Reference number(s)
4204-A

STANDARD MEDICARE PART B MANAGEMENT

TRELSTAR (triptorelin pamoate)

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 Indication
Trelstar is indicated for the palliative treatment of advanced prostate cancer

B. Compendial Uses
1. Prostate cancer
2. Gender dysphoria
3. Preservation of ovarian function
4. Breast cancer – ovarian suppression
5. Endometrial hyperplasia
6. Endometriosis
7. Fibrocystic breast changes
8. Uterine leiomyoma
9. Carcinoma of the pancreas
10. Ovarian carcinoma

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. CRITERIA FOR INITIAL APPROVAL

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

B. 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.

C. Preservation of ovarian function

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

D. Breast cancer – ovarian suppression

Authorization of 12 months may be granted for ovarian suppression in hormone-receptor positive breast cancer when all of the following criteria are met:

1. The member is premenopausal.
2. There is a higher risk for recurrence (e.g., young age, high-grade tumor, lymph-node involvement).
3. The requested medication will be used in combination with endocrine therapy.

E. Endometrial hyperplasia

Authorization of 12 months may be granted for treatment of non-atypical endometrial hyperplasia

F. Endometriosis

Authorization of up to 6 months total therapy may be granted for treatment of endometriosis.

G. Fibrocystic breast changes

Authorization of 3 months may be granted for treatment of benign fibrocystic mastopathy when either of the following criteria is met:

1. The requested medication will be used as a single agent.
2. The requested medication will be used in combination with tamoxifen or cyproterone.

H. Uterine Leiomyoma

Authorization of up to 6 months total therapy may be granted for treatment of uterine fibroids.

I. Adenocarcinoma of pancreas

Authorization of 12 months may be granted for treatment of adenocarcinoma of the pancreas.

J. Ovarian carcinoma

Authorization of 12 months may be granted for treatment of ovarian carcinoma.

IV. CONTINUATION OF THERAPY

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

A. 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 III:
      a. Adenocarcinoma of pancreas

b. Ovarian carcinoma
c. Gender dysphoria
d. Endometrial hyperplasia
e. Fibrocystic breast changes

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

B. Authorization of 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 for prostate cancer.
3. The member is receiving benefit from therapy (e.g., serum testosterone less than 50 ng/dL) and has not experienced an unacceptable toxicity.

C. Authorization of 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 for ovarian suppression in hormone receptor positive breast cancer.
3. The member was premenopausal at diagnosis and still undergoing treatment with endocrine therapy.
4. The member is receiving benefit from therapy and has not experienced an unacceptable toxicity.

D. 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 for preservation of ovarian function.
3. The member is receiving benefit from therapy and has not experienced an unacceptable toxicity.

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

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Trelstar.
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: Uterine neoplasms
4. NCCN Guideline: Prostate cancer
5. Fertility preservation in patients with cancer: ASCO clinical practice guideline update.
6. Adjuvant Endocrine Therapy for Women With Hormone Receptor-Positive Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update on Ovarian Suppression.
7. ESHRE guideline: endometriosis

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Trelstar are covered in addition to the following:
1. Prostate cancer

2. Gender dysphoria
3. Preservation of ovarian function
4. Breast cancer – ovarian suppression
5. Endometrial hyperplasia
6. Endometriosis
7. Fibrocystic breast changes
8. Uterine leiomyoma
9. Carcinoma of the pancreas
10. Ovarian carcinoma

VI. EXPLANATION OF RATIONALE

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

Support for using Trelstar to treat prostate cancer in settings not covered 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 Trelstar 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 Trelstar 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 Trelstar 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 Trelstar for ovarian suppression in patients with breast cancer can be found in the National Comprehensive Cancer Network's guideline for breast cancer. The NCCN Guideline for breast cancer supports the use of gonadotropin releasing hormone agonists during adjuvant chemotherapy in premenopausal patients with breast tumors (regardless of hormone receptor status). The use of gonadotropin releasing hormone agonists may preserve ovarian function and diminish the likelihood of chemotherapy-induced amenorrhea. Smaller historical experiences in patients with estrogen receptor-positive disease have reported conflicting results with regard to the protective effect of gonadotropin releasing hormone agonist therapy on fertility.
Additionally, support for using Trelstar for ovarian suppression in combination with endocrine therapy can be found in a study by Francis et al of 3066 premenopausal women with early-stage hormone receptor-positive breast cancer (SOFT study). Patients were randomized to receive 5 years of treatment with tamoxifen 20 mg daily, tamoxifen 20 mg daily and ovarian suppression, or exemestane 25 mg daily and ovarian suppression. Ovarian suppression could be achieved with triptorelin 3.75 mg administered by IM injection every 28 days, bilateral oophorectomy, or bilateral ovarian irradiation. Approximately one-half (53%) of patients enrolled in the study had received prior adjuvant chemotherapy. The primary analysis involved comparison of tamoxifen and ovarian suppression with tamoxifen alone. At a median follow-up of 8 years, disease-free survival and overall survival were prolonged, without a reduction in distant recurrences, in women receiving tamoxifen and ovarian suppression compared with those receiving tamoxifen alone; a disease-free survival benefit and a reduction in distant recurrences were observed, without an overall survival benefit, in women receiving exemestane and ovarian suppression compared with those receiving tamoxifen alone. Subgroup analysis in the SOFT study suggested that the relative clinical benefits of the 3 treatments generally were similar regardless of prior use of adjuvant chemotherapy; however, no difference in disease-free survival was observed with the addition of ovarian suppression to tamoxifen therapy in patients at lower risk of breast cancer recurrence (i.e., older age, node-negative disease, low-grade tumor, smaller tumor size) who had not required prior adjuvant chemotherapy. The absolute benefit of combined endocrine and ovarian suppression therapy was greater in higher-risk patients who had received adjuvant chemotherapy.
Based on current evidence, use of endocrine therapy (i.e., anastrozole, exemestane, letrozole, tamoxifen) in combination with ovarian suppression as adjuvant therapy may be considered a reasonable choice (accepted) in premenopausal women with early-stage hormone receptor-positive breast cancer at higher risk of disease recurrence (i.e., younger age, larger or high-grade tumor, increased risk of lymph node involvement) and those who received prior adjuvant chemotherapy. ASCO states that the duration of adjuvant GnRH agonist therapy should not exceed 5 years, since the toxicity of long-term (e.g., beyond 5 years) use of GnRH agonist-induced ovarian suppression has not been determined and comparative data for alternative treatment durations are lacking.

Support for using Trelstar to treat endometrial hyperplasia can be found in a study by Grimbizis et al. Long-acting triptorelin treatment returned hyperplastic endometrium to normal in most women with non-atypical hyperplasia but was ineffective in women with atypical hyperplasia. Triptorelin 3.75 mg in the form of sustained-release microcapsules was administered once every 4 weeks, on the first or second day of the menstrual cycle, for 6 months to women with simple (adenocystic) hyperplasia (n=39), complex (adenomatous) hyperplasia (n=14), or atypical complex (atypical adenomatous) hyperplasia (n=3). Among women with non-atypical forms (simple and complex), 85% responded with a return to normal endometrium, 57% functional and 29% atrophic. None of the women with atypical hyperplasia responded with a return to normal tissue. Sixty-eight percent of women experienced hot flushes, the most common side effect; 37.5% developed vaginal atrophy.

Support for using Trelstar to treat endometriosis can be found in the European Society of Human Reproduction and Endocrinology (ESHRE) endometriosis guidelines. In adults, GnRH agonists can be given to reduce endometriosis pain; evidence is limited for dosage or duration of therapy. Combined hormonal "add

back" therapy should be considered concomitantly with GnRH agonists to prevent hypoestrogenic symptoms and bone loss. GnRH agonists should be given second line (e.g., if progestins or hormonal contraceptives are not effective) due to their side effect profile. In adolescents, GnRH agonists can be prescribed to adolescents for the treatment of pain associated with laparoscopically confirmed endometriosis in cases where hormonal contraceptives or progestins have failed. Duration of therapy is up to 1 year since GnRH agonists are safe and effective in combination with add back therapy. GnRH agonist therapy in adolescents and young women should only be considered after careful consideration of potential long-term health risks and side effects.

Support for using Trelstar to treat fibrocystic breast changes can be found in a study by Monsonego et al. Intramuscular triptorelin (microsphere formulation) 3.75 mg every 28 days for 3 months has been effective in treating benign fibrocystic mastopathy. The additional use of tamoxifen (estrogen receptor-positive patients) or cyproterone (progesterone receptor-positive) with triptorelin for 3 further months has enabled complete responses to occur in about one-third of women achieving only partial response during 3 months of triptorelin monotherapy. Complete remission has been reported in over 50% of patients receiving triptorelin alone or combined with tamoxifen or cyproterone.

Support for using Trelstar to treat uterine fibroids can be found in a study by Vercellini et al. Treatment of women with triptorelin before hysterectomy for uterine leiomyomas increased the proportion that could be accomplished by a vaginal, rather than abdominal, procedure. One hundred twenty-three premenopausal women with a clinically assessed uterine volume of 12 to 16 gestational weeks were randomly assigned to receive immediate surgery or to be treated with 3 intramuscular depot injections of triptorelin 3.75 mg, separated by 28 days, before surgery. The percentage of operations that could be performed vaginally in the immediate surgery group was 16%. Of those women assigned to pre-treatment, the starting assessment was that 12% were suited to the vaginal procedure. After treatment with triptorelin, 53% were accomplished with the vaginal procedure (p less than 0.0001 between groups). This 37% reduction in risk for an abdominal surgery indicates that 3 women would need to be treated with triptorelin to avoid one abdominal surgery.
A study published by Broekmans and colleagues of 27 premenopausal women with uterine fibroids, the benefits of initial high-dose treatment for 8 weeks were prolonged by low-dose treatment for 18 additional weeks. In the initial phase of the study, all women began daily subcutaneous self-administration of aqueous triptorelin solutions. The doses were 500 mcg daily for the first week followed by a daily dose of 100 mcg for 7 weeks. The patients were then randomized to one of 3 groups using 5, 20, or 100 mcg daily for 18 weeks. After the first 8 weeks, the median uterine volume was reduced to 67.1% of the baseline volume (p=0.001) and after the full 26-week course, median uterine volume was reduced to 57.8% (p=0.001). The extent of additional decrease after 8 weeks appeared to be dose-dependent although no differences in overall volume reduction were found at 26 weeks. No significant change in median bone mineral density was observed.

Support for using Trelstar to treat adenocarcinoma of pancreas can be found in a published case report. A case report published by Gonzelez-Barcena and colleagues evaluated the use of GnRH agonists in 17 patients with unresectable and biopsy-proven adenocarcinoma of the pancreas (stage IV). Nine patients were male and 8 female, and the median age at diagnosis was 60 years. The majority of patients underwent a gastro-intestinal and biliary bypass. The therapy with D-Trp-6-LH-RH was started 3-31 days after bypass surgery. The analog was given at the dose of 1 mg/day subcutaneously for the first 7 days. Subsequently, the dose was reduced to 100 micrograms/day. One month after the start of the therapy the gonadotropin levels were in subnormal range. This therapy led to clinical improvement, better quality of life and an increase in survival time. The median survival time for all the groups was 7.2 months (men 7.4 months and women 6.9 months). LH-RH agonists appear to decrease pancreatic cancer growth by eliminating the stimulatory effect of sex steroids, and by direct effects on tumors. Further improvement in the clinical response in patients with inoperable pancreatic carcinoma might be possibly obtained by the combination of LH--RH agonists with modern somatostatin analogs.

Support for using Trelstar to treat ovarian carcinoma can be found in a study by Duffaud and colleagues. Triptorelin had only minor efficacy when used to treat ovarian carcinoma in women who had been pretreated with platinum-containing chemotherapy. Pretreated women (n=69) received intramuscular injections of microencapsulated triptorelin 3.75 mg on days 1, 8 and 28, and then every 4 weeks until disease progression. There were no objective responses. Only 11 of 69 (16%) of the patients achieved stable disease, with a median duration of 6 months. Median overall survival time for those with disease stabilization was 17 months. The drug was well tolerated, with only mild hot flushes and headaches reported in a few patients. Additionally, a partial response to triptorelin was observed in 6 of 41 advanced ovarian carcinoma patients (15%) who had relapsed after conventional therapy in one trial. Remission persisted for up to 18 months, and mean survival time was 10 months. Stable disease (6 to 12 months) was observed in an additional 5 patients (12%). Responses to triptorelin appeared to be better in older patients in this study but were not correlated with histological grade or subtype of cancer (Parmar et al).

V. REFERENCES

1. Trelstar [package insert]. Madison, NJ: Allergan Inc.; December 2021.
2. The NCCN Drugs & Biologics Compendium® © 2022 National Comprehensive Cancer Network, Inc. http://www.nccn.org. Accessed February 7, 2023.
3. DRUGDEX® System (electronic version). Truven Health Analytics, Ann Arbor, MI. Available at http://www.micromedexsolutions.com. Accessed February 7, 2023.
4. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Breast Cancer. Version 2.2022. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Accessed February 7, 2023.
5. AHFS DI (Adult and Pediatric) [database online]. Hudson, OH: Lexi-Comp, Inc.; http://online.lexi.com/lco/action/index/dataset/complete_ashp [available with subscription]. Accessed February 7, 2023.
6. Lexicomp [database online]. Hudson, OH: Lexi-Comp, Inc.; https://online.lexi.com/lco/action/home [available with subscription]. Accessed February 7, 2023.
7. Oktay K, Harvey BE, Partridge AH, et al: Fertility preservation in patients with cancer: ASCO clinical practice guideline update. J Clin Oncol 2018; 36(19):1994-2001.
8. Francis PA, Regan MM, Fleming GF et al. Adjuvant ovarian suppression in premenopausal breast cancer. N Engl J Med. 2015; 372:436-46.
9. Francis PA, Pagani O, Fleming GF et al. Tailoring Adjuvant Endocrine Therapy for Premenopausal Breast Cancer. N Engl J Med. 2018; 379:122-137.
10. Burstein HJ, Lacchetti C, Anderson H et al. Adjuvant Endocrine Therapy for Women With Hormone Receptor-Positive Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update on Ovarian Suppression. J Clin Oncol. 2016; 34:1689-701.
11. Grimbizis G, Tsalikis T, Tzioufa V, et al: Regression of endometrial hyperplasia after treatment with the gonadotrophin-releasing hormone analogue triptorelin: a prospective study. Hum Reprod 1999; 14(2):479-484.
12. Becker CM, Bokor A, Heikinheimo O, et al: ESHRE guideline: endometriosis. Hum Reprod Open 2022; 2022(2):1-24.
13. Monsonego J, Destable MD, De Saint Florent G, et al: Fibrocystic disease of the breast in premenopausal women: histohormonal correlation and response to luteinizing hormone-releasing hormone analog treatment. Am J Obstet Gynecol 1991; 164:1181-1189.
14. Vercellini P, Crosignani PG, Imparato E, et al: Treatment with a gonadotrophin releasing hormone agonist before hysterectomy for leiomyomas: results of a multicentre, randomised controlled trial. Br J Obstet Gynaecol 1998; 105(11):1148-1154.

15. Broekmans FJ, Hompes PGA, & Heitbrink MA: Two-step gonadotropin-releasing hormone agonist treatment of uterine leiomyomas: standard-dose therapy followed by reduced-dose therapy. Am J Obstet Gynecol 1996; 175:1208-1216.
16. Gonzalez-Barcena D, Ibarra-Olmos MA, Garcia-Carrasco F, et al: Influence of D-Trp-6-LH-RH on the survival time in patients with advanced pancreatic cancer. Biomed Pharmacother 1989; 43(4):313-317.
17. Duffaud F, van der Burg MEL, Namer M, et al: D-TRP-6-LHRH (Triptorelin) is not effective in ovarian carcinoma: and EORTC Gynaecological Cancer Co-operative Group Study. Anticancer Drugs 2001; 12:159-162.
18. Parmar H, Phillips RH, Rustin G, et al: Therapy of advanced ovarian cancer with D-Trp-6-LH-RH (Decapeptyl) microcapsules. Biomed Pharmacother 1988; 42:531-538.