PRIOR AUTHORIZATION POLICY

POLICY: Gonadotropin-Releasing Hormone Agonists – Injectable Long-Acting Products Prior Authorization Policy
- Lupron Depot® (leuprolide acetate suspension for intramuscular injection – AbbVie)
- Lupaneta Pack® (leuprolide acetate for depot suspension; norethindrone acetate tablets co-packaged for intramuscular use and oral use, respectively – AbbVie) [discontinued]

REVIEW DATE: 02/21/2024

Overview

Lupaneta Pack is indicated for initial management of the painful symptoms of **endometriosis** and for management of recurrence of symptoms.[1,2] Lupaneta Pack was discontinued in 2021.

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]
- **Anemia caused by uterine leiomyomata** (fibroids), preoperative hematologic improvement in women for whom 3 months of hormonal suppression is deemed necessary. (Lupron Depot in combination with iron therapy).
- **Endometriosis**, including pain relief and reduction of endometriotic lesions (Lupron Depot monotherapy).
- **Endometriosis**, initial management of the painful symptoms of endometriosis 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.
- 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 American College of Obstetricians and Gynecologists (ACOG) [2021] practice bulletin regarding the management of symptomatic uterine leiomyomas discuss that gonadotropin-releasing hormone (GnRH) agonists (either with or without add-back hormonal therapy) are recommended for bleeding associated with fibroids, uterine enlargement associated with fibroids, and as a bridge to other treatment strategies (such as surgical management, menopause, or other medical therapies).[6] Add-back hormonal therapy (such as low-dose estrogen or progestin, or both), may help mitigate the hypoestrogenic effects of GnRH agonists, such

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as decreased bone mineral density. The guidelines state that the type, dose, and route of delivery of add-back therapy depend on patient preference and the severity of symptoms.

GnRH agonists 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.[7] 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.[8] The ACOG committee opinion on options for prevention and management of menstrual bleeding in adolescent patients undergoing cancer treatment states that GnRH agonists are an option for menstrual suppression.[9]

Endometriosis

According to the ACOG practice bulletin on the management of endometriosis (2010, reaffirmed 2018), empiric therapy with a 3-month course of a 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.[10] The ACOG committee opinion on dysmenorrhea and endometriosis in the adolescent (2018) notes that patients with endometriosis who have pain after conservative surgical therapy and suppressive hormonal therapy may benefit from at least 6 months of GnRH agonist therapy with add-back medicine.[11]

Other Uses With Supportive Evidence

ACOG practice guideline (2023) suggests GnRH agonists with adjunctive combined hormonal add-back therapy for adults with severe, refractory premenstrual symptoms.[27] Premenstrual disorders include the conditions of premenstrual syndrome (PMS) and premenstrual dysphoric disorder (PMDD). The symptoms associated with these conditions can be physical and/or affective and may interfere with daily functioning. GnRH agonists are not recommended as first-line therapy and should be reserved for adult patients who have severe symptoms. GnRH agonists are not generally used to treat premenstrual symptoms in adolescents because of the lack of efficacy data in this population and concern for long-term effects on bone health. ACOG recommends selective serotonin reuptake inhibitors for the management of affective premenstrual symptoms and combined oral contraceptives for the management of overall premenstrual symptoms.

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.[12] 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 8) document also recommends the use of GnRH analogs to suppress endogenous sex hormones in transgender and gender diverse people for whom puberty blocking is indicated.[13] 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.[14] In addition to use in adolescents, GnRH analog therapy is also used in adults, particularly male-to-female patients.[15]

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In addition to the approved indications, GnRH agonists such as long-acting leuprolide, have been used for other conditions. The National Comprehensive Cancer Network (NCCN) guidelines address the use of GnRH agonists in a number of guidelines:

- **Adolescent and young adult oncology** (version 2.2024 – July 9, 2023) guidelines note GnRH agonists may be used in (oncology) protocols that are predicted to cause prolonged thrombocytopenia and present a risk for menorrhagia.[16] There are some limited data on GnRH agonists to preserve ovarian function during chemotherapy and some have shown that GnRH agonists may be beneficial for fertility preservation, although the guidelines note further investigation is needed and other fertility preservation modalities should still be pursued.
- **Breast cancer** (version 1.2024 – January 25, 2024) guidelines note that luteinizing hormone-releasing hormone agonists, such as leuprolide, can be used for ovarian suppression.[17] Leuprolide dosing per NCCN includes 3.75 mg to 7.5 mg every 4 weeks or 11.25 mg to 22.5 mg every 12 weeks. 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.
- **Head and neck cancer** (version 2.2024 – December 08, 2023) guidelines note that a significant number of advanced salivary gland tumors with distant metastases are androgen receptor-positive (AR+), and therefore, the panel recommends patients with tumors that are AR+ receive androgen receptor therapy (i.e., leuprolide, bicalutamide).[18]
- **Ovarian cancer including fallopian tube cancer and primary peritoneal cancer** (version 1.2024 – January 17, 2024) guidelines recommend leuprolide as a hormonal therapy option in various settings (e.g., primary therapy, adjuvant therapy, recurrence).[19]
- **Uterine neoplasm** guidelines (version 1.2024 – September 20, 2023) notes that GnRH analogs are included as a category 2B option for endometrial stroma sarcoma, adenosarcoma without sarcomatous overgrowth, and estrogen receptor-progesterone receptor positive uterine sarcomas.[20,23]

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 or 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 or Lupron Depot is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Endometriosis.** Approve Lupron Depot (3.75 mg or 11.25 mg) or Lupaneta Pack for 1 year if the patient has tried ONE of the following, unless contraindicated (A, B, or C):
   A) A contraceptive (e.g., combination oral contraceptives, levonorgestrel-releasing intrauterine systems [e.g., Mirena, Liletta]), OR

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B) An oral progesterone (e.g., norethindrone tablets), OR
C) A depo-medroxyprogesterone injection.
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 7.5 mg, 22.5 mg, 30 mg, or 45 mg for 1 year if prescribed by or in consultation with an oncologist.

3. **Uterine Leiomyomata (fibroids).** Approve Lupron Depot 3.75 mg or 11.25 mg for 3 months.

Other Uses with Supportive Evidence

4. **Abnormal Uterine Bleeding.** Approve Lupron Depot 3.75 mg or 11.25 mg for 6 months.

5. **Breast Cancer.** Approve Lupron Depot 3.75 mg, 7.5mg, 11.25 mg, or 22.5 mg for 1 year if prescribed by or in consultation with an oncologist.

6. **Gender Dysphoric/Gender-Incongruent Person; Person 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 3.75 mg, 7.5 mg, 11.25mg, or 22.5 mg for 1 year if the patient meets ALL of the following criteria (A, B, and C):
   A) Patient has recurrent, unresectable, or metastatic disease; AND
   B) Patient has androgen receptor-positive disease; AND
   C) The medication is prescribed by or in consultation with an oncologist.

8. **Ovarian Cancer, including Fallopian Tube Cancer and Primary Peritoneal Cancer.** Approve Lupron Depot 3.75 mg, 7.5 mg, 11.25 mg, or 22.5 mg for 1 year if prescribed by or in consultation with an oncologist.

9. **Premenstrual Disorders, including Premenstrual Syndrome and Premenstrual Dysphoric Disorder.** Approve the 3.75 mg or 11.25 mg for 1 year if the patient meets ALL of the following criteria (A, B, and C):
   A) Patient is ≥ 18 years of age; AND
   B) According to the prescriber, the patient has severe, refractory premenstrual symptoms; AND
   C) Patient has tried one of the following therapies (i or ii):
      i. A selective serotonin reuptake inhibitor (SSRI); OR
      Note: Examples of SSRI include citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline.
      ii. A combined oral contraceptive.

10. **Preservation of Ovarian Function/Fertility in Patients Undergoing Chemotherapy.** Approve Lupron Depot 3.75 mg or 11.25 mg for 1 year if prescribed by or in consultation with an oncologist.

11. **Prophylaxis or Treatment of Uterine Bleeding or Menstrual Suppression in Patients with Hematologic Malignancy, or Undergoing Cancer Treatment, or Prior to Bone Marrow/Stem Cell Transplantation (BMT/SCT).** Approve Lupron Depot 3.75 mg or 11.25 mg for 1 year if prescribed by or in consultation with an oncologist.

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12. **Uterine Cancer.** Approve Lupron Depot 7.5 mg, 22.5 mg, 30 mg, or 45 mg 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. **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.[21,22]

2. **Polycystic Ovarian Syndrome (PCOS).** Review articles do not recommend GnRH agonists as a treatment modality for this diagnosis.[24,25] Additionally, the International Evidence-based Guideline for the Assessment and Management of Polycystic Ovary Syndrome (2018) only mentions GnRH products as they relate to infertility and assisted reproductive technology procedures.[26]

3. 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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