**BENEFIT DESCRIPTION AND LIMITATIONS OF COVERAGE**

**ITEM:** Lupron®, Lupron Depot®, Eligard® (leuprolide acetate suspension [long acting])

**PRODUCT LINES:** Commercial HMO/PPO/CDHP

**COVERED UNDER:**
- HMO: Medical (provider), Rx (self-administered)
- PPO/CDHP: Rx

**DESCRIPTION:** Leuprolide is an agonist of luteinizing hormone releasing hormone (LHRH). It acts as a potent inhibitor of gonadotropin secretion. Continuous administration results in suppression of ovarian and testicular steroidogenesis due to decreased levels of LH and FSH with subsequent decrease in testosterone and/or estrogen levels.

**CPT/HCPCS Code:** J1950, J9217, J9218

**Company Supplying:** Abbott Laboratories, Sanofi Synthelabo

**Setting:** IM or SQ injection

**Coverage Criteria:** Express Scripts, Inc. monograph dated 4/20/2011; select revision 09/06/2011

**Approval Period:** up to 12 months or benefit limit

**Recommended Authorization Criteria**

Coverage of leuprolide acetate is recommended in those who meet the following criteria:

**FDA-Approved Indication**

1. **Prostate cancer.** Approve Lupron Depot or Eligard. Lupron Depot (45 mg [6-month], 30 mg [4-month], 22.5 mg [3-month] and 7.5 mg) and Eligard (7.5 mg, 22.5 mg, 30 mg and 45 mg) are FDA-approved for this condition.

2. **Endometriosis.** Approve Lupron Depot. Lupron Depot (3.75 mg and 11.25 mg [3-month]) is FDA-approved for this condition.

3. **Uterine leiomyomata.** Approve Lupron Depot. Lupron Depot (3.75 mg, and 11.25 mg [3-month]) is FDA-approved for this condition.

4. **Treatment of central precocious puberty.** Approve Lupron Depot-Ped. Lupron Depot-Ped 1-month (7.5 mg, 11.25 mg, and 15 mg) and 3-month (11.25 mg and 30 mg) are indicated for this condition.

**Other Uses with Supportive Evidence**

5. **Ovarian cancer.** Approve Lupron Depot or Lupron Depot-Ped. In an open-label, prospective trial, women with ovarian cancer (n = 32) that was considered resistant to cytotoxic drugs received leuprolide long acting 3.75 mg intramuscularly (IM) once monthly until tumor progression. Nine patients (28%) experienced clinical benefit (i.e., partial response or remission). In a case series, leuprolide long acting 7.5 mg IM once monthly was given to five evaluable women with persistent ovarian granulosa cell tumors and led to
a partial response in two patients (40%). This response lasted three and eleven months, respectively. The NCCN 2010 guidelines for ovarian cancer recommends leuprolide as an option in certain patients (e.g., stromal tumors, granulosa cell tumors, clinical relapse).

6. **Breast cancer.** Approve Lupron Depot or Lupron Depot-Ped. In an open-label study, a total of 50 pre- or perimenopausal women with early or late stage breast cancer were randomly allocated to receive either 3.75 mg leuprolide long acting IM monthly or 11.25 mg IM every three months for up to 24 months. Both preparations suppressed estrogen to a similar extent. In another trial, breast cancer patients with estrogen-receptor positive tumors received endocrine therapy with a variety of products, including leuprolide long acting (3.75 mg subcutaneously [SC] every four weeks). GnRH analogs and other LHRH analogs are used for the estrogen-suppressive effects in pre- and perimenopausal women with breast cancer. The NCCN 2010 guidelines for breast cancer note that an LHRH agonist, such as leuprolide, is an appropriate option in certain patients with breast cancer.

7. **Preserve ovarian function/fertility in women undergoing chemotherapy.** Approve Lupron Depot or Lupron Depot-Ped. Leuproli de long acting 3.75 mg IM monthly has been used to prevent ovarian insufficiency in premenopausal women undergoing chemotherapy, which provided information in a case series format.

8. **Induce amenorrhea during bone marrow transplantation (BMT).** Approve Lupron Depot or Lupron Depot-Ped. A pilot case series study involving 10 postmenarcheal women found use of leuprolide long acting 7.5 mg IM every 28 days led to successful induction of amenorrhea prior to BMT in most patients (90%).

9. **Premenstrual syndrome (PMS).** Approve Lupron Depot or Lupron Depot-Ped in patients that have tried two other therapies for this condition (e.g., selective serotonin reuptake inhibitors [SSRIs], oral contraceptives [OCs]). Several studies, including trials that were double-blind, placebo-controlled, and/or cross-over design, have investigated the use of leuprolide long acting for symptoms related to PMS. The doses used included leuprolide long acting 3.75 mg IM monthly and 7.5 mg IM monthly. A practice bulletin on PMS developed by the American College of Obstetricians and Gynecologists (ACOG) in 2000 states that improvement in PMS symptoms with GnRH agonists have been reported in some well-designed studies. However, this therapy may have limited usefulness because of the hypoestrogenic side effects (e.g., bone loss), although sometimes estrogen and/or progesterone add-back therapy may be used. For PMS, SSRIs (e.g., fluoxetine, sertraline) are recommended as initial drugs of choice and OCs have some evidence supporting use. More recent reviews have also noted the established effectiveness of SSRIs for PMS.

10. **Menstrual migraine.** Approve Lupron Depot or Lupron Depot-Ped after the patient has tried two other therapies for the treatment of acute migraine (e.g., nonsteroidal anti-inflammatory drugs [NSAIDs], triptans, ergotamines) or prophylaxis of migraine (e.g., beta-blockers, amitriptyline, divalproex). A nonrandomized, 10-month prospective trial assessed the effects of leuprolide long acting 3.75 mg IM monthly in five women with severe menstrual migraines who were not responsive to previous treatment. Treatment led to a reduction in mean cumulative monthly headache score. Also, patient global assessment of therapy was positive and a decrease in the use of analgesic medication for headache was noted. Other therapies have been useful for the treatment or prophylaxis of menstrual migraines.

11. **Catamenial pneumothorax.** Approve Lupron Depot or Lupron Depot-Ped. Catamenial pneumothorax is a rare condition affecting women in their reproductive years. Case reports have documented leuprolide long acting IM benefiting patients with catamenial pneumothorax with the doses of 3.75 mg IM monthly and 7.5 mg IM monthly being utilized.
12. **Paraphilias or other inappropriate sexual behaviors or disorders.** Approve Lupron Depot or Lupron Depot-Ped. A detailed case series reported that males (n = 12) with paraphilias had a reduction in deviant behaviors with the use of leuprolide long acting at monthly doses of 3.75 mg IM and 7.5 mg IM. Other data are also available regarding this use. A review article regarding inappropriate sexual behaviors in cognitively impaired older individuals recommended that LHRH agonists (e.g., leuprolide, triptorelin) be utilized as a third-line agent for patients.

13. **Dysfunctional uterine bleeding.** Approve for up to 6 months of therapy of Lupron Depot or Lupron Depot-Ped. GnRH analogues are used as second-line therapy for dysfunctional uterine bleeding after other medical therapies or medications (e.g., progestins, antifibrinolytics [tramekam acid], non-steroidal anti-inflammatory drugs, estrogens, estrogens plus progesterins). Studies regarding use of leuprolide long-acting for this condition are limited. Leuprolide long acting therapy may also be used for a short time period while considering other therapeutic options (e.g., surgery) and long-term (> 6 months) may lead to irreversible bone loss.

14. **Lymphangioleiomyomatosis.** Approve Lupron Depot or Lupron Depot-Ped. This condition is a rare disease of unknown etiology that can impact fertile women and is a multisystem disorder. It is characterized by the proliferation of smooth muscle cells through the body, but especially in the lungs. Prominent symptoms include coughing and dyspnea and pleural effusion may occur, as well as chronic respiratory failure. GnRH agonists, such as leuprolide, at doses of either 3.75 mg IM every 28 days or 11.25 mg IM every 84 days have been used.

**Exclusions**

Coverage of leuprolide long acting is not recommended in the following circumstances:

1. **Polycystic ovarian syndrome (PCOS).** Leuprolide long acting has been used in women with PCOS. Patients with PCOS receiving leuprolide long acting 3.75 mg IM every 4 weeks plus an OC for six months experienced a restoration of normal ovulatory cycles and a greater reduction in ovarian volume compared to women just receiving an OC. PCOS guidelines from the ACOG, updated in 2009, and review articles do not recommend this as a treatment modality.

2. **Hirsutism.** Patients with hirsutism, either idiopathic or due to PCOS, have received leuprolide long acting, usually 3.75 mg or 7.5 mg IM monthly. Sometimes conjunctive therapy with estrogen replacement or OCs was used. Patients receiving leuprolide long acting for up to 6 months experienced positive benefits such as decreases in the Ferriman-Gallwey scores, in hair growth rate and/or in the percentage hair growth rate. However, this condition is considered cosmetic.

3. **Benign Prostatic Hyperplasia (BPH).** A prospective, placebo-controlled trial investigated the effect of leuprolide long acting 3.75 mg IM every 28 days in men (n = 50) with moderate to severe BPH. Patients were given active drug or placebo for 24 weeks and received follow-up for an additional 24 weeks. Use of leuprolide long acting led to a statistically significant decrease in prostate volume, and an increased maximum flow rate at spontaneous micturition at Week 16 compared with placebo. Also, there was greater improvement in irritative symptoms with leuprolide long acting at 48 weeks (P = 0.029). However, guidelines updated in 2010 by the American Urological Association (AUA) for the management of BPH do not mention leuprolide long acting as a therapeutic modality for this condition.
4. **Functional bowel syndrome/irritable bowel syndrome (IBS).** Leuprolide long acting has been studied in functional bowel syndrome and IBS however, more studies are needed before this therapeutic modality is recommended. A review article and guidelines for the management of IBS, a related syndrome, do not recognize leuprolide long acting as an effective alternative for this condition.

5. **Orchitis/epididmyo-orchitis.** Leuprolide long acting has been studied in this condition, however, guidelines do not recommend this therapy and more studies are needed.

6. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

**APPROVAL:**

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