Gonadotropin-releasing hormone (GnRH)

EOCCO POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: EOCCO092

Description

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

Length of Authorization and Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit	Duration of approval
naferlin (Synarel)	2 mg/mL nasal spray	Endometriosis	16 mL/30 days	6 months
		Central Precocious Puberty	40 mL/30 days	6 months
leuprolide acetate (Lupron)	1 mg/0.2mL kit	Central Precocious Puberty	1 kit/14 days	6 months
Leuprolide acetate (Lupron Depot)	3.75 mg/syringe kit	Endometriosis, Cancer, Endometrial Thickness, Uterine leiomyoma, Gender Dysphoria	1 syringe kit/30 days	6 months for all indications EXCEPT - 3 months for uterine leiomyoma -2 months for Endometrial Thickness
	7.5 mg/syringe kit	Advanced Prostate Cancer	1 syringe kit/30 days	6 months
	11.25 mg/syringe kit	Advanced Prostate Cancer, Advanced Breast Endometrial Thickness, Uterine leiomyoma, Gender Dysphoria	1 syringe kit/90 days	6 months for all indications EXCEPT - 3 months for Uterine Leiomyoma -2 months for Endometrial Thickness
	22.5 mg/syringe kit	Advanced Prostate Cancer	1 syringe kit/90 days	6 months
	30 mg/syringe kit	Advanced Prostate Cancer	1 syringe kit/120 days	6 months
	45 mg/syringe kit	Advanced Prostate Cancer	1 syringe kit/180 days	6 months

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

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

	45 mg/syringe kit	Advanced Prostate Cancer	1 syringe kit/180 days	12 months
Leuprolide-norethindrone (Lupaneta)	3.75-5 mg/syringe	Endometriosis	1 syringe kit/30 days	6 months
	11.25-5 mg/syringe	Endometriosis	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 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. Member has clinical diagnosis of CPP and documented onset of secondary sexual characteristics (any physical characteristic developing at puberty) made when:
            a. The FEMALE member was < 8 years of age, and is currently less than 11 years of age; **OR**
            b. The MALE member was < 9 years of age, and is currently less than 12 years of age; **AND**

ii. Member's diagnosis of CPP has been confirmed by a pubertal response to a GnRH stimulation test; **AND**
iii. Member has bone age advanced at least one year beyond chronological age; **AND**
iv. Tumor has been ruled out by ALL of the following:
a. Beta human chorionic gonadotropin (HCG) level
b. Adrenal and pelvic ultrasound or testicular ultrasound
c. Computerized tomography (CT) of the head; **AND**
v. The request is for leuprolide acetate 1 mg/0.2mL, Lupron Depot-Ped, or Synarel; **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 has <u>not</u> been established on therapy by the use of free samples, manufacturer coupons, or otherwise; **AND**
II. Member has received a previous prior authorization approval for this agent; **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**
3. 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 inducing 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 there, 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 a FDA max of 3 months therapy.

IV. 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.

V. 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.

VI. 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

1. Synarel [Prescribing Information]. New York, NY: G.D. Searle, LLC. May 2017.
2. Lupron Depot [Prescribing Information]. North Chicago, IL: Abbvie, Inc. June 2014, April 2018.
3. Lupron Depot-ped [Prescribing Information]. North Chicago, IL: Abbvie, Inc. August 2011.
4. Eligard [Prescribing Information]. Fort Collins: CO. Sanofi-Aventis U.S., LLC. 2010.

Policy Implementation/Update:

Date Created	October 2014
Date Effective	October 2014
Last Updated	October 2019
Last Reviewed	08/2017, 10/2019

Action and Summary of Changes	Date
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