Clinical Policy: Leuprolide Acetate (Eligard, Lupaneta Pack, Lupron Depot, Lupron Depot-Ped)

Reference Number: CP.PHAR.173
Effective Date: 10.01.16
Last Review Date: 11.17
Line of Business: Medicaid

Coding Implications
Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description
Leuprolide acetate (Eligard®, Lupaneta Pack®, Lupron Depot®, Lupron Depot-Ped®) is a gonadotropin-releasing hormone (GnRH) receptor agonist.

FDA Approved Indication(s)
Leuprolide acetate is indicated for:

- Palliative treatment of advanced prostatic cancer:
  - Leuprolide acetate injection
  - Eligard (7.5, 22,5, 30, 45)
  - Lupron Depot (7.5, 22.5, 30, 45)
- Management of endometriosis, including pain relief and reduction of endometriotic lesions:
  - Lupron Depot (3.75, 11.25)
  - Lupaneta Pack (3.75, 11.25)

  Limitations of use: Initial treatment course is limited to 6 months and use is not recommended longer than a total of 12 months due to concerns about adverse impact on bone mineral density.
- Preoperative hematologic improvement of patients with anemia caused by uterine leiomyomata [fibroids] administered concomitantly with iron therapy:
  - Lupron Depot (3.75, 11.25)
- Treatment of children with central precocious puberty (CPP):
  - Leuprolide acetate
  - Lupron Depot-Ped (7.5, 11.25, 15, 30)

Policy/Criteria
Provider must submit documentation (which may include office chart notes and lab results) supporting that member has met all approval criteria.

It is the policy of health plans affiliated with Centene Corporation® that leuprolide acetate, Eligard, Lupaneta Pack, Lupron Depot, and Lupron Depot-Ped are **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Prostate Cancer (must meet all):

1. Request is for leuprolide acetate injection or Eligard/Lupron Depot (7.5 mg, 22.5 mg, 30 mg, 45 mg);

2. Diagnosis of prostate cancer;
3. Age ≥ 18 years;
4. Meets (a or b):
   a. FDA approved use:
      i. Palliative treatment of advanced prostate cancer;
   b. NCCN recommended use (any of the following):
      i. Adjuvant androgen deprivation therapy (ADT) as a single agent or in combination with an antiandrogen if positive lymph nodes found during pelvic lymph node dissection;
      ii. Initial ADT as a single agent or in combination with an antiandrogen (a, b or c):
         a) With radiation therapy for (1, 2 or 3):
            1) Intermediate risk disease;
            2) High or very high risk disease +/- docetaxel;
            3) Regional disease (any T, N1, M0);
         b) For very high risk disease if not a candidate for definitive therapy;
         c) For regional disease (any T, N1, M0) or metastatic disease (M1);
      iii. ADT as a single agent or in combination with an antiandrogen (a or b):
         a) For biochemical failure following radical prostatectomy (1 or 2):
            1) With radiation therapy if no distant metastases;
            2) +/- radiation therapy if distant metastases;
         b) For positive digital rectal examination following radiation therapy (1 or 2):
            1) If biopsy is negative and there are no distant metastases;
            2) If not a candidate for local therapy;
      iv. For progressive castration-naive disease (a, b or c):
         a) As a single agent;
         b) With an antiandrogen;
         c) With docetaxel +/- prednisone +/- an antiandrogen for metastatic (M1) disease;
      v. For castration-recurrent disease to maintain castrate levels of serum testosterone as a single agent or with an antiandrogen;
5. Request meets one of the following:
   a. Dose does not exceed leuprolide acetate injection (SC): 1 mg once daily;
   b. Dose does not exceed Eligard (SC)/Lupron Depot (IM): 7.5 mg/month, 22.5 mg/3 months, 30 mg/4 months, 45 mg/6 months;
   c. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

Approval duration: 12 months

B. Endometriosis (must meet all):
1. Request is for Lupron Depot/Lupaneta Pack (3.75 mg, 11.25 mg);
2. Diagnosis of endometriosis;
3. Prescribed by or in consultation with a gynecologist;
4. Age ≥ 18 years;
5. Endometriosis as a cause of pain is (a or b):
   a. Surgically confirmed;

   b. Clinically suspected and member has failed a 3-month trial of one of the following agents within the last year or has a documented intolerance or contraindication to the agent (i, ii or iii):
      i. A nonsteroidal anti-inflammatory drug;
      ii. An oral or depot contraceptive;
      iii. A progestin;
6. At the time of request, member is not pregnant;
7. Dose does not exceed Lupron Depot/Lupaneta Pack (IM): 3.75 mg/month, 11.25 mg/3 months.

Approval duration: 6 months

C. Uterine Fibroids (must meet all):
1. Request is for Lupron Depot (3.75 mg, 11.25 mg);
2. Diagnosis of anemia secondary to uterine leiomyomata (fibroids) confirmed by ultrasound;
3. Prescribed by or in consultation with gynecologist;
4. Age ≥ 18 years;
5. Prescribed preoperatively to reduce fibroid size and improve hematologic control;
6. At the time of request, member is not pregnant;
7. Dose does not exceed Lupron Depot (IM): 3.75 mg/month, 11.25 mg/3 months.

Approval duration: 3 months

D. Central Precocious Puberty (must meet all)**:**
1. Request is for one of the following products:
   a. Leuprolide acetate: for diagnosing or treating central precocious puberty (CPP);
   b. Lupron Depot Ped: for treating CPP (1-month formulation 7.5 mg, 11.25 mg, 15 mg; 3-month formulation 11.25 mg, 30 mg);
2. Diagnosis of CPP confirmed by (a through c):
   a. Elevated basal luteinizing hormone (LH) level > 0.2 - 0.3 mIU/L (dependent on type of assay used) and/or elevated leuprolide-stimulated LH level > 3.3 - 5 IU/I (dependent on type of assay used);
   b. Difference between bone age and chronological age was > 1 year (bone age-chronological age;
   c. Age at onset of secondary sex characteristics is < 8 years if female, or < 9 years if male;
3. Member meets the following age requirements:
   a. Female: 2 - 11 years;
   b. Male: 2 - 12 years;
4. Prescribed by or in consultation with a pediatric endocrinologist;
5. At the time of request, member is not pregnant;
6. Dose does not exceed the following:
   a. Diagnostic use: Leuprolide acetate: 20 mcg/kg or as needed;
   b. Therapeutic use: Leuprolide acetate (SC): Initial: 50 mcg/kg/day; titrate dose upward by 10 mcg/kg/day if down-regulation is not achieved (higher mg/kg doses may be required in younger children).

c. Therapeutic use: Lupron Depot-Ped (IM): 15 mg/month (1-month formulation) or 30 mg/3 months (3-month formulation) (dosing is weight-based).

Approval duration: 12 months

E. Breast Cancer (must meet all):
1. Request is for Lupron Depot (3.75 mg);
2. Diagnosis of breast cancer;
3. Age ≥ 18 years;
4. NCCN recommended use (a or b):
   a. Member is pre/peri-menopausal;
   b. In combination with (i or ii):
      i. Adjuvant endocrine therapy (e.g., tamoxifen or an aromatase inhibitor) for hormone receptor-positive disease;
      ii. Endocrine therapy for recurrent or stage IV disease;
5. At the time of request, member is not pregnant;
6. Request meets one of the following:
   a. Dose does not exceed Lupron Depot (IM): 3.75 mg/month;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

Approval duration: 12 months

F. Ovarian Cancer (must meet all):
1. Request is for Lupron Depot (3.75 mg, 11.25 mg);
2. Diagnosis of ovarian cancer;
3. NCCN recommended use (a or b):
   a. Persistent or recurrent disease and any of the following histopathologies:
      i. Carcinosarcoma (malignant mixed Mullerian tumors [MMMTs] of the ovary);
      ii. Serous carcinoma,
      iii. Endometroid carcinoma,
      iv. Clear cell carcinoma;
      v. Mucinous carcinoma;
   b. Stage II-IV granulosa cell tumor with history of clinical relapse;
4. Age ≥ 18 years;
5. At the time of request, member is not pregnant;
6. Request meets one of the following:
   a. Dose does not exceed Lupron Depot (IM): 3.75 mg/month, 11.25 mg/3 months;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

Approval duration: 12 months

G. Other diagnoses/indications
1. Refer to CP.PHAR.57 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

II. Continued Therapy

A. Prostate Cancer (must meet all):

1. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
2. Request is for leuprolide acetate injection or Eligard/Lupron Depot (7.5 mg, 22.5 mg, 30 mg, 45 mg);
3. Member is responding positively to therapy (e.g., improved quality of life; no unacceptable toxicity);
4. If request is for a dose increase, request meets one of the following:
   a. Leuprolide acetate injection (SC): 1 mg once daily;
   b. Eligard (SC)/Lupron Depot (IM): 7.5 mg/month, 22.5 mg/3 months, 30 mg/4 months, 45 mg/6 months;
   c. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

Approval duration: 12 months

B. Endometriosis (must meet all):
1. Previously received medication via Centene benefit or member has previously met initial approval criteria;
2. Request is for Lupron Depot/Lupaneta Pack (3.75 mg, 11.25 mg);
3. Member is responding positively to therapy (e.g., improvement in dysmenorrhea, dyspareunia, pelvic pain/induration/tenderness, or size of endometrial lesions);
4. If request is for a dose increase, new dose does not exceed Lupron Depot/Lupaneta Pack (IM): 3.75 mg/month, 11.25 mg/3 months.

Approval duration: 6 months
Total duration of therapy should not exceed 12 months.

C. Uterine Fibroids (must meet all):
1. Previously received medication via Centene benefit or member has previously met initial approval criteria;
2. Request is for Lupron Depot (3.75 mg, 11.25 mg);
3. Member is responding positively to therapy;
4. If request is for a dose increase, new dose does not exceed Lupron Depot (IM): 3.75 mg/month, 11.25 mg/3 months.

Approval duration: 3 months
Total duration of therapy should not exceed 6 months.

D. Central Precocious Puberty (must meet all)**:**
1. Currently receiving medication via Centene benefit or member has previously met all initial approval criteria;
2. Request is for leuprolide acetate or Lupron Depot-Ped;
3. Member is responding positively to therapy (e.g., decreased growth velocity, cessation of menses, softening of breast tissue or testes, arrested pubertal progression);
4. Member meets the following age requirement:
   a. Female: ≤ 11 years;
   b. Male: ≤ 12 years;
5. If request is for a dose increase, new dose does not exceed one of the following:

a. Leuprolide acetate (SC)): Initial: 50 mcg/kg/day; titrate dose upward by 10 mcg/kg/day if down-regulation is not achieved (higher mg/kg doses may be required in younger children);
b. Lupron Depot-Ped (IM): 15 mg/month (1-month formulation) or 30 mg/3 months (3-month formulation) (dosing is weight-based).

Approval duration: 12 months

E. Breast Cancer (must meet all):
1. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
2. Request is for Lupron Depot (3.75 mg);
3. Member is responding positively to therapy (e.g., improved quality of life; no unacceptable toxicity);
4. If request is for a dose increase, meets one of the following:
   a. New dose does not exceed Lupron Depot (IM): 3.75 mg/month.
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

Approval duration: 12 months

F. Ovarian Cancer (must meet all):
1. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
2. Request is for Lupron Depot (3.75 mg, 11.25 mg);
3. Member is responding positively to therapy (e.g., improved quality of life; no unacceptable toxicity);
4. If request is for a dose increase, request meets one of the following:
   a. New dose does not exceed Lupron Depot (IM): 3.75 mg/month, 11.25 mg/3 months;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

Approval duration: 12 months

G. Other diagnoses/indications (must meet 1 or 2):
1. Currently receiving medication via Centene benefit and documentation supports positive response to therapy.
   Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to CP.PHAR.57 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policy – CP.PHAR.57 or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

CPP: central precocious puberty
FDA: Food and Drug Administration
GnRH: gonadotropin-releasing hormone
IM: intramuscular
NCCN: National Comprehensive Cancer Network
SC: subcutaneous

V. Dosage and Administration

Drug Name	Indication	Dosing Regimen	Maximum Dose
Leuprolide acetate injection Leuprolide acetate (Lupron Depot 7.5, 22.5, 30, 45) Leuprolide acetate (Eligard 7.5, 22.5, 30, 45)	Prostate cancer*	Leuprolide acetate injection (SC): 1 mg/day	See regimen
		Lupron Depot (IM) - 7.5 mg/month; 22.5 mg/3 months; 30 mg/4 months; 45 mg/6 months	See regimen
		Eligard (SC) - 7.5 mg/month; 22.5 mg/3 months; 30 mg/4 months; 45 mg/6 months	See regimen
Leuprolide acetate (Lupron Depot 3.75, 11.25) Leuprolide acetate (Lupaneta Pack 3.75, 11.25)	Endometriosis	Lupron Depot/Lupaneta Pack (IM) - 3.75 mg/month; 11.25 mg/3 months	See regimen
Leuprolide acetate (Lupron Depot 3.75)	Uterine fibroids	Lupron Depot (IM) - 3.75 mg/month, 11.25 mg/3 months	See regimen
Leuprolide acetate injection Leuprolide acetate (Lupron Depot-Ped 7.5, 11.25, 15 [1 mo]; 11.25, 30 [3 mo])	CPP	Leuprolide acetate (SC): • Diagnostic: 20 mcg/kg or as needed; • Treatment: Initial: 50 mcg/kg/day; titrate dose upward by 10 mcg/kg/day if down-regulation is not achieved (higher mg/kg doses may be required in younger children).	See regimen
		Lupron Depot-Ped (IM): Monthly administration weight-based starting dose: 7.5 mg (≤ 25 kg), 11.25 mg (> 25 to 37.5 kg), 15 mg (> 37.5 kg) (increase as needed to 15 mg/month); 3-month administration: 11.25 mg or 30 mg	See regimen
Leuprolide acetate (Lupron Depot	Breast cancer	Lupron Depot (IM) 3.75 mg/month	See regimen

3.75)			
Leuprolide acetate (Lupron Depot 3.75, 11.25)	Ovarian cancer	Lupron Depot (IM) 3.75 mg/month, 11.25 mg/3 months	See regimen

**May be used in combination with therapies such as radiation therapy, antiandrogens, glucocorticoids, docetaxel.*

VI. Product Availability

Drug Name	Availability
Leuprolide acetate (Eligard)	Kit: 7.5 mg (1 month), 22.5 mg (3 month), 30 mg (4 month), 45 mg (6 month)
Leuprolide acetate injection	Vial: 1 mg/0.2 mL (5 mg/mL) Kit: 14 mg/2.8 mL (5 mg/mL)
Leuprolide acetate and norethindrone tablets (Lupaneta Pack)	Pack: 3.75 mg leuprolide acetate syringe (1 month) with 5 mg norethindrone tablets Pack: 11.25 mg leuprolide acetate syringe (3 month) with 5 mg norethindrone tablets
Leuprolide acetate (Lupron Depot)	Prefilled syringe: 7.5 mg (1 month), 22.5 mg (3 month), 30 mg (4 month), 45 mg (6 month)
Leuprolide acetate (Lupron Depot 3.75)	Prefilled syringe: 3.75 mg (1 month)
Leuprolide acetate (Lupron Depot 11.25)	Prefilled syringe: 11.25 mg (3 month)
Leuprolide acetate (Lupron Depot-Ped)	Prefilled syringe: 7.5 mg (1 month), 11.25 mg (1 month), 15 mg (1 month) Prefilled syringe: 11.25 mg (3 month), 30 mg (3 month)

VII. References

1. Leuprolide Acetate Injection Prescribing Information. Bedford, OH: Ben Venue Laboratories, Inc.; August 2011. Available at https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed July 26, 2017.
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4. Lupaneta Pack 11.25 Prescribing Information. North Chicago, IL: AbbVie Inc.; June 2015. http://rxabbvie.com/pdf/lupaneta_11_25_pi.pdf. Accessed July 13 2017.
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18. Kaplowitz P, Bloch C. Evaluation and referral of children with signs of early puberty. Pediatrics. 2016; 137(1): e20153732.
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Coding Implications
Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

HCPCS Codes	Description
J1950	Injection, leuprolide acetate (for depot suspension), per 3.75 mg
J9217	Leuprolide acetate (for depot suspension), 7.5 mg
J9218	Leuprolide acetate, per 1 mg
J9219	Leuprolide acetate implant, 65 mg

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy split from CP.PHAR.118.GnRH Analogs. Prostate cancer – locally confined with radiation therapy; age added 18 or older per PI; max dose added; staging restated per PI Approval period limited to 6 months total with radiation therapy per guidelines Prostate cancer – advanced/palliative; age added 18 or older per PI; max dose added; removed preferencing other than a trial of injectables before receiving implant; staging of advanced prostate cancer restated as stage T3 through T4 or high risk through nodal/metastatic disease per guidelines; added confirmation that treatment intent is palliative if designated in PI; approval period extended to q 12 months Breast cancer – advanced/palliative; age added 18 or older per PI; max dose added; defined advanced as stage IV or recurrent metastatic disease per guidelines; removed requirement for ER/PR+ status as guidelines note status not always clear and that GnRH analogs can be effective in either case; add peri-menopausal status per Zoladex guideline; FDA approved and off-label breast cancer criteria is stated the same based on Zoladex PI and guidelines; added confirmation that treatment intent is palliative as designated in Zoladex PI; approval period; extended to q 12 months Endometriosis - age added 18 or older per PI; max dose added; removed that surgical diagnosis had to be within last year; for clinical diagnosis, restated failure of one three-month trial to analgesics and/or contraceptives per UpToDate; approval period restated per PIs as follows: 6 months total if Zoladex, up to 12 months total for all others per products. Endometrial thinning prior to ablation - age added 18 or older per PI; max dose added	02.16	02.16
Endometriosis: Changed 3 month trial of analgesics and/or hormonal contraceptives to NSAIDS and/or hormonal contraceptives.	05.16	
Per the PI, pregnancy is not a contraindication in cases of advanced breast cancer so it is removed as such in sections I.B and II.B above.	10.16	
Age removed. Formulations added. Off-label NCCN recommended uses added (prostate and breast cancer; doses removed; 3-month injectable requirement removed).	01.17	02.17

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Age and dosing added to oncology criteria; age added to gynecology criteria. Positive therapeutic response examples added to oncology and endometriosis criteria. Oncology FDA/NCCN (categories 1 and 2A) indications listed separately. Pelvic pain criteria deleted with direction to suspected endometriosis if appropriate. Endometriosis step therapy edited from estrogen/progestin OC to OC or depot contraceptive or progestin. Total approval duration increased from 6 to 12 months. Concomitant iron therapy and specific time period within which surgery must be performed are removed from fibroid criteria. Total approval duration increased from 3 to 6 months. Specialist requirement added for endometriosis, fibroids, CPP. Safety information removed with exception of pregnancy.	09.17	11.17

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or

regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

Note: For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.