

PRIOR AUTHORIZATION POLICY

POLICY: Gonadotropin-Releasing Hormone Agonists – Injectable Long-Acting Products Prior Authorization Policy

- Lupaneta Pack® (leuprolide acetate for depot suspension; norethindrone acetate tablets co-packaged for intramuscular use and oral use, respectively – AbbVie Inc.)
- Lupron Depot® (leuprolide acetate suspension for intramuscular injection – Abbott Laboratories)

REVIEW DATE: 01/20/2021

Overview

Lupaneta Pack is indicated for initial management of the painful symptoms of **endometriosis** and for management of recurrence of symptoms.^{1,2}

Lupron Depot (3.75 mg intramuscular (IM) injection every month, 11.25 mg IM injection every 3 months) is indicated for the following conditions:^{3,4}

- Preoperative hematologic improvement of patients with **anemia caused by uterine leiomyomata** (fibroids) [Lupron Depot in combination with iron therapy].
- **Endometriosis**, including pain relief and reduction of endometriotic lesions (Lupron Depot monotherapy).
- **Endometriosis**, initial management and management of recurrence of symptoms (Lupron Depot in combination with norethindrone acetate 5 mg daily).

Lupron Depot (7.5 mg IM injection every month, 22.5 mg IM injection every 3 months, 30 mg IM injection every 4 months, and 45 mg IM injection every 6 months) is indicated for the **palliative treatment of advanced prostate cancer**.⁵

Duration of Treatment:

- Lupaneta Pack: Initial treatment course is limited to 6 months; a single retreatment course of up to 6 months is allowed. Total duration of treatment is limited to 12 months.^{1,2}
- Lupron Depot 3.75 mg and 11.25 mg:^{3,4}
 - Endometriosis: For the first 6 months of treatment, Lupron Depot may be used as monotherapy or in combination with norethindrone acetate. If retreatment is needed, Lupron Depot must be used in combination with norethindrone acetate (for 6 months). Total duration of treatment is limited to 12 months.
 - Uterine leiomyomata (fibroids): Recommended duration of treatment is up to 3 months. If additional treatment is contemplated, bone density should be assessed prior to initiation of therapy.
- Lupron Depot 7.5 mg, 22.5 mg, 30 mg, and 45 mg: Labeling does not specify a treatment duration.

Guidelines

Abnormal Uterine Bleeding/Uterine Leiomyomata (Fibroids)

The ACOG practice bulletin regarding the diagnosis of abnormal uterine bleeding in reproductive-aged women discusses the nomenclature of abnormal uterine bleeding. It can be classified by the acronym PALM-COEIN (polyp, adenomyosis, leiomyoma, malignancy and hyperplasia, coagulopathy, ovulatory dysfunction, endometrial, iatrogenic, and not yet classified) and can be further classified by etiology.⁶ The term abnormal uterine bleeding can also be paired with descriptive terms that describe the associated bleeding pattern such as heavy menstrual bleeding or intermenstrual bleeding.

The ACOG frequently asked questions (FAQ) #074 (2018) addresses medication use for the treatment of fibroids.⁷ GnRH agonists are noted as medications that can stop the menstrual cycle and shrink fibroids. GnRH analogs are used as short-term preoperative therapy to reduce uterine and leiomyoma volume; long-term therapy should be limited to patients who have contraindications to other medical or surgical treatments.⁸ They can also be used for acute abnormal uterine bleeding with an aromatase inhibitor or antagonist to prevent initial estrogen flare and for the treatment of heavy menstrual bleeding caused by leiomyoma-associated hormonal imbalance.⁹

A clinical practice guideline from the Society of Obstetricians and Gynaecologists of Canada notes that leuprolide acetate or combined hormonal contraception should be considered highly effective in preventing abnormal uterine bleeding when initiated prior to cancer treatment in premenopausal women at risk of thrombocytopenia.¹⁰ The ACOG committee opinion on prevention and management of heavy menstrual bleeding in adolescent patients undergoing cancer treatment lists leuprolide as an option for patients.¹¹

Endometriosis

According to the American College of Obstetricians and Gynecologists (ACOG) practice bulletin on the management of endometriosis (2010, reaffirmed 2018), empiric therapy with a 3-month course of a gonadotropin-releasing hormone (GnRH) agonist is appropriate after an appropriate pretreatment evaluation (to exclude other causes of chronic pelvic pain) and failure of initial treatment with oral contraceptives and nonsteroidal anti-inflammatory drugs (NSAIDs).¹²

Other Uses With Supportive Evidence

The Endocrine Society Guideline (2017) for the Treatment of Gender-Dysphoric/Gender-Incongruent Persons note that persons who fulfill criteria for treatment and who request treatment should initially undergo treatment to suppress physical changes of puberty.¹³ Pubertal hormonal suppression should typically be initiated after the adolescent first exhibits physical changes of puberty (Tanner stages G2/B2). However, there may be compelling reasons to initiate hormone treatment before the age of 16 years in some adolescents. The guidelines note suppression of pubertal development and gonadal function can be effectively achieved via gonadotropin suppression using GnRH analogs. Long-acting GnRH analogs are the currently preferred treatment option. An advantage to using a GnRH analog is that the effects can be reversed; pubertal suppression can be discontinued if the individual no longer wishes to transition. Upon discontinuation of therapy, spontaneous pubertal development has been shown to resume. The World Professional Association for Transgender Health (WPATH) Standards of Care (version 7) document also recommends the use of GnRH analogs in both male and female adolescents as a fully reversible intervention for pubertal suppression.¹⁴ GnRH can also be used in patients during late puberty to suppress the hypothalamic-pituitary-gonadal axis to allow for lower doses of cross-sex hormones.¹⁵ In addition to use in adolescents, GnRH analog therapy is also used in adults, particularly male-to-female patients.¹⁶

In addition to the approved indications, GnRH agonists such as long-acting leuprolide, have been used for other conditions. The NCCN guidelines for Adolescent and Young Adult Oncology (version 1.2021 – September 10, 2020)¹⁷ note there are some data to suggest menstrual suppression with GnRH agonists (before the initiation of chemotherapy) may protect ovaries in young women with breast cancer. There are conflicting data regarding the beneficial effects of GnRH agonists on fertility preservation. The NCCN guidelines for Breast Cancer (version 6.2020 – September 8, 2020) note that luteinizing hormone-releasing hormone agonists, such as leuprolide, can be used for ovarian suppression.¹⁸ The guidelines further note that randomized trials have shown that ovarian suppression with GnRH agonist therapy administered during adjuvant chemotherapy in premenopausal women with breast tumors (regardless of hormone receptor status) may preserve ovarian function and diminish the likelihood of chemotherapy-induced amenorrhea. The NCCN guidelines for Head and Neck Cancer (version 1.2021 – November 9, 2020) recommend the

use of androgen receptor therapy (i.e., leuprolide, bicalutamide) for androgen receptor-positive, advanced salivary gland tumors with distant metastases.¹⁹ The NCCN guidelines for Ovarian Cancer including Fallopian Tube Cancer and Primary Peritoneal Cancer (version 2.2020 – January 12, 2021) recommend leuprolide as a hormonal therapy option in various settings (e.g., adjuvant therapy, recurrence).²⁰

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Lupaneta Pack and Lupron-Depot. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Lupaneta Pack and Lupron-Depot as well as the monitoring required for adverse events and long-term efficacy, approval for some of the conditions requires Lupaneta Pack and Lupron-Depot to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

Recommended Authorization Criteria

Coverage of Lupaneta Pack and Lupron Depot is recommended in those who meet the following criteria:

FDA-Approved Indications

- 1. Endometriosis.** Approve Lupron Depot or Lupaneta Pack for 1 year if the patient has tried one of the following (A, B, or C):
 - A)** A contraceptive (e.g., combination oral contraceptives, levonorgestrel-releasing intrauterine systems [e.g., Mirena®, Liletta®]), OR
 - B)** An oral progesterone (e.g., norethindrone tablets), OR
 - C)** A depo-medroxyprogesterone injection, unless contraindicated.**NOTE:** An exception to the requirement for a trial of the above therapies can be made if the patient has previously used a gonadotropin-releasing hormone [GnRH] agonist (e.g., Lupron-Depot) or antagonist (e.g., Orilissa).
- 2. Prostate Cancer.** Approve Lupron Depot for 1 year if prescribed by or in consultation with an oncologist.
- 3. Uterine Leiomyomata (fibroids).** Approve Lupron Depot for 6 months.

Other Uses with Supportive Evidence

- 4. Abnormal Uterine Bleeding.** Approve Lupron Depot for 6 months.
- 5. Breast Cancer.** Approve Lupron Depot for 1 year if prescribed by or in consultation with an oncologist.
- 6. Gender Dysphoric/Gender-Incongruent Persons; Persons Undergoing Gender Reassignment (Female-To-Male [FTM] or Male-To-Female [MTF]).** Approve Lupron Depot for 1 year if prescribed by or in consultation with an endocrinologist or a physician who specializes in the treatment of transgender patients.

7. **Head and Neck Cancer – Salivary Gland Tumors.** Approve Lupron Depot for 1 year if the patient meets the following criteria (A, B, and C):
 - A) Patient has advanced salivary gland tumors with distant metastases; AND
 - B) Patient has androgen receptor (AR)-positive disease; AND
 - C) The medication is prescribed by or in consultation with an oncologist.
8. **Ovarian Cancer.** Approve Lupron Depot for 1 year if prescribed by or in consultation with an oncologist.
9. **Preservation of Ovarian Function/Fertility in Patients Undergoing Chemotherapy.** Approve Lupron Depot for 1 year if prescribed by or in consultation with an oncologist.
10. **Prophylaxis or Treatment of Uterine Bleeding in Patients with Hematologic Malignancy, or Undergoing Cancer Treatment, or Prior to Bone Marrow/Stem Cell Transplantation (BMT/SCT).** Approve Lupron Depot for 1 year if prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Lupron Depot and Lupaneta Pack is not recommended in the following situations:

1. **Hirsutism.** The Endocrine Society guidelines (2018) on the treatment of hirsutism in premenopausal women suggest against using GnRH agonists except in women with severe forms of hyperandrogenemia, such as ovarian hyperthecosis, who have had a suboptimal response to oral contraceptives and antiandrogens.²¹
2. **Menstrual Migraine.** A review article notes that GnRH analogs are effective in eliminating menstrual migraines, but their use is limited due to the significant adverse effects of estrogen deficiency, including severe vasomotor symptoms, sleep disruption, and a marked reduction in bone density.^{22,23}
3. **Premenstrual Syndrome (PMS).** On occasion, GnRH analogs are recommended as an aid in the diagnosis of PMS.²⁴ Use of GnRH analogs results in profound cycle suppression and elimination of PMS symptoms, but these agents should not be used routinely. GnRH analogs are recommended only as a third-line treatment or for the most refractory patients.
4. **Polycystic Ovarian Syndrome (PCOS).** PCOS guidelines from the Endocrine Society (2013)²⁵ and review articles^{26,27} do not recommend this as a treatment modality.
5. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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4. Lupron Depot® – 11.25 mg [prescribing information]. North Chicago, IL: AbbVie Inc.; March 2020.
5. Lupron Depot® – 1 Month 7.5 mg, 3 Month 22.5 mg, 4 Month 30 mg, 6 Month 45 mg [prescribing information]. North Chicago, IL: AbbVie Inc.; March 2019.
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