

UnitedHealthcare Pharmacy
Clinical Pharmacy Programs

Program Number	2024 P 1059-12
Program	Prior Authorization/Notification
Medication	Leuprolide acetate (bulk powder, 1 mg/0.2 mL injection)* Note: These criteria do not apply to the intramuscular (IM) formulations (Lupron® Depot, Lupron® Depot-Ped, and leuprolide acetate depot) or Eligard® which are not self-administered and are therefore not covered under the pharmacy benefit. These products are covered under the medical benefit and are subject to drug policy criteria.
P&T Approval Date	7/2012, 5/2013, 7/2014, 7/2015, 6/2016, 6/2017, 7/2018, 9/2019, 9/2020, 10/2021, 10/2022, 6/2023, 6/2024
Effective Date	9/1/2024

1. Background:

Leuprolide acetate is a synthetic nonapeptide analog of naturally occurring gonadotropin releasing hormone (GnRH) or luteinizing hormone-releasing hormone (LH-RH) which acts as a potent inhibitor of gonadotropin secretion. Leuprolide acetate is indicated in the palliative treatment of advanced prostatic cancer..

In addition to prostate cancer, the National Cancer Comprehensive Network (NCCN) recommends leuprolide acetate for the treatment of salivary gland tumors and uterine sarcoma.²

While a depot formulation of leuprolide (Lupron Depot-Ped) is FDA labeled for the treatment of central precocious puberty (CPP),³ clinical evidence supports the use of daily SC administered leuprolide acetate for the same indication.⁴ CPP is defined as early onset of secondary sexual characteristics, generally earlier than 8 years of age in girls and 9 years of age in boys, associated with pubertal pituitary gonadotropin activation. Leuprolide prescribing information states that prior to initiation of treatment, a clinical diagnosis of CPP should be confirmed by blood concentration of luteinizing hormone (LH) (basal or stimulated with a GnRH analog) and assessment of bone age versus chronological age.³ Once therapy is initiated, CPP patients should be evaluated every 3 to 6 months for pubertal development and growth, and bone age should be measured radiographically every 6 to 12 months.⁴

Clinical evidence also supports the use of leuprolide as part of an assisted reproductive technology (ART) protocol in the treatment of infertility. ‘Long protocols’ most commonly utilized in ART include leuprolide initiation on day 21-24 of the menstrual cycle that occurs prior to the planned ovarian stimulation cycle. Leuprolide administration (in combination with FSH) then continues during oocyte stimulation until sufficient follicular development is attained.⁵⁻⁷⁸

2. Coverage Criteria^a:

These criteria provide parameters for coverage of oncology indications based upon the National Comprehensive Cancer Network (NCCN) Drugs & Biologics Compendium[™]. The Compendium lists the appropriate drugs and biologics for specific cancers using US Food and Drug Administration (FDA)-approved disease indications and specific NCCN panel recommendations. Each recommendation is supported by a level of evidence category.

UnitedHealthcare recognizes indications and uses of leuprolide acetate listed in the NCCN Drugs and Biologics Compendium with Categories of Evidence and Consensus of 1, 2A, and 2B as proven and Categories of Evidence and Consensus of 3 as unproven.

Clinical evidence supporting the use of GnRH analogs for the treatment of gender dysphoria is limited and lacks long-term safety data. Statistically robust randomized controlled trials are needed to address the issue of whether the benefits outweigh the clinical risk in its use.

Some states mandate benefit coverage for off-label use of medications for some diagnoses or under some circumstances. Some states also mandate usage of other Compendium references. Where such mandates apply, they supersede language in the benefit document or in the notification criteria.

A. Patients less than 19 years of age

1. Initial Authorization

- a. **Leuprolide acetate bulk powder[‡] or generic leuprolide acetate 1 mg/0.2 mL injection kit** will be approved based on **both** of the following criteria:

(1) Patient has an oncology diagnosis

-AND-

(2) Patient is less than 19 years of age

Authorization will be issued for 12 months.

2. Reauthorization

- a. **Leuprolide acetate bulk powder[‡] or generic leuprolide acetate 1 mg/0.2 mL injection kit** will be approved based on the following criterion:

(1) Patient does not show evidence of progressive disease while on therapy

Authorization will be issued for 12 months.

B. Treatment of Prostate Cancer

1. Initial Authorization

a. **Leuprolide acetate bulk powder[†] or generic leuprolide acetate 1 mg/0.2 mL injection kit** will be approved based on the following criteria:

(1) Diagnosis of prostate cancer

-AND-

(2) Disease is **one** of the following:

(a) Advanced

(b) Metastatic

2. **Reauthorization**

a. **Leuprolide acetate bulk powder[†] or generic leuprolide acetate 1 mg/0.2 mL injection kit** will be approved based on the following criterion:

(1) Patient does not show evidence of progressive disease while on therapy

Authorization will be issued for 12 months.

C. **Salivary Gland Tumors**

1. **Initial Authorization**

a. **Leuprolide acetate bulk powder[†] or generic leuprolide acetate 1 mg/0.2 mL injection kit** will be approved based on **all** of the following criteria:

(1) Diagnosis of salivary gland tumor

-AND-

(2) Disease is **one** of the following:

(a) Recurrent

(b) Unresectable

(c) Metastatic

-AND-

(3) Disease is androgen receptor positive (AR+)

Authorization will be issued for 12 months.

2. **Reauthorization**

a. **Leuprolide acetate bulk powder[†] or generic leuprolide acetate 1 mg/0.2 mL injection kit** will be approved based on the following criterion:

(1) Patient does not show evidence of progressive disease while on therapy

Authorization will be issued for 12 months.

D. Uterine Sarcoma

1. Initial Authorization

- a. **Leuprolide acetate bulk powder[†] or generic leuprolide acetate 1 mg/0.2 mL injection kit** will be approved based on the following criterion:

- (1) Diagnosis of **one** of the following:
- (a) Low-grade endometrial stromal sarcoma (ESS)
 - (b) Adenosarcoma without sarcomatous overgrowth
 - (c) Estrogen receptor/progesterone receptor positive (ER/PR+) uterine sarcoma

Authorization will be issued for 12 months.

2. Reauthorization

- a. **Leuprolide acetate bulk powder[†] or generic leuprolide acetate 1 mg/0.2 mL injection kit** will be approved based on the following criterion:

- (1) Patient does not show evidence of progressive disease while on therapy

Authorization will be issued for 12 months.

E. Treatment of Central Precocious Puberty (CPP)

1. Initial Authorization

- a. **Generic leuprolide acetate 1 mg/0.2 mL injection kit or leuprolide bulk powder[†]** will be approved based on **all** of the following criteria:

- (1) Diagnosis of central precocious puberty (idiopathic or neurogenic)

-AND-

- (2) Onset of secondary sexual characteristics in **one** of the following:

- (a) Females at birth \leq 8 years of age
- (b) Males at birth \leq 9 years of age

-AND-

- (3) Confirmation of diagnosis as defined by **one** of the following:

- (a) A pubertal luteinizing hormone response to a GnRH stimulation test
- (b) Bone age advanced one year beyond the chronological age

Authorization will be issued for 12 months.

2. **Reauthorization**

- a. **Generic leuprolide acetate 1 mg/0.2 mL injection kit or leuprolide acetate bulk powder†** will be approved based on the following criterion:

- (1) Documentation of a positive clinical response (e.g., decrease in height velocity, cessation of menses, arrest pubertal progression, reduction in bone age advancement)

Authorization will be issued for 12 months.

F. **Infertility***

1. **Generic leuprolide acetate 1 mg/0.2 mL injection kit or leuprolide bulk powder†** will be approved based on **both** of the following criteria*:

- a. Diagnosis of infertility

-AND-

- b. Used as part of an assisted reproductive technology (ART) protocol

Authorization will be issued for 2 months.

G. **Gender dysphoria in adolescents**

1. **Initial Authorization**

- a. **Generic leuprolide acetate 1 mg/0.2 mL injection kit** will be approved based on **all** of the following criteria:

- (1) Submission of medical records (e.g., chart notes, laboratory values) documenting all the following:

- (a) Diagnosis of gender dysphoria, according to the current DSM criteria, by a mental health professional with expertise in child and adolescent psychiatry

-AND-

- (b) Medication is prescribed by or in consultation with a pediatric endocrinologist

-AND-

- (c) Patient has experienced puberty development to at least Tanner stage 2

-AND-

(d) One of the following laboratory tests, based upon the laboratory reference range, confirming:

- a. Pubertal levels of estradiol in females; **or**
- b. Pubertal levels of testosterone in males

-AND-

(2) A letter from the prescriber and/or formal documentation stating all of the following:

(a) Patient has experienced pubertal changes that have resulted in an increase of their gender dysphoria that has significantly impaired psychological or social functioning

-AND-

(b) Coexisting psychiatric and medical comorbidities or social problems that may interfere with the diagnostic procedures or treatment have been addressed or removed

-AND-

(c) Current enrollment, attendance, and active participation in psychological and social support treatment program.

-AND-

(d) Patient demonstrates knowledge and understanding of the expected outcomes of treatment and related transgender therapies.

Authorization will be issued for 12 months.

2. Reauthorization

a. **Generic leuprolide acetate 1 mg/0.2 mL injection kit** will be approved based on provider attestation to all of the following criteria:

(1) Patient will continue enrollment, attendance and active participation in psychological and social support throughout the course of treatment

-AND-

(2) Patient demonstrates knowledge and understanding of the expected outcomes of treatment and related transgender therapies

-AND-

(3) Documentation of positive clinical response to therapy

Authorization will be issued for 12 months.

^a State mandates may apply. Any federal regulatory requirements and the member specific benefit plan coverage may also impact coverage criteria. Other policies and utilization management programs may apply.

3. Additional Clinical Rules:

- Notwithstanding Coverage Criteria, UnitedHealthcare may approve initial and re-authorization based solely on previous claim/medication history, diagnosis codes (ICD-10) and/or claim logic. Use of automated approval and re-approval processes varies by program and/or therapeutic class.
- Supply limitations may be in place.

*Infertility is typically excluded from coverage for UnitedHealthcare. Please refer to member's specific benefits for coverage determination.

‡Leuprolide bulk powder is also subject to Compounds and Bulk Powders Notification criteria.

4. References:

1. Leuprolide acetate [package insert]. Princeton, NJ: Sandoz Inc; June 2020.
2. The NCCN Drugs and Biologics Compendium (NCCN Compendium™). Available at https://www.nccn.org/professionals/drug_compendium/content/. Accessed May 1, 2024..
3. Lupron Depot-Ped [package insert]. North Chicago, IL: AbbVie Inc.; April 2023.
4. Carel JC, Eugster EA, Rogol A, et al. Consensus statement on the use of gonadotropin-releasing hormone analogs in children. *Pediatrics*. 2009 Apr;123(4):e752-62. Epub 2009 Mar 30.
5. Maheshwari A, Gibreel A, Siristatidis CS, Bhattacharya S. Gonadotrophin-releasing hormone agonist protocols for pituitary suppression in assisted reproduction. *Cochrane Database of Systematic Reviews* 2011, Issue 8. Art. No.: CD006919.
6. Tummon IS, Daniel SA, Kaplan BR, et al. Randomized, prospective comparison of luteal leuprolide acetate and gonadotropins versus clomiphene citrate and gonadotropins in 408 first cycles of in vitro fertilization. *Fertil Steril*. 1992 Sep;58(3):563-8.
7. Gagliardi CL, Emmi AM, Weiss G, Schmidt CL. Gonadotropin-releasing hormone agonist improves the efficiency of controlled ovarian hyperstimulation/intrauterine insemination. *Fertil Steril*. 1991 May;55(5):939-44.
8. Albuquerque LE1, Tso LO, Saconato H, Albuquerque MC, Macedo CR. Depot versus daily administration of gonadotrophin-releasing hormone agonist protocols for pituitary down regulation in assisted reproduction cycles. *Cochrane Database Syst Rev*. 2013 Jan 31;1:CD002808.
9. Hembree WC, Cohen-Kettenis PT, Gooren L, et al. Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline [published correction appears in *J Clin Endocrinol Metab*. 2018 Feb 1;103(2):699] [published correction appears in *J Clin Endocrinol Metab*. 2018 Jul 1;103(7):2758-2759]. *J Clin Endocrinol Metab*. 2017;102(11):3869-3903. Coleman E, Radix AE, Bouman WP, et al. Standards of Care for the Health of Transgender and Gender Diverse People, Version 8. *Int J Transgend Health*. 2022;23(Suppl 1):S1-S259. Published 2022 Sep 6. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. 2013. Washington, DC. Pages 451-459.

10. Costa R, Dunsford M, Skagerberg E, et al. Psychological Support, Puberty Suppression, and Psychosocial Functioning in Adolescents with Gender Dysphoria. *J Sex Med* 2015;12:2206–2214
11. de Vries AL, McGuire JK, Steensma TD, et al. Young adult psychological outcome after puberty suppression and gender reassignment. *Pediatrics*. 2014 Oct;134(4):696-704.

Program	Prior Authorization/Notification - leuprolide acetate (bulk powder, 1 mg/0.2 mL injection)
Change Control	
7/2014	Annual review. Revised age criterion for CPP to ≤ 8 years of age in females and ≤ 9 years of age in males. Simplified criteria for leuprolide bulk powder and added note that Compounds and Bulk Powders Notification criteria apply as well.
7/2015	Annual review. Revised criterion for CPP with no change to clinical intent. Updated references.
6/2016	Annual review. No changes to criteria. Updated references.
6/2017	Annual review. No changes to criteria. Updated references.
7/2018	Annual review. Added criteria for salivary gland tumors based on NCCN guidelines & gender dysphoria. Updated references.
9/2019	Annual review. Reorganized prostate cancer section & updated references.
9/2020	Annual review. Updated Head and Neck Cancer section according to NCCN guidelines. Updated references.
10/2021	Annual review. No changes to criteria. Updated references.
10/2022	Annual review. No changes to criteria. Added state mandate footnote. Updated references.
6/2023	Removed Eligard from the program. Added leuprolide acetate depot and Eligard to list of drugs covered under medical benefit.
6/2024	Annual review. Simplified criteria for prostate and salivary gland cancer. Added criteria for uterine sarcoma. Updated reauthorization criteria for CPP. Updated background and references.