PART B DRUG MEDICAL/PHARMACY	ASPIRE HEALTH	Effective Date August 15, 2024	
	Leuprolide Long-Acting Products Lupron Depot®, Eligard® Camcevi™ Lutrate Depot™	**Policy #** **Leuprolide Long-Acting Products**	
		Review Date 05/28/2024	**Applicable to:** ☑ Medicare Advantage ☐ Commercial ☐ Elevance Health HMO ☐ Blue Shield Trio
	Approver's Name & Title QI & UM Drug Subcommittee		

Aspire Health Plan applies medical drug clinical criteria as a reference for medical policy information only. Federal and state laws or requirements, contract language, and Plan benefit may take precedence over the application of these clinical criteria. Please consult the applicable certificate or contract for benefit details. This policy is subject to revision at the discretion of the Plan and is therefore subject to change. Refer to the 'Disclaimer' section below for more information.

OVERVIEW

This policy addresses the coverage of the leuprolide acetate (Lupron®, Lupron Depot®, Eligard®, Lutrate Depot®) and leuprolide mesylate (Camcevi™), synthetic analogs of gonadotropin releasing hormone (GnRH) for the following indications:

FDA-APPROVED INDICATIONS (Adults)

- Advanced Prostate Cancer (including palliative treatment)
- Endometriosis
- Uterine leiomyomata (Uterine Fibroids)

COMPENDIAL / OFF-LABEL INDICATIONS (Adults)†

- Breast Cancer, premenopausal†
- Breast Cancer in male patients, hormone receptor–positive†
- Ovarian Cancer / Fallopian Tube Cancer / Primary Peritoneal Cancer†
- Head and Neck Cancer (salivary gland tumors)†

EXPERIMENTAL/INVESTIGATIONAL: All other uses are considered experimental or investigational and, therefore, not covered unless the indication is supported as an accepted off-label use, as defined in the Company medical policy on off-label coverage for prescription drugs and biologics.

PLACE OF SERVICE: The administration of GnRH analogs is typically an outpatient procedure which is only eligible for coverage as an inpatient procedure in special circumstances, including, but not limited to, the presence of a co-morbid condition that would require monitoring in a more controlled environment such as the inpatient setting.

APPLICABLE HCPCS

LUPRON DEPOT: J1950 Injection, leuprolide acetate (for depot suspension), per 3.75mg

Injection, suspension (Lupron Depot)
- 3.75mg (monthly)
- 11.25mg (3 months)

CAMCEVI (42 mg Kit): J1952 Leuprolide injectable, camcevi, 1 mg

Injection, emulsion (Camcevi)
- 42mg/prefilled syringe (6 months)

LUPRON DEPOT & ELIGARD: J9217 Leuprolide acetate (for depot suspension), 7.5 mg

Injection, powder for reconstitution
- 7.5mg (1-month) (Eligard)
- 22.5mg (3-month) (Eligard)
- 30mg (4-month) (Eligard)
- 45mg (6-month) (Eligard)

Injection, suspension (Lupron Depot)
- 7.5mg (1-month)
- 22.5mg (3-month)
- 30mg (4-month)
- 45mg (6-month)

LUTRATE DEPOT (22.5 MG KIT): J1954 Injection, leuprolide acetate for depot suspension (lutrate), 7.5 mg

NOT ADDRESSED IN THIS POLICY			
HCPCS	**Drug Name**	**Strength**	**Indications**
J1951	Fensolvi	45 mg	Central Precocious Puberty
J1950	Lupron Depot-Ped	7.5 mg	Central Precocious Puberty
J1950	Lupron Depot-Ped	11.25 mg	Central Precocious Puberty
J1950	Lupron Depot-Ped 3-Month	11.25 mg	Central Precocious Puberty
J1950	Lupron Depot-Ped	15 mg	Central Precocious Puberty
J1950	Lupron Depot-Ped 3-Month	30 mg	Central Precocious Puberty
J9218	Leuprolide acetate, per 1 mg	1mg/0.2mL kit	Usually self-administered form of leuprolide acetate and is not covered under Medicare Part A/B Self-Administered Drugs (SADs) List

CLINICAL CRITERIA

I. INITIAL CRITERIA

Requested drug may be authorized when ALL of the following criteria are met:

A. Documented diagnosis of **ONE** of the following AND all its respective criteria are met:

1. Prostate Cancer, Advanced*
   *The LCD does not specify a definition of advanced; until which time that it does, practitioners may consider advanced to mean metastatic or not amenable to surgery for any reason.

2. Endometriosis

3. Uterine leiomyomata (Uterine Fibroids)

4. Breast Cancer, premenopausal†

5. Breast Cancer in male patients, hormone receptor–positive†

6. Ovarian Cancer† / Fallopian Tube Cancer† / Primary Peritoneal Cancer†

7. Head and Neck Cancer (salivary gland tumors)† : *Documented diagnosis of androgen-receptor positive recurrent salivary gland tumor.*

†*Compendial / Off-Label Indications*

AND

B. Prescribed by, or in consultation with, a board-certified oncologist, hematologist, or physician specialist appropriate to treat member's condition [e.g., Oncologic indications: Oncologist; prostate cancer: oncologist or urologist; Women's health indications (endometriosis, uterine leiomyomata): obstetrician-gynecologist]. If prescribed in consultation, consultation notes must be submitted with initial request and reauthorization requests.

AND

C. Member has no known contraindication(s) to requested leuprolide product (e.g., Known hypersensitivity to GnRH analogs, or any of component of the product)

AND

D. Exclusions / Limitations

1. All other uses are considered experimental/investigational and, therefore, not covered unless the indication is supported as an accepted off-label use, as defined in the 'Off-Label Use of Drugs and Biologic Agents' policy.

2. The dose and frequency of administration is not consistent with the FDA approved labeling. Doses and frequencies that exceed the FDA recommended dosage/frequency as per the prescribing information, are considered not reasonable and necessary and not covered by Medicare.

II. REAUTHORIZATION / CONTINUATION OF THERAPY CRITERIA

Requested leuprolide product may be authorized for continuation of therapy when initial criteria have been met **AND** ALL of the following are met:

1. Documentation demonstrating the positive response or clinical benefits to the requested drug supporting continued treatment; or Requested drug is being continued in accordance with the recommended time as defined by FDA approved labeling or per recommendations of the CMS authorized compendia, or per the professional society guidelines (including but not limited to: NCCN, ASCO, ACOG or AAP standard of care guidelines); **and**

2. Prescriber attests to, or clinical reviewer has found, no evidence of intolerable adverse effects or unacceptable toxicity with the requested drug; and

STEP THERAPY

Step therapy is not applicable at this time.

Numerous leuprolide products are commercially available (e.g., Camcevi, Eligard, Lupron Depot). However, the superiority of any specific leuprolide product over others is not substantiated by reliable evidence. Certain products are more cost-effective and at least as likely to produce equivalent therapeutic results as the other leuprolide products.

AHP may recommend the most cost-effective formulary product in accordance with the FDA approved indication for the member.

DOSAGE AND AUTHORIZATION TIMEFRAMES

1. Recommended Dose: The requested dose and frequency are in accordance with FDA-approved labeling, CMS recognized compendia, and/or evidence-based practice guidelines.

Indication	Dose
Uterine Leiomyomata (fibroids)	3.75 mg **IM** monthly for up to 3 months or 11.25 mg **IM** once **(J1950)** Use concomitant iron treatment
Breast Cancer / Ovarian Cancer (Fallopian Tube Cancer / Primary Peritoneal Cancer)	**Breast cancer in male patients, hormone receptor-positive (Off-label)** *Advanced or metastatic disease:* 3.75 mg **IM** once every 4 weeks **(J1950)**. Endocrine therapy for males with advanced or metastatic, HR+, HER2-negative breast cancer may be sequenced as in females. **Breast Cancer in Premenopausal Ovarian Ablation (Off-label)** 3.75 mg **IM** every 28 days or 11.25 mg **IM** every 3 months for up to 24 months **(J1950)**
Endometriosis	3.75 mg **IM** monthly for up to 6 months or 11.25 mg **IM** every 3 months for 2 doses (6 months total) **(J1950)** Recommended duration of treatment is 6 months; may treat again for additional 6 months, but with concomitant administration of norethindrone. **Total duration of therapy (initial plus re-treatment for symptom recurrence) should not exceed 12 months.**

Prostate Cancer, Advanced	Leuprolide acetate: • Lupron: 7.5 mg **IM** monthly, 22.5 mg IM every 3 months, 30 mg IM every 4 months, or 45 mg IM every 6 months **(J9217)** • Eligard: 7.5 mg **SQ** monthly, 22.5 mg **SQ** every 3 months, 30 mg **SC** every 4 months, 45 mg **SQ** every 6 months **(J9217)** • Lutrate Depot 22.5 mg Kit: 22.5 mg IM every 3 months **(J1954)** • Leuprolide acetate: 1 mg/0.2 mL/day **SQ** (**J9218 is a self-administered form of leuprolide acetate and is not covered under Medicare Part B)** Leuprolide mesylate: • Camcevi: 42 mg **SQ** every 6 months (**J1952)**
Head and Neck Cancer (salivary gland tumors)	IM or SQ: 7.5 mg every 4 weeks, 22.5 mg every 12 weeks **(J9217)**
Do not use concurrently a fractional dose, or a combination of doses of this or any depot formulation due to different release characteristics.	

2. **Maximum Quantity:** Not to exceed the recommended dosing in FDA-approved labeling, CMS recognized compendia, and/or evidence-based practice guidelines for prescribed indication.

3. **Authorization Period (initial authorization and re-authorization)**

   a. Endometriosis
   Initial authorization: May authorize up to 6 months
   Reauthorization: One time only.
   Total duration of therapy: Not to exceed 12 months.

   b. Uterine leiomyomata (fibroids)
   Initial authorization: 3 months
   Reauthorization: 3 months
   Total duration of therapy: Not to exceed 6 months.

   c. All Other Indications (Advanced Prostate Cancer, Breast Cancer, Ovarian Cancer)
   Initial authorization: 12 months
   Reauthorization: 12 months

DRUG INFORMATION

PHARMACOLOGIC CATEGORY: Antineoplastic Agent, Gonadotropin-Releasing Hormone Agonist

ROUTE OF ADMINISTRATION: Intramuscular Administration (IM), Subcutaneous (SQ) Injection.

- IM administration: Lupron Depot and Lutrate Depot
- SQ administration: Eligard and Camcevi (must be administered by a healthcare provider).

FDA-APPROVED INDICATIONS (Adults)

- Prostate cancer, *advanced*
- Endometriosis (as monotherapy or in combination with norethindrone)
- Uterine leiomyomata (fibroids) (in combination with iron)
- *Central precocious puberty (not addressed in this policy).*

COMPENDIAL APPROVED (OFF-LABEL) USES (Adults)

- Breast cancer
- Ovarian cancer
- Premenstrual syndrome
- Prostate cancer
- Uterine leiomyoma
- Fertility preservation procedure, in women with cancer *(not addressed in this policy)*
- Gender dysphoria, Transgender female; Adjunct *(not addressed in this policy)*
- In vitro fertilization *(indication not covered; not addressed in this policy)*

CONTRAINDICATIONS

- Hypersensitivity to leuprolide, GnRH, GnRH-agonist analogs, or any component of the formulation.
- Lupron Depot 3.75 mg (monthly) and Lupron Depot 11.25 mg (3-month): Additional contraindications: patients with undiagnosed uterine bleeding; pregnancy.

OTHER CONSIDERATIONS

Concerns related to adverse effects: Metabolic changes (such as hyperglycemia, diabetes, hyperlipidemia) may occur; metabolic dysfunction–associated steatotic liver disease, including cirrhosis, has also been reported. Hyperglycemia may manifest as new-onset diabetes or worsening of glycemic control in patients with preexisting diabetes.

CLINICAL SUMMARY / APPENDIX

Leuprolide acetate (Lupron®, Lupron Depot®, Eligard®, Lutrate Depot®) and leuprolide mesylate (Camcevi™) are synthetic analogs of gonadotropin releasing hormone (GnRH). Although leuprolide has potent GnRH agonist properties during short-term or intermittent therapy, the principal effect of the drug during long-term administration is inhibition of gonadotropin secretion and suppression of ovarian and testicular steroidogenesis.

Initially, the administration of leuprolide causes stimulation of pituitary gonadotropins luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which leads to an increase in steroidogenesis in ovaries and testes; thus, resulting in increased estrogen in females and increased testosterone and dihydrotestosterone in males. With continuous administration, the levels of gonadotropins and gonadal steroids fall. Ultimately, continuous use of leuprolide decreases levels of testosterone in males and estrogen in females by inhibiting LH and FSH production.

Leuprolide acetate is administrable through an IM or SQ injection. The patient can receive injections in 1, 3, 4, or 6-month increments, and the length of time determines the specific dosage in between each injection. Dosages should not be combined because there are different release characteristics.

Professional Society Guidelines

Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

Currently, as per the NCCN Prostate Cancer Guidelines, there is no preference for any one ADT agent over another. These agents are either LHRH agonists or LHRH antagonists:

- LHRH agonists: Eligard, Lupron, Camcevi (subcutaneous 6-month injection)
  - *Not addressed in this policy: Zoladex (goserelin implant) 3.6 mg, Trelstar (triptorelin)*
- LHRH agonist: Firmagon, Orgovyx (oral drug)

The National Comprehensive Cancer Network® (NCCN) Clinical Practice Guidelines in Oncology for Breast Cancer®, the NCCN Clinical Practice Guidelines in Oncology for Head and Neck Cancers®, the NCCN Clinical Practice Guidelines in Oncology for Ovarian Cancer®, and the NCCN Clinical Practice Guidelines in Oncology for Prostate Cancer® are referenced for recommendations for coverage across each of these disease settings (LCD L39387).

REFERENCES

Government Agency

Centers for Medicare and Medicaid Services (CMS). Medicare coverage database (no NCD identified; no applicable LCD identified for MAC; search terms: Lupron; leuprolide acetate). Available from CMS.

- LCD (L39387) for Luteinizing Hormone-Releasing Hormone (LHRH) Analogs is not specific to the Medicare Part B Administrative Contractor (MAC) for CA [Jurisdiction E (1)] (Active LCDs - JE Part B – Noridian); however this LCD is considered in this policy.

Centers for Medicare and Medicaid Services (CMS). CMS IOM, Publication 100-02, Medicare Benefit Policy Manual, Chapter 15, Section 50.4.5

Prescribing Information

1. Eligard [package insert]. Fort Collins, CO; Tolmar Therapeutics, Inc; April 2019. Accessed May 2024.
2. Fensolvi [package insert]. Fort Collins, CO; Tolmar Therapeutics, Inc; May 2020. Accessed May 2024.
3. Camcevi [package insert]. Taipei City, Taiwan; Foresee Pharmaceuticals Co., Ltd.; May 2021. Accessed May 2024.
4. Leuprolide Acetate Depot [prescribing information]. Warren, NJ: Cipla USA, Inc.; July 2022.
5. Lupron Depot [prescribing information]. North Chicago, IL: AbbVie; April 2023.
6. Lutrate Depot [package insert]. Sant Quintí de Mediona, Spain; GP-PHARM, S.A..; August 2018. Accessed May 2024.

Peer-reviewed Literature, Guidelines, Consensus

National Comprehensive Cancer Network (NCCN). NCCN Guidelines Clinical Practice Guidelines in Oncology. Available at: NCCN Web site [via subscription only]. Accessed April 2024.

a. Breast Cancer Version: 2.2024. March 11, 2024.
b. Head and Neck Cancers Version 4.2024. May 1, 2024.
c. Ovarian Cancer Version 2.2024. May 13, 2024.
d. Prostate Cancer Version 3.2024. March 8, 2024.

IMPORTANT REMINDER

This Medicare Part B Step Therapy Medical Necessity Guideline is provided for informational purposes only and neither constitutes nor replaces professional medical advice. Physicians, hospitals, and other providers are expected to administer or use drugs/biologicals in the most effective and clinically appropriate manner. Treating physicians and other health care providers is solely responsible for all medical care decisions. In accordance with the member's Evidence of Coverage (EOC), every benefit plan has its own coverage provisions, limitations, and exclusions. In the event of a conflict between this policy and the member's EOC, the member's EOC provisions will take precedence.

Aspire Health Plan (AHP) adheres to Medicare guidelines, including National Coverage Determination (NCD), Local Coverage Determinations (LCDs), Local Coverage Articles (LCAs), and other relevant Medicare manuals established by CMS. Compliance with these guidelines is required when applicable. Refer to the CMS website at http://www.cms.hhs.gov. For the most up-to-date Medicare policies and coverage, please search the Medicare Coverage Database. All LCDS are the same for each state within a Jurisdiction. Medicare Part B Administrative Contractor (MAC) for CA [Jurisdiction E (1)]: Active LCDs - JE Part B – Noridian (noridianmedicare.com). In the event of a discrepancy between this policy and the Medicare NCD or LCD, the Medicare NCD/LCD will govern.

This policy is utilized by AHP to determine coverage in the absence of applicable CMS Medicare guidelines. Please refer to the links provided in the References section below to access the Medicare source materials that were used for developing this resource document. This document does not serve as a substitute for the official Medicare source materials that provide detailed information on Medicare coverage requirements. In the event of a conflict between this document and Medicare source materials, the Medicare source materials will take precedence.

The inclusion of a code in this policy does not imply that the health service it describes is covered or not covered. Benefit coverage for health services is determined by the member-specific plan document and applicable laws that may mandate coverage for a particular service. Inclusion of a code does not imply or guarantee reimbursement or payment of a claim. Other Policies and Standards may also apply. Providers are expected to retain or have access to the necessary documentation when requested to support coverage.

POLICY HISTORY

Version	Date	Summary of Changes
1	05/28/2024	New Policy