly decreased HDL levels and significantly increased LDL/HDL ratios in clinical trials. After discontinuation of treatment, mean serum lipid levels in clinical trial patients with follow-up data returned to pretreatment values.
- **Do not use LUPRON DEPOT without add-back therapy for symptom recurrence.**

Uterine Leiomyomata (Fibroids)

- Induced hypoestrogenic state results in bone loss over the course of treatment, some of which may not be reversible. The duration of therapy with LUPRON DEPOT is limited to 3 months. The symptoms associated with fibroids will recur following discontinuation of therapy. In patients with major risk factors for decreased bone mineral content, LUPRON DEPOT therapy may pose an additional risk, and the risks and benefits should be weighed carefully. In controlled clinical trials in patients with fibroids, after 3 months of therapy, vertebral bone density decreased by an average of 2.7% compared with the pretreatment values.
- In controlled clinical trials of fibroid patients, mean changes in cholesterol, LDL, HDL, and the LDL/HDL ratios were observed.

Please see accompanying full prescribing information.

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