Indications for LUPRON DEPOT® (leuprolide acetate for depot suspension)[1]

Endometriosis

LUPRON DEPOT 3.75 mg for 1-month and 11.25 mg for 3-month administration are 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 3.75 mg for 1-month and 11.25 mg for 3-month administration in combination with daily norethindrone acetate 5 mg (add-back therapy) are 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 with LUPRON DEPOT 11.25 mg, 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 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 plus add-back therapy should not exceed 12 months due to concerns about adverse impact on BMD.

Uterine Leiomyomata (Fibroids)

LUPRON DEPOT 3.75 mg for 1-month and 11.25 mg for 3-month administration concomitantly with iron therapy are 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 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

LUPRON DEPOT 3.75 mg for 1-month administration may be administered for up to 3 months. Alternatively, 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 Information for LUPRON DEPOT[1]

General Information

- LUPRON DEPOT 3.75 mg for 1-month and 11.25 mg for 3-month administration 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, 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 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.
- 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.

Indication for LUPANETA PACK™ (leuprolide acetate for depot suspension and norethindrone acetate tablets)[2]

LUPANETA PACK 1- Month 3.75 mg and 3-Month 11.25 mg are indicated for initial management of the painful symptoms of endometriosis and for management of recurrence of symptoms. The initial treatment course is limited to 6 months. If symptoms recur, a single treatment course of not more than 6 months may be administered. Use is not recommended for longer than a total of 12 months due to concerns about adverse impact on bone mineral density.

Important Safety Information for LUPANETA PACK[2]

- LUPANETA PACK 1-Month 3.75 mg and 3-Month 11.25 mg are contraindicated in:
  - Patients who are hypersensitive to gonadotropin-releasing hormone (GnRH), GnRH agonist analogs, or any of the excipients in leuprolide acetate for depot suspension, or norethindrone acetate.
  - Undiagnosed abnormal uterine bleeding.
  - Known, suspected, or planned pregnancy during the course of therapy.
  - Lactating women.
  - Known, suspected, or history of breast cancer or other hormone-sensitive cancer.
  - Current or history of thrombotic or thromboembolic disorder.
  - Liver tumors or liver disease.
- Leuprolide acetate for depot suspension induces a hypoestrogenic state resulting in loss of bone mineral density (BMD), some of which may not be reversible. In patients that are candidates for retreatment, it is recommended that bone density be assessed before retreatment. Retreatment with leuprolide acetate for depot suspension alone is not recommended.
- In patients with major risk factors for loss of bone mineral content, risks and benefits of LUPANETA PACK must be weighed carefully before therapy is instituted, as use in this population may pose additional risks.
- Leuprolide acetate may cause fetal harm if administered to a pregnant woman. Exclude pregnancy before initiating treatment with LUPANETA PACK. Use at the recommended dose usually inhibits ovulation and stops menstruation. Patients should use non-hormonal methods of contraception. Discontinue LUPANETA PACK if a patient becomes pregnant during treatment and inform the patient of potential risk to the fetus.
- Discontinue norethindrone acetate tablets, pending examination, if there is a sudden partial or complete loss of vision or sudden onset of proptosis, diplopia, or migraine. Discontinue LUPANETA PACK if examination reveals papilledema or retinal vascular lesions.
- Depression may occur or worsen during treatment with LUPANETA PACK. Carefully observe patients with a history of clinical depression and discontinue if the depression recurs to a serious degree.
- In clinical trials of LUPANETA PACK, adverse events of asthma were reported in women with pre-existing histories of asthma, sinusitis, and environmental or drug allergies. Postmarketing reports of symptoms consistent with an anaphylactoid or asthmatic process have been reported.
- Assess and manage risk factors for cardiovascular disease before starting LUPANETA PACK. Closely monitor women on norethindrone acetate who have risk factors for arterial vascular disease (e.g., hypertension, diabetes mellitus, tobacco use, hypercholesterolemia, and obesity) and/or venous thromboembolism (VTE) (e.g., family history of VTE, obesity, and smoking).
- 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 these should dissipate with continued therapy.
- Norethindrone acetate may cause some degree of fluid retention; therefore, carefully observe women with conditions that might be influenced by this effect, such as epilepsy, migraines, or cardiac or renal dysfunctions.
- Postmarketing reports of convulsions have been observed in patients on leuprolide acetate therapy, including patients with and without concurrent medications and comorbid conditions.
- Experience with LUPANETA PACK for treatment of endometriosis has been limited to women 18 years of age and older.
- In controlled clinical trials, adverse events occurring in >10% of patients were hot flashes/sweats, headache/migraine, depression/emotional lability, nausea/vomiting, nervousness/anxiety, insomnia, pain, acne, asthenia, vaginitis, weight gain, constipation/diarrhea.