BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINE

SYNAREL® (nafarelin acetate) nasal solution Generic Equivalent (if available)

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/or 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 prior authorization 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.

Medical Necessity Requirements for SYNAREL (nafarelin acetate)

Criteria for Initial Therapy:

Prescriber Qualifications
- Prescribed by an Endocrinologist, Pediatric Endocrinologist, or Gynecologist, or in consultation with one

Indication
- Central Precocious Puberty (gonadotropin dependent precocious puberty)
- Endometriosis, including pain relief and reduction of endometriotic lesions

ORIGINAL EFFECTIVE DATE: 08/15/2019 | ARCHIVE DATE: | LAST REVIEW DATE: 08/21/2025 | LAST CRITERIA REVISION DATE: 08/15/2024

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Age Requirement

- Endometriosis: 18 years or older
- Central precocious puberty
  - Female: less than 8 years old
  - Male: less than 9 years old

Baseline Clinical Evaluation

- Negative pregnancy test in a woman of childbearing potential
- **Central Precocious Puberty**
  - Early onset of secondary sexual characteristics and **ONE** of the following:
    1. Advanced through pubertal stages (Tanner stages) showing progression in 3–6 months
    2. Accelerated growth velocity greater than 6 cm per year
    3. Bone age advanced at least 1 year beyond chronological age
    4. Serum estradiol level in girls is in prepubertal to pubertal range
    5. Serum testosterone level in boys or girls (with virilization) is in pre pubertal to pubertal range
    6. Basal (unstimulated) serum luteinizing hormone is greater than 0.3 mIU/mL
    7. GNRH stimulation test shows luteinizing hormone peak greater than 5 mIU/mL
    8. GNRH stimulation test shows LH/FSH ratio greater than 0.66
  - Basal LH, FSH, estradiol in girls, testosterone in boys, GNRH stimulation test

Alternative Therapies

- **Central Precocious Puberty**
  - Failure, contraindication, intolerance, or not a candidate for **Leuprolide acetate Depot Ped**
- **Endometriosis**
  - Failure , contraindication, intolerance, or not a candidate for **BOTH** of the following:
    1. **ONE** nonsteroidal anti inflammatory agent (e.g., ibuprofen, indomethacin, naproxen, meloxicam, etc.)
    2. **ONE** hormonal product (e.g., oral estrogen/progestin contraceptive or progestin oral or depot such as medroxyprogesterone or norethindrone acetate)

Brand Specific Criteria

- Have failure, contraindication or intolerance with **THREE** generic equivalents (if available) for at least three months each. **Note**: Any failure, contraindication, or intolerance to the generic drugs should be reported to the FDA (see Definitions section)

Safety

- No FDA label contraindications:
  - Hypersensitivity to GNRH, GNRH agonist analogs, or any excipients in Synarel
  - Undiagnosed abnormal vaginal bleeding
  - Use during pregnancy or in woman of childbearing age who may become pregnant
  - Use in a woman who is breastfeeding

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Documentation Requirements

- A completed request form must be submitted, including:
  - Chart notes
  - Lab results (include all related lab values from above criteria)
  - Supporting clinical documentation

Initial Therapy Criteria Approval Duration

- **Central Precocious Puberty**
  - 6 months OR end of plan year
  - Can be renewed up to planned resumption of puberty
  - Evaluation for treatment discontinuation to start at 11 years (girls) and 12 years (boys)
  - Treatment continues until fusion of epiphyses or attainment of appropriate chronologic pubertal age
- **Endometriosis**
  - Without add back therapy: One time approval of 6 months OR end of plan year
  - With add back therapy: One time approval of 12 months OR end of plan year
  - For second treatment after recurrence without add back therapy: Bone density must be assessed, and initial criteria must be met again; approval for 6 months with hormonal add back therapy

Criteria for Continuation of Therapy (renewal therapy):

Note: Manufacturer assistance (e.g., coupons, samples, etc.) are not considered for continuation of therapy

Prescriber Qualification

- Continues to be seen by or in consultation with an Endocrinologist, Pediatric Endocrinologist, or Gynecologist

Clinical Response

- **Central Precocious Puberty**
  - Positive clinical response defined as **ALL** of the following:
    1. Progression of secondary sex characteristics has been prevented or regressed
    2. Growth rate has decreased and bone age to chronological age has decreased, but has not attained appropriate chronologic pubertal age
    3. Suppression of pituitary gonadotropins (FSH, LH) to prepubertal levels
    4. Suppression of peripheral sex steroids (testosterone and estradiol) to prepubertal levels

Adherence

- Adherence to the prescribed therapy regimen has been documented

Brand Specific Criteria

- Have failure, contraindication or intolerance with **THREE** generic equivalents (if available) for at least three months each. **Note**: Any failure, contraindication, or intolerance to the generic drugs should be reported to the FDA (see Definitions section)

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Safety

- No new contraindications or significant adverse drug effects including:
  - Hypersensitivity to GNRH, GNRH agonist analogs, or any excipients in Synarel
  - Undiagnosed abnormal vaginal bleeding
  - Use during pregnancy or in woman of childbearing age who may become pregnant
  - Use in a woman who is breastfeeding
  - Serious venous and arterial thromboembolism (e.g., DVT, PE, MI, stroke)
  - Seizures
  - Pituitary apoplexy
  - Pseudotumor cerebri
  - Serious liver injury
  - Psychiatric adverse events (e.g., emotional lability, depression, suicidal ideation or attempt)

Documentation Requirements

- Chart notes
- Supporting clinical documentation with evidence of improvement in given indication
- Lab values that confirm safe use from above criteria

Continuation Therapy Criteria Approval Duration

- **Central Precocious Puberty**
  - 6 months OR end of plan year
  - Can be renewed up to planned resumption of puberty
  - Evaluation for treatment discontinuation to start at 11 years (girls) and 12 years (boys)
  - Treatment continues until fusion of epiphyses or attainment of appropriate chronologic pubertal age

Criteria for Off-Label Use Requests:

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:

U.S. Food and Drug Administration (FDA) MedWatch Forms for FDA Safety Reporting
MedWatch Forms for FDA Safety Reporting | FDA

Clinical characteristics of forms of early pubertal development:

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

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:

Synarel (nafarelin acetate) nasal spray product information, revised by Pfizer Laboratories Div Pfizer Inc. 01-2023. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed May 13, 2025.

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