UnitedHealthcare Pharmacy
Clinical Pharmacy Programs

Program Number	2018 P 1059-6
Program	Prior Authorization/Notification
Medication	leuprolide acetate (bulk powder, 1 mg/0.2 mL injection, Eligard®)* **Note:** These criteria only apply to the SC formulations of leuprolide acetate. The intramuscular (IM) formulations (Lupron® Depot and Lupron® Depot-Ped) 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
Effective Date	10/1/2018; Oxford only: 10/1/2018

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.[10]

Subcutaneously (SC) administered leuprolide acetate (Eligard and generics) is FDA-labeled for the palliative treatment of advanced prostate cancer.[1,2]

In addition to prostate cancer, The National Cancer Comprehensive Network (NCCN) recommends leuprolide acetate for the treatment of breast cancer and ovarian cancer.[3] 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.[2]

While a depot formulation of leuprolide (Lupron Depot-Ped) is FDA labeled for the treatment of central precocious puberty (CPP),[4] clinical evidence supports the use of daily SC administered leuprolide acetate for the same indication.[5] 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. [4] 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.[5]

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.[6-8,11]

2. **Coverage Criteria:**
This criteria provides 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. **Eligard, 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. **Eligard, 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. **Eligard, 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) **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) **One** of the following:
i. Life expectancy is > 5 years
ii. Disease is symptomatic

-OR-

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

(a) as a single agent with or without abiraterone (Zytiga) and prednisone

-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-

(5) for patients who progressed on observation of localized disease

-OR-

(6) for PSA persistence/recurrence

-OR-

(7) **Both** of the following

(a) castration-naive disease

-AND-

(b) **One** of the following:
i. as a single agent for M0 or M1 disease
ii. in combination with a first-generation antiandrogen for M0 or M1disease
iii. in combination with docetaxel and concurrent steroid with or without a first-generation antiandrogen for M1 disease
iv. in combination with abiraterone and prednisone for M1 disease

-OR-

(8) M0 or M1 castration-resistant disease

Authorization will be issued for 12 months.

2. Reauthorization

a. **Eligard, 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) [off-label]

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 ≤ 8 years of age
(b) Males at birth ≤ 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[10]
(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 [off-label]*

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 [off-label]

1. Initial Authorization

a. **Eligard, 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) Disease is metastatic

-AND-

(3) Patient has a performance status of 0-3

Authorization will be issued for 12 months.

2. Reauthorization

a. **Eligard, 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 [off-label]

1. Initial Authorization

a. **Eligard,** or **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. **Eligard,** or **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.

3. Additional Clinical Rules:

Supply limitations may be in place.

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

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

4. References:

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14. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. 2013. Washington, DC. Pages 451-459.
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Program	Prior Authorization/Notification - leuprolide acetate (bulk powder, 1 mg/0.2 mL injection, Eligard)
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.