Clinical Criteria

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

Document #: ING-CC-0061 **Publish Date**: ~~07/20/2020~~09/21/2020

Status: Revised **Last Review Date**: ~~06/08/2020~~08/21/2020

Table of Contents

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)
- Lupaneta Pack (leuprolide acetate for depot suspension and norethindrone acetate tablets)
- Supprelin LA 12 month implant (histrelin acetate)
- Synarel Nasal Spray (nafarelin acetate)
- Triptodur (triptorelin pamoate extended-release)
- Vantas (histrelin acetate)
- Zoladex (goserelin acetate)

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

Agent	Endo	IET	CPP	UL
Lupaneta Pack (leuprolide acetate-norethindrone acetate) 1 month, 3 month	x			
Lupron Depot (leuprolide acetate) 1 month, 3 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			x	
Supprelin LA (histrelin acetate) 12 month			x	
Triptodur (triptorelin) 6 month			x	
Vantas (histrelin acetate)			x	
Fensolvi (leuprolide acetate) injectable suspension 45mg 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 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. Most pediatric endocrinologists will insist on reading the radiographs themselves. 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 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), Supprelin LA (histrelin acetate subcutaneous implant), and Triptodur (triptorelin pamoate intramuscular extended release) in Central Precocious Puberty

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 be approved if the following criteria are met:

I. Individual is 14 years of age or younger (clinical judgement; Kaplowitz, et al. 2016)
~~I.~~II. 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**
~~II.~~III. If individual is using Triptodur (triptorelin pamoate) IM injection is given every 6 months for those 2 years of age or older.

Zoladex (goserelin acetate), Lupron Depot or Lupron Depot-Ped (leuprolide acetate), Lupaneta Pack (leuprolide acetate for depot suspension and norethindrone), 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 noncyclical pain lasting 6 or more months that localizes to the anatomic pelvis, anterior abdominal wall at or below the umbilicus, the lumbosacral back, or the buttocks, and is of sufficient severity to cause functional disability or lead to medical care) (ACOG 2004); **OR**
II. Individual is using to induce amenorrhea (such as but not limited to menstruating women diagnosed with severe thrombocytopenia or aplastic anemia);

Approval Duration
*For Chronic Pelvic Pain: Do not continue use of agent beyond 3 months if there is no symptomatic relief.

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).

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 Lupaneta Pack (leuprolide acetate for depot suspension and norethindrone acetate) may be approved if the following criteria are met:

I. Individual is using for initial treatment or retreatment of endometriosis.

Approval Duration
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), Lupaneta Pack (leuprolide acetate for depot suspension and norethindrone acetate tablets), Synarel Nasal Spray (nafarelin acetate), and Triptodur (triptorelin pamoate intramuscular extended release) in Gender Dysphoria/Incongruence in Adolescents

Requests for all GnRH Analogs—Zoladex (goserelin acetate), Vantas or Supprelin LA (histrelin acetate), Fensolvi, Lupron Depot or Lupron Depot-Ped, (leuprolide acetate), Lupaneta Pack (leuprolide acetate for depot suspension and norethindrone acetate tablets), 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 in adolescents (greater than or equal to 10 years of age and less than 18 years of age) (Hembree 2009, 2017); **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 2009, 2017)**; AND**
IV. Individual has (early) pubertal changes that have resulted in an increase of their gender dysphoria (Hembree 2009, 2017)**; AND**
V. Individual does not suffer from a psychiatric comorbidity that interferes with the diagnostic work-up or treatment (Hembree 2009, 2017); **AND**
VI. Individual has psychological and social support during treatment confirmed (Hembree 2009, 2017); **AND**
VII. Individual has confirmed to demonstrate knowledge and understanding of the expected outcomes of GnRH analog treatment (Hembree 2009, 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)
Lupaneta Pack (leuprolide/norethindrone) 3.75 mg/5 mg	1 pack per 4 weeks
Lupaneta Pack (leuprolide/norethindrone) 11.25 mg/5 mg	1 pack per 12 weeks
Lupron Depot (leuprolide acetate) 3.75 mg	1 kit per 4 weeks
Lupron Depot (leuprolide acetate) 11.25 mg	1 kit per 12 weeks
Lupron Depot Ped (leuprolide acetate) 7.5, 11.25 or 15 mg	1 kit per 4 weeks
Lupron Depot Ped (leuprolide acetate) 11.25 or 30 mg	1 kit per 12 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)
Vantas (histrelin acetate) 50 mg	1 implant per year
Zoladex (goserelin acetate) 3.6 mg Implant	1 per 4 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, Lupaneta Pack, Fensolvi]
J3490	Unclassified drugs when specified as [Fensolvi] [Lupron Depot-Ped]
J3315	Injection, triptorelin pamoate, 3.75 mg [Trelstar, Trelstar Depot, Trelstar LA]
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, Lupaneta Pack]
J9218	Leuprolide acetate, per 1 mg [Lupron]
J9225	Histrelin implant (Vantas), 50 mg
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: 08/21/2020
Document History:

- 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.
- 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.

References

1. American College of Obstetrics and Gynecology Committee on Practice Bulletins -- Gynecology. ACOG Practice Bulletin No. 51. Chronic pelvic pain. Obstet Gynecol. 2004 (reaffirmed 2008); 103(3):589-605.
2. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. 2013. Washington, DC. Pages 451-459.
3. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.: 2020. URL: http://www.clinicalpharmacology.com. Updated periodically.
4. DailyMed. Package inserts. U.S. National Library of Medicine, National Institutes of Health website. http://dailymed.nlm.nih.gov/dailymed/about.cfm. Accessed: July 15, 2020.
5. DrugPoints® System [electronic version]. Truven Health Analytics, Greenwood Village, CO. Updated periodically.
6. Eugster E. Treatment of Central Precocious Puberty. *Journal of the Endocrine Society.* 2019: 3(5): 965-972.
7. Hembree WC, Cohen-Kettenis P, Delemarre-van de Waal HA, et al.; Endocrine Society. Endocrine treatment of transsexual persons: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2009; 94(9):3132-3154.

8. Hembree WC, Cohen-Kettenis P, Gooren L, et al.; Endocrine Society. Endocrine Treatment of Gender Dysphoric/Gender Incongruent Persons. An Endocrine Society clinical practice guideline. *J Clin Endocrinol* Metab. 2017; 102(11):1–35.
9. Kaplowitz P, Bloch C, the SECTION ON ENDOCRINOLOGY. Evaluation and Referral of Children With Signs of Early Puberty. *Pediatrics*. 2016;137(1):e20153732
10. Lethaby A, Vollenhoven B, Sowter M. Pre-operative GnRH analogue therapy before hysterectomy or myomectomy for uterine fibroids. *Cochrane Database Syst Rev*. 2001; (2):CD000547.
11. Lexi-Comp ONLINE™ with AHFS™, Hudson, Ohio: Lexi-Comp, Inc.; 2020; Updated periodically.
12. Nebesio TD, Eugster EA. Current concepts in normal and abnormal puberty. Curr Probl Pediatr Adolesc Health Care. 2007;37(2):50–72. doi: 10.1016/j.cppeds.2006.10.005.

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.