

## **Clinical Policy: Nafarelin Acetate (Synarel)**

Reference Number: CP.PHAR.174

Effective Date: 10.01.16

Last Review Date: 11.18

Line of Business: HIM, Medicaid

[Revision Log](#)

See [Important Reminder](#) at the end of this policy for important regulatory and legal information.

### **Description**

Nafarelin acetate (Synarel<sup>®</sup>) is a gonadotropin-releasing hormone (GnRH) receptor agonist.

### **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**

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

It is the policy of health plans affiliated with Centene Corporation<sup>®</sup> 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/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 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. Age ≥ 18 years;

4. 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**

**A. Other diagnoses/indications**

1. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): HIM.PHAR.21 for health insurance marketplace or CP.PMN.53 for Medicaid.

**II. Continued Therapy**

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

1. Currently receiving medication via Centene benefit or member has previously met all initial approval criteria;
2. Member is responding positively to therapy (e.g., decreased growth velocity, cessation of menses, softening of breast tissue or testes, arrested pubertal progression);
3. Member meets the following age requirement:
  - a. Female:  $\leq 11$  years;
  - b. Male:  $\leq 12$  years;
4. 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 Centene benefit or member has previously met initial approval criteria;
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: 6 months (12 months total)**

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

1. Currently receiving medication via Centene benefit and documentation supports positive response to therapy.  
**Approval duration: Duration of request or 6 months (whichever is less);** or
2. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): HIM.PHAR.21 for health insurance marketplace and CP.PMN.53 for Medicaid.

**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 policies – HIM.PHAR.21 for health insurance marketplace and CP.PMN.53 for Medicaid 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 for all relevant lines of business and may require prior authorization.*

<b>Drug Name</b>	<b>Dosing Regimen</b>	<b>Dose Limit/ Maximum Dose</b>
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, norethindrone, norgestimate, or norgestrel); estradiol valerate + dienogest; mestranol + norethindrone	Endometriosis 1 tablet PO QD (however; may vary per specific prescribing information)	1 tablet per day (however; may vary per specific prescribing information)
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

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
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<sup>®</sup> (generic) when the drug is available by brand name only and generic (Brand name<sup>®</sup>) 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

**V. Dosage and Administration**

Indication	Dosing Regimen	Maximum Dose
Central precocious puberty	1600 micrograms (8 sprays) per day administered as 2 sprays to each nostril BID; OR 1800 micrograms (9 sprays) per day administered as 3 sprays in one nostril TID (alternate nostrils throughout day).	1800 micrograms 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; OR 800 micrograms (4 sprays) per day administered as 1 spray to each nostril BID.	800 micrograms per day

**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.; 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.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
<p>Converted from CP.PHAR.118.GnRH Analogs.                      CPP - added lower age of 2 per PIs; max dose added; added additional rule-outs per PI; removed required high estradiol and testosterone levels (stimulated); edited bone age wording to be more general; approval period restated for clarity; diagnostic use: changed to leuprolide acetate (generic).                      Endometriosis - added age 18 or older per PI; max dose added; removed that surgical diagnosis timeline; for clinical diagnosis, restated failure of one three-month trial to analgesics and/or contraceptives; approval period restated per PIs.                      Pelvic pain – chronic/refractory; added age 18 or older per PI; max dose added; restated failure of one three-month trial to analgesics and/or contraceptives; approval period changed to up to 12 months total.</p>	02.16	02.16
<p>CPP: Removed lower age limit of 2 years, made bone age specifically <math>\geq 1</math> year advanced age; removed conditions that must be ruled out per specialist review.                      Endometriosis/ Pelvic Pain: Changed 3 month trial of analgesics and/or hormonal contraceptives to NSAIDS and/or hormonal contraceptives.</p>	05.16	
<p>Endometriosis and pelvic pain: age removed.</p>	01.17	02.17
<p>Pelvic pain criteria deleted.                      Age added to endometriosis; endometriosis step therapy edited from estrogen/progestin OC to OC or depot contraceptive or progestin.                      Total approval duration increased from 6 to 12 months. Positive therapeutic response examples added.                      Specialist requirement added for endometriosis, CPP.                      Safety information removed with exception of pregnancy.</p>	09.17	11.17
<p>4Q 2018 annual review: no significant changes; HIM added; references reviewed and updated.</p>	08.07.18	11.18

**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. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. “Health Plan” means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan’s affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

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**Note:**

**For Medicaid members**, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

**For Health Insurance Marketplace members**, when applicable, this policy applies only when the prescribed agent is on your health plan approved formulary. Request for non-formulary drugs must be reviewed using the non-formulary policy; HIM.PA.103.

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