Clinical Policy: Nafarelin Acetate (Synarel)

Reference Number: PA.CP.PHAR.174
Effective Date: 01/18
Last Review Date: 02/17

Coding Implications
Revision Log

Description
The intent of the criteria is to ensure that patients follow selection elements established by Pennsylvania Health and Wellness® medical policy for the use of nafarelin acetate (Synarel®).

Policy/Criteria
It is the policy of Pennsylvania Health and Wellness that Synarel is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Central Precocious Puberty (must meet all):

1. Females age ≤ 11 years or males ≤ 12 years;
2. Diagnosis of central precocious puberty (CPP) confirmed by (a through c):
   a. Elevated basal luteinizing hormone (LH) level > 0.2 - 0.3 mIU/L (dependent on type of assay used) and/or elevated leuprolide-stimulated LH level > 3.3 - 5 IU/I (dependent on type of assay used);
   b. Bone age ≥ 1 year advanced of chronological age;
   c. Age at onset of secondary sex characteristics is < 8 years, if female, or < 9 years, if male;
3. Prescribed dose of Synarel does not exceed 1800 micrograms/day administered as 600 micrograms three times a day;
4. Member has none of the following contraindications:
   a. Known hypersensitivity to gonadotropin-releasing hormone (GnRH), GnRH analogs, or any excipient in the requested product;
   b. If female, pregnancy.

Approval duration: 12 months

B. Endometriosis or Chronic Refractory Pelvic Pain (must meet all):

1. Diagnosis of one of the following:
   a. Endometriosis (i or ii):
      i. Diagnosis surgically confirmed;
      ii. Clinically diagnosed and failed a three-month trial of nonsteroidal anti-inflammatory drugs (NSAIDs) and/or combined oral estrogen-progesterone contraceptives within the last year;
   b. Chronic refractory pelvic pain (i through v):
      i. Pain for at least six months;
      ii. The pain is severe enough to cause functional disability or require treatment;
      iii. Diagnostic laparoscopy, if done, was normal;
      iv. Other causes of pelvic pain have been ruled out;
      v. Failed a three-month trial of NSAIDs and/or combined oral estrogen-progesterone contraceptives within the last year;

2. Prescribed dose does not exceed 200 micrograms administered into one nostril in the morning and 200 micrograms administered into the other nostril in the evening to start between days 2 and 4 of the menstrual cycle;
3. Member has none of the following contraindications:
   a. Known hypersensitivity to GnRH, GnRH analogs, or any excipient in the requested product;
   b. Undiagnosed vaginal bleeding;
   c. Pregnancy or breast-feeding.

Approval duration: 6 months
(Two 6-month courses total)

C. Gender Dysphoria (off-label) (must meet all):
1. Diagnosis of gender dysphoria as evidenced by meeting the DSM V criteria for gender dysphoria;
2. Prescribed by or in consultation with a pediatric endocrinologist, adolescent medicine specialist or medical provider with experience and/or training in transgender medicine;
3. Member has psychological and social support during treatment;
4. Member does not suffer from a psychiatric comorbidity that interferes with the diagnostic work-up or treatment;
5. Member demonstrates consent and understanding of the expected outcomes of GnRH analog treatment; (*For minorities, when parental consent cannot be obtained, exceptions are reviewed on a case by case basis and in conjunction with a behavioral health provider*);
6. For adults: failure to achieve physiologic hormone levels or an intolerance with use of gender-affirming hormonal therapy (e.g., estrogen, testosterone).

Approval duration: 12 months

D. Other diagnoses/indications: Refer to CP.PMN.53 - off-label policy.

II. Continued Approval

A. Central Precocious Puberty (must meet all):
1. Currently receiving medication via Pennsylvania Health and Wellness benefit or member has previously met initial approval criteria or the Continuity of Care policy applies (*see PA.LTSS.PHAR.01*);
2. Member is responding positively to therapy;
3. Females age ≤ 11 years, or males ≤ 12 years;
4. Therapeutic effect is evidenced by decreased growth velocity, cessation of menses, if female, and arrested pubertal progression;
5. Member has none of the following contraindications:
   a. Known hypersensitivity to GnRH, GnRH analogs, or any excipient in the requested product;
   b. Undiagnosed vaginal bleeding;
   c. Pregnancy or breast-feeding.

Approval duration: 12 months

B. Endometriosis or Chronic Refractory Pelvic Pain or Gender Dysphoria (off-label) (must meet all):
1. Currently receiving medication via Pennsylvania Health and Wellness benefit or member has previously met initial approval criteria or the Continuity of Care policy applies (*see PA.LTSS.PHAR.01*);
2. Member is responding positively to therapy;
3. Member has none of the following contraindications:
   a. Known hypersensitivity to GnRH, GnRH analogs, or any excipient in the requested product;
   b. Undiagnosed vaginal bleeding;
   c. Pregnancy or breast-feeding.

Approval duration:
Endometriosis or Chronic Refractory Pelvic Pain: 6 months *(Two 6-month courses total)*
Gender Dysphoria: 12 months

C. Other diagnoses/indications (must meet 1 or 2):
1. Currently receiving medication via Pennsylvania Health and Wellness benefit and documentation supports positive response to therapy, or the Continuity of Care policy applies (*see PA.LTSS.PHAR.01*); or
2. Refer to CP.PMN.53 – off-label policy.

Background
Description/Mechanism of Action:
Nafarelin acetate is a potent agonistic analog of GnRH. At the onset of administration, nafarelin stimulates the release of the pituitary gonadotropins, LH and FSH, resulting in a temporary increase of gonadal steroidogenesis. Repeated dosing abolishes the stimulatory effect on the pituitary gland. Twice-daily administration leads to decreased secretion of gonadal steroids by about 4 weeks; consequently, tissues and functions that depend on gonadal steroids for their maintenance become quiescent.

Formulations:
Synarel (nafarelin acetate): Nasal solution
- 2 mg/mL (8 mL); 200 micrograms of nafarelin per spray

FDA-Approved Indications:
Synarel is a GnRH agonist/nasal solution indicated for:
- Treatment of CPP (gonadotropin-dependent precocious puberty) in children of both sexes;
- Management of endometriosis, including pain relief and reduction of endometriotic lesions.

Appendices
Appendix A: Abbreviation Key
CPP: Central precocious puberty
GnRH: Gonadotropin-releasing hormone

LH: Luteinizing hormone
NSAIDs: Nonsteroidal anti-inflammatory drugs

Reviews, Revisions, and Approvals	Date	Approval Date

References

1. Synarel prescribing information. New York, NY: G.D. Searle, LLC., Division of Pfizer, Inc.; August 2015. Available at www.pfizer.com. Accessed December 28, 2016.
2. Harrington J and Palmert MR. Definition, etiology, and evaluation of precocious puberty. In: UpToDate, Waltham, MA: Walters Kluwer Health; 2016. Available at UpToDate.com. Accessed December 28, 2016.
3. Harrington J and Palmert MR. Treatment of precocious puberty. In: UpToDate, Waltham, MA: Walters Kluwer Health; 2016. Available at UpToDate.com. Accessed December 28, 2016.
4. Schenken RS. Endometriosis: Pathogenesis, clinical features, and diagnosis. In: UpToDate, Waltham, MA: Walters Kluwer Health; 2016. Available at UpToDate.com. Accessed December 28, 2016.
5. Schenken RS. Endometriosis: Treatment of pelvic pain. In: UpToDate, Waltham, MA: Walters Kluwer Health; 2016. Available at UpToDate.com. Accessed December 28, 2016.
6. Hornstein MD and Gibbons WE. Endometriosis: Long-term treatment with gonadotropin-releasing hormone agonists. In: UpToDate, Waltham, MA: Walters Kluwer Health; 2016. Available at UpToDate.com. Accessed December 28, 2016.
7. Barbieri RL. Evaluation of chronic pelvic pain in women. In: UpToDate, Waltham, MA: Walters Kluwer Health; 2016. Available at UpToDate.com. Accessed December 28, 2016.
8. Barbieri RL. Treatment of chronic pelvic pain in women. In: UpToDate, Waltham, MA: Walters Kluwer Health; 2016. Available at UpToDate.com. Accessed December 28, 2016.
9. The World Professional Association for Transgender Health. Standards of care for the health of transsexual, transgender, and gender nonconforming people – 7th version. September 2011. Available at www.wpath.org. Accessed December 19, 2017.
10. Hembree WC, Cohen-Kettenis PT, Gooren L, et al. Endocrine treatment of gender-dysphoric/gender-incongruent persons: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. November 2017; 102(11):3869-3903. doi: 10.1210/jc.2017-01658
11. Wylie KR, Fung RJ, Boshier C, and Rotchell M. British association for sexual and relationship therapy: recommendations of endocrine treatment for patients with gender dysphoria. Sexual and Relationship Therapy 2009; 24(2):175-187. DOI: 10.1080/14681990903023306