

Important Update to the Prescribing Information for LUPRON DEPOT[®] (leuprolide acetate for depot suspension) 3-month 11.25 mg

On April 2018, the LUPRON DEPOT Prescribing Information (PI) was updated to reflect the Physician Labeling Rule (PLR) format. These highlights do not include all of the changes; please refer to the complete PI to review additional changes. The following describes several of the changes in the LUPRON DEPOT Prescribing Information, in addition to the format change:

The following items have been ADDED to the PI:

- Section 1: INDICATION AND USAGE
 - Endometriosis
 - Added a Limitation of Use section:
Duration of use is limited due to concerns about adverse impact on bone mineral density. 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. (Previously found in Warnings and Precautions)
 - Fibroid
 - Add-back therapy with norethindrone acetate is **not** warranted for this indication.
 - Added a Limitation of Use section:
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. (Previously found in Warnings and Precautions)
- Section 14.1: CLINICAL STUDIES
 - Added: Table 10. Mean Percent Change from Baseline in Bone Mineral Density (BMD) of Lumbar Spine in Post-Treatment Follow-up

The following items pertaining to the use of norethindrone acetate have been REMOVED from the LUPRON PI. For safe and effective use of norethindrone acetate, the norethindrone acetate prescribing information should be referenced.

- *Contraindications for norethindrone acetate*
 - *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 for norethindrone acetate*
 - *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 for norethindrone acetate*
 - *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.*

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

- Section 1: INDICATIONS AND USAGE
 - Section 1.1. Endometriosis
 - *Laparoscopic staging of endometriosis does not necessarily correlate with the severity of symptoms (Previously found in Clinical Studies section)*
 - *Concomitant use of norethindrone acetate 5 mg tablet daily is intended to reduce the loss of bone mineral density (BMD) and vasomotor symptoms associated with LUPRON DEPOT therapy (Reduction of vasomotor symptoms previously found in Adverse Reactions section)*
- Section 4: CONTRAINDICATIONS
 - *When considering add-back therapy with norethindrone acetate, refer also to **Contraindications** in the norethindrone acetate package insert.*
- Section 5: WARNINGS AND PRECAUTIONS (**Updated and reordered to reflect the severity of potential reactions**)
 - *When considering add-back therapy with norethindrone acetate for endometriosis, refer also to **Warnings and Precautions** in the norethindrone acetate package insert.*
 - 5.1 Loss of Bone Mineral Density - this section updated for both endometriosis and fibroids
 - 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.*
 - 5.6 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.*
- Section 6: ADVERSE REACTIONS, Changes in Laboratory Values during Treatment
 - *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.*
- Section 17: PATIENT COUNSELING INFORMATION – now includes: loss of bone density, pregnancy warning, allergic reaction to GnRH agonists, new or worsened symptoms

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.

INDICATIONS¹

Endometriosis

LUPRON DEPOT® (leuprolide acetate for depot suspension) 11.25 mg for 3-month administration is indicated for the 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 in combination with daily norethindrone acetate 5 mg (add-back therapy) is also indicated for initial management of the painful symptoms of endometriosis and for management of recurrence of symptoms. Add-back therapy is intended to reduce the loss of bone mineral density (BMD) and reduce vasomotor symptoms associated with LUPRON DEPOT. Decide between use of LUPRON DEPOT alone or LUPRON DEPOT plus add-back therapy in consultation with the patient.

For safe and effective use of norethindrone acetate, refer to the norethindrone acetate prescribing information.

Limitation of Use

The initial treatment course of LUPRON DEPOT (whether used alone or with add-back therapy) is limited to 6 months. A single retreatment course of LUPRON DEPOT plus add-back therapy may be used for not more than 6 months 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 BMD.

Uterine Leiomyomata (Fibroids)

LUPRON DEPOT® (leuprolide acetate for depot suspension) 11.25 mg for 3-month administration used concomitantly with iron therapy is indicated for the preoperative hematologic improvement of patients with anemia caused by uterine leiomyomata (fibroids). Consider a 1-month trial period on iron alone, as some of the patients will respond to iron alone. 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 condition.

Limitation of Use

A single injection of LUPRON DEPOT 11.25 mg for 3-month administration may be used only for women for whom 3 months of hormonal suppression is deemed necessary.

IMPORTANT SAFETY INFORMATION¹

General Information

- LUPRON DEPOT 11.25 mg for 3-month administration is 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, suspected, or planned pregnancy during the course of therapy.
 - 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 11.25 mg 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 11.25 mg usually inhibits ovulation and stops menstruation. However, contraception is not ensured. Patients should use non-hormonal methods of contraception.
- 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 11.25 mg 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.
- 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 11.25 mg 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 11.25 mg 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 11.25 mg 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 full [Prescribing Information](#).