



Medical Policy

Policy:	201427-CC	Initial Effective Date: 10/30/2014
Code(s):	HCPCS J1950, J3316, J9217, J9218	Annual Review Date: 04/01/2019
SUBJECT:	<p>Leuprolide long-acting</p> <ul style="list-style-type: none"> • Lupron Depot® (leuprolide acetate suspension for intramuscular [IM] injection – Abbott Laboratories) • Lupron Depot-Ped® (leuprolide acetate suspension for IM injection – Abbott Laboratories) • Eligard® (leuprolide acetate suspension for subcutaneous [SC] injection – Sanofi-Aventis) • Lupaneta Pack® (leuprolide acetate for depot suspension; norethindrone acetate tablets co-packaged for IM use and oral use, respectively – AbbVie Inc.) • Triptodur™ (triptorelin for extended-release injectable suspension – Arbor Pharmaceuticals) 	Policy Retirement Date: 04/01/2019

As of 4/1/2019, Prior approval is not required for the procedure codes listed in this Corporate Drug Policy.

Overview

Leuprolide is a synthetic nonapeptide analog of naturally occurring gonadotropin-releasing hormone or leutinizing hormone-releasing hormone (GnRH or LHRH), which possesses greater potency compared with the natural hormone (generally considered a GnRH agonist).¹⁻⁶ It acts as a potent inhibitor of gonadotropin secretion when administered continuously in therapeutic doses. Following initial stimulation of gonadotropins, chronic administration of leuprolide leads to suppression of ovarian and testicular steroidogenesis. These effects are reversible after drug discontinuation.

This policy includes only the long-acting leuprolide acetate suspension products that are administered intramuscularly (IM) [Lupron Depot, Lupaneta Pack, and Lupron Depot-Ped]^{1-4,6} and subcutaneously (SC) [Eligard]⁵. Lupaneta Pack contains a combination pack of leuprolide acetate depot suspension administered IM and norethindrone 5 mg tablets.⁶ This policy does not cover the short-acting leuprolide products (Lupron® and Lupron® for pediatric use). The indication(s) and dosing for the long-acting leuprolide products are in Table 1.

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Table 1. Indications, Dosage and Administration for Lupron-Depot, Lupaneta Pack, Eligard, and Lupron Depot-Ped.¹⁻⁶

Products	Dosing and Administration	Indication(s)
Lupron Depot® (leuprolide acetate IM for depot suspension)	7.5 mg IM every 1 month	<u>Prostate cancer</u> : palliative treatment of advanced prostate cancer
	22.5 mg IM every 3 months	
	30 mg IM every 4 months	
	45 mg IM every 6 months	
Eligard® (leuprolide acetate suspension for SC injection)	7.5 mg SC every 1 month	<u>Prostate cancer</u> : palliative treatment of advanced prostate cancer
	22.5 mg SC every 3 months	
	30 mg SC every 4 months	
	45 mg SC every 6 months	
Lupron Depot® (leuprolide acetate IM for depot suspension)	3.75 mg IM every 1 month	<u>Endometriosis</u> : initial management and for recurrence of symptoms (including pain relief and reduction of endometriotic lesions). Limitation of Use: Duration of initial treatment or re-treatment should be limited to 6 months. <u>Uterine leiomyomata (Fibroids)</u> : preoperative hematologic improvement of patients with anemia caused by uterine leiomyomata; taken with iron therapy. Recommended duration of therapy is up to 3 months.
	11.25 mg IM every 3 months	
Lupaneta Pack® (leuprolide acetate for IM depot suspension; norethindrone acetate oral tablets co-packaged)	11.25 mg IM for 3 months Norethindrone acetate 5 mg tablets	<u>Endometriosis</u> : initial management and for recurrence of painful symptoms of endometriosis. Limitation of Use: Duration of use is limited due to adverse impact on bone mineral density. The initial treatment course is limited to 6 months. A single retreatment course of not more than 6 months may be administered if symptoms recur. Use of Lupaneta Pack for longer than total of 12 months is not recommended.
Lupron Depot-Ped® (leuprolide acetate for depot suspension)	Starting dose of 7.5 mg, 11.25 mg, or 15 mg IM for 1 month administration; starting dose based on child's weight	Central precocious puberty (CPP)
	11.25 mg IM for 3 months 30 mg IM for 3 months	
Triptodur™ (triptorelin extended-release injectable suspension)	22.5 mg IM for 24 weeks (6 months)	Central precocious puberty

IM – Intramuscular; SC – Subcutaneous.

In addition to the approved indications, GnRH agonists such as leuprolide long-acting, have been used for other conditions and various guidelines (e.g., guidelines from the National Comprehensive Cancer Center [NCCN]) discuss its use.⁷⁻⁹

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Policy Statement

Prior authorization is recommended for prescription benefit coverage of leuprolide long-acting products (e.g., Lupron Depot, Eligard, Lupron Depot-Ped, and Lupaneta Pack). Depending on the diagnosis, all approvals are provided for 6 months or 1 year in duration, as noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Recommended Authorization Criteria

Coverage of Lupron Depot, Lupron Depot-Ped, Lupaneta Pack, and Eligard are recommended in those who meet the following criteria:

Food and Drug Administration (FDA)-Approved Indications

1. Prostate Cancer. Approve Lupron Depot or Eligard for 1 year.

Lupron Depot (45 mg [6-month], 30 mg [4-month], 22.5 mg [3-month] and 7.5 mg [1-month])¹ and Eligard (7.5 mg [1 month], 22.5 mg [3 month], 30 mg [4 month] and 45 mg [6 month])⁵ are indicated for this condition.

2. Endometriosis. Approve Lupron Depot or Lupaneta Pack for 6 months if the patient meets ONE of the following criteria (A or B):

- A) Initial management of symptoms; OR
- B) Management of recurrence of symptoms after initial therapy.

Note: The recommended duration of continuous therapy (initial and recurrence) is limited to a total of 12 months. Lupron Depot and Lupaneta Pack (3.75 mg and 11.25 mg [3-month]) are both indicated for this condition.^{2-3,6} Per the prescribing information, the duration of initial treatment is for 6 months. If symptoms recur, a single retreatment course of not more than 6 months may be administered after the initial course. Use of Lupron Depot or Lupaneta Pack for longer than a total of 12 months is not recommended.

3. Uterine Leiomyomata (fibroids). Approve Lupron Depot for 6 months.

Lupron Depot (3.75 mg, and 11.25 mg [3-month]) is indicated for this condition.²⁻³ The recommended duration of therapy with Lupron Depot 3.75 mg is up to 3 months. Experience with Lupron Depot 11.25 mg (3 months) in females has been limited to women \geq 18 years of age treated for no more than 6 months.

4. Central Precocious Puberty (CPP). Approve Lupron Depot-Ped or Triptodur for 1 year.

Note: Lupron Depot-Ped and Triptodur are only indicated for **central** precocious puberty. Peripheral precocious puberty is not treated with Lupron Depot-Ped or Triptodur.

Lupron Depot-Ped (7.5 mg, 11.25 mg, and 15 mg [1-month]) and (11.25 mg and 30 mg [3-month]) and Triptodur (22.5 mg [6 months]) are indicated for this condition.⁴ The mainstay of treatment for CPP is GnRH analogs; the primary agent used in US is leuprolide acetate administered as an IM injection.¹⁰ In contrast to CPP, treatment of



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peripheral precocious puberty (PPP), or GnRH-independent precocious puberty, depends on the cause (genetic or acquired causes), and is generally not a result of central activation of the hypothalamic-pituitary-gonadal axis.¹¹

Other Uses with Supportive Evidence

- 5. Gender Reassignment (Female-To-Male [FTM] or Male-To-Female [MTF]).** Approve Lupron Depot or Eligard for 1 year if prescribed by or in consultation with an endocrinologist or a physician who specializes in the treatment of transgender patients.

The Endocrine Society guideline (2009) for treatment of transsexual persons recommends that adolescents who fulfill eligibility criteria for gender reassignment initially undergo treatment to suppress pubertal development.¹² The guidelines recommend that suppression of pubertal hormones start when girls and boys first exhibit physical changes of puberty, but no earlier than Tanner stages 2 to 3 (early puberty). According to the guidelines, suppression of pubertal development and gonadal function is most effectively accomplished by GnRH analogs and antagonists. However, since no long-acting GnRH antagonists are available, long-acting analogs are the currently preferred treatment option. An advantage of GnRH therapy is noted to be its reversibility; pubertal suppression can be discontinued and spontaneous pubertal development will resume immediately after stopping GnRH analog therapy. 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.¹³ Although too late to block endogenous pubertal development, GnRH analogs can also be used in late pubertal patients to suppress the hypothalamic-pituitary-gonadal axis, potentially allowing for lower doses of cross-sex hormones.¹⁴ In addition to use in adolescents, GnRH analog therapy is also used in adults, particularly MTF patients.¹⁵ In the professional opinion of a practicing specialist physician reviewing the available guidelines, we have adopted this criterion.

- 6. Ovarian Cancer.** Approve Lupron Depot for 1 year.

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 IM once monthly until tumor progression.⁹ Nine patients (28%) experienced clinical benefit (i.e., partial response or remission). In a case series,¹⁶ 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 3 and 11 months, respectively. The NCCN guidelines for ovarian cancer (version 1.2016) recommend leuprolide as a hormonal therapy option in various settings (e.g., adjuvant therapy, recurrence).⁹

- 7. Breast Cancer.** Approve Lupron Depot for 1 year.

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 3 months for up to 24 months.¹⁷ 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 SC every 4 weeks).¹⁸ GnRH analogues and other LHRH analogs are used for the estrogen-suppressive effects in pre- and perimenopausal women with breast cancer.¹⁹⁻²⁰ The NCCN guidelines for breast

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cancer (version 1.2017) note that LHRH agonist, such as leuprolide, can be used for ovarian suppression.⁸ It is recommended to give leuprolide as monthly injections as the 3-month depots do not reliably suppress estrogen levels in all patients.

8. **Preserve Ovarian Function/Fertility in Patients undergoing Chemotherapy.** Approve Lupron Depot for 1 year.

A case series provided information on leuprolide long-acting 3.75 mg IM monthly which has been used to prevent ovarian insufficiency in premenopausal women undergoing chemotherapy.²¹ Another prospective, non-randomized study assessed the efficacy of GnRH analogues administered before and in conjunction with chemotherapy conditioning prior to stem cell transplantation.²² The results showed a significant difference in recovery of cyclic ovarian function in patients who received GnRH agonist compared with those who did not receive co-treatment (38.3% vs. 11.1%, respectively; $P = 0.006$). A Phase II randomized study also demonstrated that leuprolide acetate 3.75 mg IM administered monthly while receiving chemotherapy reduced the risk of developing premature ovarian failure in premenopausal women ($n = 220$) with breast cancer.²³ Approximately 29% of patients in the chemotherapy-only group compared with 17% of patients in the combination chemotherapy and leuprolide group had early menopause ($P < 0.01$). Results from two meta-analysis demonstrated that temporary ovarian suppression with GnRH agonists can reduce the risk of chemotherapy-induced premature ovarian failure (POF) in young patients with cancer.²⁴⁻²⁵ The NCCN breast cancer guidelines (version 1.2017) states that randomized trials have shown that ovarian suppression with GnRH agonist therapy administered during adjuvant chemotherapy in premenopausal women with ER-negative tumors may preserve ovarian function and diminish the likelihood of chemotherapy-induced amenorrhea.⁸ A retrospective cohort study compared 286 patients who had received GnRH agonist therapy with chemotherapy to 188 women who received chemotherapy alone.²⁶ Overall, 87% of the patients who received GnRH therapy with chemotherapy retained cyclic ovarian function (COF) and 13% of patients suffered POF. In the control group 49% of the patients retained COF and 51% of patients suffered POF. Also, 69.3% of patients in the GnRH group vs. 42.3% of patients in the control group conceived; spontaneous pregnancies occurred in 65.6% of women in the GnRH group compared with 37.9% of women in the control group.

9. **Prophylaxis or Treatment of Uterine Bleeding in Patients with Hematologic Malignancy or Prior to Bone Marrow/Stem Cell Transplantation (BMT/SCT).** Approve Lupron Depot for 1 year.

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.²⁸ A commentary published on hormone use for therapeutic amenorrhea and contraception for hematopoietic stem cell transplantation recommends leuprolide 11.25 mg IM every 3 months as the preferred dosing.²⁹ Alternatively, leuprolide 3.75 mg IM can be used if tolerability is a concern, and if tolerated, can redose with leuprolide 11.25 mg IM after 3 weeks. The American College of Obstetricians and Gynecologists (ACOG) committee opinion on prevention and management of heavy menstrual bleeding in adolescent patients undergoing cancer treatment lists leuprolide as an option for patients.²⁷

10. **Abnormal Uterine Bleeding.** Approve for up to 6 months of therapy of Lupron Depot.

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Abnormal uterine bleeding (AUB) can be classified by the acronym PALM-COEIN (polyp, adenomyosis, leiomyoma, malignancy and hyperplasia, coagulopathy, ovulatory dysfunction, endometrial, iatrogenic, and not yet classified) and classifies uterine bleeding abnormalities by bleeding pattern as well as by etiology.³⁰ The term AUB can also be paired with descriptive terms that describe the associated bleeding pattern such as heavy menstrual bleeding (AUB/HMB) or intermenstrual bleeding (AUB/IMB). GnRH analogues 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.³¹ They can also be used for acute AUB with an aromatase inhibitor or antagonist to prevent initial estrogen flare and for the treatment of HMB caused by leiomyoma-associated hormonal imbalance.³² First-line therapies for medical management include combined oral contraceptives (OCs), conjugated equine estrone intravenous, and oral progestins. In addition, for long-term management, tranexamic acid, levonorgestrel intrauterine system, and non-steroidal anti-inflammatory drugs (NSAIDs) can also be used.³³⁻³⁴

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Lupron Depot, Lupron Depot-Ped, Lupaneta Pack, and Eligard have not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

- 1. Hirsutism.** Patients with hirsutism, either idiopathic or due to polycystic ovarian syndrome (PCOS), have received leuprolide long-acting, usually 3.75 mg or 7.5 mg IM monthly.³⁵⁻³⁷ 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.³⁵⁻³⁶ The Endocrine Society guidelines (2008) 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 OCs and antiandrogens.³⁸
- 2. Menstrual Migraine.** Therapies such as NSAIDs, triptans, and propranolol have been used for the treatment or prophylaxis of menstrual migraines.³⁹⁻⁴⁰ A nonrandomized, 10-month prospective trial⁴¹ 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. A review article notes that GnRH analogues 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.⁴²
- 3. Polycystic Ovarian Syndrome (PCOS).** Leuprolide long-acting has been used in women with PCOS.⁴³ 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 with women just receiving an OC. PCOS guidelines from the Endocrine Society (2013)⁴⁴ and review articles⁴⁵⁻⁴⁶ do not recommend this as a treatment modality.



- 4. Premenstrual Syndrome (PMS).** For PMS, low-dose selective serotonin reuptake inhibitors (SSRIs) [e.g., fluoxetine, sertraline] are recommended as first-line agents for severe PMS.⁴⁷ Other first-line options for PMS include exercise, vitamin B6, combined contraceptive pills, and cognitive behavioral therapy. Use of GnRH analogues results in profound cycle suppression and elimination of PMS symptoms, but these agents should not be used routinely. It is recommended sometimes to aid in the diagnosis of PMS. Otherwise it is recommended only as a third-line treatment or for the most refractory patients.
- 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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Prior approval is required for HCPCS Codes J1950, J3316, J9217, J9218

HCPCS Code(s):	
J1950	Injection, leuprolide acetate (for depot suspension), per 3.75 mg
J3316	Injection, triptorelin, extended-release, 3.75 mg (effective 1/1/19)
J9217	Leuprolide acetate, [Lupron Depot], (for depot suspension), 7.5 mg
J9218	Leuprolide acetate, [Lupron], per 1 mg