Clinical Policy: Nafarelin Acetate (Synarel)

Reference Number: PA.CP.PHAR.174
Effective Date: 01/18
Last Review Date: 10/18

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®).

FDA Approved Indication(s)
Synarel is 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.

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. Diagnosis of central precocious puberty confirmed by all of the following (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. Difference between bone age and chronological age was > 1 year (bone age-chronological age;
    c. Age at onset of secondary sex characteristics is < 8 years if female, or < 9 years if male;
2. Member meets the following age requirements:
    a. Female: 2 - 11 years;
    b. Male: 2 - 12 years;
3. Prescribed by or in consultation with a pediatric endocrinologist;
4. Dose does not exceed 1800 micrograms per day.

Approval duration: 12 months

B. Endometriosis (must meet all):

1. Diagnosis of endometriosis;
2. Prescribed by or in consultation with a gynecologist;
3. Endometriosis as a cause of pain is one of the following (a or b):
    a. Surgically confirmed;
    b. Clinically suspected and member has failed a 3-month trial of one of the following agents within the last year or has a documented intolerance or contraindication to the agent (i, ii, or iii):
        i. A non-steroidal anti-inflammatory drug;
        ii. An oral or depot injection contraceptive;

iii. A progestin;

2. Dose does not exceed 800 micrograms per day;

Approval duration: 6 months

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*);
1. Member is responding positively to therapy (e.g., decreased growth velocity, cessation of menses, softening of breast tissue or testes, arrested pubertal progression);
2. Member meets the following age requirement:
   a. Female: ≤ 11 years;
   b. Male: ≤ 12 years;
3. If request is for a dose increase, new dose does not exceed 1800 micrograms per day.

Approval duration: 12 months

B. Endometriosis (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 (e.g., improvement in dysmenorrhea, dyspareunia, pelvic pain/induration/tenderness, size of endometrial lesions);

3. If request is for a dose increase, new dose does not exceed 800 micrograms per day.

Approval duration:
Endometriosis: 6 months *(12 months total)*

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

Appendices

Appendix A: Abbreviation/Acronym Key

CPP: central precocious puberty	GnRH: gonadotropin-releasing hormone
FDA: Food and Drug Administration	LH: luteinizing hormone

Appendix B: Therapeutic Alternatives
This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent for all relevant lines of business and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
NSAIDs*: ibuprofen, naproxen, fenoprofen, ketoprofen, mefenamic acid, meclofenamate, indomethacin, tolmetin, diclofenac, etodolac, diflunisal, meloxicam, piroxicam	Endometriosis Varies – refer to specific prescribing information	Varies – refer to specific prescribing information
Combined oral estrogen-progesterone contraceptives*: ethinyl estradiol + (desogestrel, ethynodiol diacetate, drospirenone, etonogestrel, levonorgestrel, norelgestromin,	Endometriosis 1 tablet PO QD (however; may vary per specific prescribing information)	1 tablet per day (however; may vary per specific prescribing information)

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
norethindrone, norgestimate, or norgestrel); estradiol valerate + dienogest; mestranol + norethindrone		
Progestin-only oral contraceptives*: norethindrone	Endometriosis 0.35 mg PO QD	See regimen
Depot progestin contraceptives*: medroxyprogesterone acetate	Endometriosis IM: 150 mg every 3 months (every 13 weeks) SC: 104 mg every 3 months (every 12 to 14 weeks)	See regimen
Lupron Depot® 3.75 mg (leuprolide acetate)	Endometriosis 3.75 mg IM once monthly with or without norethindrone	3.75 mg per month
Lupron Depot® 11.25 mg (leuprolide acetate)	Endometriosis IM: 11.25 mg per 3 months with or without norethindrone	11.25 mg per 3 months

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.
**Examples provided may not be all-inclusive*

Appendix C: Contraindications/Boxed Warnings

- Contraindication(s):
  - Undiagnosed abnormal vaginal bleeding;
  - Pregnancy
  - Breast-feeding
- Boxed warning(s): None reported

Reviews, Revisions, and Approvals	Date	Approval Date
4Q 2018 annual review: no significant changes; references reviewed and updated.	08/18	

References

1. Synarel Prescribing Information. New York, NY: G.D. Searle, LLC., Division of Pfizer, Inc.; June 2017. Available at http://labeling.pfizer.com/ShowLabeling.aspx?id=515. Accessed July 30, 2018.
2. Committee on Practice Bulletins - Gynecology. Management of endometriosis. July 2010 (reaffirmed 2016); 116(1): 223-236.

3. Kaplowitz P, Bloch C. Evaluation and referral of children with signs of early puberty. Pediatrics. 2016; 137(1): e20153732.