Clinical Policy: Nafarelin Acetate (Synarel)

Reference Number: CP.PHAR.174
Effective Date: 10.01.16
Last Review Date: 11.20 Revision Log
Line of Business: HIM, Medicaid

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) receptor 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.

It is the policy of health plans affiliated with Centene Corporation® 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 concentration of luteinizing hormone (LH) (i.e., > 0.2 - 0.3 mIU/L) or leuprolide-stimulated LH (i.e., > 3.3 - 5 IU/L);*
      **Pubertal threshold dependent on assay used.*
   b. Bone age advanced > 1 year beyond 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 as evidenced by one of the following (a or b):

a. Surgically confirmed;
b. Clinically suspected and failure of a 3-month trial of one of the following within the last year, unless contraindicated or clinically adverse effects are experienced (i or ii):
   i. A non-steroidal anti-inflammatory drug *(see Appendix B for examples)*;
   ii. An oral or depot injectable progestin or progestin-containing contraceptive agent *(see Appendix B for examples)*;

2. Prescribed by or in consultation with a gynecologist;
3. Age ≥ 18 years;
2. Dose does not exceed 800 micrograms per day.

Approval duration: 6 months
Total duration of therapy should not exceed 12 months.

C. 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 as evidenced by, including but not limited to, improvement in any 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 requirement (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 Centene benefit 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 any of the following parameters: 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
Total duration of therapy should not exceed 12 months.

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.

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	IM: Depo-Provera: 150 mg every 13 weeks	IM: 150 mg/3 months

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
(Depo-Provera®, Depo-SubQ Provera 104®*)	SC: Depo-SubQ Provera 104: 104 mg every 12 to 14 weeks **Depo-SubQ Provera 104 also is labeled for endometriosis - same dosing regimen.*	SC: 104 mg/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
Central precocious puberty	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 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.; May 2017. Available at http://labeling.pfizer.com/ShowLabeling.aspx?id=515. Accessed July 27, 2020.
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
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.	02.16	02.16
CPP: Removed lower age limit of 2 years, made bone age specifically ≥ 1 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.	05.16	
Endometriosis and pelvic pain: age removed.	01.17	02.17
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.	09.17	11.17
4Q 2018 annual review: no significant changes; HIM added; 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

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.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. 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. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

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.