Reference number(s)
4456-A

STANDARD MEDICARE PART B MANAGEMENT

ZOLADEX (goserelin acetate)

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. Prostate cancer
   a. For use in combination with flutamide for the management of locally confined stage T2b-T4 (Stage B2-C) carcinoma of the prostate. Treatment with Zoladex and flutamide should start 8 weeks prior to initiating radiation therapy and continue during radiation therapy.
   b. In the palliative treatment of advanced carcinoma of the prostate.
2. Endometriosis
   For the management of endometriosis, including pain relief and reduction of endometriotic lesions for the duration of therapy. Experience with Zoladex for the management of endometriosis has been limited to women 18 years of age and older treated for 6 months. (Zoladex 3.6 mg strength only)
3. Endometrial thinning
   For use as an endometrial-thinning agent prior to endometrial ablation for dysfunctional uterine bleeding. (Zoladex 3.6 mg strength only)
4. Advanced breast cancer
   For use in the palliative treatment of advanced breast cancer in pre-and perimenopausal women

B. Compendial Uses
1. Breast cancer
2. Prostate cancer
3. Gender dysphoria (also known as transgender and gender diverse (TGD) persons)
4. Preservation of ovarian function
5. Prevention of recurrent menstrual related attacks in acute porphyria
6. Uterine leiomyomata (fibroids)
7. Treatment of chronic anovulatory uterine bleeding with severe anemia
8. Precocious Puberty

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. DOCUMENTATION

The following documentation must be available, upon request, for all submissions: Hormone receptor status testing results (where applicable).

III. EXCLUSIONS

Coverage will not be provided for members with any of the following exclusions: Use of the 10.8 mg strength for diagnoses other than prostate cancer, breast cancer, and gender dysphoria (if applicable).

IV. CRITERIA FOR INITIAL APPROVAL

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

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

C. Endometriosis
Authorization of a total of 6 months may be granted to members for treatment of endometriosis.

D. Endometrial-thinning agent
1. Authorization of 2 doses may be granted for endometrial thinning prior to endometrial ablation or resection for dysfunctional uterine bleeding.
2. Authorization of a total of 6 months may be granted for treatment of chronic anovulatory uterine bleeding with severe anemia.

E. 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 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.

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

G. 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.

H. Uterine leiomyomata (fibroids)
Authorization of a total of 3 months may be granted for treatment of uterine leiomyomata (fibroids) prior to surgery.

I. Precocious puberty
Authorization of 12 months may be granted for precocious puberty when all the following criteria are met:
1. Member had onset of puberty signs before age two.
2. Precocious puberty is due to hypothalamic hamartoma.

V. CONTINUATION OF THERAPY

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

A. Breast cancer

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 member is receiving benefit from therapy and has not experienced an unacceptable toxicity.

B. Prostate cancer

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 member is receiving benefit from therapy (e.g., serum testosterone less than 50 ng/dL) and has not experienced an unacceptable toxicity.

C. Gender dysphoria, precocious puberty

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

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

D. Endometriosis, endometrial-thinning agent, preservation of ovarian function, prevention of recurrent menstrual related attacks in acute porphyria, uterine leiomyomata (fibroids)

All members (including new members) requesting authorization for continuation of therapy must meet all initial authorization criteria.

VI. SUMMARY OF EVIDENCE

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

1. The prescribing information for Zoladex.
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. Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline
4. Guidance for GPs and other clinicians on the treatment of gender variant people.
5. Standards of care for the health of transsexual, transgender, and gender-nonconforming people, 8th version.
6. 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 Zoladex are covered in addition to the following:

1. Breast cancer
2. Prostate cancer
3. Gender dysphoria (also known as transgender and gender diverse (TGD) persons)
4. Preservation of ovarian function
5. Prevention of recurrent menstrual related attacks in acute porphyria
6. Uterine leiomyomata (fibroids)

7. Treatment of chronic anovulatory uterine bleeding with severe anemia
8. Precocious Puberty

VII. EXPLANATION OF RATIONALE

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

Support for using Zoladex to treat breast cancer and prostate cancer in settings not discussed in the prescribing information 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 Zoladex as an endometrial-thinning agent in patients with chronic anovulatory uterine bleeding with severe anemia. In a study by Vercellini et al, subcutaneous goserelin was found to be effective in the treatment of 23 women with chronic anovulatory uterine bleeding and severe anemia. Goserelin was administered as a 3.6-mg depot injection once a month for 6 months; all patients received ferrous sulfate 150 mg twice daily. By two months, all patients were amenorrheic; spotting was reported on 9 subsequent occasions. Hematologic values, including mean hemoglobin, hematocrit, serum iron and serum ferritin, uniformity normalized after six months of combination therapy with goserelin and supplemental iron. Adverse events included hot flashes (91%), headache (30%), insomnia (26%), paresthesia (17%), joint pain (9%), peripheral edema (9%).

Support for using Zoladex to treat 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 Zoladex 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 Zoladex 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 Zoladex for the prevention of 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 Zoladex to treat uterine leiomyoma can be found in a study by Parazzini et al. A 3-year pilot study suggests that depot goserelin may enable peri-menopausal women (with 1 or more uterine fibroids greater than 10 centimeters, symptomatic menorrhagia lasting 3 months or more, and hemoglobin of 9 g/dL) to postpone or avoid hysterectomy. Enrollees were randomized in a 1:4 ratio to immediate surgery/hysterectomy (n=13) or to goserelin treatment (n=59). Goserelin was given as 3.6-mg depot every 28 days for 4 months. If menorrhagia recurred, patients were given another 3.6-mg depot for a 3-month cycle. The same 3-month cycle could be repeated with recurring menorrhagia; however, after that, surgery/hysterectomy was scheduled. During the 3 years of follow-up after initiation of goserelin, 23 of 59 women (39%) had undergone hysterectomy.
Additionally, a study by Rees, Chamberlain and Gillmer found fewer women required hysterectomies when they underwent endometrial resection after fibroid shrinkage with goserelin than when they were treated with goserelin only (33% vs 8.3%). However, among women who completed the 12-month follow-up, there was no statistical difference between treatments in fibroid regrowth. Twenty-nine premenopausal women with fibroids and uterine sizes between 12- and 16-weeks' gestation were given goserelin 3.6 mg subcutaneously every 28 days for 12 to 20 weeks, until randomization suitability (uterine size less than 345 milliliters). Of the 25 who were randomized to receive no further treatment (group 1) or endometrial resection (group 2), 7 women from group 1 and 1 woman from group 2 failed to complete the trial because of heavy menstrual bleeding; 7 of those underwent hysterectomy and 1 (from group 1) underwent resection. In a comparison of the 6 women of group 1 and the 11 from group 2 who completed the study, there was no statistical difference in median fibroid volume.

Support for using Zoladex to treat precocious puberty can be found in a study by de Brito and colleagues. Gonadotropin releasing hormone agonists (GnRH-a) stopped or regressed secondary sexual characteristics, significantly improved mean height standard deviation for bone age, and suppressed luteinizing hormone (LH) and follicle stimulating hormone (FSH) levels in 7 of 8 children with gonadotropin-dependent precocious puberty (GDPP) due to hypothalamic hamartoma. All patients had onset of puberty signs before age 2. Magnetic resonance imaging confirmed the presence of hypothalamic hamartoma. Each patient received either goserelin 3.6 mg intramuscularly or leuprolide acetate 3.75 mg subcutaneously every 4 weeks for 2.7 to 8.4 years. One patient had only a partial response and the treatment was changed to every 3 weeks. One patient developed severe local reaction at the injection site and failed the treatment. GnRH-a arrested and regressed sexual characteristics and suppressed basal and peak LH and FSH levels after GnRH administration in 7 of 8 patients. They also significantly increased the mean height standard deviation for bone age from -0.92 to 1.11 during treatment (p less than 0.05). The hamartomas, ranged in diameter from 5 to 18 millimeters, remained the same size and shape during the follow-up period of 4 to 6 years in 6 patients. Long

term GnRH-a treatment was safe and effective in controlling precocious pubertal development in this group of patients.

VIII. REFERENCES

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