Medical Drug Clinical Criteria

Subject:	Gonadotropin Releasing Hormone Analogs for the Treatment of Non-Oncologic Indications		
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Overview

This document addresses the use of Gonadotropin Releasing Hormone (GnRH) Analogs for the Treatment of Non-Oncologic Indications. Included in this review are:

- Fensolvi (leuprolide acetate)
- Lupron Depot, Lupron Depot-Ped (leuprolide acetate)
- Supprelin LA 12 month implant (histrelin acetate)
- Synarel Nasal Spray (nafarelin acetate)
- Triptodur (triptorelin pamoate extended-release)
- Zoladex (goserelin acetate)

Summary of FDA-approved Non-Oncology related indications and commercially available GnRH Agents

Agent	Endo	IET	CPP	UL
Lupron Depot (leuprolide acetate) 1 month, 3 month, 6-month	x			x
Zoladex (goserelin acetate) 1 month	x	x		
Synarel (nafarelin acetate) 1 month	x		x	
Lupron Depot-Ped (leuprolide acetate) 1 month, 3 month, 6-month			x	
Supprelin LA (histrelin acetate) 12 month			x	
Triptodur (triptorelin) 6 month			x	
Fensolvi (leuprolide acetate) injectable suspension 45 mg kit			x	

Endo = Endometriosis, IET = Induce Endometrial Thinning, CPP = Central Precocious Puberty, UL = Uterine Leiomyomata (fibroids)

GnRH analogs are a group of hormonal drugs consisting of GnRH agonists and antagonists, both of which suppress pituitary hormones. GnRH agonists typically act over several days and GnRH antagonists act quickly within several hours. Affecting the pituitary gland in the brain, GnRH analogs suppress function of the ovaries and testes, blocking the production of testosterone in males and estrogen in females. Repeated administration of these drugs will cause gonadal hormone dependent tissues/organs to reduce or cease activity, such as the normal prostate gland that is dependent on testosterone for growth and function. This effect is reversible on discontinuation of the drug therapy.

Central Precocious Puberty (CPP) is defined as the full activation of the hypothalamic-pituitary-gonadal (HPG) axis before 8 years of age in girls and before 9 years of age in boys. The diagnosis may be considered in girls who have progressive breast development and who cross percentiles upward on the linear growth chart. CPP is far less common in boys but may be considered if there is evidence of both testicular and penile enlargement before 9 years of age (Kaplowitz 2016). The diagnostic evaluation of suspected CPP will typically include a bone age determination, which is often useful in predicting adult height. Baseline laboratory testing may include FSH, LH, and either estradiol or testosterone. The decision as to when to stop therapy is complex but typically occurs when it is apparent that continued pubertal suppression is no longer beneficial to the child. Thus, if the child is able to cope with puberty, and the predicted adult height is within the normal range, treatment may be stopped early; it often takes a year or more after cessation for menses to start. Some endocrinologists will end therapy in girls by 10 years of age, and others will continue it until 11 or 12 years of age, depending on clinical circumstances.

Gender dysphoria or gender incongruence is a condition wherein an individual's experienced gender is the opposite of his or her natal gender (usually assigned at birth based on anatomic sex). This can result in distress associated with persistent feelings, such as being "Trapped in the wrong body." Gender dysphoria is distinct from cross dressing (transvestitism), inability to accept homosexual orientation, psychotic delusions or personality disorders. Most individuals who express gender dysphoria in adolescence and later are thought to sustain the experienced gender. Guidance from the 2009 and 2017 Endocrine Society Clinical Practice Guidelines for the

endocrine treatment of Gender-Dysphoric/Gender Incongruence Persons and "Standards of Care for the Health of Transgender and Gender Diverse People, Version 8 (WPATH)" were utilized in this guideline.

Clinical Criteria

When a drug is being reviewed for coverage under a member's medical benefit plan or is otherwise subject to clinical review (including prior authorization), the following criteria will be used to determine whether the drug meets any applicable medical necessity requirements for the intended/prescribed purpose.

Fensolvi, Lupron Depot-Ped (leuprolide acetate), Synarel Nasal Spray (nafarelin acetate), or Supprelin LA (histrelin acetate subcutaneous implant), and Triptodur (triptorelin pamoate intramuscular extended release) in Central Precocious Puberty (CPP)

Requests for Fensolvi, Lupron Depot-Ped (leuprolide acetate), Synarel Nasal Spray (nafarelin acetate), or Supprelin LA (histrelin acetate subcutaneous implant), or Triptodur (triptorelin pamoate intramuscular extended release) may be approved if the following criteria are met:

I. Individual is 14 years of age or younger (clinical judgement; Kaplowitz, et al. 2016); **AND**
II. Documentation is provided that individual has a diagnosis of central precocious puberty (defined as the beginning of secondary sexual characteristics before age 8 in girls and 9 in boys) (Kaplowitz, et al. 2016); **AND**
III. Documentation is provided that the diagnosis of CPP has been confirmed by one of the following:
    A. A pubertal response to a gonadotropin hormone (GnRH) agonist test; **OR**
    B. A pubertal level of a third generation luteinizing hormone (LH) assay; **OR**
    C. A pubertal level of an ultra-sensitive luteinizing hormone (LH) assay; **OR**
    D. A pubertal level on a luteinizing hormone (LH) assay that can detect levels less than 0.2; **AND**
IV. The diagnosis has been confirmed by assessment of bone age versus chronological age.

Requests for Fensolvi, Lupron Depot-Ped (leuprolide acetate), Synarel Nasal Spray (nafarelin acetate), Vantas, Supprelin LA (histrelin acetate subcutaneous implant), or Triptodur (triptorelin pamoate intramuscular extended release) may not be approved if the following criteria are met:

I. Individual is diagnosed with peripheral precocious puberty; **OR**
II. Individual is diagnosed with benign or non-progressive precocious puberty.

Zoladex (goserelin acetate), Lupron Depot or Lupron Depot-Ped (leuprolide acetate), or Synarel Nasal Spray (nafarelin acetate) in Gynecological uses

Requests for Zoladex (goserelin acetate), Lupron Depot or Lupron Depot-Ped (leuprolide acetate), or Synarel Nasal Spray (nafarelin acetate) may be approved if the following criteria are met:

I. Individual has a diagnosis of chronic pelvic pain (defined as "pain symptoms perceived to originate from pelvic organs or structures typically lasting more than six months…with symptoms suggestive of lower urinary tract, sexual, bowel, pelvic floor, myofascial, or gynecological dysfunction") (ACOG 2020); **OR**
II. Individual is using to induce amenorrhea (such as but not limited to menstruating women diagnosed with severe thrombocytopenia or aplastic anemia);

Continuation requests for chronic pelvic pain may approved if the following criterion is met:

I. Individual has confirmation of symptomatic relief.

Requests for continuation for chronic pelvic pain may not be approved if the following criterion is met:
I. Individual has no symptomatic relief of chronic pelvic pain.

Approval Duration
For Chronic Pelvic Pain
Initial Authorization for Chronic Pelvic Pain: 3 months
Reauthorization for Chronic Pelvic Pain: 3 months

Requests for Zoladex (goserelin acetate) may be approved if the following criteria are met:

I. Individual is using for treatment of endometriosis and duration of treatment is limited to 6 months; **OR**
II. Individual is using for dysfunctional uterine bleeding; **OR**
III. Individual is using for endometrial thinning prior to endometrial ablation for dysfunctional uterine bleeding (3.6 mg implant only).

Requests for Lupron Depot or Lupron Depot-Ped (leuprolide acetate) may be approved if the following criteria are met:

I. Individual is using for initial treatment or retreatment of endometriosis; **OR**
II. Individual is using for preoperative treatment as adjunct to surgical treatment of uterine fibroids (leiomyoma uteri), such as but not limited to reducing the size of fibroids to allow for a vaginal procedure (AHFS); **OR**
III. Individual is using prior to surgical treatment (myomectomy or hysterectomy) in those with a diagnosis of confirmed anemia (Letheby et al. 2001, 2017); **OR**
IV. Individual is using for endometrial thinning prior to endometrial ablation for dysfunctional uterine bleeding.

Approval Duration
For Endometriosis:
Initial treatment: 6 months.
Retreatment: A single course may be approved for 6 months. Total duration of therapy should not exceed 12 months.

Requests for Synarel (nafarelin acetate) may be approved if the following criteria are met:

I. Individual is using for endometriosis; **AND**
II. Duration of treatment with agent is limited to 6 months.

Zoladex (goserelin acetate), Vantas or Supprelin LA (histrelin acetate), Fensolvi, Lupron Depot or Lupron Depot-Ped, (leuprolide acetate), Synarel Nasal Spray (nafarelin acetate), and Triptodur (triptorelin pamoate intramuscular extended release) in Gender Dysphoria/Incongruence

Requests for all GnRH Analogs—Zoladex (goserelin acetate), Vantas or Supprelin LA (histrelin acetate), Fensolvi, Lupron Depot or Lupron Depot-Ped, (leuprolide acetate), Synarel Nasal Spray (nafarelin acetate), or Triptodur (triptorelin pamoate intramuscular extended release) may be approved if the following criteria are met:

I. Individual has a diagnosis of gender dysphoria/incongruence (Coleman 2022); **AND**
II. Individual fulfills the DSM V criteria for gender dysphoria (American Psychiatric Association 2013); **AND**
III. Individual has experienced puberty to at least Tanner stage 2 (Hembree 2017, Coleman 2022);
IV. Individual has (early) pubertal changes that have resulted in an increase of their gender dysphoria (Hembree 2017, WPATH 2022)**; AND**
V. Individual does not suffer from a comorbidity that interferes with the diagnostic work-up or treatment (Hembree 2017); **AND**
VI. Individual has psychological and social support before and during treatment (Hembree 2017); **AND**
III. Individual has demonstrated knowledge and understanding of the expected risks and outcomes of GnRH analog treatment (Hembree 2017).

Quantity Limits

Gonadotropin Releasing Hormone Analogs for the Treatment of Non-Oncologic Indications Quantity Limits

Drug	Limit
Fensolvi (leuprolide acetate) 45 mg kit	1 kit per 24 weeks (6 months)
Lupron Depot (leuprolide acetate) 3.75 mg, 7.5 mg	1 kit per 4 weeks
Lupron Depot (leuprolide acetate) 11.25 mg, 22.5 mg	1 kit per 12 weeks
Lupron Depot (leuprolide acetate) 30 mg	1 kit per 16 weeks
Lupron Depot (leuprolide acetate) 45 mg	1 kit per 24 weeks (6 months)
Lupron Depot Ped (leuprolide acetate) (1-month kit) 7.5, 11.25 or 15 mg	1 kit per 4 weeks
Lupron Depot Ped (leuprolide acetate) (3-month kit) 11.25 or 30 mg	1 kit per 12 weeks
Lupron Depot Ped (leuprolide acetate) 45 mg	1 kit per 24 weeks
Supprelin LA (histrelin acetate) 50 mg	1 implant per year
Synarel (nafarelin acetate) 2 mg/mL (60 sprays/bottle)	5 bottles per 30 days
Triptodur (triptorelin) 22.5mg kit	1 kit per 24 weeks (6 months)
Zoladex (goserelin acetate) 3.6 mg Implant	1 per 4 weeks
Zoladex (goserelin acetate) 10.8 mg Implant	1 per 12 weeks

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement

policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

HCPCS	
J1675	Injection, histrelin acetate, 10 micrograms
J1950	Injection, leuprolide acetate (for depot suspension), per 3.75 mg [Lupron Depot, Lupron Depot-Ped]
J1951	Injection, leuprolide acetate for depot suspension (fensolvi), 0.25 mg
J1954	Injection, leuprolide acetate for depot suspension (Cipla), 7.5 mg
J3316	Injection, triptorelin, extended-release, 3.75 mg [Triptodur]
J9202	Goserelin acetate implant, per 3.6 mg [Zoladex]
J9217	Leuprolide acetate (for depot suspension), 7.5 mg [Eligard, Lupron Depot, Lupron Depot-Ped]
J9218	Leuprolide acetate, per 1 mg [Lupron]
J9226	Histrelin implant (Supprelin LA), 50 mg
S9560	Home injectable therapy; hormonal therapy (e.g., leuprolide, goserelin), including administrative services, professional pharmacy services, care coordination, and all necessary supplies and equipment (drugs and nursing visits coded separately), per diem

ICD-10 Diagnosis	
	All diagnoses excluding oncologic diagnoses

Document History

Revised: 02/21/2025
Document History:

- 02/21/2025 – Select Review: update gender dysphoria/incongruence criteria. Coding Reviewed: No changes.
- 06/10/2024 – Annual Review: remove Lupaneta and Vantas obsolete products. Coding Reviewed: Updated coding description for HCPCS J1954. Removed HCPCS J3315, J9225. Removed Lupaneta Pack from J1950, J9217. Removed Fensolvi from HCPCS J9218.
- 12/11/2023 – Select Review: update gender dysphoria heading. Coding Reviewed: No changes.
- 06/12/2023 – Annual Review: clarify types of LH assays accepted for Central precocious puberty, update gender dysphoria criteria, add Lupron Depot 45 mg and Lupron Peds Depot (6 month) 45 mg, wording and formatting. Coding Reviewed: No changes.
- 03/13/2023 – Select Review: update transgender/incongruence criteria. Coding Reviewed: No changes.
- 06/13/2022- Annual Review: update definition for central precocious puberty and chronic pelvic pain, add do not approve criteria to central precocious puberty, remove dosing in Triptodur criteria, wording and formatting. Administrative update to add documentation. Coding Reviewed: No changes. Effective 1/1/2023 Added HCPCS J1954.
- 11/19/2021- Select Review: Add quantity limit on Lupron Depot 45mg, wording change. Coding Reviewed: No changes. Effective 2/22/22 Removed HCPCS J9218.
- 09/13/2021- Select Review. Add quantity limits, clarify chronic pelvic pain approval duration. Coding reviewed: No changes.
- 05/21/2021- Annual review. Added "AND" to criteria for completeness within CPP. Coding Reviewed: Added HCPCS J1951 for Fensolvi. Removed the term Fensolvi from J1950.
- 08/21/2020 - Select review. Add age criteria for use of pharmacotherapy in CPP criteria. Define adolescents in gender dysphoria/incongruence criteria. Coding Reviewed: No changes. Removed HCPCS J3490,C9399 for Fensolvi, Lupaneta Pack. Added Fensolvi to J1950.
- 06/08/2020 - Annual review. Add new drug Fensolvi to CPP and gender dysphoria criteria. Add new quantity limit for Fensolvi. Include Vantas (histrelin acetate) for use in CPP and gender dysphoria. Add new quantity limit for Vantas. Coding reviewed: Added Fensolvi to J1950, Removed HCPCS C9399 for Lupaneta Pack
- 09/23/2019 – Administrative update to add drug specific quantity limit.
- 06/10/2019– Annual Review: Added Zoladex Quantity limit to document. Wording and formatting updates. Coding Reviewed: Reviewed: Added HCPCS J1950, J9217.
- 11/16/2018 – Annual Review: Annual review. Updated criteria with references. Minor wording and formatting updates to clarify existing override criteria. HCPCS and ICD-10 coding review: Deleted HCPCS C9016, J9155, J3490 for Triptodur. Added J3316 for Triptodur. Added C9399 for Lupaneta Pak and J3490 for Lupaneta Pack.

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Federal and state laws or requirements, contract language, and Plan utilization management programs or polices may take precedence over the application of this clinical criteria.