envolve Pharmacy Solutions

Clinical Policy: Nafarelin Acetate (Synarel)

Reference Number: ERX.SPA.148
Effective Date: 10.01.16
Last Review Date: 11.22
Line of Business: Commercial, Medicaid

Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description
Nafarelin acetate (Synarel®) is a gonadotropin-releasing hormone (GnRH) agonist.

FDA Approved Indication(s)
Synarel is indicated for:
- 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. Experience with Synarel has been limited to women 18 years of age and older treated for 6 months.

Policy/Criteria
Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.

It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ 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 CPP confirmed by all of the following (a, b, and 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/L (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 (i or ii):
      i. Female: < 8 years;
      ii. Male: < 9 years;
2. Prescribed by or in consultation with a pediatric endocrinologist;
3. Member meets one of the following age requirements (a or b):
   a. Female: 2 to ≤ 11 years;
   b. Male: 2 to ≤ 12 years;
4. Dose does not exceed 1,800 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. Age ≥ 18 years;
4. Endometriosis as a cause of pain is one of the following (a or b):
   a. Surgically confirmed;
   b. Both of the following (i and ii):
      i. Clinically suspected;

ii. Failure of a 3-month trial of one of the following within the last year, unless clinically adverse effects are experienced or all are contraindicated (1, 2, or 3):
   1) A non-steroidal anti-inflammatory drug *(see Appendix B for examples)*;
   2) An oral or injectable depot contraceptive (see Appendix B for examples);
   3) A progestin *(see Appendix B for examples)*;

5. Failure of Lupron Depot*, unless contraindicated or clinically significant adverse effects are experienced;
   **Prior authorization may be required for Lupron Depot*
6. For members currently receiving treatment with Synarel, total duration of therapy has not exceeded 12 months;
7. Dose does not exceed 800 micrograms per day.

Approval duration: 6 months

C. Other diagnoses/indications

1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

II. Continued Therapy

A. Central Precocious Puberty (must meet all)**:**

1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
2. Member is responding positively to therapy as evidenced by, including but not limited to, improvement in <u>any</u> of the following parameters: decreased growth velocity, cessation of menses, softening of breast tissue or testes, arrested pubertal progression;
3. Member meets one of the following age requirements (a or b):
   a. Female: ≤ 11 years;
   b. Male: ≤ 12 years;
4. If request is for a dose increase, new dose does not exceed 1,800 micrograms per day.

Approval duration: 12 months

B. Endometriosis (must meet all)**:**

1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
2. Member is responding positively to therapy as evidenced by, including but not limited to, improvement in <u>any</u> of the following parameters: improvement in dysmenorrhea, dyspareunia, pelvic pain/induration/tenderness, size of endometrial lesions;
3. Total duration of Synarel therapy has not exceeded 12 months;
4. If request is for a dose increase, new dose does not exceed 800 micrograms per day.

Approval duration: up to a total treatment duration of 12 months

C. Other diagnoses/indications (must meet 1 or 2)**:**

1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions and documentation supports positive response to therapy.
   Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off-label use policy – ERX.PA.01 or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

CPP: central precocious puberty
FDA: Food and Drug Administration
GnRH: gonadotropin-releasing hormone
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 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	Varies – refer to specific prescribing information	Varies – refer to specific prescribing information
Progestin-containing oral contraceptives: norethindrone*, ethinyl estradiol + (desogestrel, ethynodiol diacetate, drospirenone, etonogestrel, levonorgestrel, norelgestromin, norethindrone, norgestimate, or norgestrel); estradiol valerate + dienogest; mestranol + norethindrone	1 tablet PO QD **The progestin norethindrone also is labeled for endometriosis - see prescribing information for dosing regimen.*	1 tablet/day
Depot injection progestin contraceptives: medroxyprogesterone acetate (Depo-Provera®, Depo-SubQ Provera 104®*)	IM: Depo-Provera: 150 mg every 13 weeks SC: Depo-SubQ Provera 104: 104 mg every 12 to 14 weeks **Depo-SubQ Provera 104 also is labeled for endometriosis - same dosing regimen.*	IM: 150 mg/3 months SC: 104 mg/3 months
Lupron Depot® 3.75 mg (leuprolide acetate)	3.75 mg IM once monthly with or without norethindrone	3.75 mg per month
Lupron Depot® 11.25 mg (leuprolide acetate)	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):
  - Hypersensitivity
  - Undiagnosed abnormal vaginal bleeding
  - Pregnancy
  - Breast-feeding
- Boxed warning(s): none reported

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
CPP	1,600 micrograms (8 sprays) per day administered as 2 sprays to each nostril BID; OR 1,800 micrograms (9 sprays) per day administered as 3 sprays in one nostril TID (alternate nostrils throughout day).	1,800 mcg per day
Endometriosis	400 micrograms (2 sprays) per day administered as 1 spray to one nostril BID (alternate nostrils) starting between days 2 and 4 of the menstrual cycle. If persistent regular menstruation after 2 months of treatment with 400 micrograms daily, dose may be increased to 800 micrograms (4 sprays) per day administered as 1 spray to each nostril BID.	800 mcg per day

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VI. Product Availability
Nasal spray: 8 mL containing 2 mg/mL solution

VII. References
1. Synarel Prescribing Information. New York, NY: G.D. Searle, LLC., Division of Pfizer, Inc.; December 2020. Available at http://labeling.pfizer.com/ShowLabeling.aspx?id=515. Accessed June 21, 2021.
2. Practice bulletin no. 114: management of endometriosis. Obstet Gynecol. 2010 Jul (reaffirmed 2016);116(1):223-36. doi: 10.1097/AOG.0b013e3181e8b073.
3. Kaplowitz P, Bloch C. Evaluation and referral of children with signs of early puberty. Pediatrics. 2016; 137(1): e20153732.
4. Carel JC, Eugster EA, Rogol A, et al. Consensus statement on the use of gonadotropin-releasing hormone analogs in children. Pediatrics. 2009;123(4):e752. Epub 2009 Mar 30.
5. Krishna KB, Fuqua JS, Rogol AD, et al. Use of gonadotropin-releasing hormone analogs in children: update by an International Consortium. Horm Res Paediatr 2019;91:357–372. DOI: 10.1159/000501336.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
4Q 2018 annual review: no significant changes; references reviewed and updated.	08.07.18	11.18
4Q 2019 annual review: no significant changes: references reviewed and updated.	08.01.19	11.19
4Q 2020 annual review: no significant changes; references reviewed and updated.	08.11.20	11.20
4Q 2021 annual review: no significant changes; references reviewed and updated.	06.21.21	11.21
4Q 2022 annual review: no significant changes; clarified for endometriosis duration of therapy should not exceed 12 months by adding requirements in the criteria set, for continued approval duration modified from 6 months to “up to a total treatment duration of 12 months”; references reviewed and updated.	07.21.22	11.22

Important Reminder
This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members.

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