Pharmacy Policy Bulletin: J-0223 Synarel (nafarelin acetate) – Commercial and Healthcare Reform	
Number: J-0223	**Category:** Prior Authorization
Line(s) of Business: ☒ Commercial ☒ Healthcare Reform ☐ Medicare	**Benefit(s):** **Commercial:** **Prior Authorization (1.):** 1. Miscellaneous Specialty Drugs Oral = Yes w/ Prior Authorization **Healthcare Reform:** Not Applicable
Region(s): ☒ All ☐ Delaware ☐ New York ☐ Pennsylvania ☐ West Virginia	**Additional Restriction(s):** None
Version: J-0223-009	**Original Date:** 05/01/2019
Effective Date: 10/08/2025	**Review Date:** 09/17/2025

Drugs Product(s):	• Synarel (nafarelin acetate) nasal solution
FDA-Approved Indication(s):	• Treatment of central precocious puberty (CPP) (gonadotropin-dependent precocious puberty) in children of both sexes • Management of endometriosis, including pain relief and reduction of endometriotic lesions.

Background:	• Synarel is an analogue of gonadotropin releasing hormone (GnRH, LHRH) that suppresses release of luteinizing hormone (LH) and follicle stimulating hormone (FSH) over time which leads to reductions in ovarian and testicular steroid production. Reduction in estrogen production provides benefit for endometriosis.
	• **CPP**
	  ○ CPP is a condition that causes early sexual development in females and males. While puberty normally starts between ages 8 and 13 in females and between ages 9 and 14 in males, females with CPP begin exhibiting signs before age 8 and males before age 9 and is accompanied by significant advancement of bone age and/or a poor adult height prediction.
	  ○ The diagnosis should be confirmed by pubertal gonadal sex steroid levels and a pubertal LH response to stimulation by native GnRH. CPP is characterized by basal LH concentrations > 0.2 to 0.3 milli-international units per liter (mIU/L) and/or stimulated LH concentration post-GnRH or GnRH agonist of > 3.3 to 5.0 mIU/L.
	  ○ Magnetic resonance imaging (MRI) or computed tomography (CT)-scanning of the brain is recommended to detect hypothalamic or pituitary tumors or anatomical changes associated with increased intracranial pressure. Other causes of sexual precocity, such as congenital adrenal hyperplasia, testotoxicosis, testicular tumors and/or other autonomous feminizing or masculinizing disorders must be excluded by proper clinical hormonal and diagnostic imaging examinations.

	○ Bone age is the degree of maturation of a child's bones and is measured by taking an X-ray of the left wrist, hand, and fingers. In CPP, a child's bone age is advanced beyond their chronological age due to linear growth acceleration and acceleration of bone maturation, which can lead to short adult height. ○ Efficacy assessments in CPP include the suppression of gonadotropins (luteinizing hormone and follicle stimulating hormone) and gonadal sex steroids (estrogen in girls and testosterone in boys, respectively) during pharmacologic treatment. • **Endometriosis** ○ The American College of Obstetricians and Gynecologists lists first line therapy for pain associated with endometriosis as NSAIDs, other non-opioid analgesia, combined hormonal contraceptives, and progestins. Second line therapy includes GnRH agonists, progestin IUD, and danazol. Third line therapy includes surgery such as laproscopy, laparotomy, interruption of nerve pathways, and hysterectomy and oophorectomy. • ICD-10 Code Information: ○ ICD-10: E30.1 "Precocious puberty" may apply to Synarel; however, the prescriber must confirm that the member has central precocious puberty. • Prescribing Considerations: ○ Artificial reproductive therapy is not an FDA-approved indication. ○ Synarel is contraindicated in patients with undiagnosed abnormal vaginal bleeding, use in pregnancy or in women who may become pregnant while receiving the drug, and use in women who are breastfeeding. ○ **CPP** ▪ Assessment of growth velocity and bone age velocity should begin within 3 to 6 months of treatment initiation. ○ **Endometriosis** ▪ Experience with Synarel for the management of endometriosis has been limited to women 18 years of age and older treated for 6 months. Retreatment cannot be recommended since safety data beyond 6 months are not available. During one six-month treatment period, bone loss should not be significant. In patients with major risk factors for decreased bone mineral content such as chronic alcohol and/or tobacco use, strong family history of osteoporosis, or chronic use of drugs that can reduce bone mass such as anticonvulsants or corticosteroids, therapy with Synarel may pose an additional risk. In these patients the risks and benefits must be weighed carefully before therapy with Synarel is instituted. Repeated courses of treatment with gonadotropin-releasing hormone analogs are not advisable in patients with major risk factors for loss of bone mineral content.

Approval Criteria

I. Approval Criteria

A. Central Precocious Puberty (CPP)

1. Initiation

When a benefit, coverage of Synarel for initiation may be approved when all of the following criteria are met **(a. through f.)**:

a. Synarel is prescribed by or in consultation with an endocrinologist.

b. The member has a diagnosis of CPP (no ICD-10 code).

c. The member meets one (1) of the following criteria for the onset of secondary sexual characteristics **(i., ii., or iii.)**:
  i. The member is less than 8 years of age if female.
  ii. The member is less than 9 years of age if male.
  iii. If age is greater than the above, clear medical necessity of further treatment is outlined with clinical documentation (for example, patient chart/progress notes).
d. The member has advancement of bone age ≥ 12 months beyond chronological age.
e. The member has had an MRI or CT scan performed to rule out presence of central nervous system (CNS) lesions.
f. The member meets one (1) of the following criteria **(i. or ii.)**:
  i. The member has elevated basal luteinizing hormone (LH) level > 0.2 – 0.3 mIU/L
  ii. The member has elevated leuprolide-stimulated LH level > 3.3 – 5.0 mIU/L.

2. Maintenance

When a benefit, coverage of Synarel for maintenance may be approved when all the following criteria are met **(a. through g.)**:
a. Synarel is prescribed by or in consultation with an endocrinologist.
b. The member has a diagnosis of CPP (no ICD-10 code).
c. The member meets one (1) of the following criteria for the onset of secondary sexual characteristics **(i., ii., or iii.)**:
  i. The member is less than 8 years of age if female.
  ii. The member is less than 9 years of age if male.
  iii. If age is greater than the above, clear medical necessity of further treatment is outlined with clinical documentation (for example, patient chart/progress notes).
d. The member has advancement of bone age ≥ 12 months beyond chronological age.
e. The member has had an MRI or CT scan performed to rule out presence of central nervous system (CNS) lesions.
f. The member meets one (1) of the following criteria **(i. or ii.)**:
  i. The member has elevated basal luteinizing hormone (LH) level > 0.2 – 0.3 mIU/L
  ii. The member has elevated leuprolide-stimulated LH level > 3.3 – 5.0 mIU/L.
g. The member has experienced positive clinical response to therapy defined as one (1) of the following criteria **(i. through vi.)**:
  i. Pre-pubertal slowing or decline
  ii. Normalization of FSH
  iii. Normalization of LH
  iv. Normalization of bone age
  v. Normalization of estradiol level
  vi. Normalization of testosterone level

B. Endometriosis

When a benefit, coverage of Synarel may be approved when all of the following criteria are met **(1. through 6.)**:
1. The member is 18 years of age or older.
2. The member is female.
3. The member has a diagnosis of endometriosis (ICD-10: N80).
4. For females of childbearing age, the provider attests that the member is not pregnant.
5. The member has experienced therapeutic failure, contraindication, or intolerance to two (2) standard of care treatments **(a. through e.):**
  a. NSAIDs
  b. Combined hormonal contraceptive
  c. Progestin (i.e., medroxyprogesterone injection)
  d. GnRH agonist (leuprolide)
  e. Danazol

6. The member has experienced therapeutic failure, contraindication, or intolerance to plan-preferred Orilissa.

II. An exception to some or all of the criteria above may be granted for select members and/or circumstances based on state and/or federal regulations.

Limitations of Coverage

I. Coverage of drug(s) addressed in this policy for disease states outside of the FDA-approved indications should be denied based on the lack of clinical data to support effectiveness and safety in other conditions unless otherwise noted in the approval criteria.
II. For Commercial and HCR members with a closed formulary, a non-formulary product will only be approved if the member meets the criteria for a formulary exception in addition to the criteria outlined within this policy.

Authorization Duration

- Commercial and HCR Plans:
  - **Central Precocious Puberty (CPP)**
    - Initiation: if approved, up to a 6 month authorization may be granted.
    - Maintenance: if approved, up to a 12 month authorization may be granted.

  - **Endometriosis**
    - If approved, up to a 6 month authorization may be granted. Reauthorizations will not be approved due to lack of safety data beyond 6 months of therapy.

Automatic Approval Criteria

None.

References:

1. Synarel [package insert]. New York, NY: Pfizer Inc.; January 2023.
2. Becker CM, Bokor A, Heikinheimo O, et al. ESHRE guideline: endometriosis. *Hum Reprod Open*. 2022;2022(2): hoac009.
3. Zhao SZ, Kellerman LA, Francisco, CA, et al. Impact of nafarelin and leuprolide for endometriosis on quality of life and subjective clinical measures. *J Reprod Med*. 1999;44:1000-6.
4. Carel JC, Eugster EA, Rogol A, et al. Consensus Statement on the Use of Gonadotropin-Releasing Hormone Analogs in Children. *Pediatrics*. 2009; 123: e752-e762.
5. Falcone T, Lebovic DI. Clinical management of endometriosis. *Obstetrics & Gynecology*. 2011;118(3):691-705.