



CIGNA MEDICAL COVERAGE POLICY

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

Subject **Goserelin (Zoladex[®], Zoladex[®] LA)**

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Hyperlink to Related Coverage Policies

- Histrelin (Vantas[™])
- Leuprolide (Lupron[®], Lupron Depot[®])
- Nafarelin (Synarel[®])
- Leuprolide (Eligard[®])

INSTRUCTIONS FOR USE

Coverage Policies are intended to provide guidance in interpreting certain **standard** CIGNA HealthCare benefit plans. Please note, the terms of a customer'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 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 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 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. Proprietary information of CIGNA. Copyright ©2011 CIGNA

Coverage Policy

CIGNA covers goserelin (Zoladex[®]) as medically necessary for ANY of the following indications:

- advanced breast cancer
- advanced prostate cancer
- dysfunctional uterine bleeding
- endometriosis

CIGNA covers goserelin (Zoladex[®] LA) as medically necessary for EITHER of the following indications:

- advanced prostate cancer
- endometriosis

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 goserelin (Zoladex[®], Zoladex[®] LA) therapy.

FDA Approved Indications

Zoladex 3.6mg

Advanced Breast Cancer

Zoladex is indicated for use in the palliative treatment of advanced breast cancer in pre- and perimenopausal women. The estrogen and progesterone receptor values may help to predict whether Zoladex therapy is likely to be beneficial.

Endometriosis

Zoladex is indicated for the management of endometriosis, including pain relief and reduction of endometriotic lesions for the duration of therapy. Experience with Zoladex for the management of endometriosis had been limited to women 18 years of age and older treated for 6 months.

Endometrial Thinning

Zoladex is indicated for use as an endometrial-thinning agent prior to endometrial ablation for dysfunctional uterine bleeding.

Prostatic Carcinoma

Zoladex is indicated in the palliative treatment of advanced carcinoma of the prostate.

Stage B2-C Prostatic Carcinoma

Zoladex is indicated for use in combination with flutamide for the management of locally confined Stage T2b-T4 (Stage B2-C) carcinoma of the prostate. Treatment with Zoladex and flutamine should start 8 weeks prior to initiating radiation therapy and continue during radiation therapy.

Zoladex LA

Prostate Cancer

Zoladex LA is used for the palliative treatment of patients with hormone-dependent advanced carcinoma of the prostate (Stage D2); in combination with a non-steroidal antiandrogen and radiation therapy for the management of locally advanced (T3, T4) or bulky Stage T2b, T2c carcinoma of the prostate; or as adjuvant hormone therapy to external beam irradiation for patients with locally advanced prostate cancer (Stage T3-T4).

Endometriosis

Zoladex LA is indicated for the hormonal management of endometriosis, including pain relief and reduction of endometriotic lesions. Experience with Zoladex for the management of endometriosis has been limited to women 18 years of age and older, treated for 6 months.

FDA Recommended Dosing

Zoladex 3.6mg

Zoladex, at a dose of 3.6 mg, should be administered subcutaneously every 28 days.

Stage B2-C Prostatic Carcinoma

When Zoladex is given in combination with radiotherapy and flutamide for patients with Stage T2b-T4 (Stage B2-C) prostatic carcinoma, treatment should be started 8 weeks prior to initiating radiotherapy and should continue during radiation therapy. A treatment regimen using a Zoladex 3.6 mg depot 8 weeks before radiotherapy, followed in 28 days by the Zoladex 10.8 mg depot, can be administered. Alternatively, four injections of 3.6 mg depot can be administered at 28-day intervals, two depots preceding and two during radiotherapy.

Prostatic Carcinoma

For the management of advanced prostate cancer, Zoladex is intended for long-term administration unless clinically inappropriate.

Endometriosis

For the management of endometriosis, the recommended duration of administration is 6 months. Currently, there are no clinical data on the effect of treatment of benign gynecological conditions with Zoladex for periods in excess of 6 months.

Retreatment cannot be recommended for the management of endometriosis since safety data for retreatment are not available. If the symptoms of endometriosis recur after a course of therapy, and further treatment with Zoladex is contemplated, consideration should be given to monitoring bone mineral density. Clinical studies suggest the addition of Hormone Replacement Therapy (estrogens and/or progestins) to Zoladex is effective in reducing the bone mineral loss which occurs with Zoladex alone without compromising the efficacy of Zoladex in relieving the symptoms of endometriosis.

Endometrial Thinning

For use as an endometrial-thinning agent prior to endometrial ablation, the dosing recommendation is one or two depots (with each depot given four weeks apart). When one depot is administered, surgery should be performed at four weeks. When two depots are administered, surgery should be performed within two to four weeks following administration of the second depot.

Breast Cancer

For the management of advanced breast cancer, Zoladex is intended for long-term administration unless clinically inappropriate.

Zoladex LA

Prostate Cancer

One depot of Zoladex LA containing goserelin acetate equivalent to 10.8 mg goserelin, should be injected subcutaneously into the anterior abdominal wall every 3 months. If in exceptional circumstances repeat dosing does not occur at 3 months, data indicate that castrate levels of testosterone are maintained for up to 16 weeks in the majority of patients. When Zoladex LA is given in combination with a non-steroidal antiandrogen and radiotherapy for patients with Stage T2b-T4 prostatic carcinoma, treatment should be started 8 weeks prior to initiating radiotherapy and should continue until completion of the radiation therapy.

Endometriosis

One depot of Zoladex LA containing goserelin acetate equivalent to 10.8 mg goserelin, should be injected subcutaneously into the anterior abdominal wall every 12 weeks

Drug Availability

Zoladex 3.6mg

Zoladex is supplied as a sterile and totally biodegradable D,L-lactic and glycolic acids copolymer (13.3-14.3 mg/dose) impregnated with goserelin acetate equivalent to 3.6 mg of goserelin in a disposable syringe device fitted with a 16-gauge x 36 +/-0.5 mm siliconized hypodermic needle with protective needle sleeve [SafeSystem™ Syringe]. The unit is sterile and comes in a sealed, light and moisture proof, aluminum foil laminate pouch containing a desiccant capsule.

Zoladex LA

Zoladex LA comes in a hard, cream-coloured, rod-shaped depot which contains 10.8mg of goserelin as goserelin acetate.

General Background

Pharmacology

Goserelin 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 and 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.

Guidelines

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

Invasive Breast Cancer

Grade 2A

Treatment of premenopausal women with hormone receptor-positive disease as a consideration with adjuvant therapy or in combination with endocrine therapy for 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

Prostate Cancer

Grade 1

Initial long-term (2-3 years) neoadjuvant/concomitant/adjuvant androgen deprivation therapy in combination with radiation therapy for clinically localized disease with high risk of recurrence or locally advanced disease with very high risk of recurrence.

Grade 2A

Adjuvant treatment if positive lymph nodes were found during pelvic lymph node dissection.

Initial short-term (4-6 months) neoadjuvant/concomitant/adjuvant androgen deprivation therapy in combination with radiation therapy with or without brachytherapy for clinically localized disease with intermediate risk of recurrence with brachytherapy for clinically localized disease with high risk of recurrence or with brachytherapy for locally advanced (T3b-4) disease with very high risk of recurrence for metastatic disease.

Initial treatment for locally advanced (T3b-4) or metastatic disease

For postprostatectomy recurrence with radiation therapy in patients without distant metastases or in patients with distant metastases.

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 or who are not candidates for local therapy or with distant metastases.

Single agent or in combination with antiandrogen for disease progression in androgen deprivation therapy-naïve patients. 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.

Neoadjuvant therapy in conjunction with brachytherapy in patients with high-risk disease or a large prostate where neoadjuvant therapy can shrink the prostate to an acceptable size for brachytherapy.

Adverse Reactions

Common side effects reported in adults are those typical of hypogonadism. Hot flashes occur in the majority of patients, regardless of gender. In men, the agents frequently cause sexual dysfunction, impotence or decreased erections. In women, vaginal dryness, vaginal atrophy, headaches, and reduced libido are common. Transient changes in blood pressure (hypotension or hypertension) have occasionally occurred in patients receiving goserelin. Other side effects in women have included emotional lability, sweating, depression, acne, breast atrophy, seborrhea, and peripheral edema. Other side effects in men have included lower urinary tract symptoms, lethargy, and pain (worsened in the first month). During post-marketing surveillance, rare cases of pituitary apoplexy have been reported after the administration of gonadotropin-releasing hormone agonists.

Long-term therapy (> 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 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. 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.

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 with antiandrogen monotherapy or combined androgen blockade.

No drug-drug interaction studies have been conducted, and no confirmed interactions have been reported between goserelin and other drugs.

Goserelin is contraindicated in women with known or suspected pregnancy or lactation. Goserelin can cause fetal harm (Pregnancy Category X); embryotoxicity and fetotoxicity has been observed in animals. Before initiating goserelin therapy, pregnancy must be excluded.

The signs and symptoms of prostate or breast cancer may worsen during the first weeks of treatment because goserelin may initially cause a transient increase in serum levels of testosterone or estrogen, respectively. Patients may experience worsening of symptoms or onset of new symptoms, including bone pain. In patients with prostate cancer, isolated cases of spinal cord compression and ureteral obstruction have been reported. Additionally, hypercalcemia has been reported in some prostate and breast cancer patients with bone metastases after initiating goserelin treatment.

Cervical dilation should be performed carefully in patients undergoing endometrial ablation following use of goserelin as an endometrial thinning agent because the pharmacologic effect that goserelin exerts on the uterus and cervix may cause an increase in cervical resistance.

Coding/Billing Information

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

Covered when medically necessary:

HCPCS Codes	Description
J9202	Goserelin acetate implant, per 3.6 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
185	Malignant neoplasm of prostate
617.0-617.9	Endometriosis
626.2	Excessive or frequent menstruation
626.8	Other disorders of menstruation and other abnormal bleeding from female genital tract

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