

## Drug Class Update: Gonadotropin-Releasing Hormone Agonists

**Date of Review:** August 2023

**Date of Last Review:** December 2021

(fibroids/endometriosis focused review on GnRH antagonists)  
March 2019 (Endometriosis); Nov 2019 (Elagolix); Jan 2019  
(Hormone replacement); May 2015 (GnRH Agonists)

**Dates of Literature Search:** 01/01/2015 – 06/20/2023

**Current Status of PDL Class:**

See **Appendix 1**.

### Plain Language Summary:

- This review looks at new evidence for using medications to treat early onset puberty also called central precocious puberty. This rare condition means females will begin menstruating, develop breasts, or develop pubic hair before 8 years of age. Males will develop enlarged testicles, deepen their voice, or grow pubic hair before 9 years of age. This condition can be stressful for a child that is experiencing physical changes before their peers.
- This review also looks at new evidence for using medications to manage gender dysphoria. Gender dysphoria is a sense of unease a person may have because of a difference between their biological sex at birth and their gender identity. This discomfort can cause anxiety, depression, and thoughts of suicide. Medical management of gender dysphoria is covered under the Oregon Health Plan.
- Medicines that stop the production of hormones which cause changes during puberty are used to treat central precocious puberty and manage gender dysphoria. These medicines are called gonadotropin-releasing hormone agonists and include goserelin, histrelin, leuprolide, nafarelin, and triptorelin.
- Medicines should only be used for a short time (3 years) to stop puberty in children with central precocious puberty. Once the child has reached the age of 11 or 12 years, the medicines can be stopped and puberty will begin again within 12 to 18 months.
- Positive outcomes associated with using these medicines in children are less depression, less anxiety, and improved growth to normal height as an adult.
- Adverse events associated with use of these medicine include slowed growth, increased mood swings, and decreased bone turnover.
- Providers must explain to the Oregon Health Authority why someone needs goserelin, histrelin, leuprolide, nafarelin, and triptorelin before Medicaid will pay for it. This process is called prior authorization.

### Purpose for Class Update:

- Examine recently published evidence for safety and efficacy of gonadotropin-releasing hormone (GnRH) agonists (e.g., goserelin, histrelin, leuprolide, nafarelin, triptorelin) for management of pediatric patients with central precocious puberty (CPP) and off-label use of GnRH agonists for puberty suppression in adolescents with gender dysphoria.

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## Research Questions:

1. What is the evidence of efficacy and safety for GnRH agonists when used to manage CPP or suppress puberty in adolescents with gender dysphoria?
2. Are there any subgroups of patients who, based on age, ethnicity, comorbidities, disease duration or severity, would particularly benefit or be harmed by a specific GnRH agonist?
3. What is the most current guidance for use of GnRH agonists to manage CPP or gender dysphoria?

## Conclusions:

- Two high-quality systematic reviews<sup>1,2</sup> and 2 high-quality clinical practice guidelines<sup>3,4</sup> have been published since the GnRH agonists were last reviewed for CPP and gender dysphoria. No evidence was identified that directly compared on GnRH agonist with another agonist for either CPP or gender dysphoria.
- A 2020 systematic review with meta-analysis examined the effects of long-acting GnRH agonist treatment (triptorelin or leuprolide) on adult height in females with precocious puberty (onset before 10 years of age).<sup>1</sup> Adult height, duration of the treatment, and age at the start of treatment were analyzed.<sup>1</sup> Adult height increased in females who received GnRH agonists compared to those who did not receive treatment (mean difference [MD] 3.2 cm; 95% confidence interval [CI] 1.3 to 5.1 cm,  $I^2 = 84%$ ; low QoE).<sup>1</sup> Mean height difference in females who started treatment before 8 years of age was 5.1 cm compared to 2.5 cm in females who started treatment at 8 years of age or older.<sup>1</sup> In females who were treated for less than 3 years, adult height was increased by an average of 0.4 cm compared to 5.9 cm in those who were treated for more than 3 years.<sup>1</sup> Duration of treatment was associated with greater height ( $p=0.005$ ) than age at start of treatment ( $p=0.084$ ) when compared with females who were not treated (low QoE).
- A 2021 systematic review investigated the long-term efficacy and safety of GnRH agonist treatment in children with CPP.<sup>2</sup> GnRH agonists leuprolide, triptorelin, nafarelin, goserelin, and histrelin were used in studies. Primary outcomes included in the studies were final adult height, body mass index (BMI), incidence of polycystic ovary syndrome (PCOS) in females and androgen excess in males.<sup>2</sup> Compared with no treatment, GnRH agonists increased final adult height and decreased BMI in females with CPP (low QoE).<sup>2</sup> GnRH agonists did not increase the risk of PCOS in females with CPP (low QoE).<sup>2</sup> Evidence was insufficient to make conclusions about androgen excess in males.<sup>2</sup>
- In 2017, the international Endocrine Society published guidance for endocrine treatment of persons with gender dysphoria.<sup>3</sup> They recommend puberty suppression with long-acting GnRH agonists in adolescents with gender dysphoria who have entered puberty at Tanner Stage 2.<sup>3</sup> The primary risks of pubertal suppression in gender-dysphoric adolescents may include adverse effects on bone mineralization, compromised fertility, and unknown effects on brain development.<sup>3</sup>
- An update of World Professional Association for Transgender Health (WPATH) Standards of Care was published in 2022.<sup>4</sup> They recognize that the body of evidence to support the effectiveness of early medical intervention is growing but is still limited, and there are few studies that follow youth into adulthood.<sup>4</sup> WPATH recommends health care professionals use GnRH agonists in eligible transgender and gender diverse people for whom suppressing puberty is indicated.<sup>4</sup> The adolescent should have reached Tanner stage 2 of puberty for pubertal suppression to be initiated with GnRH agonists.<sup>4</sup>
- No populations were identified based on age, race, ethnicity, or comorbidities who would particularly benefit or be harmed from treatment with a specific GnRH agonist.
- In June 2023 House Bill 2002-C was enacted to modify provisions relating to protections for individuals receiving gender-affirming health services.<sup>5</sup> The bill specifies criteria for medical necessity and requires that any denial of services be reviewed and approved by a provider with experience providing or delivering gender-affirming treatment.

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## Recommendations:

- No changes to the Oregon Health Plan (OHP) Preferred Drug List (PDL) are recommended based on review of the clinical evidence.
- Revise clinical prior authorization (PA) criteria to include Early and Periodic Screening, Diagnostic and Treatment (EPSDT) assessment and recently enacted state legislation.
- After executive session, the committee recommended making all Lupron Depot-Ped kit formulations (1 month, 3 month, and 6 month) preferred on the PDL.

## Summary of Prior Reviews and Current Policy:

- Puberty suppression in adolescents with gender dysphoria is a funded under the OHP Prioritized List of Health Services. In April 2015, the Pharmacy and Therapeutics (P&T) Committee approved use of GnRH agonists in adolescents with documented gender dysphoria at the beginning of puberty.
- The GnRH modulators were last reviewed by the P&T Committee in December 2021 in a review focused on fibroids and endometriosis treatments. Clinical PA criteria for GnRH modulators were separated into two PA documents for GnRH agonists and GnRH antagonists (see **Appendix 3**).
- The PDL status of each GnRH agonist is presented in **Appendix 1**. All GnRH agonists are non-preferred and require PA in patients under 18 years of age to ensure appropriate use for conditions funded under OHP.

## Background:

### Central Precocious Puberty

Central precocious puberty is defined as the full activation of the hypothalamic-pituitary-gonadal (HPG) axis before 8 years of age in females and before 9 years of age in males.<sup>6</sup> In a population-based study of data from Danish national registries from 1993 to 2001, the incidence of precocious puberty was 20 per 10,000 females and less than 5 per 10,000 males.<sup>7</sup> Although usually idiopathic in females, CPP can be induced by head trauma, neoplasm, radiation, or genetic conditions.<sup>8</sup> Pathologic causes due to physical injury of the central nervous system are more common in males with CPP.<sup>8</sup> In contrast, peripheral precocious puberty occurs when hormonal influences originating outside of the HPG axis (e.g., androgen-secreting tumor, estrogen secreting-tumor, congenital adrenal hyperplasia) produce incomplete, atypically sequenced or rapid pubertal progression.<sup>8</sup>

Central precocious puberty is characterized by sequential maturation of breasts and pubic hair in females and of testicular and penile enlargement and pubic hair in males.<sup>6,8</sup> Tanner stages are used to evaluate pubertal development.<sup>9</sup> Children are rated on a scale of 1-5 with 1 being preadolescent and 5 being fully developed.<sup>9</sup> The onset of puberty is marked by breast development in females (Tanner stage 2 breast development) and testicular enlargement in males (Tanner stage 2 genital development).<sup>10,11</sup> Children with CPP have accelerated linear growth for age, advanced bone age, and pubertal levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH).<sup>8</sup> An LH level of more than 0.3 IU/L is the most reliable laboratory finding for CPP.<sup>8,12</sup> CPP may result in premature cessation of growth and short stature as an adult.

The goal of CPP therapy is to halt pubertal progression and delay epiphyseal maturation, which leads to improvement of final adult height.<sup>13</sup> GnRH agonists are indicated in idiopathic CPP.<sup>6</sup> They work by providing continuous stimulation of the pituitary gonadotrophs, leading to desensitization and decreases in the release of LH and FSH.<sup>14</sup> In open-label, noncomparative, longitudinal studies, the use of GnRH agonists consistently resulted in the regression or stabilization of pubertal symptoms.<sup>15,16</sup> The duration of GnRH agonist therapy should be long enough to optimize final adult height, yet still allow progression of pubertal characteristics at an age that is concurrent with the individual's peers.<sup>17</sup> When GnRH agonist therapy with monthly depot preparations is stopped, normal puberty returns, on average, within 12 to 18 months.<sup>17</sup> Adverse effects with GnRH agonist treatment are rare, but may include allergic reactions, sterile abscess formation after injection, fracture of implant upon removal, vaginal bleeding, hot flashes, and seizures.<sup>12</sup> Medications approved by FDA for puberty suppression in children with CPP are presented in **Table 1**.

**Table 1. Gonadotropin-Releasing Hormone Agonists for Central Precocious Puberty.<sup>18</sup>**

Drug/Formulation	Age and Weight (if appropriate)	Dose
Histrelin (SUPPRELIN LA) SC Implant	≥ 2 years	50 mg implant surgically inserted SC every 12 months
Leuprolide (FENSOLVI) 6-month 45 mg SC Suspension	≥ 2 years	45 mg SC every 6 months; discontinue at the appropriate age of puberty onset
Leuprolide (LUPRON DEPOT-PED) 1-month IM Suspension (7.5 mg, 11.25mg, 15 mg)	≥ 1 years and ≤ 25 kg	7.5mg IM once a month; discontinue at the appropriate age of puberty onset
	≥ 1 years and > 25 kg to 37.5 kg	11.25 mg IM once a month; discontinue at the appropriate age of puberty onset
	≥ 1 years and > 37.5 kg	15 mg IM once a month; discontinue at the appropriate age of puberty onset
Leuprolide (LUPRON DEPOT-PED) 3-month IM Suspension (11.25 mg and 30 mg)	≥ 1 years	11.25 mg IM every 3 months or 30 mg IM every 3 months; discontinue at the appropriate age of puberty onset
Leuprolide (LUPRON DEPOT-PED) 6-month IM Suspension (45 mg)	≥ 1 years	45 mg IM every 6 months; discontinue at the appropriate age of puberty onset
Nafarelin (SYNAREL) Nasal Spray	Initiate before 8 years of age in females and before 9 years of age in males	2 sprays (400 mcg) into each nostril twice daily (total daily dose = 1600 mcg)
Triptorelin (TRIPTODUR) 6-month IM Suspension	≥ 2 years	22.5 mg IM every 6 months
Abbreviations: IM = intramuscular; kg = kilograms; mcg = microgram; mg = milligram; SC = subcutaneous		

### Gender Dysphoria

Gender dysphoria is the distress experienced by an individual when their gender identity and their gender assigned at birth are discordant.<sup>19</sup> Gender dysphoria is more specifically defined by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5; American Psychiatric Association) as a diagnosis.<sup>20</sup> Gender dysphoria can result in psychologic dysfunction, depression, and suicidal ideation.<sup>20</sup> The prevalence of gender dysphoria is difficult to determine in the general population. Previously, the prevalence in adults was thought to range from 0.005% to 0.014% for people assigned male gender at birth and 0.002% to 0.003% for people assigned female gender at birth.<sup>20</sup> More recent studies suggest that 0.39% to 0.60% of adults identify as transgender, with an increasing prevalence over the past decade.<sup>21</sup> Youth may present to providers stating overtly that they are transgender and requesting a gender assessment, or they may present less overtly with a mood disorder, anxiety or depressive traits, or a caregiver may have concern about social problems such as a change in academic performance or school truancy.<sup>19</sup> Not all children and youth who report gender identities different from their gender assigned at birth will experience persistent gender dysphoria. Retrospective studies suggest gender dysphoria persists from childhood into adulthood in the range of 12% to 27%.<sup>22</sup>

The Oregon Health Authority's Health Evidence Review Commission (HERC) Guideline Note 127 provides guidance on the treatment of gender dysphoria in OHP members.<sup>23</sup> Treatment with GnRH agonists is funded under the OHP if used to delay the onset of puberty.<sup>23</sup> The HERC recommends therapy be initiated at first

physical signs of puberty, confirmed by pubertal hormone levels, but no earlier than Tanner stages 2-3.<sup>23</sup> Prior to initiation of puberty suppression therapy, adolescents must fulfill eligibility and readiness criteria and have a comprehensive mental health evaluation.<sup>23</sup> Ongoing psychological care is strongly encouraged for continued puberty suppression therapy.<sup>23</sup>

The World Professional Association for Transgender Health (WPATH) Standards of Care recommend regimens for hormone therapy in adolescents with gender dysphoria that are substantially different from those used in adults. These regimens are adapted to account for the somatic, emotional and mental development that occurs throughout adolescence.<sup>4</sup> Although none of the GnRH agonists are approved by FDA for gender dysphoria, evidence from the use of GnRH agonists in treating CPP is oftentimes extrapolated to individuals with gender dysphoria to delay puberty.<sup>24</sup> GnRH agonists are covered under the OHP medical benefit for management of gender dysphoria. Compendial dosing information for GnRH agonists studied in gender dysphoria is presented in **Table 2**.

**Table 2. Gonadotropin-Releasing Hormone Agonists Studied in Gender Dysphoria<sup>18</sup>**

Drug/Formulation	Off-Label Dose
Goserelin (ZOLADEX) SC Implant	3.6 mg SC every month
Leuprolide (LUPRON) Suspension	3.75 mg IM every month
Leuprolide (LUPRON DEPOT-PED) 1-month or 3-month IM Suspension	3.75 mg IM every month 11.25 mg IM every 3 months
Triptorelin (TRELSTAR) IM Suspension	3.75 mg IM every month
Abbreviations: IM = intramuscular; kg = kilograms; SC = subcutaneous	

### 2023 Oregon Legislative Update

In June 2023 House Bill 2002-C was enacted to modify provisions relating to protections for providers and individuals receiving reproductive or gender-affirming health services. The bill specifies criteria for medical necessity and requires that any denial of services be reviewed and approved by a provider with experience providing or delivering gender-affirming treatment. Section 24 states: “Gender-affirming treatment means a procedure, service, drug, device or product that a physical or behavioral health care provider prescribes to treat an individual for incongruence between the individual’s gender identity and the individual’s sex assignment at birth. The Oregon Health Authority or a coordinated care organization may not: a) Deny or limit coverage under the plan for gender-affirming treatment that is: 1) medically necessary as determined by the physical or behavioral health care provider who prescribes the treatment; and 2) prescribed in accordance with accepted standards of care; b) Deny or limit gender-affirming treatment unless a physical or behavioral health care provider with experience prescribing or delivering gender-affirming treatment has first reviewed and approved the denial of or the limitation on access to the treatment.”<sup>5</sup> This legislation will take effect 1/1/24.

### Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) that assessed clinically relevant outcomes of GnRH agonists to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 2**, which includes dates, search terms and limits used. The Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based clinical practice guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

### **New Systematic Reviews:**

#### Adult Height After GnRH Agonist Treatment in Female Children with Precocious Puberty

A 2020 meta-analysis examined the effects of long-acting GnRH agonist treatment on adult height in female children younger than 10 years of age with precocious puberty.<sup>1</sup> Studies published from 1980 through 2018 were identified.<sup>1</sup> Of the 14 studies that met inclusion criteria, 9 were from Europe, 4 were from the Middle East, and one was from Asia.<sup>1</sup> Leuprolide was assessed in one study, either triptorelin or leuprolide were assessed in another study, and triptorelin was assessed in all of the other studies.<sup>1</sup> The GnRH agonist was administered every 28 days in almost all of the studies except two studies which used 21- to 25-day intervals.<sup>1</sup> The mean duration of treatment ranged from 1.9 to 4.2 years.<sup>1</sup> Only 2 studies were randomized. One study used a historical control.<sup>1</sup> The RoB was evaluated as follows: randomization of sequence generation (high RoB), allocation sequence concealment (high RoB), blinding of participants and personnel (high RoB), blinding of outcome assessors (moderate RoB), incomplete outcome data (low RoB), and selective outcome reporting (low RoB).<sup>1</sup>

A total of 608 treated and 395 untreated females were included in the meta-analysis.<sup>1</sup> The age in each study ranged from 6.3 to 9.0 years.<sup>1</sup> Adult height, duration of the treatment, and age at the start of treatment were analyzed.<sup>1</sup> The adult height increased in the females who were treated with GnRH agonists compared to those who did not receive treatment for early puberty.<sup>1</sup> The meta-analysis showed a pooled mean difference in adult height of 3.2 cm between treated and untreated individuals (95% CI 1.3 to 5.1 cm,  $I^2=84%$ ; low QoE).<sup>1</sup> The mean height difference in the females who started the treatment before 8 years of age was 5.1 cm (95% CI 0.4 to 9.8,  $I^2=94%$ ; low QoE).<sup>1</sup> In a subgroup of females older than 8 years of age at start of treatment, the mean height difference was smaller at 2.5 cm (95% CI 0.9 to 4.0,  $I^2=53%$ ; low QoE).<sup>1</sup> In females treated for less than 3 years, differences in adult height were not statistically significant, with an average increase of 0.4 cm versus those who were not treated (95% CI -1.8 to 2.7,  $I^2=74%$ ). In females treated for more than 3 years, adult height was increased by an average of 5.9 cm versus those who were not treated (95% CI 3.7 to 8.1,  $I^2=77%$ ; low QoE).<sup>1</sup>

This systematic review provides low-quality evidence that the adult height achieved with puberty suppression with GnRH agonists is associated with duration of treatment ( $p=0.005$ ) but does not provide evidence that the age at treatment initiation improves the adult height achieved ( $p=0.084$ ).<sup>1</sup> Use of an GnRH agonist for more than 3 years increased adult height; however, this meta-analysis did not find that treatment for less than 3 years had an effect on adult height achieved.<sup>1</sup> However, significant heterogeneity was identified between the studies in this meta-analysis, so there is high uncertainty of the effects found and more studies are needed.<sup>1</sup>

#### Long-Term Efficacy and Safety of GnRH Agonist Treatment in Children with Central Precocious Puberty

A 2021 systematic review investigated the long-term efficacy and safety of GnRH agonist treatment in children with CPP.<sup>2</sup> Literature was searched through November 2019.<sup>2</sup> Ninety-eight studies with a total of 5475 individuals (98.5% were female) met inclusion criteria.<sup>2</sup> The average age of CPP onset in each study ranged from 4.5 to 8 years, and the average age of GnRH agonist treatment initiation in each study ranged from 5 to 9.3 years.<sup>2</sup> The GnRH agonists used in the studies included leuprolide, triptorelin, nafarelin, goserelin, and histrelin.<sup>2</sup> Of the 98 total studies, 18 were RCTs ( $n=1303$ ) with moderate to high RoB and the remaining 81 ( $n=4172$ ) were single-arm studies with high RoB.<sup>2</sup> Thirteen studies ( $n=1047$ ) compared GnRH agonist treatment with no treatment, and six studies ( $n=310$ ) compared GnRH agonist treatment with GnRH agonist plus growth hormone.<sup>2</sup> Treatment duration in the studies ranged from 3 months to 5 years.<sup>2</sup> Selection bias and attrition bias were the primary concerns for the RCTs.<sup>2</sup> The QoE for each outcome were graded as very low to moderate.<sup>2</sup>

The primary efficacy outcome was final adult height. Harm outcomes included BMI, the incidence of polycystic ovary syndrome (PCOS) among females and androgen excess among males.<sup>2</sup> The RCTs showed that GnRH agonist treatment increased final adult height compared to no treatment by a mean difference [MD] of 4.83 cm (95% CI 2.32 to 7.34;  $I^2 = 49%$ ; 4 studies;  $n=242$ ; low QoE).<sup>2</sup> Lower BMI was observed in females treated with GnRH agonists compared with no treatment (MD  $-1.01$  kg/m<sup>2</sup>; 95% CI  $-1.64$  to  $-0.37$ ;  $I^2 = 0%$ ; 3 studies;  $n=334$ ; low QoE).<sup>2</sup> The incidence of PCOS was not found to be impacted by GnRH agonist treatment (RR 1.21; 95% CI 0.46 to 3.15;  $I^2 = 48%$ ; 3 studies;  $n=179$ ; low QoE).<sup>2</sup> There is insufficient evidence to know the effects of GnRH agonists on androgen excess in males.<sup>2</sup>

Compared with no treatment, there is low QoE that GnRH agonists increase final adult height.<sup>2</sup> GnRH agonists did not increase the risk of PCOS or obesity in females with CPP (low QoE).<sup>2</sup> Evidence regarding other key long-term outcomes (such as infertility and malignant or metabolic diseases) was considered insufficient to make conclusions.<sup>2</sup>

After review, 7 systematic reviews were excluded due to poor quality (e.g., indirect network-meta-analyses or failure to meet AMSTAR criteria), wrong study design or included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).<sup>25-31</sup>

### **New Clinical Practice Guidelines:**

#### Endocrine Society Clinical Practice Guideline: Gender Dysphoria

In 2017, the global Endocrine Society updated a 2009 practice guideline titled “Endocrine Treatment of Transsexual Persons” and renamed the guidance as “Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons”.<sup>3</sup> This nomenclature change reflects updated medical perspectives on management of gender dysphoria. This publication was co-sponsored by the American Association of Clinical Endocrinologists, American Society of Andrology, European Society for Pediatric Endocrinology, European Society of Endocrinology, Pediatric Endocrine Society, and WPATH.<sup>3</sup> Gender incongruence is an umbrella term used when the gender identity or gender expression differs from what is typically associated with the designated gender.<sup>3</sup> Not all individuals with gender incongruence have gender dysphoria or seek treatment.<sup>3</sup> Two systematic reviews supported the evidence-based recommendations developed by the guideline task force.

The guideline recommends treatment of gender-dysphoric/gender-incongruent adolescents who have entered puberty at Tanner Stage 2 by suppression with long-acting GnRH agonists.<sup>3</sup> An advantage of using GnRH agonists is the reversibility of the intervention.<sup>3</sup> If the individual no longer desires transition, they can discontinue pubertal suppression.<sup>3</sup> A benefit of pubertal suppression at early puberty may be better psychological and physical outcomes compared with starting gender-affirming treatment long after the first phases of puberty.<sup>3</sup> Although there is sparse evidence regarding the use of GnRH agonists in adolescents with gender dysphoria; in adolescents with CPP spontaneous pubertal development has been shown to resume after patients discontinue taking GnRH agonists.<sup>3</sup>

The primary risks of pubertal suppression in gender-dysphoric/gender-incongruent adolescents may include adverse effects on bone mineralization (which can theoretically be reversed with sex hormone treatment), compromised fertility if the person subsequently is treated with sex hormones, and unknown effects on brain development.<sup>3</sup> Few data are available on the effect of GnRH agonists on bone mineral density (BMD) in adolescents with gender-dysphoric/gender incongruence.<sup>3</sup> In children with CPP, treatment with GnRH agonists has been found to result in a decrease of BMD during treatment by some, but not others.<sup>3</sup> Recommended monitoring for individuals taking GnRH agonists includes Tanner staging, blood pressure, height and weight measurements every 3 to 6 months; LH, FSH, estradiol (transgender females), and testosterone levels (transgender males) every 6 to 12 months; and BMD using dual-energy X-ray absorptiometry (DEXA) every 1 to 2 years.<sup>3</sup>

Clinicians may add gender-affirming hormones to induce puberty (oral or transdermal estradiol in transgender women and intramuscular or subcutaneous testosterone in transgender men) after a multidisciplinary team has confirmed the persistence of gender dysphoric/gender incongruence and sufficient mental capacity to give informed consent to this partially irreversible treatment.<sup>3</sup> Most adolescents have this capacity by age 16 years old.<sup>3</sup> There may be compelling reasons to initiate sex hormone treatment prior to age 16 years, although there is minimal published experience treating prior to 13.5 to 14 years of age.<sup>3</sup> The care of peripubertal youths and older adolescents, should be cared for by an expert multidisciplinary team comprised of medical professionals and mental health professionals.<sup>3</sup> The treating physician must confirm the criteria for treatment used by the referring mental health practitioner and collaborate with them in decisions about gender-affirming surgery in older adolescents.<sup>3</sup>

Specific graded recommendations and the quality of evidence regarding use of GnRH agonists in children and adolescents are summarized below:

- Recommend against puberty blocking and gender-affirming hormone treatment in prepubertal children with gender-dysphoric/gender incongruence. (Strong Recommendation, Moderate QoE).<sup>3</sup>
- Suggest that adolescents who meet diagnostic criteria for gender-dysphoric/gender incongruence who are requesting treatment, and fulfill criteria for treatment, initially undergo treatment to suppress pubertal development. (Weak Recommendation, Moderate QoE).<sup>3</sup>
- Recommend that where indicated, long-acting GnRH agonists are used to suppress pubertal hormones. (Strong Recommendation, Moderate QoE).<sup>3</sup>
- Suggest that clinicians begin pubertal hormone suppression after first signs of physical changes of puberty. (Weak Recommendation, Moderate QoE).<sup>3</sup>

#### World Professional Association for Transgender Health

An update of WPATH Standards of Care was published in 2022 due to growing scientific evidence for the care of transgender and gender diverse people.<sup>4</sup> This professional organization was founded in 1979 to create an international community of providers committed to understanding the treatment of gender dysphoria. Recommendations were based on data derived from systematic literature review.<sup>4</sup> Most of the research and experience in this field comes from a North American and Western European perspective.<sup>4</sup> The term gender incongruence is recognized as a condition in the International Classification of Diseases and Related Health Problems, 11th Version of the World Health Organization (ICD-11) and will replace the term gender dysphoria in subsequent publications.<sup>4</sup>

A key challenge in adolescent transgender care is the quality of evidence evaluating the effectiveness of medically necessary gender-affirming medical and surgical treatments over time.<sup>4</sup> Despite the slowly growing body of evidence supporting the effectiveness of early medical intervention, the number of studies is still low, and there are few outcome studies that follow youth into adulthood.<sup>4</sup> WPATH recommends health care professionals assessing transgender and gender diverse adolescents only recommend gender-affirming medical or surgical treatments requested by the patient when:

- The adolescent meets the diagnostic criteria of gender incongruence as per the ICD-11 in situations where a diagnosis is necessary to access health care.<sup>4</sup>
- The experience of gender diversity/incongruence is marked and sustained over time.<sup>4</sup>
- The adolescent demonstrates the emotional and cognitive maturity required to provide informed consent/assent for the treatment.<sup>4</sup>
- The adolescent's mental health is assessed and any concerns that may interfere with diagnostic clarity, capacity to consent, and gender-affirming medical treatments have been addressed.<sup>4</sup>
- The adolescent has been informed of the reproductive effects, including the potential loss of fertility and the available options to preserve fertility, and these have been discussed in the context of the adolescent's stage of pubertal development.<sup>4</sup>
- The adolescent has reached Tanner stage 2 of puberty for pubertal suppression to be initiated.<sup>4</sup>
- WPATH recommends health care professionals use GnRH agonists to suppress endogenous sex hormones in eligible transgender and gender diverse people for whom puberty blocking is indicated.<sup>4</sup>



- WPATH recommends health care professionals prescribe 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 (past Tanner stage 3) but are unsure about or do not wish to begin sex steroid hormone therapy.<sup>4</sup>

#### New FDA Safety Alerts:

**Table 1. Description of new FDA Safety Alert<sup>32</sup>**

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Histrelin	SUPPRELIN LA	4/22	Warnings and Precautions	Pseudo tumor cerebri (idiopathic intracranial hypertension) have been reported in pediatric patients receiving GnRH agonists. Monitor patients for signs and symptoms of pseudo tumor cerebri, including headache, papilledema, blurred vision, diplopia, loss of vision, pain behind the eye or pain with eye movement, tinnitus, dizziness, and nausea.
Leuprolide	LUPRON DEPOT-PED, FENSOLVI			
Nafarelin	SYNAREL			
Triptorelin	TRIPTODUR			

#### Randomized Controlled Trials:

A total of 46 citations were manually reviewed from the initial literature search. After further review, 46 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

#### References:

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**Appendix 1: Current Preferred Drug List**

<b><u>Generic</u></b>	<b><u>Brand</u></b>	<b><u>Form</u></b>	<b><u>Route</u></b>	<b><u>PDL</u></b>
histrelin acetate	SUPPRELIN LA	KIT	IL	N
histrelin acetate	SUPPRELIN	KIT	SQ	N
leuprolide acetate	LUPRON DEPOT-PED	KIT	IM	N
leuprolide acetate	LUPRON DEPOT	SYRINGEKIT	IM	N
leuprolide acetate	LUPRON DEPOT	SYRINGEKIT	IM	N
leuprolide acetate	LUPRON DEPOT (LUPANETA)	SYRINGEKIT	IM	N
leuprolide acetate	LUPRON DEPOT-PED	SYRINGEKIT	IM	N
leuprolide acetate	LEUPROLIDE ACETATE	KIT	SQ	N
leuprolide acetate	ELIGARD	SYRINGE	SQ	N
leuprolide acetate	FENSOLVI	SYRINGE	SQ	N
leuprolide acetate	LEUPROLIDE ACETATE	VIAL	SQ	N
leuprolide mesylate	CAMCEVI	SYRINGE	SQ	N
leuprolide/norethindrone acet	LUPANETA PACK	KT SYR TAB	MC	N
nafarelin acetate	SYNAREL	SPRAY	NS	N
triptorelin pamoate	TRELSTAR	VIAL	IM	N
triptorelin pamoate	TRIPTODUR	VIAL	IM	N

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## Appendix 2: Medline Search Strategy

### Search # 1: Ovid MEDLINE(R) 1996 to November Week 2 2022; Ovid MEDLINE(R) In-Process & In-Data-Review Citations 1946 to **November 17, 2022**

1. central precocious puberty.mp. or exp Puberty, Precocious/	2688
2. exp Gender Dysphoria/	842
3. exp Goserelin/	1098
4. exp Leuprolide/	2241
5. exp Nafarelin/	129
6. Gonadotropin-Releasing Hormone/ or histrelin.mp.	16174
7. Triptorelin Pamoate/	1242
8. 1 or 2	3527
9. 3 or 4 or 5 or 6 or 7	18895
10. 8 and 9	784
<b>11. limit 10 to (english language and humans and yr="2015 -Current")</b>	<b>279</b>
12. limit 11 to (clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or guideline or meta-analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review")	41

### Search # 2: Ovid MEDLINE(R) 1996 to June Week 2 2023; Ovid MEDLINE(R) In-Process & In-Data-Review Citations 1946 to **June 19, 2023**

1. central precocious puberty.mp. or exp Puberty, Precocious/	2790
2. exp Gender Dysphoria/	909
3. exp Goserelin/	1106
4. exp Leuprolide/	2266
5. exp Nafarelin/	129
6. Gonadotropin-Releasing Hormone/ or histrelin.mp.	16530
7. Triptorelin Pamoate/	1247
8. 1 or 2	3696
9. 3 or 4 or 5 or 6 or 7	19275
10. 8 and 9	824
<b>11. limit 10 to (english language and humans and yr="2022 -Current")</b>	<b>70</b>
12. limit 11 to (clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or guideline or meta analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review")	5

## Gonadotropin-Releasing Hormone Agonists

**Goals:**

- Restrict use of gonadotropin-releasing hormone (GnRH) agonists to medically appropriate conditions funded under the Oregon Health Plan.
- Promote use that is consistent with medical evidence and product labeling.

**Length of Authorization:**

- Up to 6 months

**Requires PA:**

- All GnRH agonists

**Covered Alternatives:**

- Current PMPDP preferred drug list per OAR 410-121-0030 at [www.orpdl.org](http://www.orpdl.org)
- Searchable site for Oregon FFS Drug Class listed at [www.orpdl.org/drugs/](http://www.orpdl.org/drugs/)

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the diagnosis funded by OHP?	<b>Yes:</b> Go to #4	<b>No: For current age ≥ 21 years:</b> Pass to RPh. Deny; not funded by the OHP  <b>For current age &lt; 21 years:</b> Go to #3.
3. Will the prescriber consider switching to a preferred product, if appropriate? Message: <ul style="list-style-type: none"> <li>• Preferred products do not require a PA.</li> <li>• Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy &amp; Therapeutics Committee.</li> </ul>	<b>Yes:</b> Inform prescriber of covered alternatives in class.	<b>No:</b> Go to #4

Approval Criteria		
4. Is there documentation that the condition is of sufficient severity that it impacts the patient's health (e.g., quality of life, function, growth, development, ability to participate in school, perform activities of daily living, etc)?	<b>Yes:</b> Go to #5	<b>No:</b> Pass to RPh. Deny; medical necessity.
5. Is the diagnosis central precocious puberty or other endocrine disorder?	<b>Yes:</b> Go to #6	<b>No:</b> Go to #7
6. Is the prescriber a pediatric endocrinologist?	<b>Yes:</b> Approve for up to 6 months.	<b>No:</b> Pass to RPh; deny for medical appropriateness.
7. Is the diagnosis gender dysphoria?	<b>Yes:</b> Approve for 1 year	<b>No:</b> Go to #8
8. Is the patient of childbearing potential and pregnant or actively trying to conceive?	<b>Yes:</b> Pass to RPh. Deny; medical appropriateness	<b>No:</b> Go to #9
9. Is there documentation that the provider and patient have discussed the teratogenic risks of the drug if the patient were to become pregnant?	<b>Yes:</b> Go to # 10	<b>No:</b> Pass to RPh. Deny; medical appropriateness.
10. Is this request for treatment of breast cancer or prostate cancer?	<b>Yes:</b> Approve up to 1 year	<b>No:</b> Go to #11
11. Is this request for leuprolide for the management of preoperative anemia due to uterine fibroids (leiomyoma)?	<b>Yes:</b> Approve for up to 3 months	<b>No:</b> Go to #12
12. Is this request for management of moderate to severe pain associated with endometriosis in a woman $\geq 18$ years of age?	<b>Yes:</b> Go to #13	<b>No:</b> Pass to RPh. Deny; medical appropriateness

## Approval Criteria

13. Has the patient tried and failed an adequate trial of at least 1 of the preferred first line endometriosis therapy options for at least 3 months including administration of combined hormonal contraceptives or progestins (oral, depot injection, or intrauterine) alone?  
OR  
Does the patient have a documented intolerance, FDA-labeled contraindication, or hypersensitivity the first-line therapy options?

**Yes:** Approve for 6 to 12 months, depending on selected medication.  
  
\*Note maximum recommended duration of therapy for nafarelin and goserelin is 6 months. Leuprolide therapy should not exceed 12 months. If requesting continuation of therapy beyond FDA-approved duration, pass to RPh. Deny; medical appropriateness.

**No:** Go to #14  
  
\*First-line therapy options such as hormonal contraceptives or progestins do not require PA

14. RPh only:  
All other indications need to be evaluated as to whether it is funded under the OHP. Refer unique situations to Medical Director of DMAP.

P&T / DUR Review: 8/23 (DM); 12/21 (DM); 3/19 (DM); 5/15  
Implementation: 9/1/23; 1/1/22; 5/1/19