BlueCross BlueShield Arizona

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PHARMACY COVERAGE GUIDELINE

SYNAREL® (nafarelin acetate) nasal solution

This Pharmacy Coverage Guideline (PCG):
- Provides information about the reasons, basis, and information sources we use for coverage decisions
- Is not an opinion that a drug (collectively "Service") is clinically appropriate or inappropriate for a patient
- Is not a substitute for a provider's judgment (Provider and patient are responsible for all decisions about appropriateness of care)
- Is subject to all provisions e.g. (benefit coverage, limits, and exclusions) in the member's benefit plan; and
- Is subject to change as new information becomes available.

Scope
- This PCG applies to Commercial and Marketplace plans
- This PCG does not apply to the Federal Employee Program, Medicare Advantage, Medicaid or members of out-of-state Blue Cross and/or Blue Shield Plans

Instructions & Guidance
- To determine whether a member is eligible for the Service, read the entire PCG.
- This PCG is used for FDA approved indications including, but not limited to, a diagnosis and/or treatment with dosing, frequency, and duration.
- Use of a drug outside the FDA approved guidelines, refer to the appropriate Off-Label Use policy.
- The "Criteria" section outlines the factors and information we use to decide if the Service is medically necessary as defined in the Member's benefit plan.
- The "Description" section describes the Service.
- The "Definition" section defines certain words, terms or items within the policy and may include tables and charts.
- The "Resources" section lists the information and materials we considered in developing this PCG
- **We do not accept patient use of samples as evidence of an initial course of treatment, justification for continuation of therapy, or evidence of adequate trial and failure.**
- Information about medications that require precertification is available at www.azblue.com/pharmacy. You must fully complete the request form and provide chart notes, lab workup and any other supporting documentation. The prescribing provider must sign the form. Fax the form to BCBSAZ Pharmacy Management at (602) 864-3126 or email it to Pharmacyprecert@azblue.com.

Criteria:

➢ **Criteria for initial therapy:** Synarel (nafarelin acetate) is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met:

1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with an Endocrinologist, Pediatric Endocrinologist, or Gynecologist.

2. Individual has a confirmed diagnosis of **ONE** of the following:
    a. Central precocious puberty (CPP) (gonadotropin-dependent precocious puberty) in children who have early onset of secondary sexual characteristics and **ALL** of the following:
        i. **Female** at < 8 years of age **or Male**< 9 years of age
        ii. With **ONE** of the following:
            1. Advanced through pubertal stages (Tanner stages) showing progression to the next stage in 3-6 months

2. Accelerated growth velocity > 6 cm per year
3. Advanced bone age for height age (bone age that has advanced at least 1 year beyond chronological age
4. Serum estradiol level in girls is pre-pubertal to pubertal range
5. Serum testosterone level in boys or girls (with virilization) is pre-pubertal to pubertal range
6. Basal (unstimulated) serum LH is in the pubertal range (> 0.3 mIU/mL)
7. GnRH stimulation test shows LH peak is elevated into the pubertal range (> 5 mIU/mL)
8. GnRH stimulation test shows LH/FSH ratio is > 0.66

b. Management of endometriosis, including pain relief and reduction of endometriotic lesions in an individual 18 years of age or older.

3. **Additional criteria for CPP only:** Failure, contraindication per FDA label, or intolerance to leuprolide acetate Depot-Ped. **[Note: requires Precertification: See Lupron Depot PED guideline]**

4. **Additional criteria for endometriosis only,** failure, contraindication per FDA label, or intolerance to **ALL** the following preferred step therapy agents:
   a. **ONE** Non-steroidal anti-inflammatory agent such as ibuprofen, indomethacin, naproxen, meloxicam, and others
   b. Oral estrogen-progestin contraceptive or depot medroxyprogesterone or norethindrone acetate

5. The individual has received and completed **ALL** the following **baseline tests** before initiation of treatment and with continued monitoring of the individual as clinically appropriate:
   a. **For CPP only:** basal LH, FSH, estradiol in girls, testosterone in boys, GnRH stimulation test
   b. Negative pregnancy test in a woman of childbearing potential

6. There are **NO** FDA-label contraindications, such as:
   a. Hypersensitivity to GnRH, GnRH agonist analogs or any of the excipients in Synarel
   b. Undiagnosed abnormal vaginal bleeding
   c. Use in pregnancy or in woman who may become pregnant
   d. Use in a woman who is breast-feeding

Initial approval duration:
- **For CPP:** 6 months, can be renewed up to planned resumption of puberty **AND** evaluations for treatment discontinuation to start at 11 and 12 years of age, respectively in girls and boys, treatment will be continued until there is fusion of the epiphyses or attainment of appropriate chronologic pubertal age is achieved
- **For endometriosis:** one-time approval of 6 months

➢ **Criteria for continuation of coverage (renewal request):** Synarel (nafarelin acetate) is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met **(samples are not considered for continuation of therapy**):

1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with an Endocrinologist, Pediatric Endocrinologist, or Gynecologist.

2. **For CPP**, individual's condition has responded while on therapy with response defined as **ALL** of the following:
    a. Progression of secondary sex characteristics has been prevented or regressed
    b. Growth rate has decreased and bone age to chronological age has decreased, but has not attained appropriate chronologic pubertal age yet
    c. There is suppression of pituitary gonadotropins (FSH, LH) to pre-pubertal levels
    b. There is suppression of peripheral sex steroids (testosterone and estradiol) to pre-pubertal levels

3. Individual has been adherent with the medication

4. Individual has not developed any contraindications or other significant adverse drug effects that may exclude continued use as follow:
    a. Contraindications as listed in the criteria for initial therapy section
    b. Significant adverse effect such as:
        i. Pregnancy
        ii. Undiagnosed abnormal vaginal bleeding
        iii. Seizures
        iv. Pituitary apoplexy
        v. Pseudotumor cerebri
        vi. Psychiatric adverse events such as emotional lability (such as crying, irritability, impatience, anger, and aggression), depression, suicidal ideation and attempt

Renewal duration:

- **For CPP:** 6 months, can be renewed up to planned resumption of puberty **AND** evaluations for treatment discontinuation to start at 11 and 12 years of age, respectively in girls and boys, treatment will be continued until there is fusion of the epiphyses or attainment of appropriate chronologic pubertal age is achieved

➢ Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

1. **Off-Label Use of Non-Cancer Medications**

2. **Off-Label Use of Cancer Medications**

Description:

Synarel (nafarelin acetate) is indicated for treatment of **central precocious puberty (CPP)** (gonadotropin-dependent precocious puberty) in children of both sexes. Synarel (nafarelin acetate) is also indicated for **management of endometriosis, including pain relief and reduction of endometriotic lesions**. Experience with Synarel (nafarelin acetate) for the management of endometriosis has been limited to women 18 years of age and older treated for 6 months. Retreatment cannot be recommended since safety data beyond 6 months is not available.

Nafarelin acetate is a potent agonistic analog of gonadotropin-releasing hormone (GnRH). At the onset of administration, nafarelin stimulates the release of the pituitary gonadotropins, LH and FSH, resulting in a temporary increase of gonadal steroidogenesis. Repeated dosing abolishes the stimulatory effect on the pituitary

gland. Twice daily administration leads to decreased secretion of gonadal steroids by about 4 weeks; consequently, tissues and functions that depend on gonadal steroids for their maintenance become quiescent.

When used regularly in girls and boys with CPP at the recommended dose, Synarel (nafarelin acetate) suppresses LH and sex steroid hormone levels to prepubertal levels, affects a corresponding arrest of secondary sexual development, and slows linear growth and skeletal maturation. In some cases, initial estrogen withdrawal bleeding may occur, generally within 6 weeks after initiation of therapy. Thereafter, menstruation should cease.

The diagnosis of CPP is suspected when premature development of secondary sexual characteristics occurs at or before the age of 8 years in girls and 9 years in boys and is accompanied by significant advancement of bone age and/or a poor adult height prediction. The diagnosis should be confirmed by pubertal gonadal sex steroid levels and a pubertal LH response to stimulation by native GnRH.

Endometriosis is defined as endometrial glands and stroma that occur outside the uterine cavity. The lesions are usually located in the pelvis but can occur at other sites including the bowel, diaphragm, and pleural cavity. Endometriosis is an estrogen-dependent, benign, inflammatory disease that can affect a woman during their premenarcheal, reproductive, and postmenopausal hormonal stages. Ectopic endometrial tissue and inflammation may cause dysmenorrhea, dyspareunia, chronic pelvic pain, pelvic tenderness, pelvic induration, infertility and/or an ovarian mass. Less common symptoms include bowel and bladder dysfunction (e.g., dyschezia and dysuria), abnormal uterine bleeding, low back pain, or chronic fatigue. For some, the disease is asymptomatic and is an incidental finding at the time of surgery or imaging done for other indications.

A progestin, danazol, extended-cycle combined oral contraceptive, nonsteroidal anti-inflammatory drug (NSAIDs), or GnRH agonist can be used for the initial treatment of pain in women with suspected endometriosis. In women with a history of endometriosis who wish to preserve their fertility, NSAIDs or combined oral contraceptive can be used to treat recurrent pain. Oral or depot medroxyprogesterone acetate is also an effective treatment option. If none of these therapies are successful, a progestin, GnRH agonist, or androgen may be used. If treatment with a GnRH agonist is successful, the use of an add-back regimen can reduce or eliminate bone mineral loss and provide symptomatic relief without reduction in pain.

Add-back therapy refers to the addition of hormone replacement therapy to GnRH agonists, in order to avoid adverse effects that are caused by GnRH agonist-induced hormone suppression. Evidence suggests that add-back therapy is more effective for symptomatic relief than use of a GnRH agonist alone, both immediately after treatment and at 6 months. Add-back therapy increases estrogen levels but does not reduce the efficacy of GnRH agonists for treating dysmenorrhea and dyspareunia. Add-back regimens have been used in women undergoing long-term therapy; they may include a progestin alone, low dose progestin, progestin plus bisphosphonate, or estrogen.

In controlled clinical studies of endometriosis, Synarel (nafarelin acetate) at doses of 400 and 800 µg/day for 6 months was shown to be comparable to danazol, 800 mg/day, in relieving the clinical symptoms of endometriosis (pelvic pain, dysmenorrhea, and dyspareunia) and in reducing the size of endometrial implants as determined by laparoscopy. In a single controlled clinical trial, intranasal Synarel (nafarelin acetate) at a dose of 400 µg per day was shown to be clinically comparable to intramuscular leuprolide depot, 3.75 mg monthly, for the treatment of the symptoms (dysmenorrhea, dyspareunia and pelvic pain) associated with endometriosis.

Synarel (nafarelin acetate) lowers estrogen levels and may result in hypoestrogenic effects such as hot flashes, decreased libido, vaginal dryness, emotional lability, insomnia, and headache. The induced hypoestrogenic state also results in a small loss in bone density over the course of treatment, some of which may not be reversible. In patients with major risk factors for decreased bone mineral content such as chronic alcohol and/or tobacco use,

strong family history of osteoporosis, or chronic use of drugs that can reduce bone mass such as anticonvulsants or corticosteroids, therapy with Synarel (nafarelin acetate) may pose an additional risk. Repeated courses of treatment with gonadotropin-releasing hormone analogs are not advisable in patients with major risk factors for loss of bone mineral content.

Definitions:

Clinical characteristics of forms of early pubertal development:

	Non-progressive precocious puberty	Central precocious puberty (CPP)	Peripheral precocity
Physical examination: Advancement through pubertal stages (Tanner stage)	No progression in Tanner staging during 3 to 6 months of observation	Progression to next pubertal stage in 3 to 6 months	Progression
Growth velocity	Normal for bone age	Accelerated (> 6 cm per year)*	Accelerated*
Bone age	Normal to mildly advanced	Advanced for height age	Advanced for height age
Serum estradiol concentration (girls)¶	Pre-pubertal$^{\Delta}$	Pre-pubertal to pubertal	Increased in ovarian causes of peripheral precocity, or with exogenous estrogen exposure
Serum testosterone concentration (boys, or girls with virilization)¶	Pre-pubertal$^{\Delta}$	Pre-pubertal to pubertal	Pubertal and increasing
Basal (unstimulated) serum LH concentration¶	Pre-pubertal$^{\Delta\lozenge}$	Pubertal$^{\lozenge}$	Suppressed or pre-pubertal$^{\lozenge}$
GnRH (or GnRHa) stimulation test¶	LH peak in the pre-pubertal range$^{\Delta\S}$ Lower stimulated LH to FSH ratio$^{¥}$	LH peak elevated (in the pubertal range)§ Higher stimulated LH to FSH ratio$^{¥}$	No change from baseline, or LH peak in the pre-pubertal range

CPP: central precocious puberty; LH: luteinizing hormone; GnRH: gonadotropin-releasing hormone; GnRHa: gonadotropin-releasing hormone agonist; FSH: follicle-stimulating hormone.

***** UNLESS the patient has concomitant growth hormone deficiency (as in the case of a neurogenic form of CPP), or has already passed his or her peak height velocity at the time of evaluation, in which case growth velocity may be normal or decreased for chronological age.

¶ Using most commercially available immunoassays, serum concentrations of gonadal steroids have poor sensitivity to differentiate between pre-pubertal and early pubertal concentrations.

Δ In most cases these levels will be pre-pubertal, however in children with intermittently progressive CPP, these levels may reach pubertal concentrations during times of active development.

◊ Using ultrasensitive assays with detection limit of LH <0.1 mIU/L, pre-pubertal basal LH concentrations are <0.2 to 0.3 mIU/mL.

§ In most laboratories, the upper limit of normal for LH after GnRH stimulation is 3.3-5.0 mIU/mL. Stimulated LH concentrations above this normal range suggests CPP.

¥ A peak stimulated LH/FSH ratio < 0.66 usually suggests non-progressive precocious puberty, whereas a ratio > 0.66 is typically seen with CPP.

Reference:
Oerter KE, Uriarte MM, Rose SR, et al. Gonadotropin secretory dynamics during puberty in normal girls and boys. J Clin Endocrinol Metab 1990; 71:1251.

Resources:

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