



CIGNA PHARMACY COVERAGE POLICY

This Coverage Policy should NOT be used for Great-West benefit plans.

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Subject Nafarelin (Synarel®)

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Hyperlink to Related Coverage Policies

Goserelin (Zoladex®) Leuprolide (Lupron®),
Lupron Depot®, Lupron Depot-PED®)

INSTRUCTIONS FOR USE

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Coverage Policy

CIGNA covers nafarelin (Synarel®) as medically necessary for EITHER of the following indications:

- central precocious puberty with onset of secondary sexual characteristics earlier than 8 years in females and 9 years in males
- endometriosis in women 18 years of age and older with treatment not to exceed six months

General Background

FDA Approved Indications

Synarel is indicated for treatment of central precocious puberty (CPP) (gonadotropin-dependent precocious puberty) in children of both sexes. Synarel is indicated for management of endometriosis, including pain relief and reduction of endometriotic lesions. Experience with Synarel for the management of endometriosis has been limited to women 18 years of age and older treated for 6 months.

FDA Recommended Dosing

CPP - For the treatment of central precocious puberty (CPP), the recommended daily dose of Synarel is 1600 µg. The dose can be increased to 1800 µg daily if adequate suppression cannot be achieved at 1600 µg/day. Endometriosis - For the management of endometriosis, the recommended daily dose of Synarel is 400 µg. This is achieved by one spray (200 µg) into one nostril in the morning and one spray into the other nostril in the evening. Treatment should be started between days 2 and 4 of the menstrual cycle.

Nafarelin 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. Table 1 provides a brief comparison of the available GnRH agonists.

Following intranasal administration, nafarelin is rapidly absorbed into the systemic circulation. Peak serum concentrations are usually attained between 10 to 45 minutes. Bioavailability after a 400 mcg dose averaged 2.8% (range 1.2–5.6%). Nasal congestion/rhinitis does not appear to affect the bioavailability of nafarelin nasal solution. Following intranasal administration, the average serum half-life of nafarelin is approximately three hours. Approximately 80% of nafarelin is protein bound. The drug undergoes metabolism and is eliminated in urine and feces. A small amount is excreted unchanged in urine.

Clinical Studies

Central Precocious Puberty (CPP): Eighteen clinical trials evaluating efficacy in children with central precocious puberty (CPP) were reviewed. Study design varied, including: one randomized placebo-controlled trial, one randomized active-controlled trial, 13 nonrandomized trials with no comparison group, and two nonrandomized trials with historical controls. The specific GnRH agonist and route used varied with the individual trials, including: goserelin depot (one trial), triptorelin depot (11 trials), triptorelin subcutaneous injection (one trial), nafarelin intranasal spray (one trial), buserelin intranasal spray (one trial), or leuprolide depot (six trials). Treatment duration ranged from 0.6 years to 7.7 years.

The available data suggest that GnRH agonists increase final height, reduce growth velocity, and arrest pubertal development. The agents significantly reduce serum concentrations of LH, FSH, and sex hormones (i.e., estradiol, testosterone) during therapy. Table 1 summarizes the results of the included trials.

Table 1. Results of GnRH Agonist Therapy in Central Precocious Puberty

Agent	Dosage Regimens Used	Increase (%) in Predicted or Actual Final Height	Reduction (%) in Growth Velocity	Number of Included Studies
Goserelin	10.8 mg SQ every three months	Not reported	31	1
Leuprolide	30–50 mcg/kg SQ daily 0.3 mg/kg IM once monthly 1.87–15 mg IM once monthly 7.5 mg SQ once monthly 11.25 mg SQ every three months	3.5	20–36	6
Nafarelin	1200–1600 mcg/d IN given in two divided doses	Increased	Not reported	1
Triptorelin	1.5–3 mcg/kg SQ daily 42–120 mcg/kg IM once monthly 3.75 mg IM once monthly	1.1–4.4	29–51	11

Abbreviations: **IM** = intramuscular; **IN** = intranasal; **SQ** = subcutaneous

Clinical studies in children with CPP showed that the peak response of LH to GnRH stimulation was reduced from a pubertal response to a prepubertal response within one month of nafarelin treatment. Additionally, in most children receiving nafarelin treatment, linear growth velocity is reduced within the first year to 5–6 cm per year or less; bone age velocity approaches normal during the first year; and the height for chronologic age approaches normal during the second or third year of treatment. Nafarelin therapy leads to regression of

secondary sexual characteristics in children. In clinical studies, breast development regressed in 82% of girls, and genital development regressed in 100% of boys. The inhibitory effects of nafarelin are reversible following discontinuance of the drug, resulting in normal progression of pubertal development.

Endometriosis:

A meta-analysis of clinical trials evaluating the GnRH agonists in premenopausal women with symptomatic endometriosis, diagnosed by laparoscopy, was reviewed. The investigators included a total of 26 randomized trials comparing GnRH agonists with placebo (one trial); GnRH agonists plus estrogen/progestin add-back therapy (five trials); other GnRH agonists (four trials); danazol (15 trials); gestrinone (one trial); or oral contraceptives (one trial). The specific GnRH agonist and route used varied with the individual trials, including: leuprolide subcutaneous injection for seven days followed by leuprolide intranasal spray (one trial), goserelin depot (seven trials), triptorelin depot (two trials), nafarelin intranasal spray (four trials), buserelin intranasal spray (three trials), buserelin subcutaneous injection (two trials), or leuprolide depot (seven trials). The usual duration of treatment was six months.

The GnRH agonists have comparable efficacy to other pharmacologic treatments for endometriosis, including danazol, oral contraceptives, or GnRH agonists plus estrogen/progestin add-back therapy. The GnRH agonists are more effective than placebo. Because adverse events differ between pharmacologic classes, treatment decisions should be based on tolerability rather than efficacy. In a single endometriosis trial comparing GnRH agonists with oral contraceptives, hot flushes, insomnia, and vaginal dryness were more frequent with the GnRH agonists. Therefore, after a trial of oral contraceptives, GnRH agonists may be used in patients with inadequate symptom relief; use of concomitant estrogen-progestin add-back is preferred to reduce hypoestrogenic side effects. Table 2 summarizes results of the meta-analysis.

Table 2 Results of Endometriosis Meta-Analysis

Comparator	Reduction in Endometriosis Pain	Objective Efficacy by rAFS Score*	Discontinuation due to Inefficacy
Placebo/No treatment	GnRH agonist > placebo	Not reported	Placebo > GnRH agonists
Danazol	GnRH agonist = danazol	GnRH agonist = danazol	Not reported
Oral Contraceptives	GnRH agonist = oral contraceptives	GnRH agonist = oral contraceptives	Not reported
Combination therapy (GnRH agonist plus estrogen and progestin add-back)	GnRH agonist monotherapy = combination therapy	GnRH agonist monotherapy = combination therapy	Not reported

*Revised American Fertility Society score, an objective measure of endometriosis severity and response to therapy.

Three clinical trials have compared the individual GnRH agonists with each other in patients with endometriosis. All the agents effectively reduce pain and other endometriosis symptoms, as shown in Table 3. There were no significant differences between the individual agents in efficacy measures in any of the trials.

Table 3. Results of GnRH Agonist Therapy in Comparative Endometriosis Trials

Agent	Dosage Regimens Compared	Pain Score, Change (%) from Baseline	Patients (%) with $\geq 50\%$ Decrease in Disease Severity	Withdrawals (%) due to Adverse Effects	Number of Included Studies
Goserelin	3.6 mg SQ monthly	45	37–39	7	1
Leuprolide	3.75 mg IM monthly	61	Not reported	13	2
Nafarelin	200 mcg IN BID	43–59	34–39	6–7	2
Triptorelin*	3.75 mg IM monthly	Not reported	Not reported	Not reported	1

Abbreviations: **BID** = twice daily; **IM** = intramuscular; **IN** = intranasal; **SQ** = subcutaneous

*Study evaluated effects on biochemical markers (i.e., estradiol, LH, FSH), rather than effects on symptoms.

A quality of life study (Zhao, et al., 1999) was conducted using data collected in the leuprolide vs. nafarelin trial by Agarwal, et al., (1997). The investigators found that both treatments improved disease-related quality of life to a similar extent. In patients with severe disease, quality of life was similar during treatment but was better with nafarelin at 1.5, 3, and 6 months after treatment completion ($p < 0.05$ vs. leuprolide for all comparisons).

Common side effects reported in adult women are those typical of hypoestrogenism. Hot flashes, vaginal dryness, and reduced libido are common. Other side effects have included headache, emotional lability, acne, myalgia, reduction in breast size (adults), transient breast enlargement (children), and nasal irritation/rhinitis.

In a single endometriosis trial comparing GnRH agonist with oral contraceptives, hot flashes, insomnia, and vaginal dryness were more frequent with the GnRH agonists. Similarly, hot flashes 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 flashes 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.

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 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.

No drug-drug interaction studies have been conducted. However, drug interactions would not be expected to occur because nafarelin is not primarily degraded by cytochrome P-450 enzymes and it has limited protein binding. Use of a topical nasal decongestant should be delayed until at least two hours after administration of nafarelin.

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

Careful establishment of a diagnosis of CPP is essential before treatment is initiated. Regular monitoring, especially during the initial six to eight weeks of treatment, is important to ensure rapid suppression of pituitary-gonadal function. Bone age and growth velocity assessment should begin within three to six months of initiation of nafarelin treatment.

Ovarian cysts have occurred in the first two months of nafarelin therapy in adult women with endometriosis, mostly in those with polycystic ovarian disease. These cystic enlargements may resolve spontaneously (usually by four to six weeks of therapy) or require discontinuance of the drug and/or surgical intervention. The relevance of these findings to children is not known.

Coding/Billing Information

Note: This section not is use

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