# Clinical Policy: Nafarelin Acetate (Synarel)

Reference Number: CP.PHAR.174
Effective Date: 10.01.16
Last Review Date: 05.24
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®) 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 luteinizing hormone (LH) level > 0.2 - 0.3 mIU/mL (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. For members currently receiving treatment with Synarel, total duration of therapy has not exceeded 6 months;
6. Dose does not exceed 800 micrograms per day.

**Approval duration: 6 months**

**C. Gender Dysphoria, Gender Transition (off-label)** (must meet all)**:**
1. Diagnosis of gender dysphoria or request is for gender transition;
2. Prescribed by or in consultation with both of the following (a and b):
   a. Endocrinologist;
   b. Provider with expertise in gender dysphoria and transgender medicine based on a certified training program or affiliation with local transgender health services (e.g., mental health professional such as psychologist, psychiatrist, see *Appendix D*);
3. Age and pubertal development - meets (a or b):
   a. Member is < 18 years of age and has reached or passed through Tanner Stage 2*;
   **Age ranges approximating Tanner Stage 2 pubertal development extend from 8 to 13 years of age in girls and 9 to 14 years of age in boys.*
   b. Member is ≥ 18 years of age and has failed to achieve physiologic hormone levels with gender-affirming hormonal therapy (e.g., estrogen, testosterone) unless contraindicated or clinically significant adverse effects are experienced;
4. Member demonstrates understanding of expected GnRH analogue treatment outcomes and has given consent for such treatment;
5. If member has a psychiatric comorbidity, member is followed by mental health provider;
6. Psychosocial support will be provided during treatment;
7. Dose is within FDA maximum limit for any FDA-approved indication (see Section V) or is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

**Approval duration: 12 months**

**D. Other diagnoses/indications** (must meet 1 or 2)**:**
1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):

a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: HIM.PA.33 for health insurance marketplace and CP.PMN.255 for Medicaid; or
b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: HIM.PA.103 for health insurance marketplace and CP.PMN.16 for Medicaid; or

2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: HIM.PA.154 for health insurance marketplace and CP.PMN.53 for Medicaid.

## II. Continued Therapy

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

1. Member meets one of the following (a or b):
   a. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
   b. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (*refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B);*
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. Total duration of Synarel therapy has not exceeded 6 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 6months**

**C. Gender Dysphoria, Gender Transition (off-label)** (must meet all)**:**

1. Member meets one of the following (a or b):
   a. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;

b. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (*refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B*);

2. Member is responding positively to therapy;
3. If request is for a dose increase, new dose is within FDA maximum limit for any FDA-approved indication (see Section V) or is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

**Approval duration:**
**Medicaid/HIM –** 12 months

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

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: HIM.PA.33 for health insurance marketplace and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: HIM.PA.103 for health insurance marketplace and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: HIM.PA.154 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.PA.154 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, | Varies – refer to specific prescribing information | Varies – refer to specific |

| Drug Name | Dosing Regimen | Dose Limit/ Maximum Dose |
|---|---|---|
| mefenamic acid, meclofenamate, indomethacin, tolmetin, diclofenac, etodolac, diflunisal, meloxicam, piroxicam | | 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<br>**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<br><br>SC: Depo-SubQ Provera 104: 104 mg every 12 to 14 weeks<br>**Depo-SubQ Provera 104 also is labeled for endometriosis - same dosing regimen.* | IM: 150 mg/3 months<br><br>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

*Appendix D: General Information*

- World Professional Association for Transgender Health (WPATH) offers their Global Education Institute (GEI) Certified Training Courses: Best Practices in Transgender Medical and Mental Health Care. Additionally, the following link provides a search tool to locate WPATH member providers: https://www.wpath.org/provider/search
- Transgender Care Therapy Certification Training is also offered by the International Transgender Certification Association (ITCA). Professionals with expertise in transgender care can be located using the following search tool: https://transgendercertification.com/locate-a-professional/
- The WPATH Standards of Care Version 8 recommend that adolescents are managed by a multidisciplinary care team that involves both medical and mental health professionals.

The list of key disciplines includes but is not limited to: adolescent medicine/primary care, endocrinology, psychology, psychiatry, speech/language pathology, fertility, social work, support staff, and the surgical team. The need to include a healthcare professional with some expertise in mental health does not dictate the inclusion of a psychologist, psychiatrist or social work in each assessment. Instead, a general practitioner, nurse or other qualified clinician could fulfill this requirement as long as they have sufficient expertise to identify gender incongruence, recognize mental health concerns, distinguish between these concerns and gender dysphoria, incongruence, and diversity, assist a transgender person in care planning and preparation for gender affirmative medical and surgical treatments, and refer to a mental health professional if needed.

## 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<br>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. If persistent regular menstruation after 2 months of treatment with 400 micrograms daily, dose may be increased to<br>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

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2. Practice bulletin no. 114: management of endometriosis. Obstet Gynecol. 2010 Jul (reaffirmed 2016);116(1):223-36. doi: 10.1097/AOG.0b013e3181e8b073.
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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.
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*Gender Dysphoria*
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12. Emmanual M, Bokor BR. Tanner Stages. Treasure Island, FL: StatPearls Publishing; 2019 Jan. Available at https://www.ncbi.nlm.nih.gov/books/NBK470280/. Last update: December 11, 2022. Accessed January 24, 2024.
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14. Coleman E, Radix AE, Bouman WP, et al. WPATH: World Professional Association for Transgender Health Standards of Care for the Health of Transgender and Gender Divrse People, Version 8. Available at: https://www.wpath.org/soc8. Accessed January 18, 2024.

| Reviews, Revisions, and Approvals | Date | P&T Approval Date |
|---|---|---|
| 4Q 2020 annual review: no significant changes; references reviewed and updated. | 08.11.20 | 11.20 |
| 4Q 2021 annual review: no significant changes; HIM.PHAR.21 changed to HIM.PA.154; 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. Template changes applied to other diagnoses/indications and continued therapy section. | 07.21.22 | 11.22 |
| Added off-label use criteria for gender dysphoria or gender transition. | 02.16.23 | 05.23 |

| Reviews, Revisions, and Approvals | Date | P&T Approval Date |
|---|---|---|
| 2Q 2024 annual review: for endometriosis reduced total treatment duration from 12 to 6 months per prescribing information; for CPP clarified for bone age the requirement is that the difference between bone age and chronological age was > 1 year (bone age-chronological age); corrected units for basal luteinizing hormone level to mIU/mL; references reviewed and updated. | 01.09.24 | 05.24 |

**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.