



# CIGNA MEDICAL COVERAGE POLICY

The following Coverage Policy applies to all plans administered by CIGNA Companies including plans administered by Great-West Healthcare, which is now a part of CIGNA.

**Subject** Leuprolide (Lupron<sup>®</sup>, Lupron Depot<sup>®</sup>, Lupron Depot-PED<sup>®</sup>)

**Effective Date** ..... 1/15/2011  
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**Coverage Policy Number** ..... 6117

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## Hyperlink to Related Coverage Policies

[Degarelix \(Firmagon<sup>®</sup>\)](#)  
[Goserelin \(Zoladex<sup>®</sup>\)](#)  
[Histrelin \(Vantas<sup>™</sup>\)](#)  
[Nafarelin \(Synarel<sup>®</sup>\)](#)  
[Triptorelin \(Trelstar<sup>®</sup> Depot, Trelstar<sup>®</sup> LA\)](#)  
[Leuprolide \(Eligard<sup>®</sup>\)](#)

### INSTRUCTIONS FOR USE

Coverage Policies are intended to provide guidance in interpreting certain **standard** CIGNA HealthCare benefit plans as well as benefit plans formerly administered by Great-West Healthcare. Please note, the terms of a participant's particular benefit plan document [Group Service Agreement (GSA), 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 participant'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 participant's benefit plan document **always supercedes** 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 group 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. Proprietary information of CIGNA. Copyright ©2011 CIGNA

## Coverage Policy

**CIGNA covers leuprolide (Lupron<sup>®</sup>) as medically necessary for EITHER of the following indications:**

- advanced prostate cancer
- advanced breast cancer

**CIGNA covers leuprolide (Lupron Depot<sup>®</sup>) as medically necessary for ANY of the following indications:**

- advanced prostate cancer
- uterine fibroids or leiomyomata
- endometriosis
- epithelial ovarian carcinoma (3.75 mg ONLY)
- ovarian stromal tumors

**CIGNA covers leuprolide (Lupron Depot-PED<sup>®</sup>) as medically necessary for central precocious puberty (CPP) with onset of secondary sexual characteristics earlier than 8 years in females and 9 years in males.**

**Note: Injectable fertility medications are specifically excluded under most benefit plans. Please refer to the applicable benefit plan document to determine benefit availability and the terms and conditions of coverage.**

If coverage is available for injectable fertility medications, then CIGNA covers leuprolide (Lupron Depot<sup>®</sup>) as medically necessary for documented infertility when used in conjunction with urofollitropin or menotropins to suppress luteinizing hormone (LH) production in a woman with premature LH surge, or when used for prevention of severe ovarian hyperstimulation syndrome associated with in vitro fertilization.

When coverage is available and medically necessary, the dosage, frequency, site of administration, and duration of therapy should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to leuprolide (Lupron<sup>®</sup>, Lupron Depot<sup>®</sup>, Lupron Depot-PED<sup>®</sup>) therapy.

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## **FDA Approved Indications**

### **Lupron**

Lupron injection (leuprolide acetate) is indicated in the palliative treatment of advanced prostatic cancer.

### **Lupron Depot**

Endometriosis – Lupron Depot 3.75 mg and 3-Month 11.25 mg, is indicated for management of endometriosis, including pain relief and reduction of endometriotic lesions. Lupron Depot monthly with norethindrone acetate 5 mg daily is also indicated for initial management of endometriosis and for management of recurrence of symptoms. Duration of initial treatment or retreatment should be limited to 6 months. Uterine Leiomyomata (Fibroids) – Lupron Depot 3.75 mg and 3-Month 11.25 mg concomitantly with iron therapy is indicated for the preoperative hematologic improvement of patients with anemia caused by uterine leiomyomata. The clinician may wish to consider a one-month trial period on iron alone inasmuch as some of the patients will respond to iron alone. Lupron may be added if the response to iron alone is considered inadequate. Recommended duration of therapy with Lupron Depot 3.75 mg is up to three months or a single injection of Lupron Depot 3-month 11.25 mg. Experience with Lupron Depot in females has been limited to women 18 years of age and older. Lupron Depot 7.5 mg, 3-month 22.5 mg, and 4-month 30 mg are all indicated in the palliative treatment of advanced prostatic cancer. They offer an alternative treatment of prostatic cancer when orchiectomy or estrogen administration is either not indicated or unacceptable to the patient. In clinical trials, the safety and efficacy of Lupron Depot 3-month 22.5 mg were similar to that of the original daily subcutaneous injection and the monthly depot formulation.

### **Lupron Depot-PED**

Lupron Depot-PED is indicated in the treatment of children with central precocious puberty (CPP). Children should be selected using the following criteria: Clinical diagnosis of CPP (idiopathic or neurogenic) with onset of secondary sexual characteristics earlier than 8 years in females and 9 years in males; Clinical diagnosis should be confirmed prior to initiation of therapy by confirmation of diagnosis by a pubertal response to a GnRH stimulation test. The sensitivity and methodology of this assay must be understood. Bone age advanced one year beyond the chronological age. Baseline evaluation should also include - height and weight measurements; sex steroid levels; adrenal steroid level to exclude congenital adrenal hyperplasia; beta human chorionic gonadotropin level to rule out a chorionic gonadotropin-secreting tumor; pelvic/adrenal/testicular ultrasound to rule out a steroid secreting tumor; computerized tomography of the head to rule out intracranial tumor.

## **FDA Recommended Dosing**

### **Lupron**

The recommended dose of Lupron is 1 mg (0.2 mL or 20 unit mark) administered as a single daily subcutaneous injection. Each 0.2 mL contains 1 mg of leuprolide acetate.

### **Lupron Depot**

Endometriosis - the recommended duration of treatment with Lupron Depot 3.75 mg or 3-month 11.25 mg alone or in combination with norethindrone acetate is six months. If the symptoms of endometriosis recur after a course of therapy, retreatment with a six-month course of Lupron Depot monthly and norethindrone acetate 5

mg daily may be considered. Retreatment beyond this one six-month course cannot be recommended. It is recommended that bone density be assessed before retreatment begins to ensure that values are within normal limits. Lupron Depot alone is not recommended for retreatment. If norethindrone acetate is contraindicated for the individual patient, then retreatment is not recommended. An assessment of cardiovascular risk and management of risk factors such as cigarette smoking is recommended before beginning treatment with Lupron Depot and norethindrone acetate. Uterine Leiomyomata (Fibroids) - recommended duration of therapy with Lupron Depot 3.75 mg is up to 3 months or one injection of Lupron Depot 3-month 11.25 mg. The symptoms associated with uterine leiomyomata will recur following discontinuation of therapy. If additional treatment with Lupron Depot 3.75 mg is contemplated, bone density should be assessed prior to initiation of therapy to ensure that values are within normal limits. Due to different release characteristics, a fractional dose of the 3-month depot formulation is not equivalent to the same dose of the monthly formulation and should not be given.

### **Lupron Depot-PED**

The dose of Lupron Depot-PED must be individualized for each child. The dose is based on a mg/kg ratio of drug to body weight. Younger children require higher doses on a mg/kg ratio. For each dosage form, after 1-2 months of initiating therapy or changing doses, the child must be monitored with a GnRH stimulation test, sex steroids, and Tanner staging to confirm downregulation. Measurements of bone age for advancement should be monitored every 6-12 months. The dose should be titrated upward until no progression of the condition is noted either clinically and/or by laboratory parameters. The first dose found to result in adequate downregulation can probably be maintained for the duration of therapy in most children. However, there are insufficient data to guide dosage adjustment as patients move into higher weight categories after beginning therapy at very young ages and low dosages. It is recommended that adequate downregulation be verified in such patients whose weight has increased significantly while on therapy. Discontinuation of Lupron Depot-PED should be considered before age 11 for females and age 12 for males. The recommended starting dose is 0.3 mg/kg/4 weeks (minimum 7.5 mg) administered as a single intramuscular injection. The starting dose will be dictated by the child's weight ( $\leq 25$  kg 7.5 mg;  $>25$ -37.5 kg 11.25 mg;  $>37.5$  kg 15 mg). If total downregulation is not achieved, the dose should be titrated upward in increments of 3.75 mg every 4 weeks. This dose will be considered the maintenance dose.

### **Drug Availability**

#### **Lupron Depot 3.75mg**

Each syringe contains sterile lyophilized microspheres, which is leuprolide incorporated in a biodegradable copolymer of lactic and glycolic acids. When mixed with diluent, Lupron Depot 3.75 mg is administered as a single monthly IM injection.

#### **Lupron Depot 11.25mg**

Each syringe contains sterile lyophilized microspheres which are leuprolide acetate incorporated in a biodegradable polymer of polylactic acid. When mixed with 1.5 mL of the diluent, Lupron Depot-3 Month 11.25 mg is administered as a single IM injection every three months.

#### **Lupron Depot PED**

Lupron Depot PED is packaged in a pre-filled dual chamber syringe that comes in 7.5mg, 11.25mg, and 15mg strengths.

### **General Background**

#### **Pharmacology**

Leuprolide is a synthetic analog of endogenous gonadotropin-releasing hormone (GnRH), or gonadorelin. GnRH regulates follicle-stimulating hormone (FSH) and luteinizing hormone (LH) synthesis and secretion by the anterior pituitary gland. In response to GnRH, FSH and LH synthesis initially increase, causing a transient increase in circulating levels of sex hormones. With continued administration for more than one to three weeks, the pituitary gland down-regulates and desensitizes GnRH receptors, reducing FSH and LH secretion. Although the physiologic effects are complicated, the end result of continuous GnRH use is chemical castration, or markedly reduced estrogen levels in females and testosterone levels in males. In men, testosterone increases transiently during the first week after the initial dose, then falls to castrate levels after two to four weeks of continued therapy. Similarly, in women, estradiol increases transiently and then falls to postmenopausal levels by three weeks after initiating continuous therapy. Consequently, physiologic functions and tissues that are dependent on gonadal steroids for their maintenance become quiescent. Normal pituitary and gonadal function

typically returns within three months of discontinuing GnRH agonist therapy. Leuprolide is not active when administered orally. The average terminal elimination half-life of leuprolide is approximately three hours. Approximately 46% of leuprolide is protein bound. The drug is eliminated via a combination of hepatic metabolism and urinary excretion.

## **Guidelines**

The National Comprehensive Cancer Network (NCCN) recommends leuprolide acetate for the following:

### **Invasive Breast Cancer**

Lupron

For consideration in the treatment of premenopausal women with hormone receptor-positive disease for whom adjuvant therapy is considered. The combination of ovarian ablation/suppression plus endocrine therapy may be superior to suppression alone. The benefit of ovarian ablation/suppression in premenopausal women who have received adjuvant chemotherapy is uncertain; in combination with endocrine therapy for the treatment of premenopausal women with hormone receptor-positive recurrent or metastatic disease (men with breast cancer should be treated similarly to postmenopausal women, except that use of an aromatase inhibitor is ineffective without concomitant suppression of testicular steroidogenesis) (Grade 2A).

### **Epithelial Ovarian Cancer**

Lupron Depot 3.75mg

Recurrence hormonal therapy as a single agent for recurrence as evidenced by serially rising CA-125 levels in patients who have received prior chemotherapy or progressive or stable disease on primary chemotherapy or relapse after complete remission following primary chemotherapy or stage II-IV disease showing partial response to primary treatment; single-agent hormonal recurrence therapy for low-grade or focal recurrences after a disease-free interval of more than 6 months as immediate treatment or with secondary cytoreductive surgery or following secondary cytoreductive surgery (Grade 2A)

### **Ovarian Stromal Tumors**

Lupron Depot 3.25mg & 3-month 11.25mg

Hormonal therapy for clinical relapse following initial treatment in patients with stage II-IV granulosa cell tumors (Grade 2A).

### **Prostate Cancer**

Lupron and Lupron Depot

Initial treatment for locally advanced (T3b-4) disease for short-term neoadjuvant/concomitant/adjuvant androgen deprivation therapy (ADT; 4-6 months) in combination with radiation therapy or long-term ADT (2-3 years) (Grade 1).

Adjuvant treatment if pelvic lymph node dissection was performed and positive lymph nodes were found at initial prostatectomy; initial short-term neoadjuvant/concomitant/adjuvant androgen deprivation therapy (4-6 months) in combination with radiation therapy with or without brachytherapy for clinically localized disease with intermediate risk of recurrence (Grade 2A).

Initial treatment in combination with radiation therapy for clinically localized disease with high risk of recurrence, short-term neoadjuvant/concomitant/adjuvant androgen deprivation therapy (ADT; 4-6 months) with radiation therapy may be recommended in selected patients with a single adverse high-risk factor (T3a disease, Gleason score 8 to 10, or prostate-specific antigen levels greater than 20 ng/mL) (Grade 2A).

For postprostatectomy recurrence with or without radiation therapy in patients without distant metastases; for metastatic or recurrent disease as short-term neoadjuvant/concomitant/adjuvant androgen deprivation therapy (ADT; 4-6 months) in combination with radiation therapy for metastatic (any T, N1) disease at initial presentation or long-term ADT (2-3 years) for metastatic (any T, N1 or any T, any N, M1 ) disease at initial presentation or following prostatectomy in patients with distant metastases or following radiation therapy in patients with rising prostate-specific antigen levels or positive digital rectal examination who are not candidates for local therapy or in patients with distant metastases (Grade 2A).

Salvage therapy following radiation therapy in patients with rising prostate-specific antigen levels or positive digital rectal examination with a negative biopsy and no metastatic disease (Grade 2A).

Single agent or in combination with antiandrogen for treatment of disseminated disease without neuroendocrine features. If there is relapse following initial treatment, discontinue antiandrogen. In patients who are at risk of developing symptoms associated with the flare in testosterone levels with luteinizing hormone-releasing hormone (LHRH) agonist therapy alone, LHRH agonist should be given in combination with antiandrogen for at least 7 days (Grade 2A).

Neoadjuvant therapy in conjunction with brachytherapy in patients with any of the following: high-risk disease or a large prostate where neoadjuvant therapy can shrink the prostate to an acceptable size for brachytherapy (Grade 2A).

The Centers for Disease Control and Prevention (CDC) recommend GnRH medicines for women who don't ovulate regularly each month. Women who ovulate before the egg is ready can also use these medicines. GnRH analogs act on the pituitary gland to change when the body ovulates.

### **Clinical Efficacy**

#### **Advanced Prostate Cancer**

Leuprolide appears to be at least as effective as orchiectomy or estrogen therapy (specifically diethylstilbestrol [DES], no longer commercially available in the US) in previously untreated patients with advanced prostate cancer and is associated with fewer serious adverse effects than estrogen therapy (at least when DES is given in a dosage of 3 mg daily). In the treatment of advanced prostate cancer, leuprolide has produced an objective response in about 80% of previously untreated patients. Patients who respond to leuprolide therapy usually exhibit disease stabilization or, to a lesser extent, partial responses; complete responses occur rarely. The duration of clinical response with leuprolide appears to be comparable to that following orchiectomy or estrogen therapy; however, further long-term study is needed to clearly establish the duration of response to leuprolide. Patients whose disease responds to or is stabilized with hormonal manipulation (e.g., orchiectomy, estrogen therapy) appear to have increased survival compared with those whose disease progresses; however, there are insufficient data to date to determine the effect of leuprolide on long-term survival in patients with prostate cancer. Leuprolide is not recommended for use in patients with recurrent, advanced prostate cancer who previously underwent orchiectomy and/or previously received estrogen therapy. Patients most likely to respond to leuprolide probably are those whose tumors are relatively androgen dependent (approximately 80% of cases of newly diagnosed prostate cancer are androgen dependent). In the treatment of advanced prostate cancer, it has not been clearly established whether immediate or delayed hormonal manipulation is optimal in asymptomatic patients. Many clinicians suggest that hormonal manipulation for newly diagnosed, advanced prostate cancer should be withheld until symptoms appear in patients who are asymptomatic and sexually potent; however, other clinicians suggest initiation of therapy at the time of diagnosis in asymptomatic patients to prevent further disease progression and delay of potentially effective treatment. A difference in survival between patients with stage D prostate tumors receiving immediate hormonal manipulation and those receiving delayed therapy has not been clearly demonstrated.

#### **Advanced Breast Cancer** (off-label indication which is NCCN recommended)

Leuprolide has been used with some success for the treatment of breast cancer in a limited number of pre-menopausal and post-menopausal women. Clinical studies with leuprolide for the treatment of breast cancer generally have been performed in women who have received mastectomy, radiation, and/or previous anti-neoplastic and/or anti-estrogenic therapy. In one study in pre-menopausal women with breast cancer, leuprolide produced an objective response rate of 64%; median duration of response was 39 or 19 weeks in patients having a partial response or disease stabilization, respectively. In post-menopausal women with breast cancer, leuprolide has produced an objective response in 35% of patients and remission was generally of short duration. Many patients with breast cancer who respond to leuprolide therapy have tumors that are estrogen-receptor positive; however, responses have occurred in some patients with estrogen-receptor-negative tumors, suggesting that the drug may have a direct anti-tumor effect in addition to its inhibitory effect on ovarian function. Many clinicians currently recommend that leuprolide be limited to use in pre-menopausal women with breast cancer.

#### **Endometriosis**

In controlled clinical studies, Lupron Depot monthly for six months was shown to be comparable to danazol 800 mg/day in relieving the clinical sign/symptoms of endometriosis (pelvic pain, dysmenorrhea, dyspareunia, pelvic tenderness, and induration) and in reducing the size of endometrial implants as evidenced by laparoscopy. The

clinical significance of a decrease in endometriotic lesions is not known at this time, and in addition laparoscopic staging of endometriosis does not necessarily correlate with the severity of symptoms. Lupron Depot induced amenorrhea in 74% and 98% of the patients after the first and second treatment months respectively. Most of the remaining patients reported episodes of only light bleeding or spotting. In the first, second and third post-treatment months, normal menstrual cycles resumed in 7%, 71% and 95% of patients, respectively, excluding those who became pregnant.

Two clinical studies with treatment duration of 12 months indicate that concurrent hormonal therapy (norethindrone acetate 5 mg daily) is effective in significantly reducing the loss of bone mineral density associated with Lupron without compromising the efficacy of Lupron in relieving symptoms of endometriosis. (All patients in these studies received calcium supplementation with 1000 mg elemental calcium). One controlled, randomized and double-blind study included 51 women treated with Lupron Depot alone and 55 women treated with Lupron plus norethindrone acetate 5 mg daily. The second study was an open label study in which 136 women were treated with Lupron plus norethindrone acetate 5 mg daily. This study confirmed the reduction in loss of bone mineral density that was observed in the controlled study. Suppression of menses was maintained throughout treatment in 84% and 73% of patients receiving Lupron plus norethindrone in the controlled study and open label study, respectively. The median time for menses resumption after treatment with Lupron plus norethindrone was 8 weeks.

If the symptoms of endometriosis recur after a course of therapy, retreatment with a six-month course of leuprolide and norethindrone acetate 5 mg daily may be considered. Retreatment beyond this one six-month course cannot be recommended. It is recommended that bone density be assessed before retreatment begins to ensure that values are within normal limits. Leuprolide alone is not recommended for retreatment. If norethindrone acetate is contraindicated for the individual patient, then retreatment is not recommended. An assessment of cardiovascular risk and management of risk factors such as cigarette smoking is recommended before beginning treatment with leuprolide and norethindrone acetate.

#### **Uterine Fibroids or Leiomyomata**

In controlled clinical trials, administration of Lupron Depot for a period of three or six months was shown to decrease uterine and fibroid volume, thus allowing for relief of clinical symptoms (abdominal bloating, pelvic pain, and pressure). Excessive vaginal bleeding (menorrhagia and menometrorrhagia) decreased, resulting in improvement in hematologic parameters. In three clinical trials, enrollment was not based on hematologic status. Mean uterine volume decreased by 41% and myoma volume decreased by 37% at final visit as evidenced by ultrasound or MRI. These patients also experienced a decrease in symptoms including excessive vaginal bleeding and pelvic discomfort. Benefit occurred by three months of therapy, but additional gain was observed with an additional three months of Lupron Depot. Ninety-five percent of these patients became amenorrheic with 61%, 25%, and 4% experiencing amenorrhea during the first, second, and third treatment months respectively. Post-treatment follow-up was carried out for a small percentage of Lupron Depot patients among the 77% who demonstrated a  $\geq 25\%$  decrease in uterine volume while on therapy. Menses usually returned within two months of cessation of therapy. Mean time to return to pretreatment uterine size was 8.3 months. Regrowth did not appear to be related to pretreatment uterine volume. In another controlled clinical study, enrollment was based on hematocrit  $\leq 30\%$  and/or hemoglobin  $\leq 10.2$  g/dL. Administration of Lupron Depot, concomitantly with iron, produced an increase of  $\geq 6\%$  hematocrit and  $\geq 2$  g/dL hemoglobin in 77% of patients at three months of therapy. The mean change in hematocrit was 10.1% and the mean change in hemoglobin was 4.2 g/dL. Clinical response was judged to be a hematocrit of  $\geq 36\%$  and hemoglobin of  $\geq 12$  g/dL, thus allowing for autologous blood donation prior to surgery. At three months, 75% of patients met this criterion. At three months, 80% of patients experienced relief from either menorrhagia or menometrorrhagia. As with the previous studies, episodes of spotting and menstrual-like bleeding were noted in some patients. In this same study, a decrease of  $\geq 25\%$  was seen in uterine and myoma volumes in 60% and 54% of patients respectively. Lupron Depot was found to relieve symptoms of bloating, pelvic pain, and pressure. There is no evidence that pregnancy rates are enhanced or adversely affected by the use of Lupron Depot.

#### **Epithelial Ovarian Cancer and Ovarian Stromal Tumors** (off-label indication which is NCCN recommended)

Results of clinical trials conducted by the NCCN resulted in positive outcomes for the use of leuprolide acetate in epithelial ovarian carcinoma for recurrent hormonal therapy as a single agent. The NCCN also recommends use of leuprolide for ovarian stromal tumors as hormonal therapy.

## **CPP**

In children with CPP, stimulated and basal gonadotropins are reduced to prepubertal levels. Testosterone and estradiol are reduced to prepubertal levels in males and females respectively. Reduction of gonadotropins will allow for normal physical and psychological growth and development. Natural maturation occurs when gonadotropins return to pubertal levels following discontinuation of leuprolide acetate. The following physiologic effects have been noted with the chronic administration of leuprolide acetate in this patient population: Skeletal Growth - a measurable increase in body length can be noted since the epiphyseal plates will not close prematurely; Organ Growth - reproductive organs will return to a prepubertal state; Menses - menses, if present, will cease. In a study of 22 children with CPP, doses of Lupron Depot were given every 4 weeks and plasma levels were determined according to weight categories.

## **Infertility**

Gonadotrophin-releasing hormone antagonists produce immediate suppression of gonadotrophin secretion, hence, they can be given after starting gonadotrophin administration. This has resulted in dramatic reduction in the duration of treatment cycle. Two different regimes have been described. The multiple-dose protocol involves the administration of 0.25 mg cetrorelix (or ganirelix) daily from day six to seven of stimulation, or when the leading follicle is 14 to 15 mm, until human chorionic gonadotrophin (HCG) administration and the single-dose protocol involves the single administration of 3 mg cetrorelix on day seven to eight of stimulation. Assuming comparable clinical outcome, these benefits would justify a change from the standard long protocol of GnRH agonists to the new GnRH antagonist regimens. Cochrane Menstrual Disorders and Subfertility Group's Specialised Register was searched, MEDLINE and EMBASE databases from 1987 to February 2006, and handsearched bibliographies of relevant publications and reviews, and abstracts of scientific meetings. Randomized controlled studies comparing different protocols of GnRH antagonists with GnRH agonists in assisted conception cycles were included in this review. Twenty seven RCTs comparing the GnRH antagonist to the long protocol of GnRH agonist fulfilled the inclusion criteria. Clinical pregnancy rate was significantly lower in the antagonist group. The ongoing pregnancy/ live-birth rate showed the same significant lower pregnancy in the antagonist group. However, there was statistically significant reduction in incidence of severe OHSS with antagonist protocol. In addition, interventions to prevent OHSS (e.g. coasting, cycle cancellation) were administered more frequently in the agonist group. GnRH antagonist protocol is a short and simple protocol with good clinical outcome with significant reduction in incidence of severe ovarian hyperstimulation syndrome and amount of gonadotrophins but the lower pregnancy rate compared to the GnRH agonist long protocol necessitates counseling subfertile couples before recommending change from GnRH agonist to antagonist.

## **Adverse Reactions**

Leuprolide common side effects reported in adults are those typical of hypogonadism. Hot flushes occur in the majority of patients, regardless of gender. In men, the agents frequently cause sexual dysfunction, and impotence or decreased erections. In women, vaginal dryness, vaginal atrophy, headaches, and reduced libido are common. Hypogonadal side effects are infrequent in children. Instead, local reactions such as injection site reactions are the most common adverse effects. During postmarketing surveillance, rare cases of pituitary apoplexy have been reported after the administration of GnRH agonists.

Long-term therapy (more than six months) with GnRH agonists has a detrimental effect on bone mass, causing a reduction in bone mineral density. Although this effect is partially reversible, bone mineral density may remain below pretreatment values for more than one year after discontinuation. For benign gynecologic conditions (e.g., endometriosis, uterine leiomyomata), duration of therapy should not exceed six months unless concomitant estrogen is given to minimize effects on bone density. In a randomized trial in 40 females with CPP, supplementation with elemental calcium 2 g/day prevented or reversed bone demineralization, despite continued GnRH agonist therapy for up to two years.

In a single endometriosis trial comparing GnRH agonist with oral contraceptives, hot flushes, insomnia, and vaginal dryness were more frequent with the GnRH agonists. Similarly, hot flushes and reduced libido were more common with GnRH agonist monotherapy than either placebo or GnRH agonist combined with estrogen/progestin add-back therapy. Comparative adverse effects were evaluated in the three comparative endometriosis trials and the endometriosis quality of life study. There was generally no difference between the GnRH agonists in the incidence or type of adverse effects reported. Hot flushes may occur in more than 90% of patients treated with GnRH agonists. One study suggests that leuprolide may cause more hypoestrogenic

symptoms and bone demineralization than nafarelin. More studies are needed to evaluate whether actual differences exist.

In several of the meta-analyses, side effects accounted for most of the differences between treatments. In men, impotence and hot flushes were more common with GnRH agonists, while gynecomastia was more common with nonsteroidal antiandrogens. Treatment withdrawals due to side effects may occur less frequently with GnRH agonists than other hormonal agents. Men were less likely to discontinue GnRH agonist monotherapy compared to antiandrogen monotherapy or combined androgen blockade.

Leuprolide is contraindicated in women with the following conditions: known or suspected pregnancy, lactation, or undiagnosed abnormal vaginal bleeding. Leuprolide can cause fetal harm (Pregnancy Category X); embryotoxicity and fetotoxicity has been observed in animals. Before initiating leuprolide therapy, pregnancy must be excluded.

The signs and symptoms of prostate cancer or endometriosis may worsen during the first weeks of treatment because goserelin may initially cause a transient increase in serum levels of testosterone or estrogen, respectively. Prostate cancer patients may experience worsening of symptoms or onset of new symptoms, including bone pain. In patients with prostate cancer, isolated cases of ureteral obstruction and spinal cord compression have been reported, which may contribute to paralysis with or without fatal complications. Observe patients with metastatic vertebral lesions and/or with upper or lower urinary tract obstruction very closely during the first few weeks of treatment.

Please Note: Bayer HealthCare Pharmaceuticals Inc. discontinued marketing of Viadur (leuprolide acetate implant). Based on diminished market demand and growing manufacturing costs, Bayer HealthCare Pharmaceuticals has concluded that Viadur has limited long-term market viability. The decision to discontinue marketing of Viadur is not the result of safety or efficacy issues.

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## Coding/Billing Information

**Note:** This list of codes may not be all-inclusive.

**Covered when medically necessary:**

HCPCS Codes	Description
J1950	Injection, Leuprolide acetate (for depot suspension), per 3.75 mg
J9217	Leuprolide acetate [Lupron Depot] (for depot suspension), 7.5 mg
J9218	Leuprolide acetate (Lupron), per 1 mg

ICD-9-CM Diagnosis Codes	Description
174.0-174.9	Malignant neoplasm of female breast
175.0-175.9	Malignant neoplasm of male breast
183.0	Malignant neoplasm of ovary
185	Malignant neoplasm of prostate
218.0-218.9	Uterine leiomyoma
259.1	Precocious sexual development and puberty, not elsewhere classified
617.0-617.9	Endometriosis

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