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

Reference Number: PA.CP.PHAR.173
Effective Date: 01/18
Last Review Date: 10/18

Coding Implications
Revision Log

Description
The intent of the criteria is to ensure that patients follow selection elements established by Pennsylvania Health and Wellness® medical policy for the use of leuprolide acetate (Eligard®, Lupaneta Pack®, Lupron Depot®, Lupron Depot-Ped®).

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

- Palliative treatment of advanced prostate 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)

  Limitation(s) 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
It is the policy of Pennsylvania Health and Wellness that leuprolide acetate, Eligard, Lupaneta Pack, Lupron Depot, Lupron Depot-Ped are **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Prostate Cancer (must meet all):

1. Diagnosis of prostate cancer;
2. Request is for leuprolide acetate injection or Eligard/Lupron Depot (7.5 mg, 22.5 mg, 30 mg, 45 mg);
3. Prescribed by or in consultation with an oncologist or urologist;
4. Request meets one of the following:
   a. Dose does not exceed any of the following:

i. leuprolide acetate injection (SC): 1 mg per day;
ii. Eligard (SC)/Lupron Depot (IM): 7.5 mg per month, 22.5 mg per 3 months, 30 mg per 4 months, 45 mg per 6 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

B. Central Precocious Puberty (must meet all, *for diagnosis use 5a only*):

1. 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;
2. Request is for one of the following products:
   a. Leuprolide acetate;
   b. Lupron Depot Ped: 7.5 mg, 11.25 mg, 15 mg, 30 mg;
3. Prescribed by or in consultation with a pediatric endocrinologist;
4. Member meets the following age requirements:
   a. Female: 2 - 11 years;
   b. Male: 2 - 12 years;
5. 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 per day; titrate dose upward by 10 mcg/kg per 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 per month (1-month formulation) or 30 mg per 3 months (3-month formulation) (dosing is weight-based).

Approval duration: 12 months

C. Endometriosis (must meet all):

1. Diagnosis of endometriosis;
2. Request is for Lupron Depot/Lupaneta Pack (3.75 mg, 11.25 mg);
3. Prescribed by or in consultation with a gynecologist;
4. Age ≥ 18 years;
5. Endometriosis as a cause of pain is one of the following (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 injectable depot contraceptive;
iii. A progestin;

6. Dose does not exceed Lupron Depot/Lupaneta Pack (IM): 3.75 mg per month, 11.25 mg per 3 months.

Approval duration: 6 months

D. 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. Prescribed preoperatively to reduce fibroid size and improve hematologic control;
5. Dose does not exceed Lupron Depot (IM): 3.75 mg per month, 11.25 mg per 3 months.

Approval duration: 3 months total

E. Breast and Ovarian Cancer (off-label) (must meet all):
1. Diagnosis of breast or ovarian cancer;
2. Request is for Lupron Depot (3.75 mg, breast or ovarian cancer or 11.25 mg for ovarian cancer);
3. Prescribed by or in consultation with an oncologist;
4. Request meets one of the following:
   a. Breast or ovarian cancer: Dose does not exceed 3.75 mg per month;
   b. Ovarian cancer: Dose does not exceed 11.25 mg per 3 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

F. Gender Dysphoria (off-label) (must meet all):
1. Diagnosis of gender dysphoria as evidenced by meeting the DSM V criteria for gender dysphoria;
2. Prescribed by or in consultation with a pediatric endocrinologist, adolescent medicine specialist or medical provider with experience and/or training in transgender medicine;
3. Member has psychological and social support during treatment;
4. Member does not suffer from a psychiatric comorbidity that interferes with the diagnostic work-up or treatment;
5. Member demonstrates consent and understanding of the expected outcomes of GnRH analog treatment (*For minorities, when parental consent cannot be obtained,*

exceptions are reviewed on a case by case basis and in conjunction with a behavioral health provider);

6. For adults: failure to achieve physiologic hormone levels or an intolerance with use of gender-affirming hormonal therapy (e.g., estrogen, testosterone).

Approval duration: 12 months

G. Other diagnoses/indications: Refer to CP.PMN.53

II. Continued Approval

A. Prostate Cancer (must meet all):

1. Currently receiving medication via Pennsylvania Health and Wellness benefit or member has previously met initial approval criteria or the Continuity of Care policy applies (*see PA.LTSS.PHAR.01*);
1. Request is for leuprolide acetate injection or Eligard/Lupron Depot (7.5 mg, 22.5 mg, 30 mg, 45 mg);
2. Member is responding positively to therapy;
3. If request is for a dose increase, request meets one of the following:
   a. New dose does not exceed leuprolide acetate injection (SC): 1 mg per day;
   b. New dose does not exceed Eligard (SC)/Lupron Depot (IM): 7.5 mg per month, 22.5 mg per 3 months, 30 mg per 4 months, 45 mg per 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

Approval duration: 12 months

B. Central Precocious Puberty (must meet all):

1. Currently receiving medication via Pennsylvania Health and Wellness benefit or member has previously met initial approval criteria or the Continuity of Care policy applies (*see PA.LTSS.PHAR.01*):
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 per day; titrate dose upward by 10 mcg/kg per day if down-regulation is not achieved (higher mg/kg doses may be required in younger children);
   b. Lupron Depot-Ped (IM): 15 mg per month (1-month formulation) or 30 mg per 3 months (3-month formulation) (dosing is weight-based).

Approval duration: 12 months

C. Endometriosis (must meet all):
1. Currently receiving medication via Pennsylvania Health and Wellness benefit or member has previously met initial approval criteria or the Continuity of Care policy applies (*see PA.LTSS.PHAR.01*);
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 3.75 mg per month, 11.25 mg per 3 months.

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

D. Breast and Ovarian Cancer (off-label) (must meet all):
1. Currently receiving medication via Pennsylvania Health and Wellness benefit or member has previously met initial approval criteria or the Continuity of Care policy applies (*see PA.LTSS.PHAR.01*);
2. Request is for Lupron Depot (3.75 mg, breast or ovarian cancer or 11.25 mg for ovarian cancer);
3. Member is responding positively to therapy;
4. If request is for a dose increase, request meets one of the following:
    a. Breast or ovarian cancer: New dose does not exceed 3.75 mg per month;
    b. Ovarian cancer: New dose does not exceed 11.25 mg per 3 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

E. Uterine Fibroids (must meet all):
1. Currently receiving medication via Pennsylvania Health and Wellness benefit or member has previously met initial approval criteria or the Continuity of Care policy applies (*see PA.LTSS.PHAR.01*);
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 3.75 mg per month or 11.25 mg per 3 months.

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

F. Gender Dysphoria (off-label) (must meet all):
5. Currently receiving medication via Pennsylvania Health and Wellness benefit or member has previously met initial approval criteria or the Continuity of Care policy applies (*see PA.LTSS.PHAR.01*);
6. Member is responding positively to therapy;

7. Member has none of the following contraindications:
   a. Known hypersensitivity to GnRH, GnRH analogs, or any excipient in the requested product;
   b. Undiagnosed vaginal bleeding;
   c. Pregnancy or breast-feeding.

Approval duration: 12 months

G. Other diagnoses/indications (must meet 1 or 2):
1. Currently receiving medication via Pennsylvania Health and Wellness benefit and documentation supports positive response to therapy, or the Continuity of Care policy applies (*see PA.LTSS.PHAR.01*); or
2. Refer to CP.PMN.53 – off-label policy.

Background

Description/Mechanism of Action:

Leuprolide acetate is a GnRH agonist/synthetic nonapeptide analog of naturally occurring GnRH and acts as an inhibitor of gonadotropin secretion.

Formulations:

Subcutaneous (SC) formulations:

Leuprolide acetate injection

Eligard:

7.5 mg for 1-month administration
22.5 mg for 3-month administration
30 mg for 4-month administration
45 mg for 6 month administration

Intramuscular (IM) formulations:

Lupron Depot:

7.5 mg for 1-month administration
22.5 mg for 3-month administration
30 mg for 4-month administration
45 mg for 6 month administration

Lupron Depot:

3.75 mg for 1-month administration

Lupron Depot:

11.25 mg for 3-month administration

Lupron Depot-Ped

7.5 mg for 1-month administration
11.25 mg for 1-month administration
15 mg for 1-month administration

Lupron Depot-Ped

11.25 mg for 3-month administration
30 mg for 3-month administration

Lupaneta Pack:

3.75 mg for 1-month administration; packaged with norethindrone acetate 5 mg daily (oral)

Lupaneta Pack:

11.25 mg for 3-month administration; packaged with norethindrone acetate 5 mg daily (oral)

Appendices

Appendix A: Abbreviation/Acronym Key

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

Appendix B: Therapeutic Alternatives

This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent for all relevant lines of business and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
NSAIDs: ibuprofen, naproxen, fenoprofen, ketoprofen, mefenamic acid, meclofenamate, indomethacin, tolmetin, diclofenac, etodolac, diflunisal, meloxicam, piroxicam	Endometriosis Varies – refer to specific prescribing information	Varies – refer to specific prescribing information
Combined oral estrogen-progesterone contraceptives: ethinyl estradiol + (desogestrel, ethynodiol diacetate, drospirenone, etonogestrel, levonorgestrel, norelgestromin, norethindrone, norgestimate, or norgestrel); estradiol valerate + dienogest; mestranol + norethindrone	Endometriosis 1 tablet PO QD (may vary per specific prescribing information)	1 tablet per day (may vary per specific prescribing information)
Progestin-only oral contraceptives: norethindrone	Endometriosis 0.35 mg PO QD	0.35 mg PO QD
Depot injection progestin contraceptives: medroxyprogesterone acetate	Endometriosis IM: 150 mg per 3 months (every 13 weeks) SC: 104 mg per 3 months (every 12 to 14 weeks)	IM: 150 mg/3 months SC: 104 mg/3 months

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

Appendix C: Contraindications/Boxed Warnings

- Contraindication(s):

- Known hypersensitivity to GnRH, GnRH agonist analogs or any of the components of the individual products;
- Pregnancy;
- Lupron 3.75 mg/11.25 mg and Lupaneta Pack - the above, plus:
  - Undiagnosed abnormal vaginal bleeding;
  - Breast-feeding;
  - If used with norethindrone acetate:
    - Thrombophlebitis, thromboembolic disorders, cerebral apoplexy, or a past history of these conditions;
    - Markedly impaired liver function or liver disease;
    - Known or suspected carcinoma of the breast.

- Boxed warning(s): None reported

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	Approval Date
4Q 2018 annual review; no significant changes; for oncology, summarized NCCN and FDA-approved uses for improved clarity (limited to diagnosis); specialist involvement in care and continuation of care added; references reviewed and updated.	08/18	

References
1. Leuprolide Acetate Injection Prescribing Information. Bedford, OH: Ben Venue Laboratories, Inc.; August 2011. Available at www.accessdata.fda.gov. Accessed July 27, 2018.
2. Eligard Prescribing Information. Fort Collins CO: TOLMAR Pharmaceuticals, Inc.; November 2017. Available at https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=b78d1919-9dee-44fa-90f9-e0a26d32481d&type=display. Accessed July 27, 2018.
3. Lupaneta Pack 3.75 Prescribing Information. North Chicago, IL: AbbVie Inc.; June 2015. http://rxabbvie.com/pdf/lupaneta_3_75_pi.pdf. Accessed July 27, 2018.

Lupaneta Pack 11.25 Prescribing Information. North Chicago, IL: AbbVie Inc.; June 2015. http://rxabbvie.com/pdf/lupaneta_11_25_pi.pdf. Accessed July 27, 2018.

4. Lupron Depot 3.75 Prescribing Information. North Chicago, IL: AbbVie Inc.; April 2018. Available at http://www.rxabbvie.com/pdf/lupron3_75mg.pdf. Accessed July 26, 2017.

5. Lupron Depot 11.25 mg Prescribing Information. North Chicago, IL: AbbVie Inc.; June 2015. Available at http://www.rxabbvie.com/pdf/lupron3month11_25mg.pdf. Accessed July 27, 2018.
6. Lupron Depot 7.5, 22.5, 30, 45 mg Prescribing Information. North Chicago, IL: AbbVie, Inc., June 2016. Available at http://www.rxabbvie.com/pdf/lupronuro_pi.pdf. Accessed July 27, 2018.
7. Lupron Depot-PED Prescribing Information. North Chicago, IL: AbbVie Inc.; May 2017. Available at: http://www.rxabbvie.com/pdf/lupronpediatric.pdf. Accessed July 27, 2018.
8. National Comprehensive Cancer Network Drugs and Biologics Compendium. Leuprolide acetate. Available at nccn.org. Accessed July 26, 2017.
9. National Comprehensive Cancer Network Drugs and Biologics Compendium. Leuprolide acetate for depot suspension. Available at nccn.org. Accessed July 27, 2018.
10. National Comprehensive Cancer Network. Prostate cancer (Version 3.2018). Available at nccn.org. Accessed July 27, 2018.
11. National Comprehensive Cancer Network. Breast cancer (Version 1.2018). Available at nccn.org. Accessed July 27, 2018.
12. National Comprehensive Cancer Network. Ovarian cancer (Version 2.2018). Available at nccn.org. Accessed July 27, 2018.
13. Committee on Practice Bulletins - Gynecology. Management of endometriosis. July 2010 (reaffirmed 2016); 116(1): 223-236.
14. Donnez J, Dolmans MM. Uterine fibroids management: From the present to the future. Hum Reprod Update. November 2016; 22(6): 665-686.
15. MS DeLaCruz, EM Buchanan. Uterine fibroids: Diagnosis and treatment. Am Fam Physician. January 15, 2017; 95(2): 100-107.
16. Marret H, Fritel X, Ouldamer L et al. Therapeutic management of uterine fibroid tumors: Updated French guidelines. Eur J Obstet Gynecol Reprod Biol. December 2012; 165(2): 156–164.
17. Kaplowitz P, Bloch C. Evaluation and referral of children with signs of early puberty. Pediatrics. 2016; 137(1): e20153732.