LifeWise
Health Plan of Washington

PHARMACY / MEDICAL POLICY – 5.01.625

Gonadotropin Releasing Hormone (GnRH) Analogs

Effective Date:	**Feb. 7 , 2025***	RELATED MEDICAL POLICIES:
Last Revised:	Oct. 8 , 2024	7.01.557 Gender Transition/Affirmation Services
Replaces:	N/A	
*View current version here.		

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Introduction

The gonadotropin-releasing hormone (GnRH) agonists and antagonists are short protein analogs of GnRH that reduce the production of sex hormones, such as estrogen and testosterone. These agents are used to treat conditions that respond to hormonal inhibition, including advanced prostate cancer, endometriosis, uterine fibroids, central precocious puberty, and gender dysphoria.

Gonadotropin-releasing hormone (GnRH) is produced naturally in the hypothalamus of the brain and acts on receptors in the pituitary gland, stimulating the release of luteinizing hormone (LH) and follicular stimulating hormone (FSH). These hormones, in turn, signal the release of testosterone from the male testes and estrogen from the female ovaries. The use of GnRH agonists activates receptors to cause an initial and temporary surge in sex hormones, but with continued use will inhibit the production of LH and FSH resulting in estrogen and testosterone levels to decline. In contrast, GnRH antagonists block receptors directly to reduce the production of LH and FSH, and ultimately the sex hormones. Although the efficacy of GnRH agonists and antagonists are similar, antagonists reach clinical effect faster and without an initial surge in sex hormone release characteristic of the agonists.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can

be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria

Drug	Medical Necessity
Covered Indications	
Breast cancer	****Lupron Depot (leuprolide acetate), ***Trelstar (triptorelin pamoate), or Zoladex (goserelin) may be considered medically necessary for the palliative treatment of advanced breast cancer in *pre- and perimenopausal women.** ****Lupron Depot (leuprolide acetate), ***Trelstar (triptorelin pamoate), or Zoladex (goserelin) may be considered medically necessary for the adjuvant treatment of adult individuals for the treatment of early breast cancer in *pre- and perimenopausal women when the following are met:** • Individual has HR+ breast cancer **AND** • Individual is receiving treatment with tamoxifen or an aromatase inhibitor (e.g., anastrozole, exemestane, letrozole) ****Lupron Depot (leuprolide acetate), ***Trelstar (triptorelin pamoate), or Zoladex (goserelin) may be considered medically necessary for the adjuvant treatment of adult individuals with HR+/HER2-negative, lymph node-positive, early breast cancer at ****high risk of recurrence and a Ki-67 score ≥20% when used in combination with:** • Verzenio (abemaciclib) **AND** • Tamoxifen or an aromatase inhibitor (e.g., anastrozole, exemestane, letrozole) **Note:** *Pre- and perimenopausal status requires documentation of ongoing menses or normal estradiol, FSH, and LH levels.

Drug	Medical Necessity
Covered Indications	
	Note: **Only Lupron Depot 3.75 mg administered monthly or Lupron Depot 11.25 mg administered every 3 months. **Note:** ***Only Trelstar 3.75 mg administered every 4 weeks or Trelstar 11.25 mg administered every 12 weeks. **Note:** ****High-risk in Verzenio trial was defined as ≥4 positive pathologic axillary lymph nodes OR 1-3 positive axillary lymph nodes with one or more of the following: Grade 3 disease, Tumor size ≥5 cm, Ki-67 score of ≥ 20%.
Central precocious puberty	**Fensolvi (leuprolide acetate), generic leuprolide, Lupron Depot PED (leuprolide acetate), Supprelin LA (histrelin implant), Synarel (nafarelin), Triptodur (triptorelin), and Vantas (histrelin implant) may be considered medically necessary for the treatment of children with central precocious puberty when the following criteria are met:** • Diagnosis confirmed by one of the following: ○ Pubertal basal level of luteinizing hormone (based on laboratory reference ranges; see **Appendix**) **OR** ○ Positive response to GnRH stimulation test (peak LH concentration ≥5 IU/L) **OR** ○ Bone age advanced by at least one year beyond the chronological age **AND** • Documented onset of secondary sexual characteristics (genital maturation, pubic hair growth, and/or menses in female) in one of the following: ○ Female ≤8 years of age **OR** ○ Male ≤9 years of age **AND** • Medication is prescribed by or in consultation with an endocrinologist
Endometriosis	**Generic leuprolide, brand leuprolide depot, Lupaneta Pack (leuprolide/norethindrone), Lupron Depot (leuprolide acetate), Synarel (nafarelin), and Zoladex (goserelin) may be considered**

Drug	Medical Necessity
Covered Indications	
	medically necessary for women when the following criteria are met: • Individual is aged 18 years or older **AND** • Individual has a documentation showing confirmed diagnosis of endometriosis **AND** • Individual is being treated for the management of endometriosis, including pain relief and reduction of endometriotic lesions **Myfembree (relugolix/estradiol/norethindrone acetate) may be considered medically necessary when the following criteria are met:** • Individual is aged 18 years or older **AND** • Individual is premenopausal and is being treated for moderate to severe pain associated with endometriosis **AND** • Individual does not have osteoporosis **AND** • The dose is ≤40 mg of relugolix per day (taken as relugolix 40 mg, estradiol 1 mg, norethindrone acetate 0.5 once daily) **AND** • The total treatment duration is ≤ 24 months **Note:** Requests for Myfembree after completing 24 months of therapy is considered not medically necessary. **Approval of Myfembree can be granted for the labeled duration of therapy (24 months).** **Orilissa (elagolix) may be considered medically necessary when the following criteria are met:** • Individual is aged 18 years or older **AND**

Drug	Medical Necessity
Covered Indications	
	• Individual is premenopausal and is being treated for moderate to severe pain associated with endometriosis **AND** • Individual does not have osteoporosis or severe hepatic impairment (Child-Pugh C) **AND** • Treatment duration does not exceed: ○ 150 mg once daily for 24 months **OR** ○ 200 mg twice daily for 6 months **Note:** Requests for Orilissa 150 mg after completing 6 months of therapy with Orilissa 200 mg is considered not medically necessary. **Approval of Orilissa (elagolix) can be granted for the labeled duration of therapy (24 months for 150 mg and 6 months for 200 mg).**
Gender dysphoria	**Eligard (leuprolide acetate), Fensolvi (leuprolide acetate), generic leuprolide, brand leuprolide depot, Lupron Depot (leuprolide acetate), Lupron Depot PED (leuprolide acetate), Supprelin LA (histrelin implant), Synarel (nafarelin), Trelstar (triptorelin pamoate), Triptodur (triptorelin), Vantas (histrelin implant), and Zoladex (goserelin) may be considered medically necessary for the treatment of gender dysphoria when all of the following are met:** • One of the following: ○ Individual is ≥ 14 years of age **OR** ○ Tanner stage 2 or higher puberty onset based on physical examination **OR** ○ Tanner stage 2 or higher puberty onset based on serum testosterone level, serum estradiol level, serum estrone level, serum luteinizing hormone level (only individuals assigned female at birth), or serum follicle stimulating hormone level (only individuals assigned female at birth)

Drug	Medical Necessity
Covered Indications	

	AND
	• All of the following:
	  ○ Individual has not undergone a gonadectomy
	  ○ Confirmation of the diagnosis of gender dysphoria, including verification that all diagnostic criteria for gender dysphoria are met as specified in the current version of the Diagnostic and Statistical Manual of Mental Disorders (DSM)
	  ○ Documentation that the individual has no comorbid psychiatric disorders. Alternatively, if the individual has any comorbid psychiatric disorders, documentation that the individual's gender incongruence and desire to be of a gender other than the individual's assigned gender are not due to any psychiatric disorders (e.g., psychotic disorders) other than gender dysphoria
	  ○ Medication is prescribed by or in consultation with an endocrinologist, transgender specialist, providers in an adolescent medicine gender clinic, or providers in a gender health clinic for adult individuals
	  ○ Documentation that potential adverse effects have been discussed including specifically possible effects on fertility, and, if the individual is not taking a cross-sex hormone aka gender affirming hormone (a testosterone formulation for transgender males; an estrogen or progesterone formulation for transgender females), possible effects on bone mineralization, and bone density
	  ○ If the individual is starting a GnRH analog at 23 years of age or older, or after reaching Tanner stage 5, or after irreversible physical/anatomic secondary sexual characteristics are well developed, documentation that a GnRH analog is necessary to suppress characteristics of the gender assigned at birth that are not evident by observation or on physical examination (e.g., menses or penile erections)
	  ○ If the individual is starting a GnRH analog while already taking a cross-sex hormone (aka a gender affirming

Drug	Medical Necessity
Covered Indications	
	hormone), documentation that cross-sex hormone is not resulting in adequate suppression of natal (gender assigned at birth) secondary sex characteristics or is not resulting in adequate suppression of endogenous hormones (e.g., testosterone for individuals assigned male at birth; estrogens or luteinizing hormone or follicle stimulating hormone for individuals assigned female at birth) **Note:** Due to overlapping values between Tanner stages 1 and 2, for individuals assigned male at birth, total testosterone of at least 24 ng/dL or at least 0.17-0.8 nmol/L is required to confirm Tanner stage 2, or serum estradiol of at least 14 pg/mL is required to confirm Tanner stage 2, or serum estrone level of at least 17 pg/mL is required to confirm Tanner stage 2. Due to overlapping values between Tanner stages 1 and 2, for individuals assigned female at birth, total testosterone of at least 11 ng/dL or 0.36 nmol/L is required to confirm Tanner stage 2, or serum estradiol of at least 21 pg/mL is required to confirm Tanner stage 2, or serum estrone of at least 30 pg/mL is required to confirm Tanner stage 2, or luteinizing hormone >0.3 IU/L is required to confirm Tanner stage 2, or serum follicle stimulating hormone >4.1 IU/L is required to confirm Tanner stage 2. Luteinizing hormone levels and follicle stimulating hormone levels do not reliably confirm Tanner stage for individuals assigned male at birth due to the extent of overlapping values between Tanner stages 1 and all higher Tanner stages. **Note:** Use of these products is investigational for individuals <14 years of age with gender dysphoria who have not reached Tanner stage 2 puberty onset. Use of these products is also investigational for the treatment of gender dysphoria for individuals who have completed puberty. Use of any other products in this policy for the treatment of gender dysphoria is considered investigational.
Ovulation suppression	**Generic leuprolide may be considered medically necessary to suppress ovulation for a frozen embryo transfer (FET)** **Note:** Coverage is subject to infertility and assisted reproduction benefits
Prostate cancer	**Camcevi (leuprolide mesylate), Firmagon (degarelix), generic leuprolide, brand leuprolide depot, Lupron Depot (leuprolide acetate), Orgovyx (relugolix), Trelstar (triptorelin pamoate), and Zoladex (goserelin) may be considered medically**

Drug	Medical Necessity
Covered Indications	
	necessary for the palliative treatment of advanced* prostate cancer when used: • As adjuvant therapy for: ○ Stages T2b-T4 N0 M0 (Jewett stage B2-C) **OR** ○ Stages T1-4 N1 M0 **OR** ○ Individuals with unfavorable risk stratification as evidence by: ▪ Stage T1c with PSA >10 ng/mL and Gleason score 7 with Gleason pattern 4+3 **OR** ▪ Stage T1c and ≥50% biopsy cores positive (e.g., ≥ 6 of 12 cores) **OR** • For recurrence or metastatic disease as documented by: ○ Stages T1-4 N0-2 M1 **OR** ○ Rising PSA after curative attempt with surgery and/or radiation **Eligard (leuprolide acetate) may be considered medically necessary for the treatment of advanced* prostate cancer** **Note:** *Advanced prostate cancer is cancer that cannot be cured with surgery or radiation may or may not be metastatic. **Zoladex (goserelin) may be considered medically necessary for the treatment of locally confined Stage T2b-T4 (Stage B2-C) prostate cancer when used in combination with flutamide.**
Uterine fibroids	**Generic leuprolide, brand leuprolide depot, and Lupron Depot (leuprolide acetate) may be considered medically necessary when the following criteria are met:** • For the treatment of anemia due to uterine fibroids (leiomyomas) that are inadequately controlled by 1-month trial of iron supplementation. **OR**

Drug	Medical Necessity
Covered Indications	
	• To reduce the size of fibroids prior to surgery (e.g., myomectomy, hysterectomy). **Initial approval will be for 90-days.** **Note:** Coverage for Lupron Depot 4-month and 6-month formulations will be prohibited. **Re-authorization criteria:** • Continuous use of generic leuprolide, brand leuprolide depot, and Lupron Depot for the treatment of uterine fibroids beyond 90-days is not recommended per FDA labeling due to the risk of bone toxicity. **Myfembree (relugolix/estradiol/norethindrone acetate) may be considered medically necessary when ALL of the following criteria are met:** • Individual is aged 18 years of or older **AND** • Individual is premenopausal and is being treated for the management of heavy menstrual bleeding associated with uterine fibroids (leiomyomas) **AND** • Individual has tried and failed one contraceptive for the management of symptoms **AND** • The dose is ≤40 mg of relugolix per day (taken as relugolix 40 mg, estradiol 1 mg, norethindrone acetate 0.5 once daily) **AND** • The total treatment duration is ≤ 24 months **Myfembree approval can be granted for the labeled duration of therapy (24 months).**

Drug	Medical Necessity
Covered Indications	
	Oriahnn (elagolix/estradiol/norethindrone acetate) may be considered medically necessary when ALL of the following criteria are met: • Individual is aged 18 years or older **AND** • Individual is premenopausal and is being treated for the management of heavy menstrual bleeding associated with uterine fibroids (leiomyomas) **AND** • Individual has tried and failed one contraceptive for the management of symptoms **AND** • The dose is ≤600 mg of elagolix per day (taken as elagolix 300 mg, estradiol 1 mg, norethindrone acetate 0.5 mg in the morning and elagolix 300 mg in the evening) **AND** • The total treatment duration is ≤ 24 months **Oriahnn approval can be granted for the labeled duration of therapy (24 months).** **Zoladex (goserelin) may be considered medically necessary for use as an endometrial-thinning agent prior to endometrial ablation for dysfunctional uterine bleeding.**

Drug	Investigational
As listed	**All other uses of GnRH analogs for conditions not outlined in this policy are considered investigational.** **Use of any other products in this policy for the treatment of gender dysphoria, outside of those listed within the Medical Necessity section, is considered investigational.**

Drug	Investigational
	Use of GnRH analogs that does not meet the age or diagnosis requirements within the Medical Necessity section is considered investigational. **Use of GnRH analogs that meets the age and diagnosis requirements within the Medical Necessity section but does not meet other policy criteria within the Medical Necessity section is considered not medically necessary.**

Length of Approval	
Approval	**Criteria**
Initial authorization	**The drugs listed in this policy may be approved up to 12 months, unless noted otherwise.** **Authorization of Zoladex (goserelin) for the treatment of endometriosis beyond 6 months total treatment duration is considered not medically necessary since safety data for retreatment is not available (per FDA labeling).** **Authorization of Zoladex (goserelin) for use as an endometrial-thinning agent prior to endometrial ablation for dysfunctional uterine bleeding beyond 6 months total treatment duration is considered investigational.** **Authorization of generic leuprolide, brand leuprolide depot, and Lupron Depot (leuprolide acetate) for the treatment of uterine fibroids beyond 3 months total treatment duration is considered not medically necessary.**
Indications	**Ongoing Use**
Breast cancer	**Re-authorization of Lupron Depot (leuprolide acetate), Trelstar (triptorelin pamoate), or Zoladex (goserelin) may be approved for 12 months for the palliative treatment of advanced breast cancer in pre- and perimenopausal women when the following are met:** • Documentation of positive clinical response • Individual is tolerating therapy

Length of Approval	
	Re-authorization of Lupron Depot (leuprolide acetate), Trelstar (triptorelin pamoate), or Zoladex (goserelin) may be approved for 12 months for the adjuvant treatment of early breast cancer in pre- and perimenopausal women when the following are met: • Documentation of positive clinical response • Individual is tolerating therapy
Central precocious puberty	**Re-authorization of Fensolvi (leuprolide acetate), generic leuprolide, Lupron Depot PED (leuprolide acetate), Supprelin LA (histrelin implant), Synarel (nafarelin), Triptodur (triptorelin), and Vantas (histrelin implant) may be approved for 12 months for the ongoing treatment of central precocious puberty when the following are met:** • Documentation of positive clinical response • Individual is younger than the appropriate onset of puberty: o Female <11 years of age **OR** o Male <12 years of age
Endometriosis	**Re-authorization of generic leuprolide, brand leuprolide depot, Lupaneta Pack, Lupron Depot (leuprolide acetate), and Synarel (nafarelin) beyond 12 months total treatment duration is considered not medically necessary.** **Re-authorization of Zoladex (goserelin) beyond 6 months total treatment duration is considered not medically necessary since safety data for retreatment is not available (per FDA labeling).** **Re-authorization of Myfembree (relugolix/estradiol/norethindrone acetate) beyond 24 months is considered not medically necessary.** **Re-authorization of Orilissa (elagolix)150 mg beyond 24 months or Orilissa 200 mg beyond 6 months is considered not medically necessary.**
Gender dysphoria	**Re-authorization of Fensolvi (leuprolide acetate), generic leuprolide, brand leuprolide depot, Lupron Depot (leuprolide**

Length of Approval	
	acetate), Lupron Depot PED (leuprolide acetate), Supprelin LA (histrelin implant), Synarel (nafarelin), Trelstar (triptorelin pamoate), Triptodur (triptorelin), Vantas (histrelin implant), and Zoladex (goserelin) may be approved for 12 months for the ongoing treatment of gender dysphoria when the following are met: • Individual has not undergone a gonadectomy **AND** • Documentation of suppression of secondary sex characteristics based on physical examination OR documentation of suppression of characteristics of the gender assigned at birth that are not evident by observation or on physical examination (e.g., menses or penile erections) **AND** • Documentation of annual testing of bone age or bone density unless the individual is concurrently taking a cross-sex hormone aka a gender affirming hormone (a testosterone formulation for transgender males; an estrogen or progesterone formulation for transgender females) **AND** • For the first re-authorization request, if the previous coverage was under a non-Company plan, documentation that the initial authorization requirements have also been met **Note:** Suppression of characteristics of the gender assigned at birth can consist of either prevention of continued progression of puberty, or regression of secondary sexual characteristics of the gender assigned at birth. **Note:** Documentation of regression to a lower Tanner stage or of prevention of progression to a higher Tanner stage is acceptable as physical examination documentation of suppression of secondary sexual characteristics. **Note:** The purpose of GnRH analog treatment for gender dysphoria is to suppress observable secondary sexual characteristics of the gender assigned at birth or to suppress characteristics of the gender assigned at birth that are not evident by observation or on physical examination (e.g., menses or penile erections). The purpose is not just to attain certain lab values in the absence of suppression of observable secondary sexual characteristics of the gender assigned at birth or suppression of

Length of Approval	
	characteristics of the gender assigned at birth that are not evident by observation or on physical examination.
Ovulation suppression	**Re-authorization of generic leuprolide may be approved for 12 months to suppress ovulation for a frozen embryo transfer (FET) when the following are met:** • Documentation of positive clinical response • Individual is tolerating therapy **Note:** Coverage is subject to infertility and assisted reproduction benefits
Prostate cancer	**Re-authorization of Camcevi (leuprolide mesylate), Eligard (leuprolide acetate), Firmagon (degarelix), generic leuprolide, brand leuprolide depot, Lupron Depot (leuprolide acetate), Orgovyx (relugolix), Trelstar (triptorelin pamoate), Zoladex (goserelin), and may be approved for 12 months for the treatment of prostate cancer when the following are met:** • Documentation of positive clinical response • Individual is tolerating therapy
Uterine fibroids	**Treatment for uterine fibroids with generic leuprolide, brand leuprolide depot, and Lupron Depot (leuprolide acetate) can only be approved for a maximum of 3 months total. Re-authorization will not be granted.** **Re-authorization of Myfembree (relugolix/estradiol/norethindrone acetate) and Oriahnn (elagolix/estradiol/norethindrone acetate) beyond 24 months is considered not medically necessary.** **Re-authorization of Zoladex (goserelin) for use as an endometrial-thinning agent prior to endometrial ablation for dysfunctional uterine bleeding beyond the initial 6 months is considered investigational.**

Documentation Requirements

The individual's medical records submitted for review for all conditions should document that medical necessity criteria are met. The record should include the following:

- Office visit notes that contain the diagnosis, relevant history, physical evaluation, and lab values.

Coding

Code	Description
HCPCS	
J1950	Injection, leuprolide acetate (for depot suspension), (Lupron Depot 11.25 mg, 3.75; Lupron Depot PED 11.25, 15 mg, 30 mg, 7.5 mg) per 3.75 mg
J1951	Injection, leuprolide acetate for depot suspension (Fensolvi) 0.25 mg
J1952	Leuprolide injectable, Camcevi, 1 mg
J1954	Injection, leuprolide acetate for depot suspension (Cipla), 7.5 mg
J3315	Injection, triptorelin pamoate, (Trelstar) 3.75 mg
J3316	Injection, triptorelin, extended-release, (Triptodur) 3.75 mg
J3490	Unclassified drugs (Use to report Lupaneta Pack and Synarel)
J9155	Injection, degarelix, (Firmagon)1 mg
J9202	Goserelin acetate implant, (Zoladex) per 3.6 mg
J9217	Leuprolide acetate (for depot suspension) (Lupron Depot 22.5 mg, 30 mg, 45 mg, 7.5 mg and (Eligard)), 7.5 mg
J9218	Leuprolide acetate, per 1 mg
J9225	Histrelin implant (Vantas), 50 mg
J9226	Histrelin implant (Supprelin LA), 50 mg

Note: HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

Related Information

Benefit Application

Pharmacy Benefit

Myfembree (relugolix/estradiol/norethindrone acetate), Orgovyx (relugolix), Oriahnn (elagolix/estradiol/norethindrone), and Orilissa (elagolix) are managed through the pharmacy benefit.

Pharmacy / Medical Benefit

Camcevi (leuprolide mesylate), Fensolvi (leuprolide acetate), Eligard (leuprolide acetate), Firmagon (degarelix), generic leuprolide acetate, Lupaneta Pack (leuprolide acetate/norethindrone), Lupron Depot PED (leuprolide acetate), Lupron Depot (leuprolide acetate), brand leuprolide depot, Supprelin LA (histrelin acetate), Trelstar (triptorelin pamoate), Triptodur (triptorelin ER), Vantas (histrelin acetate), and Zoladex (goserelin acetate) are managed through both the pharmacy and medical benefit.

Evidence Review

Uterine Fibroids (leiomyomas)

Uterine fibroids (or leiomyomas) are noncancerous tumors originating from the smooth muscles of the myometrium. Symptoms typically present as heavy or prolonged menstrual bleeding, urinary tract or bowel issues, and/or pelvic pain or pressure. Due to afflicting women of child-bearing age, complications from uterine fibroids can result in infertility and adverse pregnancy outcomes. There have been no reported cases of uterine fibroids in prepubertal girls to date, with most individuals experiencing shrinkage of fibroids post-menopause. Clinical diagnosis involves pelvic examination and ultrasound imaging accompanied by symptom history. Despite being the most common pelvic tumor in women, the true prevalence is difficult to determine due to the scarcity of longitudinal studies. One systematic review in 2017 noted a range of between 4.5-68.6% of women will experience uterine fibroids in their lifetime.

The incidence rates of fibroids are threefold greater in Black women versus White women, with tumors proliferating to greater sizes in the former population. No clear etiology has been

established, but differences in genetic factors, diet, lifestyle, psychosocial stress, and environmental exposures have been considered to contribute to the disparity. Other notable factors with an increased correlation to fibroid risk include obesity, hypertension, increased red meat consumption, alcohol, and smoking. Individuals with symptomatic fibroids report lower quality of life scores than other chronic diseases on measures relating to psychosocial stressors, such as bodily pain, mental health, and social functioning. Uterine fibroids also cause approximately 40% of all hysterectomies, which adds to the approximately $9.4 billion US healthcare dollars spent annually. Annual costs per individual was estimated around $4,600.

Advanced Prostate Cancer

Prostate cancer is a neoplastic disease of the prostate gland. Prostate cancer arises from mutations in cells of the prostate that cause overexpression of enzymes that support androgen biosynthesis, loss of regulation of cell death within the tumor cells, and up regulation of androgen receptors. Androgen receptor binding by androgens plays a crucial role in prostate cancer progression. Most prostate cancers respond to androgen deprivation.

Approximately 60% of all cases of prostate cancer are diagnosed in men 65 years of age or older and 97% occur in men 50 and older. Prostate cancers typically progress slowly and there is a high rate of survival for disease detected in early stages, but not for advanced disease stages. In the US, the 5-year survival rate is effectively 100% when the disease is local or regional, but this drops to 31% for disease with distant metastases.

Prostate cancer is the second most common cause of cancer death in American men. In 2021, an estimated 248,530 men are expected to be diagnosed with prostate cancer, and approximately 34,130 are expected to have died from the disease. The condition is associated with a substantial economic burden, due to high incidence rates and high costs associated with management of advanced cancer stages. The high management cost burden arises from the requirement for hospitalizations, chemotherapy, palliative surgical procedures, and computed tomography (CT) or magnetic resonance imaging (MRI) scans to monitor potential bone metastases. In 2007, per-patient per-month CRPC costs for men over the age of 40 were approximately $1,800, with ambulatory visits ($1,152) and inpatient stays ($559) comprising the majority of these costs. Total all-cause healthcare costs for these same individuals totaled $3,500 per-patient per-month.

Central Precocious Puberty

Precocious puberty is defined as the development of secondary sex characteristics before the age of 8 years in girls and 9 years in boys. These lower age limits were determined as 2 to 2.5 standard deviations below the population norm, where the mean age of onset of puberty is approximately 10.5 years in girls and 11.5 years in boys. Central precocious puberty (CPP) is caused by an early activation of the hypothalamic-pituitary-gonadal axis, with 40-75% of cases present in boys compared with 10-20% in girls. These individuals experience early onset of advanced bone age and pubertal levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). CPP can be treated with gonadotropin-releasing hormone (GnRH) agonists by downregulating the pituitary response to endogenous GnRH, thereby preserving adult stature and sexual characteristics.

CPP is idiopathic in 80-90% of cases in girls but only 25-60% of boys, which can be attributed to genetic variations. Other cases are caused by lesions of the central nervous system which can be detected as tumors, signs of trauma, and congenital defects via magnetic resonance imaging (MRI), but also second-hand exposure to high serum levels of sex steroids.

Gender Dysphoria

Gender dysphoria (formerly referred to as gender identity disorder) is defined as psychological distress caused by a mismatch between a person's gender identity and their sex assigned at birth based on genital anatomy and chromosomes. According to the American Psychiatric Association, the crucial element of gender dysphoria is "clinically significant distress". This contrasts with gender nonconformity which does not always lead to dysphoria or distress. Early-onset gender dysphoria is behaviorally visible in childhood while cases of late-onset dysphoria occur into adolescence and adulthood. Epidemiologic studies are lacking, but a review of 10 studies in a population presenting for gender-transition care at specialist centers noted prevalence ranging from 0.00220-0.0083% for transgender females and 0.0005-0.0033% for transgender males. Although specific causes of gender dysphoria remain unknown, it is likely to involve various genetic, biological, environmental, and cultural factors.

Diagnosis is generally conducted by a mental health professional using the criteria outlined in the latest edition of the Diagnostic and Statistical Manual of Mental Disorders. The core components of diagnosis revolve around longstanding distress with divergence between one's gender identity and external sexual characteristics at birth, coupled with difficulties with social interactions and functions of daily living. Treatment for gender dysphoria may include psychotherapy, behavioral counseling, hormone therapy, and/or surgery. Medical interventions,

such as hormonal treatment and gender reassignment surgery, are intended to reduce the distress resulting from the transgender status.

Endometriosis

Endometriosis is a condition that involves outgrowths of endometrial tissue that extend past the uterine cavity. Lesions are categorized based on their affected sites which can occur in the pelvis, bowel, diaphragm, and/or the pleural cavity. It occurs in approximately 10% of women in reproductive age globally, with underlying inflammation presenting clinical symptoms such as dysmenorrhea, dyspareunia, chronic pain, and infertility. Factors associated with an increased risk for developing endometrial lesions include early menarche, late menopause, heavy menstrual bleeding, low body mass index, and exposure to physical/sexual abuse in childhood or adolescence.

Although some experts claim visual confirmation of endometriosis is sufficient, definitive diagnosis requires a histologic evaluation of lesions through biopsy. Endometriosis progression is estrogen-dependent, thus treatment involves hormone therapy with the use of gonadotropin-releasing hormone (GnRH) agonists to reduce chronic pelvic pain. Chronic pain management and surgery may also be appropriate for managing symptoms, but no treatment options result in a cure for endometriosis.

References

1. LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Gonadotropin Releasing Hormone (GnRH) Analogues. [Updated 2018 Mar 20]. Available from: **https://www.ncbi.nlm.nih.gov/books/NBK547863/** Accessed February 19, 2024.
2. Test ID: LHPED luteinizing Hormone (lh), pediatrics, serum. (n.d.). Retrieved May 07, 2021, from **https://www.mayocliniclabs.com/test-catalog/Clinical+and+Interpretive/62999 Accessed** February 19, 2024.
3. Management of transgender and gender-diverse children and adolescents. Uptodate. (n.d.). **https://www.uptodate.com/contents/management-of-transgender-and-gender-diverse-children-and-adolescents?search=gender+dysphoria&source=search_result&selectedTitle=4~15&usage_type=default&display_rank=4#** Accessed February 19, 2024.
4. Treatment of precocious puberty. Uptodate. (n.d.). **https://www.uptodate.com/contents/treatment-of-precocious-puberty?search=central+precocious+puberty&source=search_result&selectedTitle=2~29&usage_type=default&display_rank=2#H568107578** Accessed February 19, 2024.
5. Key statistics for prostate cancer: Prostate cancer facts. (n.d.). Retrieved May 07, 2021, from **https://www.cancer.org/cancer/prostate-cancer/about/key-statistics.html** Accessed February 19, 2024.

6. Uterine fibroids (leiomyomas): Epidemiology, clinical features, diagnosis, and natural history. Uptodate. (n.d.). **https://www.uptodate.com/contents/uterine-fibroids-leiomyomas-epidemiology-clinical-features-diagnosis-and-natural-history?search=uterine+fibroids&source=search_result&selectedTitle=2~150&usage_type=default&display_rank=2** Accessed February 19, 2024.

7. Stewart EA, Cookson CL, Gandolfo RA, Schulze-Rath R. Epidemiology of uterine fibroids: a systematic review. BJOG. 2017 Sep;124(10):1501-1512. doi: 10.1111/1471-0528.14640. Epub 2017 May 13. PMID: 28296146.

8. Definition, etiology, and evaluation of precocious puberty. Uptodate. (n.d.). **https://www.uptodate.com/contents/definition-etiology-and-evaluation-of-precocious-puberty?search=central+precocious+puberty&source=search_result&selectedTitle=1~29&usage_type=default&display_rank=1#H29** Accessed February 19, 2024.

9. Gender development and clinical presentation of gender diversity in children and adolescents. Uptodate. (n.d.). **https://www.uptodate.com/contents/gender-development-and-clinical-presentation-of-gender-diversity-in-children-and-adolescents?search=gender+dysphoria&source=search_result&selectedTitle=2~15&usage_type=default&display_rank=2#H172535427** Accessed February 19, 2024.

   Endometriosis: Pathogenesis, epidemiology, and clinical impact. Uptodate. (n.d.). **https://www.uptodate.com/contents/endometriosis-pathogenesis-clinical-features-and-diagnosis?search=endometriosis&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1** Accessed February 19, 2024.

Appendix

Laboratory Reference Ranges for Basal Luteinizing Hormone

Age	Females	Males
<1 year	<0.02-18.3 IU/L	<0.02-5.0 IU/L
1-8 years	<0.02-0.3 IU/L	<0.02-0.5 IU/L
9-10 years	<0.02-4.8 IU/L	<0.02-3.6 IU/L
11-13 years	<0.02-11.7 IU/L	0.1-5.7 IU/L
14-17 years	<0.02-16.7 IU/L	0.8-8.7 IU/L

History

Date	Comments
06/01/21	New policy, approved May 11, 2021, effective for dates of service on or after September 3, 2021, following 90-day provider notification. Add to Prescription Drug section. Drugs added to the policy include generic leuprolide acetate SC, Lupron Depot (leuprolide acetate) IM, Lupron Depot PED (leuprolide acetate) SC, Lupaneta Pack (leuprolide acetate/norethindrone) IM/PO, Fensolvi (leuprolide acetate) SC, Eligard (leuprolide acetate) SC, Trelstar (triptorelin pamoate) IM, Triptodur (triptorelin ER) IM, Vantas (histrelin acetate) SC implant, Supprelin LA (histrelin acetate) SC implant, Zoladex (goserelin acetate) SC implant, Firmagon (degarelix) SC, Orgovyx (relugolix) PO, Orilissa (elagolix) PO, and Oriahnn (elagolix/estradiol/norethindrone) PO. Indications added to the policy include uterine fibroids, endometriosis, central precocious puberty, advanced prostate cancer, and gender dysphoria.
08/01/21	Interim Review, approved July 22, 2021. Added Camcevi (leuprolide mesylate) to policy for the treatment of prostate cancer. Added Myfembree (relugolix/estradiol/ norethindrone acetate) to policy for the treatment of uterine fibroids. Updated re-authorization criteria for generic leuprolide, Lupron Depot (leuprolide acetate), and Lupaneta Pack (leuprolide/norethindrone) when used for the treatment of endometriosis.
01/01/22	Coding update. Added HCPCS code J1952.
02/01/22	Interim Review, approved January 31, 2022. Added coverage criteria for Lupron Depot (leuprolide acetate) and Trelstar (triptorelin pamoate) for the palliative treatment of advanced breast cancer in pre- and perimenopausal women. Added coverage criteria for Lupron Depot, Trelstar, and Zoladex (goserelin) for the adjuvant treatment of early breast in pre- and perimenopausal women. Added coverage criteria for Lupron Depot, Trelstar, and Zoladex when used in combination with Verzenio (abemaciclib) for the treatment of early breast cancer at high risk of recurrence and a Ki-67 score ≥20% in pre- and perimenopausal women. Added notes to breast cancer coverage regarding pre- and perimenopausal status and for Lupron Depot and Trelstar. Added note on advance prostate cancer. Updated criteria for gender dysphoria to include providers in an adolescent medicine gender clinic.
05/01/22	Interim Review, approved April 25, 2022. Updated criteria for generic leuprolide and Lupron Depot (leuprolide acetate) for uterine fibroids to specify that the trial of iron supplementation is a 1-month trial.
09/01/22	Annual Review, approved August 9, 2022. Updated criteria for the adjuvant treatment of early breast cancer removing requirement the patient has high-risk of recurrence. Updated coverage criteria for gender dysphoria removing "adolescent" and changing to patient is ≥ 12 years of age (or Tanner stage 2 or higher puberty onset) to 19 years of age. Updated re-authorization criteria for gender dysphoria to include patient is ≤19 years of age. Added a note to Orilissa under coverage criteria that requests for Orilissa 150 mg after completing 6 months of therapy with Orilissa 200 mg is considered not medically necessary. Added under ongoing use for endometriosis that re-authorization of Orilissa 150 mg beyond 24 months or Orilissa 200 mg beyond 6 months is considered not medically necessary. Updated HCPCS J1950 to indicate

Date	Comments
	Lupron Depot and Lupron Depot PED**.** Updated HCPCS J9217 to indicate Eligard. Removed Eligard from HCPCS J9218.
10/01/22	Interim Review, approved September 13, 2022. Updated prostate cancer criteria to include coverage for individuals with unfavorable risk stratification. Added a new indication to Myfembree for the treatment of moderate to severe pain associated with endometriosis. Updated Orilissa criteria to limit use to individuals 18 years of age or older and to premenopausal individuals. Added under ongoing use for uterine fibroids that re-authorization of Myfembree and Oriahnn beyond 24 months is considered not medically necessary. Changed the wording from "patient" to "individual" throughout the policy for standardization.
05/01/23	Annual Review, approved April 19, 2023. Added brand leuprolide depot to Lupron Depot 22.5 mg administered every 3 months coverage criteria. Added coverage for generic leuprolide to suppress ovulation for a frozen embryo transfer (FET). Updated gender dysphoria criteria to require documentation that potential adverse effects have been discussed including specifically impaired bone mineralization, loss of bone density, or bone demineralization. Added a note under the gender dysphoria criteria that states use of other products in this policy are considered investigational for the treatment of gender dysphoria. Updated gender dysphoria criteria to require that the individual is 14 years of age (or Tanner stage 2 or higher puberty onset) to 22 years of age.
08/01/23	Interim Review, approved July 11, 2023. Updated gender dysphoria criteria to require documentation that the individual's gender incongruence and desire to be of a gender other than the individual's assigned gender are not due to any other psychiatric disorders (e.g., psychotic disorders). Added Eligard (leuprolide acetate) to the list of Gender Dysphoria.
09/01/23	Interim Review, approved August 21, 2023. Updated the wording for endometriosis criteria to have a documentation of confirmed diagnosis of endometriosis.
12/01/23	Interim Review, approved November 14, 2023, effective for dates of service on or after March 7, 2024, following 90-day provider notification. Removed Eligard's coverage for the palliative treatment of advanced prostate cancer and added coverage for the treatment of advanced prostate cancer. Updated initial gender dysphoria criteria to require documentation that the individual has no comorbid psychiatric disorders and that potential adverse effects have been discussed including specifically possible effects on fertility. Updated initial gender dysphoria criteria to clarify that an individual must be ≥ 14 years of age, Tanner stage 2 or higher puberty onset based on physical examination, or Tanner stage 2 or higher puberty onset based on serum testosterone level in addition to being less than 23 years of age. Updated initial gender dysphoria criteria to clarify that the individual has not undergone a gonadectomy. Added a note under the gender dysphoria criteria that states that due to overlapping values between Tanner stages 1 and 2, for individuals assigned male at birth, total testosterone of at least 24 ng/dL or at least 0.17-0.8 nmol/L is required to confirm Tanner stage 2. For

Date	Comments
	individuals assigned female at birth, total testosterone of at least 11 ng/dL or 0.36 nmol/L is required to confirm Tanner stage 2. Levels of estrogens such as estradiol or estrone do not reliably confirm Tanner stage due to the extent of overlapping values between all Tanner stages. Added a note that use of these products is also investigational for the treatment of gender dysphoria for individuals who have completed puberty. Updated gender dysphoria re-authorization criteria to require documented specific rationale for why the individual has not undergone a gonadectomy if the individual ≥ 22 years of age, that suppression of secondary sex characteristics is based on physical examination, and documentation of annual testing of bone age or bone density.
02/01/24	Coding update. Added HCPC code J1954.
04/01/24	Annual Review, approved March 12, 2024. Updated initial gender dysphoria criteria from requiring diagnosis of confirmed gender dysphoria according to DSM-5 criteria to confirmation of the diagnosis of gender dysphoria, including verification that all diagnostic criteria for gender dysphoria are met as specified in the current version of the Diagnostic and Statistical Manual of Mental Disorders (DSM).
11/01/24	Interim Review, approved October 8, 2024, effective for dates of service on or after February 7, 2025, following 90-day provider notification. Updated initial authorization duration from up to 6 months to up to 12 months. Added the following clarification to the Investigational section of the policy: Use of GnRH analogs that does not meet the age or diagnosis requirements within the Medical Necessity section is considered investigational. Use of GnRH analogs that meets the age and diagnosis requirements within the Medical Necessity section but does not meet other policy criteria within the Medical Necessity section is considered not medically necessary. Updated initial gender dysphoria criteria to clarify that Tanner stage 2 or higher puberty onset is based on serum testosterone level, serum estradiol level, serum estrone level, serum luteinizing hormone level (only individuals assigned female at birth), or serum follicle stimulating hormone (only individuals assigned female at birth). Updated initial gender dysphoria criteria to clarify that documentation that potential adverse effects have been discussed, including specifically possible effects on fertility, and, if the individual is not taking a cross-sex hormone aka a gender affirming hormone (a testosterone formulation for transgender males; an estrogen or progesterone formulation for transgender females), possible effects on bone mineralization and bone density. Updated initial gender dysphoria criteria to clarify that if the individual is starting a GnRH analog at age 23 or older, or after reaching Tanner stage 5, or after irreversible physical/anatomic secondary sexual characteristics are already well developed, documentation that a GnRH analog is necessary to suppress characteristics of the gender assigned at birth that are not evident by observation or on physical examination (e.g., menses or penile erections). Updated initial gender dysphoria criteria to clarify that if the individual is starting a GnRH analog while already taking a cross-sex hormone (aka a gender affirming hormone), documentation that cross-sex hormone/gender affirming hormone treatment is not resulting in adequate suppression of natal (gender assigned at birth) secondary sex characteristics or is not

Date	Comments
	resulting in adequate suppression of endogenous hormones (e.g., testosterone for individuals assigned male at birth; estrogens or luteinizing hormone or follicle stimulating hormone for individuals assigned female at birth). Updated initial gender dysphoria criteria notes to clarify that due to overlapping values between Tanner stages 1 and 2, for individuals assigned male at birth, total testosterone of at least 24 ng/dL or at least 0.17-0.8 nmol/L is required to confirm Tanner stage 2, or serum estradiol of at least 14 pg/ml is required to confirm Tanner stage 2, or serum estrone level of at least 17 pg/ml is required to confirm Tanner stage 2. Due to overlapping values between Tanner stages 1 and 2, for individuals assigned female at birth, total testosterone of at least 11 ng/dL or 0.36 nmol/L is required to confirm Tanner stage 2, or serum estradiol of at least 21 pg/ml is required to confirm Tanner stage 2, or serum estrone level of at least 30 pg/ml is required to confirm Tanner stage 2, or serum luteinizing hormone > 0.3 IU/L is required to confirm Tanner stage 2, or serum follicle stimulating hormone > 4.1 IU/L is required to confirm Tanner stage 2. Luteinizing hormone levels and follicle stimulating hormone levels do not reliably confirm Tanner stage for individuals assigned male at birth due to the extent of overlapping values between Tanner stage 1 and all higher Tanner stages. Updated re-authorization gender dysphoria criteria to clarify that documentation of suppression of secondary sex characteristics based on physical examination OR documentation of suppression of characteristics of the gender assigned at birth that are not evident by observation or on physical examination (e.g., menses or penile erections) is required. Updated re-authorization gender dysphoria criteria to clarify that documentation of annual testing of bone age or bone density unless the individual is concurrently taking a cross-sex hormone aka a gender affirming hormone (a testosterone formulation for transgender males; an estrogen or progesterone formulation for transgender females) is required. Updated re-authorization gender dysphoria criteria to clarify that, for the first re-authorization request, if the previous coverage was under a non-Company plan, documentation that the initial authorization requirements have also been met is required. Added the following re-authorization gender dysphoria criteria notes: Suppression of characteristics of the gender assigned at birth can consist of either prevention of continued progression of puberty, or regression of secondary sexual characteristics of the gender assigned at birth. Documentation of regression to a lower Tanner stage or of prevention of progression to a higher Tanner stage is acceptable as physical examination documentation of suppression of secondary sex characteristics. The purpose of GnRH analog treatment for gender dysphoria is to suppress observable secondary sex characteristics of the gender assigned at birth or to suppress characteristics of the gender assigned at birth that are not evident by observation or on physical examination (e.g., menses or penile erections). The purpose is not just to attain certain lab values.in the absence of suppression of observable secondary sex characteristics of the gender assigned at birth or suppression of characteristics of the gender assigned at birth that are not evident by observation or on physical examination. Added coverage criteria for Synarel (nafarelin).

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply.

Scope: Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.