Gonadotropin-releasing hormone (GnRH)

EOCCO POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: EOCCO092

Description

The listed treatments are synthetic gonadotropin-releasing hormone (GnRHs) analogs that exhibit a potent reversible inhibition of gonadotropin secretion through suppression of testicular and ovarian steroidogenesis.

Length of Authorization and Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit	Duration of approval
nafarelin (Synarel)	Endometriosis	2 mg/mL nasal spray	16 mL/30 days	6 months
	Central Precocious Puberty		40 mL/30 days	6 months
leuprolide acetate (Lupron)	Central Precocious Puberty	1 mg/0.2mL kit	1 kit/14 days	6 months
Leuprolide acetate (Lupron Depot)	Endometriosis, Cancer, Endometrial Thickness, Uterine leiomyoma, Gender Dysphoria	3.75 mg/syringe kit	1 syringe kit/30 days	6 months for all indications EXCEPT - 3 months for uterine leiomyoma -2 months for Endometrial Thickness
	Advanced Prostate Cancer, Central Precocious Puberty	7.5 mg/syringe kit	1 syringe kit/30 days	6 months
	Advanced Prostate Cancer, Advanced Breast Endometrial Thickness, Uterine leiomyoma, Central Precocious Puberty, Gender Dysphoria	11.25 mg/syringe kit	1 syringe kit/90 days	6 months for all indications EXCEPT - 3 months for Uterine Leiomyoma -2 months for Endometrial Thickness
	Advanced Prostate Cancer	22.5 mg/syringe kit	1 syringe kit/90 days	6 months

	Advanced Prostate, Cancer Central Precocious Puberty	30 mg/syringe kit	1 syringe kit/120 days	6 months
	Advanced Prostate Cancer	45 mg/syringe kit	1 syringe kit/180 days	6 months
Leuprolide acetate (Lupron Depot-Ped)	Central Precocious Puberty	7.5 mg/syringe kit	1 syringe kit/30 days	6 months
	Central Precocious Puberty	11.25 mg/syringe kit	1 syringe kit/30 days OR 1 syringe kit/90 days	6 months
	Central Precocious Puberty	15 mg/syringe kit	1 syringe kit/30 days	6 months
	Central Precocious Puberty	30 mg/syringe kit	1 syringe kit/90 days	6 months
Leuprolide acetate (Eligard)	Advanced Prostate Cancer	7.5 mg/syringe kit	1 syringe kit/30 days	6 months
	Advanced Prostate Cancer	22.5 mg/syringe kit	1 syringe kit/90 days	6 months
	Advanced Prostate Cancer	30 mg/syringe kit	1 syringe kit/120 days	6 months
	Advanced Prostate Cancer	45 mg/syringe kit	1 syringe kit/180 days	6 months
Leuprolide-norethindrone (Lupaneta)	Endometriosis	3.75-5 mg/syringe	1 syringe kit/30 days	6 months
	Endometriosis	11.25-5 mg/syringe	1 syringe kit/90 days	6 months
Renewal				
nafarelin (Synarel)	Central Precocious Puberty	2 mg/mL nasal spray	40 mL/30 days	6 months
leuprolide acetate	Central Precocious Puberty	1 mg/0.2mL kit (each kit contains 2.8 mL of leuprolide acetate and 14 disposable syringes)	1 kit/14 days	6 months
	Endometriosis,	3.75 mg/syringe kit	1 syringe kit/30 days	- 12 months for Advanced Breast

Leuprolide acetate (Lupron Depot)	Cancer, Endometrial Thickness, Uterine leiomyoma, Gender Dysphoria			Cancer and Gender Dysphoria EXCEPT - 6 months for Endometriosis (**MAX #1 renewal allow**) - NO RENEWAL for Uterine leiomyoma and Endometrial Thickness
	Advanced Prostate Cancer, Central Precocious Puberty	7.5 mg/syringe kit	1 syringe kit/30 days	12 months
	Advanced Prostate Cancer, Advanced Breast Endometrial Thickness, Uterine leiomyoma, Central Precocious Puberty, Gender Dysphoria	11.25 mg/syringe kit	1 syringe kit/90 days	- 12 months for Advanced Breast Cancer, Central Precocious Puberty, and Gender Dysphoria EXCEPT - 6 months for Endometriosis (**MAX #1 renewal**) - NO RENEWAL for Uterine leiomyoma and Endometrial Thickness
	Advanced Prostate Cancer	22.5 mg/syringe kit	1 syringe kit/90 days	12 months
	Advanced Prostate, Cancer Central Precocious Puberty	30 mg/syringe kit	1 syringe kit/120 days	12 months
	Advanced Prostate Cancer	45 mg/syringe kit	1 syringe kit/180 days	12 months
Leuprolide acetate (Lupron Depot-Ped)	Central Precocious Puberty	7.5 mg/syringe kit	1 syringe kit/30 days	6 months
	Central Precocious Puberty	11.25 mg/syringe kit	1 syringe kit/30 days OR 1 syringe kit/90 days	6 months

	Central Precocious Puberty	15 mg/syringe kit	1 syringe kit/30 days	6 months
	Central Precocious Puberty	30 mg/syringe kit	1 syringe kit/90 days	6 months
Leuprolide acetate (Eligard)	Advanced Prostate Cancer	7.5 mg/syringe kit	1 syringe kit/30 days	12 months
	Advanced Prostate Cancer	22.5 mg/syringe kit	1 syringe kit/90 days	12 months
	Advanced Prostate Cancer	30 mg/syringe kit	1 syringe kit/120 days	12 months
	Advanced Prostate Cancer	45 mg/syringe kit	1 syringe kit/180 days	12 months
Leuprolide-norethindrone (Lupaneta)	Endometriosis	3.75-5 mg/syringe	1 syringe kit/30 days	6 months
	Endometriosis	11.25-5 mg/syringe	1 syringe kit/90 days	6 months (**MAX #1 renewal allow**)

Initial Evaluation

I. **Synthetic gonadotropin-releasing hormones (GnRHs)** may be considered medically necessary when the following criteria below are met:
   A. Medication is prescribed by, or in consultation with, a gynecologist, endocrinologist, or oncologist; **AND**
   B. A diagnosis of one of the following:
      1. **Endometriosis**; **AND**
         i. Member is 18 years of age or older; **AND**
         ii. Member requires pain relief and reduction of endometriotic lesions; **AND**
         iii. Treatment with an oral contraceptive has been ineffective, contraindicated, or was not tolerated; **AND**
         iv. The request is for Lupron Depot (3.75 mg, 11.25 mg), Synarel, OR Lupaneta; **OR**
      2. **Uterine leiomyoma (fibroids); AND**
         i. Member is 18 years of age or older; **AND**
         ii. The diagnosis of uterine leiomyoma has been confirmed by ultrasound or hysteroscopy; **AND**

iii. Member requires therapy for anemia associated with preoperative management (e.g., hysterectomy, uterine artery embolization, myomectomy, hysteroscopy, etc.) of uterine leiomyoma; **AND**
iv. Member will be on iron therapy concomitantly; **AND**
v. The request is for Lupron Depot (3.75 mg, 11.25 mg); **OR**

3. **Central Precocious Puberty (CPP)**; **AND**
   i. Documented onset of secondary sexual characteristics (e.g., genital maturation, pubic hair growth, and/or menses in female); **AND**
      a. Symptom onset before 8 years of age for FEMALE, 9 years of age for MALE; **AND**
   ii. FEMALE member is less than 11 years of age, MALE member is less than 12 years of age; **AND**
   iii. Member has clinical diagnosis of CPP confirmed by a pubertal response to a GnRH stimulation test or a pubertal basal level of luteinizing hormone (LH); **AND**
   iv. Provider attestation that the member has bone age advanced at least one year beyond chronological age; **OR**
4. **Advanced prostate cancer; AND**
   i. The request is for Lupron-Depot, or Eligard; **OR**
5. **Advanced breast cancer in premenopausal women; AND**
   i. The request is for Lupron-Depot 11.25 mg; **OR**
6. **Reduction of endometrial thickness prior to endometrial ablation; AND**
   i. The request is for Lupron Depot (3.75 mg, 11.25 mg), **OR**
7. **Gender Dysphoria**

II. Gonadotropin-releasing hormone (GnRH) analogs are considered <u>not medically necessary</u> when criteria above are not met and/or when used for:
   A. In vitro fertilization
   B. Premenstrual syndrome

Renewal Evaluation

I. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
II. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
III. A diagnosis of one of the following:

A. **Endometriosis**; **AND**
    1. Member is responding positively to therapy (e.g., pain relief and reduction of endometriotic lesions); **AND**
    2. Provider attests that the member's bone mineral density been assessed and has been deemed appropriate to continue GnRH therapy; **AND**
    3. The total duration of treatment with a GnRH analog has not exceed a total of 12 months; **AND**
    4. The request is for leuprolide acetate (Lupron Depot) in combination with norethindrone, or Lupaneta; **OR**

B. **Central Precocious Puberty (CPP); AND**
    1. Member is responding positively to therapy (e.g., lack of progression or stabilization of secondary sexual characteristics, decrease in growth rate, decrease in bone age to chronological age); **AND**
    2. Female member is less than 11 years of age; **OR**
        i. Male member is less than 12 years of age; **OR**

C. **Advanced prostate cancer; AND**
    1. Provider attest that member has exhibited improvement in or stability of disease symptoms; **OR**

D. **Advanced breast cancer in premonopausal women**; **AND**
    1. Provider attests that member has exhibited improvement in or stability of disease symptoms; **OR**

E. **Gender Dysphoria; AND**
    1. A renewal approval of 12 months is allowed

Supporting Evidence

I. In clinical trials, leuprolide acetate (Lupron Depot), when compared to danazol 800 mg per day, significantly reduced symptoms of endometriosis (e.g., pelvic pain, dysmenorrhea, dyspareunia, pelvic tenderness, and induration) and induced laparoscopic improvement; however, due to decrease in bone mineral density, the total duration of therapy with leuprolide acetate for depot suspension should not exceed 12 months. If retreatment is needed after the initial six months, an addition of hormone therapy with norethindrone acetate is recommended. Clinical studies demonstrated that concurrent norethindrone acetate and calcium supplementation daily with leuprolide acetate (Lupron Depot) have shown to significantly reduce the loss of bone mineral density that occurs with GnRH treatment, without compromising the efficacy of relieving symptoms of endometriosis.

II. In a study, women with stage III-IV endometriosis were randomized to receive either laparoscopic surgery first followed by 6 months of nafarelin (Synarel) 200 mcg twice daily

followed by a second-look laparoscopy (n=28) or no initial surgical procedure with nafarelin (Synarel) 200 mcg twice daily followed by a second-look laparoscopy with appropriate surgery (n=25). There was no difference in efficacy. Additionally, per label, safety and efficacy has not been established beyond 6 months.

III. In a randomized study, leuprolide acetate (Lupron depot) plus iron demonstrated clinical response (HCT of 36% or greater and Hb of 12 g/dL or greater) compared with iron alone at week 4 (40% vs 17%), week 8 (71% vs 39%), and week 12 (75% vs 49%). In the leuprolide acetate (Lupron depot) arm: excessive vaginal bleeding decreased in 80% of patients at 3 months; uterine and myoma volume decreases of 25% or greater occurred in 60% and 54% of patients, respectively; and mean fibroid diameter decreased from 6.3 cm to 5.6 cm. The use of leuprolide acetate (Lupron depot) for uterine leiyomyoma should not exceed an FDA max of 3 months therapy.

IV. Precocious puberty is defined as the onset of secondary sexual development before the age of eight years in females and nine years in males. Central precocious puberty (CPP), also known as gonadotropin-dependent precocious puberty or true precocious puberty, is caused by early maturation of the hypothalamic-pituitary-gonadal axis. CPP is characterized by sequential maturation of breasts and pubic hair in females, and maturation of the testes, penis, and pubic hair in males. Average age of puberty onset in females is 11 and 12 in males. The decision to discontinue treatment factors in the patient's bone age and height balanced with a desire to have pubertal progression with their peers.

V. GnRH stimulation tests have been the gold standard for confirmation of CPP diagnosis. However, new studies support the use of pubertal basal LH levels in diagnosis. The American Family Physician and Gonadotropin-Releasing Hormone Analogs in Children guidelines support use of basal LH levels to confirm the diagnosis of CPP after onset of symptoms. One study attempted to diagnose young girls with CPP based off pubertal basal LH levels. In over 90% of instances, basal LH levels was able to differentiate prepubertal patients from those with CPP using third-generation assays. The basal LH level threshold to diagnose CPP has not been definitively set, but a typical threshold of 0.3 U/L is used.

VI. Patients with CPP typically demonstrate early bone maturation and accelerated growth. Height velocity is considered accelerated if it exceeds 6 cm per year. As bones mature, CPP could lead to early closure of epiphysis, eventually resulting in a decreased adult height. The decision to treat is based on pubertal progression (sexual maturation), height velocity, and rate of bone age advancement. The goal of GnRH treatment is preservation of height potential and growth to normal adult height and to address the psychosocial impact of early entry into puberty.

VII. MRI imaging is completed to rule out intracranial pathology such as hamartomas (tumor-like growth), CNS tumors, arachnoid cysts, and other lesions. Imaging can be used to identify the cause of CPP to determine if other treatments are needed. The American Academy of Pediatrics, American Family Physician, and European Society for Paediatric Endocrinology have released consensus statements that brain imaging should be performed in all boys and girls who are 6

years or younger. However, recommendations were also given to discuss the pros and cons of MRI scanning with the parents to assist in making an informed decision. Intracranial pathology occurs in up to 38% of boys and up to 6.3% in girls with CPP. A meta-analysis of CPP MRI findings found that only 1.6% of girls had CNS abnormalities required an intervention. Investigators suggest there is a lower incidence of tumors in girls older than 6 years and imaging above 6 years old will likely lead to incidental positive findings not related to CPP. Ultimately, treatment for CPP with a GnRH agent will occur independent of imaging or the presence of a tumor. Therefore MRI/imaging is not required for coverage of GnRH therapy.

VIII. In an open-label study, nafarelin acetate (Synarel) for the treatment of central precocious puberty in children, demonstrated a growth rate reduction from 11.5 cm/year to 5.8 cm/year after 6 months of therapy.

IX. In open-label studies, monthly or once every 3 months of leuprolide acetate administration in children with central precocious puberty naïve to GnRH therapy demonstrated clinical and physical signs of puberty suppression. These clinical/physical signs include stopped or regressed secondary sexual characteristics, significantly improved mean height standard deviation for bone age, and suppressed luteinizing hormone and follicle stimulating hormone.

X. In an open-label, non-comparative, multicenter clinical trial, leuprolide acetate (Lupron depot) demonstrated a reduction and maintenance in serum testosterone level to castrate range (≤50 ng/dL). In the study, serum testosterone suppressed to the castrate range within 30 days of the initial depot injection in 94% (51/54) of patients for whom testosterone suppression was achieved (2 patients withdrew prior to onset of suppression) and within 66 days in all 54 patients. In a separate open-label study (AGL9904), leuprolide acetate (Eligard) 7.5 mg, 22.5 mg, 30 mg and 45 mg demonstrated castration suppression and maintenance.

Investigational or Not Medically Necessary Uses

I. In vitro fertilization
   A. This is an excluded indication per the plan benefit.

II. Premenstrual syndrome
   A. There is currently insufficient evidence regarding safety and/or efficacy with leuprolide acetate in this setting.

References

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9. Eugster EA. Treatment of Central Precocious Puberty. J Endocr Soc. 2019;3(5):965-972. Published 2019 Mar 28.
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13. Kaplowitz PB. Do 6-8 year old girls with central precocious puberty need routine brain imaging?. *Int J Pediatr Endocrinol*. 2016;2016:9.

Policy Implementation/Update:

Action and Summary of Changes	Date
Addition of CPP indication to the Lupron Depot injection products with corresponding strengths of Lupron Depot Ped. Updated criteria for central precocious puberty. Changed wording in the age criteria to specify "onset of symptoms" before specified age. Included basal serum LH levels in addition to GnRH stimulation test required for confirmation of diagnosis. Removed lines "beta human chorionic gonadotropin (HCG) level and adrenal and pelvic ultrasound or testicular ultrasound" as tests are specifically performed in the peripheral setting. Added evidence to support changes. Removed criteria requiring imaging prior to treatment with GnRH analogues. Updated supporting evidence with disease state background and guideline recommendations for diagnosis and treatment.	05/2022
Criteria transitioned into policy format. With the following updates made: added supporting evidence, added indications that are medically not necessary, added renewal criteria, limit renewal for endometriosis to a total duration of 12 months, limit initial approval for uterine leiomyoma to 3 months per FDA max, require bone mineral density evaluation upon renewal for the treatment of endometriosis, require concomitant iron therapy for uterine leiomyoma indication, updated Lupron-depot strength for advanced breast cancer, and no renewal for uterine leiyomyoma and endometrial thickness.	10/2019
Previous reviews	08/2017
Policy created	10/2014