

UnitedHealthcare Pharmacy
Clinical Pharmacy Programs

Program Number	2023 P 1059-11
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, 06/2023
Effective Date	8/1/2023; Oxford only: 8/1/2023

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 when given continuously in therapeutic doses. Consequently, tissues and functions that depend on gonadal steroids for their maintenance become quiescent.⁹

In addition to prostate cancer, The National Cancer Comprehensive Network (NCCN) recommends leuprolide acetate for the treatment of breast cancer and ovarian cancer.² However, the NCCN recommendations for these cancers are for the depot formulations of leuprolide, which are covered under the medical benefit. The NCCN also recommends leuprolide acetate for the treatment of salivary gland tumors.¹

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.^{5-7, 10}

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) For the palliative treatment of advanced prostate cancer

-OR-

(2) **All** of the following:

(a) Disease is asymptomatic

-AND-

(b) Life expectancy is ≤ 5 years

-AND-

(c) **One** of the following:

i. Disease is regional

ii. Disease is metastatic

-OR-

(3) **All** of the following:

(a) As a single agent with or without abiraterone (Zytiga) and prednisone or in combination with a first-generation antiandrogen (e.g., nilutamide, flutamide, or bicalutamide)

-AND-

(b) Patient is in the regional risk group

-AND-

(c) **One** of the following:

i. Life expectancy is > 5 years

ii. Disease is symptomatic

-OR-

(4) For patients who progressed on observation of localized disease

-OR-

(5) **Both** of the following:

(a) As a single agent or in combination with a first-generation antiandrogen (e.g., nilutamide, flutamide, or bicalutamide)

-AND-

- (b) Patient is in the M0 PSA persistence/recurrence after RP or EBRT risk group

-OR-

(6) **Both** of the following:

- (a) As a single agent or in combination with a first-generation antiandrogen (e.g., nilutamide, flutamide, or bicalutamide) or in combination with docetaxel and concurrent steroid with or without a first-generation antiandrogen or in combination with abiraterone and prednisone

-AND-

- (b) Patient is in the M1 Castration-Naïve/resistant disease risk group

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.

C. 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 test¹⁰

(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 bone age monitoring (e.g., radiographic imaging)

Authorization will be issued for 12 months.

D. Treatment of 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.

E. 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) Disease is androgen receptor positive

-AND-

(2) **One** of the following:

(a) Disease is metastatic and patient has a performance status of 0-3

-OR-

(b) Disease is one of the following:

- i. Recurrent unresectable locoregional
- ii. Second primary with prior radiation therapy

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.

F. 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 September 7, 2022.
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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.
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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.
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13. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. 2013. Washington, DC. Pages 451-459.
14. 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
15. 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.