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Leuprolide – Long Acting

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INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Overview

This policy supports medical necessity review for the following leuprolide products:

- **Leuprolide acetate**
- **Lupaneta Pack**® (leuprolide acetate for depot suspension; norethindrone acetate tablets)
- **Lupron Depot**® (leuprolide acetate suspension for intramuscular [IM] injection)

The use of leuprolide (Leuprolide acetate, Lupaneta Pack, Lupron Depot) for oncology indications and infertility are addressed in separate coverage policies. Please refer to the related coverage policy links above (Oncology Medications, Infertility Injectables).

Coverage Policy

Leuprolide (leuprolide acetate, Lupaneta Pack, and Lupron Depot) are considered medically necessary when ONE of the following are met:

1. **Management of endometriosis**
2. **Uterine fibroids or leiomyomata (Lupron Depot only)**

3. **Gender-Dysphoric/Gender-Incongruent Persons; Persons Undergoing Gender Reassignment (Female-To-Male or Male-To-Female).** Individual meets the following criteria:
    a. Prescribed by or in consultation with an endocrinologist or a physician who specializes in the treatment of transgender patients
4. **Abnormal Uterine Bleeding (Lupron Depot only)**
5. **Use as a stimulation test to confirm a diagnosis of central precocious puberty prior to initiation of treatment (leuprolide acetate only)**

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Note: Receipt of sample product does not satisfy any criteria requirements for coverage.

Reauthorization Criteria

Leuprolide acetate, Lupaneta Pack, and Lupron Depot are considered medically necessary for continued use when initial criteria are met AND documentation of beneficial response.

Authorization Duration

Initial approval duration up to 12 months for all indications except the following:

- Lupaneta Pack: Initial treatment course is limited to 6 months;
- Uterine leiomyomata (fibroids): Recommended duration of treatment is up to 3 months [no reauthorization]
- Abnormal Uterine Bleeding. Approve Lupron Depot for 6 months

Reauthorization duration is up to 12 months for all indications except the following:

- Lupaneta Pack: a single retreatment course of up to 6 months is allowed. Total duration of treatment is limited to 12 months

Conditions Not Covered

Leuprolide acetate, Lupaneta Pack, and Lupron Depot are considered experimental, investigational or unproven for ANY other use including the following (this list may not be all inclusive):

1. **Hirsutism.** Patients with hirsutism, either idiopathic or due to polycystic ovarian syndrome (PCOS), have received long-acting leuprolide, usually 3.75 mg or 7.5 mg IM monthly.[21-23] Sometimes conjunctive therapy with estrogen replacement or oral contraceptives was used. Patients receiving long-acting leuprolide 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.[21,22] 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 oral contraceptives and antiandrogens.[24]

2. **Menstrual Migraine.** Therapies such as NSAIDs, triptans, and propranolol have been used for the treatment or prophylaxis of menstrual migraines.[25,26] A nonrandomized, 10-month prospective trial[27] assessed the effects of long-acting leuprolide 3.75 mg IM monthly in five women with severe menstrual migraines who were not responsive to prior 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.[28]

3. **Polycystic Ovarian Syndrome (PCOS).** Long-acting leuprolide has been used in women with PCOS.[29] Patients with PCOS receiving long-acting leuprolide 3.75 mg IM every 4 weeks plus an oral contraceptive for 6 months experienced a restoration of normal ovulatory cycles and a greater reduction in ovarian volume compared with women just receiving an oral contraceptive. PCOS guidelines from the Endocrine Society (2013)[30] and review articles[31,32] do not recommend this as a treatment modality.

4. **Premenstrual Syndrome (PMS).** Low-dose selective serotonin reuptake inhibitors (SSRIs) [e.g., fluoxetine, sertraline] are recommended as first-line agents for severe PMS.[33] 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.

Background

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 women with **anemia caused by uterine leiomyomata** (fibroids) 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
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).[6]

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.[7] 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.[8] GnRH agonists are noted as medications that can stop the menstrual cycle and shrink fibroids. 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.[9] 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.[10]

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.[11] 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.[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, and various guidelines (e.g., guidelines from the National Comprehensive Cancer Center [NCCN]) discuss its use. The NCCN guidelines for Ovarian Cancer including Fallopian Tube Cancer and Primary Peritoneal Cancer (version 3.2019 – November 26, 2019) recommend leuprolide as a hormonal therapy option in various settings (e.g., adjuvant therapy, recurrence).[17] The NCCN guidelines for Breast Cancer (version 3.2019 – September 6, 2019) note that luteinizing hormone-releasing hormone agonists, such as leuprolide, can be used for ovarian suppression.[18] For this use, leuprolide should be given as monthly injections as the 3-month depots do not reliably suppress estrogen levels in all patients. 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 Adolescent and Young Adult Oncology (version 1.2020 – July 11, 2019)[19] note there are some data to suggest menstrual suppression with GnRH agonists may protect ovaries in young women with breast cancer before the initiation of chemotherapy. There are conflicting data regarding the beneficial effects of GnRH agonists on fertility preservation. The NCCN guidelines for Head and Neck Cancer (version 3.2019 – September 6, 2019) recommend the use of androgen receptor therapy (i.e., leuprolide, bicalutamide) for androgen receptor-positive, recurrent salivary gland tumors with distant metastases.[20]

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