Medical Benefit Drug Policy

Gonadotropin-Releasing Hormone Agonists (Non-Oncology Indications)

Policy Number: MC/PC 016
Effective Date: June 1, 2026

Instructions for Use

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Related Policies

- Oncology Medication Clinical Coverage

Coverage Rationale

Central Precocious Puberty (CPP)

For initial coverage of Fensolvi, Lupron Depot-PED, Supprelin LA and Triptodur for Central Precocious Puberty (CPP) the following will be required:

- Diagnosis of central precocious puberty (idiopathic or neurogenic) **and**
- Early onset of secondary sexual characteristics in one of the following:
  - Females less than 8 years of age
  - Males less than 9 years of age **and**
- Advanced bone age of at least one year compared with chronological age **and**
- One of the following:
  - Both of the following:
    - Peak luteinizing hormone (LH) level above pre-pubertal range
    - Pubertal luteinizing hormone (LH) level response to a gonadotrophin releasing hormone (GnRH) stimulation test **or**
  - Patient has a random LH level in the pubertal range **and**
- One of the following:
  - Patient had one of the following diagnostic evaluations to rule out tumors, when suspected:
    - Diagnostic imaging of the brain (MRI or CT scan) (in patients with symptoms suggestive of a brain tumor or in those 6 years of age or younger)
    - Pelvic/testicular/adrenal ultrasound (if steroid levels suggest suspicion)
    - Adrenal steroids to rule out congenital adrenal hyperplasia (when pubarche precedes thelarche or gonadarche) **or**
  - Patient has no suspected tumors **and**
- Prescribed by or in consultation with an endocrinologist

For reauthorization coverage of Fensolvi, Lupron Depot-PED, Supprelin LA and Triptodur for Central Precocious Puberty (CPP) the following will be required

- Patient demonstrates positive clinical response to therapy (e.g., lack of progression or stabilization of secondary sexual characteristics, decrease in height velocity, a decrease in the ratio of bone age to chronological age, improvement in final height prediction, LH levels have been suppressed to pre-pubertal levels) **and**
- Patient is currently younger than the appropriate time point for the onset of puberty (e.g., females younger than 11 years of age, males younger than 12 years of age) **and**
- Prescribed by or in consultation with an endocrinologist

Gender Dysphoria/Gender Incongruence (off-label)

For initial coverage of Lupron Depot-PED, Supprelin LA, Triptodur and Fensolvi for Gender Dysphoria/Gender Incongruence (off-label) the following will be required:

- Using gonadotropin for suppression of puberty **and**
- Diagnosis of gender dysphoria/gender incongruence **and**
- Prescribed in consultation with an endocrinologist or provider with expertise in transgender hormone therapy

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

HCPCS Code	Description
J1950	Injection, leuprolide acetate (for depot suspension), per 3.75 mg
J1951	Injection, leuprolide acetate for depot suspension (fensolvi), 0.25 mg
J3316	Injection, triptorelin, extended-release, 3.75 mg
J9226	Histrelin implant (Supprelin LA), 50 mg

ICD-10 Code	Description
E22.8	Other hyperfunction of pituitary gland, central precocious puberty
E30.1	Precocious puberty
F64.0	Transsexualism
F64.1	Dual role transvestism
F64.2	Gender identity disorder of childhood
F64.8	Other gender identity disorders
F64.9	Gender identity disorder, unspecified
Z87.890	Personal history of sex reassignment

Background

Central Precocious Puberty (CPP)

Puberty is a period of physical, hormonal, and psychological transition from childhood to adulthood, with accelerated linear growth and achievement of reproductive function (Britto et al 2016). Pubertal timing is influenced by complex interactions of genetic, nutritional, environmental, and socioeconomic factors (Macedo et al 2014). While there has been extensive discussion with regard to the definition of puberty, most pediatricians give an age limit of 8 years in girls

and 9 to 9.5 years in boys for the lower limit of normal pubertal development (Carel et al 2004). Central Precocious Puberty(CPP) is characterized by the early onset of pubertal manifestations in girls and boys (Carel et al 2004). CPP is caused by the disruption of the hypothalamic-pituitary-gonadal axis, which results in the early activation of pulsatile gonadotropin-releasing hormone (GnRH) secretion (Carel and Léger 2008). These manifestations consist primarily of breast development in girls and testicular enlargement in boys (Carel and Léger 2008).

Gonadotropin-Releasing Hormone Agonists (GnRH agonists) are the treatment of choice for CPP. Chronic administration of potent GnRH agonists causes down-regulation of pituitary GnRH receptors, suppression of gonadotropin (luteinizing hormone [LH] and follicle-stimulating hormone [FSH]) secretion, and finally suppression of the release of gonadal sex hormones (Fuqua 2013, Klein et al 2016). There are several GnRH agonists available in varying doses and formulations. The intramuscular (IM) depot and long-acting subcutaneous (SC) formulations are generally preferred due to improved compliance (Guaraldi et al 2016; Popovic et al 2022). The GnRH agonists that are Food and Drug Administration (FDA)-approved for the treatment of CPP include:

- Fensolvi (leuprolide acetate), administered as a long-acting SC injection every 6 months.
- Lupron Depot-Ped (leuprolide acetate), available as monthly or every-3-month IM injections.
- Supprelin LA (histrelin), available as a 1-year SC implant device.
- Triptodur (triptorelin), administered as a single IM injection every 24 weeks. Of note, Trelstar (triptorelin pamoate) IM injection was the first FDA-approved triptorelin formulation; it was used off-label to treat CPP until Triptodur was made available in 2017 (Klein et al 2016).

The optimal time to discontinue a GnRH agonist has not been established. Older analyses suggest that discontinuation around the age of 11 years is associated with optimal height outcomes (Carel and Léger 2008). However, more recent data stress the importance of individualizing the decision of when to discontinue therapy based on bone age progression and rate of linear growth, amongst other variables (Popovic et al 2022).

Gender Dysphoria/Gender Incongruence (off-label)
Gender dysphoria is defined as the discomfort arising in some individuals from the incongruence between their gender identities and their external sexual anatomy at birth. The diagnosis of gender dysphoria is generally done by a mental health professional; however, other health care professionals who have the appropriate experience and training can also diagnose gender dysphoria. Mental health providers typically use the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) to make a diagnosis (American Psychiatric Association 2013).

Clinical Evidence

Fensolvi
In a single-arm trial (N = 64) in GnRH agonist-naïve pediatric patients with CPP (mean age, 7.5 years; range, 4 to 9 years), subcutaneously (SC) leuprolide acetate once every 24 weeks adequately suppressed LH in 87% of patients at month 6 and 86% of patients at month 12. Furthermore, SC leuprolide acetate adequately reduced FSH levels in 66% and 55% of patients at months 6 and 12, respectively. Progression of clinical signs of puberty were arrested or reversed with reduction in growth velocity and bone age (Fensolvi Product Information 2022, Klein et al 2020).

Lupron Depot Ped
A RCT with 54 patients compared the 1-month (7.5 mg) and 3-month (11.25 mg and 22.5 mg) leuprolide formulations for the treatment of CPP. There were more patients with inadequate pubertal suppression in the 11.25 mg 3-month leuprolide depot group (as measured by mean stimulated LH levels > 4 IU/L) compared to the 7.5 mg monthly and 22.5 mg 3-month groups. Mean LH and FSH levels in the 22.5 mg 3-month dose group were not different from the monthly depot injections. No differences in estradiol levels, growth velocity, or bone age progression were observed between the dosing groups (Fuld et al 2011). In a phase 3, randomized, open-label (OL) study (N = 84), leuprolide 11.25 mg 3-month depot was compared to leuprolide 30 mg 3-month depot in children with CPP. There were 9 treatment failures (peak

stimulated LH > 4 IU/L) in the 11.25 mg group and 2 in the 30 mg group. Basal sex steroid suppression, growth rates, pubertal progression, bone age advancement, and AEs were similar between both doses (Lee et al 2012).

In a phase 3, single-arm, OL study, 27 treatment-naïve and 18 previously-treated children with CPP were treated with leuprolide acetate 45 mg 6-month depot. At 24 weeks, 86.7% of patients had adequately suppressed LH. Through week 48, adequate suppression of LH, estradiol, and testosterone was achieved, as well as suppression of physical signs of puberty (Klein et al 2023).

Supprelin LA
In a multicenter trial (MC) with histrelin implant for the treatment of CPP, peak LH and estradiol or testosterone were effectively suppressed, and no significant AEs were noted. Positive long-term safety and efficacy data were reported in 2 studies (a 2- and a 6-year study) that evaluated long-term hormonal suppression in CPP patients post histrelin implant insertion. More specifically, peak LH and FSH levels remained suppressed in both the 2- and the 6-year trial (Harrington and Palmert 2024, Rahhal et al 2009, Silverman et al 2015).

Triptodur
The efficacy of triptorelin 6-month injection was evaluated in an open-label, single-arm clinical trial in females and males with CPP, ages 2 to 9 years (N = 44). At 12 months, 97.7% of patients achieved pre-pubertal LH levels. Mean stimulated FSH and mean basal FSH levels were also lower at 12 months, compared to baseline. Additionally, the Tanner stage (a scale of physical development) was stable or reduced (manifested by a reduction in physical development) in 88.6% of patients (Klein et al 2016).

Note: Clinical evidence supporting the use of GnRH analogs for the treatment of gender dysphoria and transgender individuals is limited and lacks long-term safety data. Statistically robust randomized controlled trials are needed to address the issue of whether the benefits outweigh the clinical risk in its use.

Clinical Guidelines
Central Precocious Puberty (CPP)
American Academy of Pediatrics (AAP) has published an evaluation and referral guideline of children with signs of early puberty (Kaplowitz and Bloch 2016). In this guideline, the AAP advises that treatment with GnRH agonists such as leuprolide can be administered via injection at monthly or 3-month intervals or with annual insertion of SC histrelin implant. If suppression of menses is the primary concern (rather than preservation of linear growth potential), then medroxyprogesterone depot IM injection every 3 months can be considered. Therapy should be continued until the physician determines that continued pubertal suppression is no longer beneficial to the child. The guidelines have not been updated to include leuprolide long-acting SC injection.

Gender Dysphoria/Gender Incongruence (off-label)
In 2017, the Endocrine Society published a clinical practice guideline on the 'Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons'. This guideline recommends treating gender-dysphoric/gender-incongruent adolescents who have entered puberty at Tanner Stage G2/B2 by suppression with gonadotropin-releasing hormone agonists (Hembree et al 2017). In view of the increasing scientific evidence, the World Professional Association for Transgender Health (WPATH) commissioned a new version of the Standards of Care, the SOC-8 in 2022 (Coleman et al 2022). The approach to gender-affirming hormone therapy differs and depends on the developmental stage of the individual at the time of initiation of hormone therapy as well as their treatment goals. Hormone therapy is not recommended for children who have not begun endogenous puberty. In eligible youth who have reached the early stages of puberty, the focus is usually to delay further pubertal progression with gonadotropin releasing hormone agonists until an appropriate time.

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

LUPRON DEPOT-PED is a gonadotropin releasing hormone (GnRH) agonist indicated for the treatment of pediatric patients with central precocious puberty.

FENSOLVI is a gonadotropin releasing hormone (GnRH) agonist indicated for the treatment of pediatric patients 2 years of age and older with central precocious puberty.

SUPPRELIN LA is a gonadotropin releasing hormone (GnRH) agonist indicated for the treatment of children with central precocious puberty (CPP)

TRIPTODUR is a gonadotropin releasing hormone (GnRH) agonist indicated for the treatment of pediatric patients 2 years and older with central precocious puberty

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Policy History/Revision Information

Date	Summary of Changes
12/13/2023	Approved by OptumRx P&T Committee
8/15/2024	Annual Review. Removed "pediatric" from pediatric endocrinologist prescriber requirement for central precocious puberty (CPP) indication.
8/21/2025	Annual Review. Added: Patient has a random LH level in the pubertal range for central precocious puberty (CPP) indication. Added additional study to the clinical evidence section for Lupron Depot Ped. Updated references.

Instructions for Use

This Medical Benefit Drug Policy provides assistance in interpreting standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, please check the member specific benefit plan document and any applicable federal or state mandates. The insurance reserves the right to modify its Policies and Guidelines as necessary. This Medical Benefit Drug Policy is provided for informational purposes. It does not constitute medical advice.

OptumRx may also use tools developed by third parties to assist us in administering health benefits. OptumRx Medical Benefit Drug Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

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- Qualified sign language interpreters.
- Written information in other formats (large print, audio, accessible electronic formats, other formats).

Provides free language assistance services to people whose primary language is not English, which may include:

- Qualified interpreters.
- Information written in other languages.

If *you* need reasonable modifications, appropriate auxiliary aids and services, or language assistance services, contact the Nondiscrimination Grievance Coordinator at the address, phone number, fax number, or email address below.

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Nondiscrimination Grievance Coordinator
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PO Box 1890
Southampton, PA 18966-9998
Phone: 1-866-631-5404 (TTY: 711)
Fax: 763-847-4010
Email: customerservice@aspirushealthplan.com

You can file a *grievance* in person or by mail, fax, or email. If *you* need help filing a *grievance*, the Nondiscrimination Grievance Coordinator is available to help *you*.

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at:

U.S. Department of Health and Human Services
200 Independence Avenue, SW
Room 509F, HHH Building
Washington, D.C. 20201
1.800.368.1019, 800.537.7697 (TDD)

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Albanian: KUJDES: Nëse flitni shqip, për ju ka në dispozicion shërbime të asistencës gjuhësore, pa pagesë.Telefononi në 1-800-332-6501 (TTY: 711).

Arabic تنبيه: إذا كنت تتحدث اللغة العربية، فإن خدمات المساعدة اللغوية متاحة لك مجاناً. اتصل بن اعلى رقم الهاتف1-800-332-6501(رقم هاتف الصم والبك : 711)

French: ATTENTION: Si vous parlez français, des services d'aide linguistique vous sont proposés gratuitement. Appelez le 1-800-332-6501 (ATS: 711).

German: ACHTUNG: Wenn Sie Deutsch sprechen, stehen Ihnen kostenlos sprachliche Hilfsdienstleistungen zurVerfügung. Rufnummer: 1-800-332-6501 (TTY: 711).

Hindi: _यान द_: य_द आप ि हंदी बोलते ह_ तो आपके ि लए मु_त म_ भाषा सहायता सेवाएं उपल_ध ह_।1-800-332-6501 (TTY: 711) पर कॉल कर_।

Hmong: LUS CEEV: Yog tias koj hais lus Hmoob, cov kev pab txog lus, muaj kev pab dawb rau koj. Hu rau 1-800-332-6501 (TTY: 711).

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Tagalog: PAUNAWA: Kung nagsasalita ka ng Tagalog, maaari kang gumamit ng mga serbisyo ng tulong sa wika nangwalang bayad. Tumawag sa 1-800-332-6501 (TTY: 711).

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Pennsylvania Dutch: Wann du Deitsch (Pennsylvania German / Dutch) schwetzscht, kannscht du mitaus Koschte ebbergricke, ass dihr helft mit die englisch Schprooch. Ruf selli Nummer uff: Call 1-800-332-6501 (TTY: 711).

Lao: ໂປດຊາບ: ຖ້າວ່າ ທ່ານເວົ້າພາສາ ລາວ, ການບໍລິການຊ່ວຍເຫຼືອດ້ານພາສາ,ໂດຍບໍ່ເສັງຄ່າ, ແມ່ນມີພ້ອມໃຫ້ທ່ານ. ໂທຣ 1-800-332-6501 (TTY: 711).