PHARMACY / MEDICAL POLICY – 5.01.625
Gonadotropin Releasing Hormone (GnRH) Analogs

Effective Date: Sept. 1, 2023*
Last Revised: Aug. 21, 2023
Replaces: N/A

*This policy has been updated. View the upcoming policy here.

Select a hyperlink below to be directed to that section.

POLICY CRITERIA | DOCUMENTATION REQUIREMENTS | CODING
RELATED INFORMATION | EVIDENCE REVIEW | REFERENCES | APPENDIX | HISTORY

∞ Clicking this icon returns you to the hyperlinks menu above.

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

<table>
<thead>
<tr>
<th>Drug</th>
<th>Medical Necessity</th>
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</thead>
</table>
| **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  
  • 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.  
  **Zoladex (goserelin)** may be considered medically necessary for use as an endometrial-thinning agent prior to endometrial ablation for dysfunctional uterine bleeding.  
  **Oriahnn (elagolix/estradiol/norethindrone acetate)** may be considered medically necessary when ALL of the following criteria are met:  
  • Individual is 18 years of age and older |
Myfembree approval can be granted for the labeled duration of therapy (24 months).
<table>
<thead>
<tr>
<th>Drug</th>
<th>Medical Necessity</th>
</tr>
</thead>
</table>
| **Prostate cancer**  | Camcevi (leuprolide mesylate), Eligard (leuprolide acetate), Firmagon (degarelix), generic leuprolide, brand leuprolide depot, Lupron Depot (leuprolide acetate), Orgovyx (relugolix), Trelstar (triptorelin pamoate), and Zoladex (goserelin) may be considered medically necessary for the palliative treatment of advanced* prostate cancer when used:  
  - As adjuvant therapy for:  
    - Stages T2b-T4 N0 M0 (Jewett stage B2-C)  
    - Stages T1-4 N1 M0  
    - Individuals with unfavorable risk stratification as evidence by:  
      - Stage T1c with PSA >10 ng/mL and Gleason score 7 with Gleason pattern 4+3  
      - Stage T1c and ≥50% biopsy cores positive (e.g., ≥ 6 of 12 cores)  
  - For recurrence or metastatic disease as documented by:  
    - Stages T1-4 N0-2 M1  
    - Rising PSA after curative attempt with surgery and/or radiation  

  **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. |
<p>| <strong>Breast cancer</strong>     | **Lupron Depot (leuprolide acetate), ***Trelstar (triptorelin pamoate), or Zoladex (goserelin) may be considered medically necessary for the palliative treatment of advanced breast cancer in <em>pre- and perimenopausal women.</em> |</p>
<table>
<thead>
<tr>
<th>Drug Medical Necessity Covered Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>**Lupron Depot (leuprolide acetate), **<em>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 <em>pre- and perimenopausal women when the following are met:</em></em></td>
</tr>
<tr>
<td>• Individual has HR+ breast cancer AND • Individual is receiving treatment with tamoxifen or an aromatase inhibitor (e.g., anastrozole, exemestane, letrozole)</td>
</tr>
</tbody>
</table>

| **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.

**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%.

<table>
<thead>
<tr>
<th>Central precocious puberty</th>
<th>Generic leuprolide, Lupron Depot PED (leuprolide acetate), Fensolvi (leuprolide acetate), Triptodur (triptorelin), Vantas (histrelin implant), and Supprelin LA (histrelin implant) may be considered medically necessary for the treatment of children with central precocious puberty when the following are met:</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>CENTRAL PRECOCIOUS PUBERTY</th>
<th><strong>G</strong>eneric <strong>leuprolide</strong>, <strong>Lupron Depot PED</strong> (leuprolide acetate), <strong>Fensolvi</strong> (leuprolide acetate), <strong>Triptodur</strong> (triptorelin), <strong>Vantas</strong> (histrelin implant), and <strong>Supprelin LA</strong> (histrelin implant) may be considered medically necessary for the treatment of children with central precocious puberty when the following are met:</th>
</tr>
</thead>
</table>
### Drug Medical Necessity

| Covered Indications |  
|---------------------|----------------------------------|
| • Diagnosis confirmed by one of the following:  
  o Pubertal basal level of luteinizing hormone (based on laboratory reference ranges; see Appendix)  
  OR  
  o Positive response to GnRH stimulation test (peak LH concentration ≥5 IU/L)  
  OR  
  o 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:  
  o Female ≤8 years of age  
  OR  
  o Male ≤9 years of age  

  **AND**  
  • Medication is prescribed by or in consultation with an endocrinologist  

| Gender dysphoria | Gender dysphoria  
|------------------|-------------------------------------------------------------|
| Generic leuprolide, brand leuprolide depot, Lupron Depot (leuprolide acetate), Lupron Depot PED (leuprolide acetate), Eligard (leuprolide acetate), Fensolvi (leuprolide acetate), Triptodur (triptorelin), Trelstar (triptorelin pamoate), Vantas (histrelin implant), Supprelin LA (histrelin implant), and Zoladex (goserelin) may be considered medically necessary for the treatment of gender dysphoria when the following are met:  
  • Individual is ≥ 14 years of age (or Tanner stage 2 or higher puberty onset) to 22 years of age and has not undergone a gonadectomy  
  **AND**  
  • Diagnosis of confirmed gender dysphoria according to DSM-5 criteria  
  **AND**  
  • Documentation that the individual’s gender incongruence and desire to be of a gender other than the individual’s assigned
<table>
<thead>
<tr>
<th>Drug</th>
<th>Medical Necessity</th>
</tr>
</thead>
</table>
| **Covered Indications**       | gender are not due to any other psychiatric disorders (e.g., psychotic disorders)  
AND  
• Medication is prescribed by or in consultation with an endocrinologist, transgender specialist, or providers in an adolescent medicine gender clinic  
AND  
• Documentation that potential adverse effects have been discussed including specifically impaired bone mineralization, loss of bone density, or bone demineralization  

**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 any other products in this policy for the treatment of gender dysphoria is considered investigational.                                                                                                                                 |
| **Endometriosis**             | **Generic leuprolide, brand leuprolide depot, Lupron Depot (leuprolide acetate), Lupaneta Pack (leuprolide/norethindrone), and Zoladex (goserelin)** may be considered medically necessary for women when the following criteria are met:  
• Individual is 18 years of age 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 18 years of age or older  
AND  
• Individual is premenopausal and is being treated for moderate to severe pain associated with endometriosis |
## Drug Medical Necessity

### Covered Indications

| 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 18 years of age or older
- Individual is premenopausal and is being treated for moderate to severe pain associated with endometriosis
- Individual does not have osteoporosis or severe hepatic impairment (Child-Pugh C)
- Treatment duration does not exceed:
  - 150 mg once daily for 24 months
  - 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).

### Ovulation Suppression

**Generic leuprolide may be considered medically necessary to suppress ovulation for a frozen embryo transfer (FET)**
<table>
<thead>
<tr>
<th>Drug</th>
<th>Medical Necessity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Covered Indications</td>
<td></td>
</tr>
<tr>
<td>Note:</td>
<td>Coverage is subject to infertility and assisted reproduction benefits</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug</th>
<th>Investigational</th>
</tr>
</thead>
<tbody>
<tr>
<td>As listed</td>
<td>All other uses of GnRH analogs for conditions not outlined in this policy are considered investigational.</td>
</tr>
</tbody>
</table>

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.

<table>
<thead>
<tr>
<th>Length of Approval</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approval</td>
<td>The drugs listed in this policy may be approved up to 6 months, unless noted otherwise.</td>
</tr>
<tr>
<td>Indications</td>
<td>Ongoing Use</td>
</tr>
<tr>
<td>Uterine fibroids</td>
<td>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.</td>
</tr>
</tbody>
</table>

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.

Prostate cancer    | Re-authorization of generic leuprolide, Camcevi (leuprolide mesylate), brand leuprolide depot, Lupron Depot (leuprolide acetate), Eligard (leuprolide acetate), Trelstar (triptorelin
<table>
<thead>
<tr>
<th>Length of Approval</th>
<th></th>
</tr>
</thead>
</table>
| **Prostate cancer** | Pamoate (degarelix), Firmagon (degarelix), Zoladex (goserelin), and Orgovyx (relugolix) 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 |

| **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 |
|-------------------| 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 generic leuprolide, Lupron Depot PED (leuprolide acetate), Fensolvi (leuprolide acetate), Triptodur (triptorelin), Vantas (histrelin implant), and Supprelin LA (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 |
| **Gender dysphoria** | Re-authorization of generic leuprolide, brand leuprolide depot, Lupron Depot (leuprolide acetate), Lupron Depot PED (leuprolide acetate), Fensolvi (leuprolide acetate), Triptodur (triptorelin), Trelstar (triptorelin pamoate), Vantas (histrelin implant), and Supprelin LA (histrelin implant) may be approved for 12 months for the prophylactic treatment of gender dysphoria 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 |
Length of Approval

<table>
<thead>
<tr>
<th>Length of Approval</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>approved for 12 months for the ongoing treatment of gender dysphoria when the following are met:</strong></td>
<td></td>
</tr>
<tr>
<td>• Individual is ≤ 22 years of age and has not undergone a gonadectomy AND • Documentation of suppression of secondary sex characteristics.</td>
<td></td>
</tr>
</tbody>
</table>

**Endometriosis**

- Re-authorization of generic leuprolide, brand leuprolide depot, Lupron Depot (leuprolide acetate), and Lupaneta Pack (leuprolide/norethindrone) may be approved for an additional 6 months (maximum of 12 months total treatment duration) when the following are met:
  - Documentation of positive clinical response
  - Individual is tolerating therapy

  Re-authorization of generic leuprolide, brand leuprolide depot, Lupron Depot (leuprolide acetate), and Lupaneta Pack 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.

**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
**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**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>J1950</td>
<td>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</td>
</tr>
<tr>
<td>J1951</td>
<td>Injection, leuprolide acetate for depot suspension (Fensolvi) 0.25 mg</td>
</tr>
<tr>
<td>J1952</td>
<td>Leuprolide injectable, Camcevi, 1 mg</td>
</tr>
<tr>
<td>J3315</td>
<td>Injection, triptorelin pamoate, (Trelstar) 3.75 mg</td>
</tr>
<tr>
<td>J3316</td>
<td>Injection, triptorelin, extended-release, (Triptodur) 3.75 mg</td>
</tr>
<tr>
<td>J3490</td>
<td>Unclassified drugs (Use to report Lupaneta Pack)</td>
</tr>
<tr>
<td>J9155</td>
<td>Injection, degarelix, (Firmagon)1 mg</td>
</tr>
<tr>
<td>J9202</td>
<td>Goserelin acetate implant, (Zoladex) per 3.6 mg</td>
</tr>
<tr>
<td>J9217</td>
<td>Leuprolide acetate (for depot suspension) (Lupron Depot 22.5 mg, 30 mg, 45 mg, 7.5 mg and (Eligard)), 7.5 mg</td>
</tr>
<tr>
<td>J9218</td>
<td>Leuprolide acetate, per 1 mg</td>
</tr>
<tr>
<td>J9225</td>
<td>Histrelin implant (Vantas), 50 mg</td>
</tr>
<tr>
<td>J9226</td>
<td>Histrelin implant (Supprelin LA), 50 mg</td>
</tr>
</tbody>
</table>

**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 childbearing 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 $4600.

**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 U.S., 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 Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). 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**


**Appendix**

### Laboratory Reference Ranges for Basal Luteinizing Hormone

<table>
<thead>
<tr>
<th>Age</th>
<th>Females</th>
<th>Males</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1 year</td>
<td>&lt;0.02-18.3 IU/L</td>
<td>&lt;0.02-5.0 IU/L</td>
</tr>
<tr>
<td>1-8 years</td>
<td>&lt;0.02-0.3 IU/L</td>
<td>&lt;0.02-0.5 IU/L</td>
</tr>
<tr>
<td>9-10 years</td>
<td>&lt;0.02-4.8 IU/L</td>
<td>&lt;0.02-3.6 IU/L</td>
</tr>
<tr>
<td>11-13 years</td>
<td>&lt;0.02-11.7 IU/L</td>
<td>0.1-5.7 IU/L</td>
</tr>
<tr>
<td>14-17 years</td>
<td>&lt;0.02-16.7 IU/L</td>
<td>0.8-8.7 IU/L</td>
</tr>
</tbody>
</table>

**History**
<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>06/01/21</td>
<td>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, Fenvelol (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.</td>
</tr>
<tr>
<td>08/01/21</td>
<td>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.</td>
</tr>
<tr>
<td>01/01/22</td>
<td>Coding update. Added HCPCS code J1952.</td>
</tr>
<tr>
<td>02/01/22</td>
<td>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.</td>
</tr>
<tr>
<td>05/01/22</td>
<td>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.</td>
</tr>
<tr>
<td>09/01/22</td>
<td>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 &quot;adolescent&quot; 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</td>
</tr>
<tr>
<td>Date</td>
<td>Comments</td>
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<tr>
<td>10/01/22</td>
<td>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 &quot;patient&quot; to &quot;individual&quot; throughout the policy for standardization.</td>
</tr>
<tr>
<td>05/01/23</td>
<td>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.</td>
</tr>
<tr>
<td>08/01/23</td>
<td>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.</td>
</tr>
<tr>
<td>09/01/23</td>
<td>Interim Review, approved August 21, 2023. Updated the wording for endometriosis criteria to have a documentation of confirmed diagnosis of endometriosis.</td>
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</table>

**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. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2023 Premera All Rights Reserved.

**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.
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Alaska residents: Contact the Alaska Division of Insurance via email at insurance@alaska.gov, or by phone at 907-269-7900 or 1-800-INSURAK (in-state, outside Anchorage).

Language Assistance

ATENCIÓN: si habla español, tiene a su disposición servicios gratuitos de asistencia lingüística. Llame al 800-722-1471 (TTY: 711).


注意: 如果您使用繁體中文,您可以免費獲得語言援助服務。請致電 800-722-1471 (TTY: 711)。


Note: 800-722-1471 (TTY: 711) is a toll-free number and is available 24 hours a day, 7 days a week, to people with disabilities wishing to file a complaint.