Reference number(s)
4728-A

STANDARD MEDICARE PART B MANAGEMENT

LUPRON DEPOT 3.75 mg
LUPRON DEPOT-3 Month 11.25 mg
(leuprolide acetate for depot suspension)

POLICY

I. 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.

A. FDA-Approved Indications

1. Endometriosis

Lupron Depot 3.75 mg and Lupron Depot-3 Month 11.25 mg are indicated for management of endometriosis, including pain relief and reduction of endometriotic lesions. Lupron Depot 3.75 mg monthly and Lupron Depot-3 Month 11.25 mg with norethindrone acetate 5 mg daily are also indicated for initial management of the painful symptoms of endometriosis and for management of recurrence of symptoms.

Use of norethindrone acetate in combination with Lupron Depot 3.75 mg and Lupron Depot 11.25 mg is referred to as add-back therapy, and is intended to reduce the loss of bone mineral density (BMD) and reduce vasomotor symptoms associated with use of Lupron Depot 3.75 mg and Lupron Depot 11.25 mg.

2. Uterine Leiomyomata (Fibroids)

When used concomitantly with iron therapy, Lupron Depot 3.75 mg and Lupron Depot-3 Month 11.25 mg are indicated for preoperative hematologic improvement of women with anemia caused by fibroids for whom three months of hormonal suppression is deemed necessary. The clinician may wish to consider a one-month trial period on iron alone, as some women will respond to iron alone. Lupron Depot may be added if the response to iron alone is considered inadequate.

Limitations of Use:

For endometriosis: The total duration of therapy with Lupron Depot 3.75 mg and 11.25 mg plus add-back therapy should not exceed 12 months due to concerns about adverse impact on bone mineral density.

For uterine leiomyomata: Lupron Depot 3.75 mg and 11.25 mg is not indicated for combination use with norethindrone acetate add-back therapy for the preoperative hematologic improvement of women with anemia caused by heavy menstrual bleeding due to fibroids.

B. Compendial Uses

1. Breast cancer
2. Ovarian Cancer
   i. Epithelial ovarian cancer/fallopian tube cancer/primary peritoneal cancer
   ii. Carcinosarcoma (Malignant mixed Müllerian tumors)

iii. Grade 1 endometrioid carcinoma
iv. Low-grade serous carcinoma
v. Mucinous carcinoma of the ovary
vi. Clear cell carcinoma of the ovary

3. Salivary gland tumors
4. Gender dysphoria (also known as transgender and gender diverse (TGD) persons)
5. Preservation of ovarian function
6. Prevention of recurrent menstrual related attacks in acute porphyria
7. Adrenocorticotropic hormone (ACTH)-dependent Cushing's syndrome
8. Catamenial pneumothorax
9. Irritable bowel syndrome
10. Premenstrual syndrome
11. Use in combination with growth hormone for children with growth failure and advancing puberty
12. Induction of amenorrhea

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

II. CRITERIA FOR INITIAL APPROVAL

A. Endometriosis

Authorization of up to 6 months (one treatment course) may be granted to members for initial treatment of endometriosis.

B. Uterine leiomyomata (fibroids)

Authorization of up to 3 months may be granted for initial treatment of uterine leiomyomata (fibroids) when either of the following criteria is met:

1. Member has anemia due to uterine leiomyomata, or
2. Lupron Depot will be used prior to surgery for uterine leiomyomata.

C. Breast cancer

Authorization of 12 months may be granted for treatment of hormone receptor-positive breast cancer.

D. Ovarian cancer

Authorization of 12 months may be granted for treatment of the following types of ovarian cancer:

1. Epithelial ovarian cancer
2. Fallopian tube cancer
3. Primary peritoneal cancer
4. Grade 1 endometrioid carcinoma
5. Low-grade serous carcinoma
6. Carcinosarcoma (malignant mixed Müllerian tumors)
7. Mucinous carcinoma of the ovary
8. Clear cell carcinoma of the ovary

E. Salivary gland tumors

Authorization of 12 months may be granted for treatment of recurrent salivary gland tumors when the tumor is androgen receptor positive.

F. Gender dysphoria

1. Authorization of 12 months may be granted for pubertal hormonal suppression in an adolescent member when all of the following criteria are met:
   a. The member has a diagnosis of gender dysphoria.
   b. The member has reached Tanner stage 2 of puberty or greater.
2. Authorization of 12 months may be granted for gender transition when all of the following criteria are met:
   a. The member has a diagnosis of gender dysphoria.
   b. The member will receive the requested medication concomitantly with gender-affirming hormones.

G. Preservation of ovarian function
Authorization of 3 months may be granted for preservation of ovarian function when the member is premenopausal and undergoing chemotherapy.

H. Prevention of recurrent menstrual related attacks in acute porphyria
Authorization of 12 months may be granted for prevention of recurrent menstrual related attacks in members with acute porphyria when the requested medication is prescribed by or in consultation with a physician experienced in the management of porphyrias.

I. Adrenocorticotropic hormone (ACTH)-dependent Cushing's syndrome
Authorization of 12 months may be granted for treatment of ACTH-dependent Cushing's syndrome.

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

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

L. Premenstrual syndrome
Authorization of 3 months may be granted for treatment of premenstrual syndrome.

M. Advancing puberty and growth failure
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.

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

III. CONTINUATION OF THERAPY

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

A. Authorization for 6 months (for a lifetime maximum of 12 months total) may be granted when all of the following criteria are met:
   1. The member is currently receiving therapy with the requested medication.
   2. The requested medication is being used to treat endometriosis.
   3. The member is receiving benefit from therapy.
   4. The member has had a recurrence of symptoms.
   5. The member has a bone mineral density within normal limits.

B. Authorization for 3 months (for a lifetime maximum of 6 months total) may be granted when all of the following criteria are met:
   1. The member is currently receiving therapy with the requested medication.
   2. Lupron Depot is being used to treat uterine leiomyomata (fibroids).
   3. The member is receiving benefit from therapy.
   4. The member meets one of the following:
      i. The member has anemia due to uterine leiomyomata.
      ii. The requested medication will be used prior to surgery for uterine leiomyomata.

C. Authorization for 12 months may be granted when all of the following criteria are met:
   1. The member is currently receiving therapy with the requested medication.
   2. The requested medication is being used to treat breast cancer, ovarian cancer, or salivary gland tumors.
   3. The member is receiving benefit from therapy and has not experienced unacceptable toxicity.

D. Authorization for 12 months may be granted when all of the following criteria are met:
   1. The member is currently receiving therapy with the requested medication.
   2. The requested medication is being used to treat one of the following indications enumerated in Section II:
      i. Gender dysphoria
      ii. Prevention of recurrent menstrual related attacks in acute porphyria
      iii. ACTH-dependent Cushing's syndrome
      iv. Advancing puberty and growth failure in combination with growth hormone
   3. The member is receiving benefit from therapy.

E. Authorization for 6 months may be granted when all of the following criteria are met:
   1. The member is currently receiving therapy with the requested medication.
   2. The requested medication is being used to treat one of the following indications enumerated in Section II:
      i. Irritable bowel syndrome
      ii. Induction of amenorrhea
   3. The member is receiving benefit from therapy.

F. Authorization for 3 months may be granted when all of the following criteria are met:
   1. The member is currently receiving therapy with the requested medication.
   2. The requested medication is being used to treat one of the following indications enumerated in Section II:
      i. Preservation of ovarian function
      ii. Catamenial pneumothorax
      iii. Premenstrual syndrome
   3. The member is receiving benefit from therapy.

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Lupron Depot 3.75 mg and 11.25 mg.
2. The available compendium
   a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
   b. Micromedex DrugDex
   c. American Hospital Formulary Service- Drug Information (AHFS-DI)
   d. Lexi-Drugs

e. Clinical Pharmacology
3. NCCN Guideline: Head and neck cancers
4. NCCN Guideline: Breast cancer
5. NCCN Guideline: Ovarian cancer/fallopian tube cancer/primary peritoneal cancer
6. Management of symptomatic uterine leiomyomas: ACOG Practice Bulletin No. 228. American College of Obstetricians and Gynecologists
7. Therapeutic management of uterine fibroid tumors: updated French guidelines
8. Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline
9. Guidance for GPs and other clinicians on the treatment of gender variant people
10. Standards of care for the health of transsexual, transgender, and gender-nonconforming people, 8th version
11. British and Irish Porphyria Network. Best practice guidelines on clinical management of acute attacks of porphyria and their complications.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Lupron Depot 3.75 mg and 11.25 mg are covered in addition to the following:

1. Breast cancer
2. Ovarian Cancer
   i. Epithelial ovarian cancer/fallopian tube cancer/primary peritoneal cancer
   ii. Carcinosarcoma (Malignant mixed Müllerian tumors)
   iii. Grade 1 endometrioid carcinoma
   iv. Low-grade serous carcinoma
   v. Mucinous carcinoma of the ovary
   vi. Clear cell carcinoma of the ovary
3. Salivary gland tumors
4. Gender dysphoria (also known as transgender and gender diverse (TGD) persons)
5. Preservation of ovarian function
6. Prevention of recurrent menstrual related attacks in acute porphyria
7. Adrenocorticotropic hormone (ACTH)-dependent Cushing's syndrome
8. Catamenial pneumothorax
9. Irritable bowel syndrome
10. Premenstrual syndrome
11. Use in combination with growth hormone for children with growth failure and advancing puberty
12. Induction of amenorrhea

V. EXPLANATION OF RATIONALE

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

Support for using Lupron Depot to treat breast cancer, ovarian cancer, and salivary gland tumors 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 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). According to the Standards of Care for the Health of Transgender and Gender Diverse People, Version 8, prescribing 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. PATH 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 progestins 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 for preservation of ovarian function can be found in the ASCO Clinical Practice Guidelines for fertility preservation in patients with cancer. The guideline indicates gonadotropin-releasing hormone receptor agonist therapy may be offered to young women, especially those with breast cancer, in the hope of reducing the likelihood of chemotherapy-induced ovarian insufficiency when proven fertility preservation methods (i.e., oocyte, embryo, or ovarian tissue cryopreservation) are not feasible. Gonadotropin-releasing hormone receptor agonists should not be used in place of proven fertility preservation methods.

Support for using Lupron Depot to prevent recurrent menstrual-related attacks in acute porphyria can be found in the British and Irish Porphyria Network on clinical management of acute attacks of porphyria and their complications (Stein, et al., 2012). In women with recurrent premenstrual attacks of porphyria, GnRH analogues can be administered to prevent ovulation. A number of preparations are available (busrelin, goserelin, histrelin, leuprorelin or triptorelin) and published studies have reported use of differing regimens, sometimes in extremely low doses.29,30 As an example, Zoladex 3.6 (containing goserelin acetate 3.6 mg) a long acting analogue of GnRH, can be given as an implant by subcutaneous injection into the anterior abdominal wall every 28 days, with the first injection being given during the first few days of the menstrual cycle. Administration of GnRH analogues may induce a hormone surge that can trigger an acute attack. Side-effects include depression, hot flushes, reduced libido, osteoporosis, and other menopausal symptoms. These can be reduced by use of a low dose estrogen patch. Pretreatment assessment of skeletal health (including bone mineral density [BMD] determination) should be arranged with regular gynecology review and annual BMD while treatment continues. Treatment with GnRH analogues should be reviewed after one year.

Support for using Lupron Depot to treat adrenocorticotropic hormone (ACTH)-dependent Cushing's syndrome can be found in a case report by Lacroix, Hamet and Boutin. A 63-year-old woman with bilateral adrenal hyperplasia and corticotropin-independent Cushing syndrome had her symptoms reversed with leuprolide therapy. The woman presented with hypertension, numbness, proximal muscle weakness of the lower extremities, hot flashes, weight gain, and a decrease in concentration and memory. Her Cushing syndrome had been manifested transiently during her pregnancies and became constant after menopause. It was determined that her Cushing syndrome resulted from corticotropin-independent bilateral macronodular hyperplasia. Her cortisol production was stimulated by gonadotropin-releasing hormone, and luteinizing hormone, and by drugs that activate serotonin 5-hydroxy-tryptamine receptors. With long-term leuprolide therapy (3.75 mg IM every 4 weeks), her urinary cortisol dropped into the normal range and her morning and evening plasma cortisol concentrations normalized. Her weight decreased and her blood pressure became normal.

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 to treat premenstrual syndrome can be found in a study by Schmidt and colleagues. Ovarian suppression with leuprolide treatment can reduce the symptoms of premenstrual syndrome (PMS) in some women. Twenty women with PMS, substantiated by symptom diaries for 3 menstrual cycles, were randomized to receive 3 monthly IM injections of either leuprolide depot 3.75 mg or and an equal amount of saline (placebo) in a double-blind manner. Women having 2 normal menstrual periods and no hot flashes were presumed to be taking placebo. Their codes were broken, and they were then offered the opportunity to take leuprolide in an open-label manner. For the leuprolide group, average PMS symptom scores at week 4 of treatment were significantly lower than at week 4 of baseline and lower than those in the group receiving placebo (p values all less than 0.05). No woman responded to placebo with a lessening of symptoms. Ten of 18 women who received leuprolide under either double-blind or open-label conditions responded.

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. Combination treatment with growth hormone and luteinizing hormone-releasing hormone analog in pubertal growth hormone-deficient patients resulted in a significant decrease in the rate of bone maturation and an increase in final height. A prospective trial randomized 21 growth hormone-deficient pediatric patients to growth hormone plus luteinizing hormone-releasing hormone analog or growth hormone alone for 3 years. A significant decrease in bone age maturation was observed for the combination treatment group (1.5 years) compared with the growth hormone 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).

Support for using Lupron Depot to induce amenorrhea prior to undergoing bone marrow transplantation 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.

VI. REFERENCES

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