Reference number(s)
4694-A

Standard Medicare Part B Management leuprolide depot products

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Lupron Depot 1-Month 7.5 Mg	leuprolide acetate 1-Month 7.5 Mg
Lupron Depot 3-Month 22.5 Mg	leuprolide acetate 3-Month 22.5 Mg
Lupron Depot 4-Month 30 Mg	leuprolide acetate 4-Month 30 Mg
Lupron Depot 6-Month 45 Mg	leuprolide acetate 6-Month 45 Mg

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication[1,2]

Lupron Depot 1-Month 7.5 mg, Lupron Depot 3-Month 22.5 mg, leuprolide acetate depot 3-month 22.5 mg, Lupron Depot 4-Month 30 mg, and Lupron Depot 6-Month 45 mg are indicated in the treatment of advanced prostate cancer.

Compendial Uses

- Prostate cancer[3]
- Ovarian cancer - Malignant sex cord-stromal tumors (granulosa cell tumors) (7.5 mg and 22.5 mg)[3]

- Gender dysphoria (also known as transgender and gender diverse [TGD] persons)[4-6]
- Induction of amenorrhea[7]
- Catamenial pneumothorax[7]
- Irritable bowel syndrome[7]
- Breast cancer (7.5 mg and 22.5 mg)[3,11]
- Use in combination with growth hormone for children with growth failure and advancing puberty[7]

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Coverage Criteria

Prostate cancer[1-3]

Authorization of 12 months may be granted for treatment of prostate cancer.

Gender dysphoria[4-7]

Authorization of 12 months may be granted for pubertal hormonal suppression in an adolescent member when all of the following criteria are met:

- The member has a diagnosis of gender dysphoria.
- The member has reached Tanner stage 2 of puberty or greater.

Authorization of 12 months may be granted for gender transition when all of the following criteria are met:

- The member has a diagnosis of gender dysphoria.
- The member will receive the requested medication concomitantly with gender-affirming hormones.

Ovarian cancer (7.5 mg and 22.5 mg only)[3]

Authorization of 12 months may be granted for treatment of malignant sex cord-stromal tumors (granulosa cell tumors) as a single agent.

Induction of amenorrhea[7]

Authorization of 6 months may be granted for induction of amenorrhea prior to undergoing bone marrow transplantation.

Catamenial pneumothorax[7]

Authorization of 3 months may be granted for treatment of catamenial pneumothorax.

Irritable bowel syndrome[7]

Authorization of 6 months may be granted for treatment of irritable bowel syndrome.

Breast cancer (7.5 mg and 22.5 mg only)[3,11]

Authorization of 12 months may be granted for ovarian suppression in premenopausal members with hormone-receptor positive breast cancer at higher risk for recurrence (e.g., young age, high-grade tumor, lymph-node involvement) when used in combination with endocrine therapy.

Advancing puberty and growth failure[7]

Authorization of 12 months may be granted for treatment of advancing puberty and growth failure in a pediatric member when used in combination with growth hormone.

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Ovarian Cancer

Authorization for 12 months may be granted when both of the following criteria are met:

- The member is currently receiving therapy with the requested medication.
- The member is receiving benefit from therapy. Benefit is defined as:
    - No evidence of unacceptable toxicity while on the current regimen AND
    - No evidence of disease progression while on the current regimen

Prostate Cancer

Authorization for 12 months may be granted when both of the following criteria are met:

- The member is currently receiving therapy with the requested medication.
- The member is receiving benefit from therapy (e.g., serum testosterone less than 50 ng/dL) and has not experienced unacceptable toxicity.

Breast Cancer - Ovarian Suppression

Authorization of 12 months (up to 5 years total) may be granted when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication.
- The requested medication is being used for ovarian suppression in hormone receptor positive breast cancer.
- The member was premenopausal at diagnosis and still undergoing treatment with endocrine therapy.
- The member is receiving benefit from therapy and has not experienced an unacceptable toxicity.

Gender Dysphoria

Authorization for 12 months may be granted when both of the following criteria are met:

- The member is currently receiving therapy with the requested medication.
- The member is receiving benefit from therapy.

Advancing Puberty and Growth Failure

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication.
- The requested medication is being used in combination with growth hormone.
- The member is receiving benefit from therapy.

Induction of Amenorrhea and Irritable Bowel Syndrome

Authorization for 6 months may be granted when both of the following criteria are met:

- The member is currently receiving therapy with the requested medication.
- The member is receiving benefit from therapy.

Catamenial Pneumothorax

All members (including new members) requesting authorization for continuation of therapy for catamenial pneumothorax must meet all requirements in the coverage criteria section.

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Lupron Depot 7.5 mg, 22.5 mg, 30 mg, 45 mg, and leuprolide

acetate depot 22.5 mg.

- The available compendium
  - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
  - Micromedex DrugDex
  - American Hospital Formulary Service- Drug Information (AHFS-DI)
  - Lexi-Drugs
  - Clinical Pharmacology
- NCCN Guideline: Prostate Cancer
- NCCN Guideline: Ovarian Cancer
- NCCN Guideline: Breast Cancer
- Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline
- Gender Identity Research and Education Society. Guidance for GPs and other clinicians on the treatment of gender variant people.
- Standards of Care for the Health of Transgender and Gender Diverse People, Version 8

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Lupron Depot 7.5 mg, 22.5 mg, 30 mg, 45 mg, and leuprolide acetate depot 22.5 mg are covered in addition to the following:

- Prostate cancer
- Ovarian cancer - Malignant sex cord-stromal tumors (granulosa cell tumors)
- Gender dysphoria (also known as transgender and gender diverse [TGD] persons)
- Induction of amenorrhea
- Catamenial pneumothorax
- Irritable bowel syndrome
- Breast cancer
- Use in combination with growth hormone for children with growth failure and advancing puberty

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Lupron Depot to treat malignant sex cord-stromal tumors (granulosa cell tumors), prostate cancer, and breast cancer can be found in the NCCN Drugs and Biologics Compendium. 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).

Support for using Lupron Depot for gender dysphoria can be found in the Endocrine Society Clinical Practice Guideline for Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons. The guidelines support gonadotropin-releasing hormone (GnRH) agonist use in both transgender males and transgender females. Specific products are not listed; therefore, coverage is applied to the entire class of GnRH agonists.

Support for using Lupron Depot for gender dysphoria can also be found in the World Professional Association for Transgender Health (WPATH). The Standards of Care for the Health of Transgender and Gender Diverse People, Version 8, suggests to prescribe GnRH agonists to suppress sex steroids without concomitant sex steroid hormone replacement in eligible transgender and gender diverse adolescents seeking such intervention who are well into or have completed pubertal development (defined as past Tanner stage 3) but are unsure about or do not wish to begin sex steroid hormone therapy. WPATH also recommends beginning pubertal hormone suppression in eligible transgender and gender diverse adolescents after they first exhibit physical changes of puberty (Tanner stage 2).

WPATH recommends health care professionals prescribe progestogens or a GnRH agonist for eligible transgender and gender diverse adolescents with a uterus to reduce dysphoria caused by their menstrual cycle when gender-affirming testosterone use is not yet indicated.

WPATH also recommends health care professionals prescribe testosterone-lowering medications (including GnRH agonists) for eligible transgender and gender diverse people with testes taking estrogen as part of a hormonal treatment plan if their individual goal is to approximate levels of circulating sex hormone in cisgender women.

Support for using Lupron Depot to induce amenorrhea can be found in a study by Laufer and colleagues. Leuprolide was an effective way of inducing amenorrhea prior to women undergoing bone marrow transplantation. In 10 women, leuprolide 7.5 mg IM was given every 28 days before bone marrow transplantation and continued until the platelet count was greater than 50,000. Nine of the 10 women experienced amenorrhea. One woman with an "18-week" sized uterus containing a submucous myoma had continued spotting.

Support for using Lupron Depot to treat catamenial pneumothorax can be found in a case study published by Garris and Sokol. A 35-year-old nulligravida black female diagnosed with catamenial pneumothorax was successfully treated with depot leuprolide 7.5 mg monthly for 3 months followed by 3.75 mg monthly for 3 months. Prior to leuprolide treatment, the patient had undergone a right partial pleurectomy and partial right upper lobectomy without resolution of her catamenial respiratory symptoms. With leuprolide treatment, her symptoms resolved without recurrence in 2 years of followup. Because of severe vasomotor and emotional side effects which developed with leuprolide therapy, daily doses of continuous conjugated estrogens of 0.625 mg and medroxyprogesterone acetate 2.5 mg were instituted as a hormonal add-back regimen without apparent exacerbation of respiratory symptoms.

Support for using Lupron Depot to treat irritable bowel syndrome can be found in a study by Mathias et al. In a multicenter, double-blind study, women receiving leuprolide depot 7.5 mg monthly had improved abdominal pain and nausea as compared with placebo. Female patients with functional bowel disease were randomized to receive monthly intramuscular injections of either leuprolide 3.75 mg (n=32), leuprolide 7.5 mg (n=33), or placebo (n=35) for 16 weeks. Total symptom scores (pain, nausea, vomiting,

bloating, anorexia, early satiety, altered bowel habits) were not statistically different for the leuprolide group compared with the placebo group. However, scores for pain and nausea for the leuprolide 7.5 mg group were significantly better than placebo at 16 weeks (p=0.044 and p less than 0.001, respectively). In both leuprolide groups, patient evaluations and physician global evaluations were statistically better (p less than 0.001).

Support for using Lupron Depot in combination with growth hormone for children with growth failure and advancing puberty can be found in a study by Mericq et al. (2000). Combination treatment with growth hormone (GH) and luteinizing hormone-releasing hormone analog (LHRH-A) in pubertal growth hormone-deficient patients resulted in a significant decrease in the rate of bone maturation and an increase in final height. The prospective trial randomized 21 growth hormone-deficient pediatric patients to GH plus LHRH-A or GH alone for 3 years. A significant decrease in bone age maturation was observed for the combination treatment group (1.5 years) compared with the GH only group (4.2 years; p less than 0.05). The delay in bone age maturation produced a significant increase in final height in the combination group (p less than 0.05).

References

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