BlueCross BlueShield of Arizona
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PHARMACY COVERAGE GUIDELINES	**ORIGINAL EFFECTIVE DATE: 5/17/18**
SECTION: DRUGS	**LAST REVIEW DATE: 5/16/19**
	LAST CRITERIA REVISION DATE: 5/16/19
	ARCHIVE DATE:

LUPRON DEPOPT® (leuprolide acetate) intramuscular suspension
LUPRON DEPOT PED® (leuprolide acetate) intramuscular suspension

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.**

LUPRON DEPOPT® (leuprolide acetate) intramuscular suspension
LUPRON DEPOT PED® (leuprolide acetate) intramuscular suspension

Criteria:

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

  1. Prescriber is a physician specializing in pediatric Endocrinology or is in consultation with a Pediatric Endocrinologist

  2. Individual is 2 years of age or older

  3. A confirmed diagnosis of **central precocious puberty** by **ONE** of the following:
     - Bone age that has advanced at least 1 year beyond chronological age
     - GnRH stimulation test showing LH response is > 5 mIU/mL
     - Basal, unstimulated LH level is > 0.3 mIU/L (in the pubertal range)
     - Peak stimulated LH/FSH ratio is > 0.66

  4. Has early onset of secondary sexual characteristics
     - Female at < 8 years of age
     - Male < 9 years of age

  5. There are **NO** contraindications
     - Contraindications include:
       - Hypersensitivity to GnRH, GnRH agonist or any excipients
       - Pregnancy

  6. Will **not** use partial syringes, combination of syringes, or other Lupron Depot forms to achieve a dose that is not an FDA-approve dose for the condition

  Initial approval duration:
  - Lupron Depot-PED 7.5 mg, 11.25 mg, or 15 mg for 1-month dosing: **12 months (total 12 injections)**
  - Lupron Depot-PED 11.25 mg or 30 mg for 3-month dosing: **12 months (total 4 injections)**

- **Criteria for continuation of coverage (renewal request): Lupron Depot-PED** (leuprolide 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 pediatric Endocrinology or is in consultation with a Pediatric Endocrinologist

  2. Individual's condition has responded while on therapy
     - Response is defined as:
       - LH level have been suppressed to pre-pubertal levels
       - Progression of secondary sex characteristics have 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. Will **not** use partial syringes, combination of syringes, or other Lupron Depot forms to achieve a dose that is not an FDA-approve dose for the condition

5. Individual has not developed any contraindications that may exclude continued use
   - Contraindications as listed in the criteria for initial therapy section

Renewal approval duration:
- Lupron Depot-PED 7.5 mg, 11.25 mg, or 15 mg for 1-month dosing: 12 months (total 12 injections) **AND** evaluations for treatment discontinuation to start before 11 years in girls and 12 years in boys, treatment will be discontinued with fusion of the epiphyses or achievement of appropriate chronologic pubertal age

- Lupron Depot-PED 11.25 mg or 30 mg for 3-month dosing: 12 months (total 4 injections) **AND** evaluations for treatment discontinuation to start before 11 years in girls and 12 years in boys, treatment will be discontinued with fusion of the epiphyses or achievement of appropriate chronologic pubertal age

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➢ **Criteria for initial therapy: Lupron Depot** (leuprolide acetate) is considered ***medically necessary*** and will be approved with the following criteria:

1. Prescriber is a physician specializing in Gynecology or is in consultation with a Gynecologist

2. Individual is a woman 18 years of age or older

3. **For a confirmed diagnosis of endometriosis** or prior to **surgical endometrial ablation**

4. **For endometriosis**, individual failure, contraindication or intolerance to **ALL** the following 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. **For a confirmed diagnosis of uterine leiomyomata (fibroids)** use is before fibroid surgery to manage anemia caused by uterine leiomyomata (fibroids)

6. **For uterine leiomyomata (fibroids)**, individual has failure, contraindication or intolerance to 1-month trial of iron supplementation **and** the iron supplementation will be continued

7. There are **NO** contraindications

- Contraindications include:
  - Hypersensitivity to GnRH, GnRH agonist or any excipients
  - Pregnancy
  - Undiagnosed abnormal vaginal bleeding

8. Will **not** be used in a woman who is breast feeding an infant or child

9. Will **not** use partial syringes, combination of syringes, or other Lupron Depot forms to achieve a dose that is not an FDA-approve dose for the condition

Initial approval duration:
For endometriosis is 6 months with **ONE** of the following:
- Lupron Depot 3.75 mg for 1-month dosing: total 6 injections
- Lupron Depot 11.25 mg for 3-month dosing: total 2 injections

For uterine leiomyomata (fibroids) is 3 months with **ONE** of the following
- Lupron Depot 3.75 mg for 1-month dosing: total 3 injections
- Lupron Depot 11.25 mg for 3-month dosing: total 1 injection

➢ **Criteria for continuation of coverage (renewal request): Lupron Depot** (leuprolide acetate) is considered ***medically necessary*** and will be approved with the following criteria:

1. Individual continues to be seen by a physician specializing in Gynecology or is in consultation with a Gynecologist

2. Individual's endometriosis has worsened while on therapy or symptoms have recurred
   - For endometriosis, worsening or recurrence is defined as:
     - Recurrence of symptoms of endometriosis after initial course of therapy with return of pelvic pain, dysmenorrhea, dyspareunia, pelvic tenderness, or pelvic induration

3. **For endometriosis**, only one time retreatment course of 6 months will be approved and it must be used with norethindrone acetate 5 mg daily add-back therapy

4. Individual has been adherent with the medication

5. Will **not** use partial syringes, combination of syringes, or other Lupron Depot forms to achieve a dose that is not an FDA-approve dose for the condition

6. Individual has not developed any contraindications that may exclude continued use
   - Contraindications as listed in the criteria for initial therapy section

Renewal approval duration:
For endometriosis is 6 months with **ONE** of the following:
- Lupron Depot 3.75 mg for 1-month dosing: total of 6 injections for 1 retreatment course only
- Lupron Depot 11.25 mg for 3-month dosing: total of 2 injections for 1 retreatment course only

LUPRON DEPOPT® (leuprolide acetate) intramuscular suspension
LUPRON DEPOT PED® (leuprolide acetate) intramuscular suspension

Description:

Leuprolide is a synthetic analog of endogenous gonadotropin-releasing hormone (GnRH), or gonadorelin. GnRH regulates the anterior pituitary gland synthesis and secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH). In response to GnRH, FSH and LH synthesis initially increases, causing a short-term increase in circulating levels of sex hormones. With continuous use for one to three weeks, the pituitary gland down-regulates and desensitizes GnRH receptors, reducing FSH and LH secretion.

The end result of continuous GnRH use is markedly reduced testosterone levels in males and estrogen levels in females. In men, testosterone levels increase briefly during the first week after the initial dose, then falls to castration levels after two to four weeks of therapy. Correspondingly, in women, estradiol levels transiently increase and then falls to postmenopausal levels by three weeks after initiating therapy. The physiologic functions and tissues that are dependent on gonadal steroids for their maintenance become inactive. Normal pituitary and gonadal function usually returns within three months of discontinuing GnRH agonist therapy.

Precocious Puberty:
Precocious puberty is the onset of pubertal development at an age that is earlier than the average age. It is traditionally defined as onset of secondary sexual characteristics before the age of 8 years in girls and 9 years in boys. Precocious puberty is classified on the underlying pathologic process.

Central precocious puberty (CPP, also known as gonadotropin-dependent precocious puberty or true precocious puberty) is due to early maturation of the hypothalamic-pituitary-gonadal axis. Children with CPP have accelerated linear growth for age, advanced bone age, and pubertal levels of LH and FSH. CPP can be treated with a GnRH agonist, to downregulate the pituitary response to endogenous GnRH, to produce a pre-pubertal hormonal state, and to stop the progression of secondary sexual development, accelerated growth, and bone age advancement

Peripheral precocity (also known as peripheral precocious puberty or gonadotropin-independent precocious puberty) is caused by excess secretion of sex hormones (estrogens or androgens) from the gonads or adrenal glands, exogenous sources of sex steroids, or ectopic production of gonadotropin from a germ cell tumor. FSH and LH levels are suppressed (in the pre-pubertal range) and do not increase substantially with GnRH stimulation. The approach to treatment for peripheral precocity depends on the cause. GnRH agonist therapy is ineffective

Benign or non-progressive pubertal variants include isolated breast development in girls (premature thelarche), or isolated androgen-mediated sexual characteristics (such as pubic and/or axillary hair, acne, and apocrine odor) in boys or girls that result from early activation of the hypothalamic pituitary adrenal axis as confirmed by mildly elevated levels of dehydroepiandrosterone sulfate (DHEAS) for age (premature adrenarche). Early development of secondary sexual characteristics does not signal underlying pathology and is not followed by progressive development. Serum LH and estradiol concentrations are typically in the pre-pubertal range.

Basal LH, FSH, and either estradiol and/or testosterone concentrations are used to differentiate between CPP and peripheral precocity.

Basal serum LH can identify activation of the hypothalamic-pituitary-gonadal axis. Measurement of basal LH concentration (ideally in the morning), using sensitive assays with a lower limit of detection of ≤ 0.1 mIU/L. LH

concentrations in the pre-pubertal range (< 0.2 mIU/L) are consistent with either peripheral precocity or a benign pubertal variant. LH concentrations > 0.2-0.3 mIU/L (depending on the assay used) can identify progressive CPP with high sensitivity and specificity. Serum LH after GnRH agonist stimulation value of 3.3-5 mIU/mL defines the upper limit of normal for stimulated LH values in pre-pubertal children, concentrations above this normal range suggest CPP. Basal FSH concentrations are often higher in children with CPP compared with benign pubertal variants, but there is substantial overlap.

High serum estradiol concentrations are associated with suppression of gonadotropins and are generally indicative of peripheral precocity. Elevated serum testosterone concentrations may be due to testicular testosterone production in boys, or of adrenal testosterone production or exogenous exposure in both sexes. Very high concentrations, with associated suppression of gonadotropins, are generally indicative of peripheral precocity

Endometriosis:
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 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.

Uterine leiomyomas (fibroids):
Uterine leiomyomas (also known as fibroids or myomas) are the most common benign pelvic tumor in women. The tumors develop from the smooth muscle cells of the myometrium. They develop in reproductive aged women and usually present with symptoms of abnormal uterine bleeding and/or pelvic pain/pressure. Uterine fibroids may affect fertility and lead to adverse pregnancy outcomes. In most cases, they are asymptomatic or mildly symptomatic and can usually be followed without intervention.

Anecdotal data suggest medical therapy provides adequate symptom relief in women who have bleeding as the dominant or only symptom. GnRH agonists are the most effective medical therapy for uterine fibroids but long term use is complicated by bone loss. GnRH decrease uterine and fibroid volume, allowing for relief of abdominal bloating, pelvic pain and pressure. Excessive vaginal bleeding (menorrhagia and menometrorrhagia) is decreased resulting in improved hematologic parameters. GnRH agonists are primarily used as preoperative therapy with iron supplementation to reduce the volume of blood loss and improve anemia caused by uterine fibroids. Bone loss may be minimized by giving so-called “add-back” therapy with norethindrone.

Definitions:

Clinical characteristics of forms of early pubertal development

	Central precocious puberty (CPP)	Peripheral precocity	Non-progressive precocious puberty

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Physical examination: Advancement through pubertal stages (Tanner stage)	Progression to next pubertal stage in 3-6 months	Progression	No progression in Tanner staging during 3-6 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 Δ
Serum testosterone concentration (boys, or girls with virilization) ¶	Pre-pubertal to pubertal	Pubertal and increasing	Pre-pubertal Δ
Basal (unstimulated) serum LH concentration ¶	Pubertal ◊	Suppressed or pre-pubertal ◊	Pre-pubertal Δ◊
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 Δ§ 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/L.

§ 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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Off Label Use of Cancer Medications: A.R.S. §§ 20-826(R) & (S). Subscription contracts; definitions.

Off Label Use of Cancer Medications: A.R.S. §§ 20-1057(V) & (W). Evidence of coverage by health care service organizations; renewability; definitions.

Lupron Depot-Ped product information accessed 05-09-18 at DailyMed: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=e99f47d2-da10-3127-ecb3-e5d942ae6e81

Lupron Depot product information accessed 05-09-18 at DailyMed: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=00c486b0-bd7b-4898-834d-8c656e5e73cb

UpToDate: Definition, etiology, and evaluation of precocious puberty. Current through Apr 2018. https://www-uptodate-com.mwu.idm.oclc.org/contents/definition-etiology-and-evaluation-of-precocious-puberty?search=precocious%20puberty&source=search_result&selectedTitle=1~135&usage_type=default&display_rank=1

UpToDate: Treatment of precocious puberty. Current through Apr 2018. https://www-uptodate-com.mwu.idm.oclc.org/contents/treatment-of-precocious-puberty?search=precocious%20puberty&source=search_result&selectedTitle=2~135&usage_type=default&display_rank=2

UpToDate: Endometriosis: Pathogenesis, clinical features, and diagnosis. Current through Apr 2018. https://www-uptodate-com.mwu.idm.oclc.org/contents/endometriosis-pathogenesis-clinical-features-and-diagnosis?search=endometriosis&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1

UpToDate: Endometriosis: Treatment of pelvic pain. Current through Apr 2018. https://www-uptodate-com.mwu.idm.oclc.org/contents/endometriosis-treatment-of-pelvic-pain?search=endometriosis&source=search_result&selectedTitle=3~150&usage_type=default&display_rank=3

UpToDate: Uterine leiomyomas (fibroids): Epidemiology, clinical features, diagnosis, and natural history. Current through Apr 2018. https://www-uptodate-com.mwu.idm.oclc.org/contents/uterine-leiomyomas-fibroids-epidemiology-clinical-features-diagnosis-and-natural-history?search=Uterine%20Leiomyomata&source=search_result&selectedTitle=2~150&usage_type=default&display_rank=2

UpToDate: Overview of treatment of uterine leiomyomas (fibroids). Current through Apr 2018. https://www-uptodate-com.mwu.idm.oclc.org/contents/overview-of-treatment-of-uterine-leiomyomas-fibroids?search=Uterine%20Leiomyomata&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1

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Fax completed prior authorization request form to 602-864-3126 or email to pharmacyprecert@azblue.com.
Call 866-325-1794 to check the status of a request.
All requested data must be provided. **Incomplete forms or forms without the chart notes will be returned.**
Pharmacy Coverage Guidelines are available at www.azblue.com/pharmacy.

Pharmacy Prior Authorization Request Form

Do not copy for future use. Forms are updated frequently.
REQUIRED: Office notes, labs, and medical testing relevant to the request that show medical justification are required.

Member Information

Member Name (first & last):	Date of Birth:	Gender:	BCBSAZ ID#:
Address:	City:	State:	Zip Code:

Prescribing Provider Information

Provider Name (first & last):	Specialty:	NPI#:	DEA#:
Office Address:	City:	State:	Zip Code:
Office Contact:	Office Phone:	Office Fax:	

Dispensing Pharmacy Information

Pharmacy Name:	Pharmacy Phone:	Pharmacy Fax:

Requested Medication Information

Medication Name:	Strength:		Dosage Form:
Directions for Use:	Quantity:	Refills:	Duration of Therapy/Use:

☐ Check if requesting **brand** only ☐ Check if requesting **generic**

☐ Check if requesting continuation of therapy (prior authorization approved by BCBSAZ expired)

Turn-Around Time For Review

☐ Standard ☐ Urgent. Sign here: _____ ☐ Exigent (requires prescriber to include a written statement)

Clinical Information

1. **What is the diagnosis? Please specify below.**

   ICD-10 Code: _____ **Diagnosis Description:** _____

2. ☐ Yes ☐ No **Was this medication started on a recent hospital discharge or emergency room visit?**

3. ☐ Yes ☐ No **There is absence of ALL contraindications.**

4. **What medication(s) has the individual tried and failed for this diagnosis? Please specify below.**
Important note: Samples provided by the provider are not accepted as continuation of therapy or as an adequate trial and failure.

Medication Name, Strength, Frequency	Dates started and stopped or Approximate Duration	Describe response, reason for failure, or allergy

5. **Are there any supporting labs or test results? Please specify below.**

Date	Test	Value

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Pharmacy Prior Authorization Request Form

6. Is there any additional information the prescribing provider feels is important to this review? Please specify below.
For example, explain the negative impact on medical condition, safety issue, reason formulary agent is not suitable to a specific medical condition, expected adverse clinical outcome from use of formulary agent, or reason different dosage form or dose is needed.

Signature affirms that information given on this form is true and accurate and reflects office notes

Prescribing Provider's Signature: Date:

Please note: Some medications may require completion of a drug-specific request form.

Incomplete forms or forms without the chart notes will be returned.

Office notes, labs, and medical testing relevant to the request that show medical justification are required.