BlueCross BlueShield of Arizona
An Independent Licensee of the Blue Cross and Blue Shield Association

PHARMACY COVERAGE GUIDELINES
SECTION: DRUGS

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Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Pharmacy Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Pharmacy Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Pharmacy Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Pharmacy Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.

This Pharmacy Coverage Guideline does not apply to FEP or other states' Blues Plans.

Information about medications that require precertification is available at www.azblue.com/pharmacy.

Some large (100+) benefit plan groups may customize certain benefits, including adding or deleting precertification requirements.

All applicable benefit plan provisions apply, e.g., waiting periods, limitations, exclusions, waivers and benefit maximums.

Precertification for medication(s) or product(s) indicated in this guideline requires completion of the request form in its entirety with the chart notes as documentation. **All requested data must be provided.** Once completed the form must be signed by the prescribing provider and faxed back to BCBSAZ Pharmacy Management at (602) 864-3126 or emailed to Pharmacyprecert@azblue.com. **Incomplete forms or forms without the chart notes will be returned.**

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Criteria:

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

  1. Prescriber is a physician specializing in endocrine disorders or is in consultation with an Endocrinologist, Pediatric Endocrinologist, or Gynecologist

  2. A confirmed diagnosis of **ONE** of the following:
     - Central precocious puberty (CPP) (gonadotropin-dependent precocious puberty) in children who have early onset of secondary sexual characteristics and **ALL** of the following:
       - Female at < 8 years of age or Male< 9 years of age
       - With **ONE** of the following:
         - Advanced through pubertal stages (Tanner stages) showing progression to the next stage in 3-6 months
         - Accelerated growth velocity > 6 cm per year
         - Advanced bone age for height age (bone age that has advanced at least 1 year beyond chronological age
         - Serum estradiol level in girls is pre-pubertal to pubertal range
         - Serum testosterone level in boys or girls (with virilization) is pre-pubertal to pubertal range
         - Basal (unstimulated) serum LH is in the pubertal range (> 0.3 mIU/mL)
         - GnRH stimulation test shows LH peak is elevated into the pubertal range (> 5 mIU/mL)
         - GnRH stimulation test shows LH/FSH ratio is > 0.66

     - 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, or intolerance to Leuprolide Acetate Depot-Ped **[Note: requires Precertification: See Lupron Depot PED guideline]**

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

  5. **ALL** of the following baseline tests have been completed before initiation of treatment with continued monitoring as clinically appropriate:
     - **For CPP only:** basal LH, FSH, estradiol in girls, testosterone in boys, GnRH stimulation test
     - Negative pregnancy test in a woman of child bearing potential

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6. There are **NO** contraindications
    - Contraindications include:
        - Hypersensitivity to GnRH, GnRH agonist analogs or any of the excipients in Synarel
        - Undiagnosed abnormal vaginal bleeding
        - Use in pregnancy or in women who may become pregnant
        - Use in women who are 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** of the following criteria are met:

1. Individual continues to be seen by a physician specializing in endocrine disorders or is in consultation with an Endocrinologist, Pediatric Endocrinologist, or Gynecologist

2. Individual's condition responded while on therapy
    - **For CPP**, response is defined as:
        - LH levels that have been suppressed to pre-pubertal levels
        - Progression of secondary sex characteristics has been prevented
        - Growth rate has decreased and bone age to chronological age has decreased, but has not attained appropriate chronologic pubertal age yet
        - There is suppression of pituitary gonadotropins (FSH, LH) to pre-pubertal levels
        - 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 level 4 adverse drug effects that may exclude continued use
    - Contraindications as listed in the criteria for initial therapy section
    - Significant adverse effect such as:
        - Pregnancy
        - Undiagnosed abnormal vaginal bleeding
        - Seizures
        - Pituitary apoplexy

5. There are no significant interacting drugs

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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

- Synarel (nafarelin acetate) for all other indications not previously listed or if above criteria not met is considered ***experimental or investigational*** based upon:

1. Lack of final approval from the Food and Drug Administration, and
2. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes, and
3. Insufficient evidence to support improvement of the net health outcome, and
4. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives, and
5. Insufficient evidence to support improvement outside the investigational setting.

These indications include, *but are not limited to:*

- Treatment with dosing or frequency outside the FDA-approved dosing and frequency

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 women 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.

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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-pubertalΔ	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-pubertalΔ	Pre-pubertal to pubertal	Pubertal and increasing
Basal (unstimulated) serum LH concentration¶	Pre-pubertalΔ◊	Pubertal◊	Suppressed or pre-pubertal◊
GnRH (or GnRHa) stimulation test¶	LH peak in the pre-pubertal rangeΔ§ 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.

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§ 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.

Gonadotropin releasing hormone analog (GnRH analog):

Supprelin LA (histrelin acetate) subcutaneous implant
Lupron Depot-Ped (leuprolide acetate) intramuscular injection
Synarel (nafarelin acetate) intranasal
Triptodur (triptorelin) intramuscular injection

Resources:

Synarel (nafarelin acetate) product information accessed 07-24-19 at DailyMed

UpToDate: Definition, etiology, and evaluation of precocious puberty. Current through June 2019

UpToDate: Treatment of precocious puberty. Current through June 2019

UpToDate: Endometriosis: Pathogenesis, clinical features, and diagnosis. Current through June 2019

UpToDate: Endometriosis: Treatment of pelvic pain. Current through June 2019