Drug Coverage Policy

Effective Date 3/15/2026
Coverage Policy Number.....IP0415
Policy Title.....Synarel

Gonadotropin-Releasing Hormone Agonist – Synarel

- Synarel® (nafarelin acetate nasal solution – Pfizer)

INSTRUCTIONS FOR USE

The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment where appropriate and have discretion in making individual coverage determinations. Where coverage for care or services does not depend on specific circumstances, reimbursement will only be provided if a requested service(s) is submitted in accordance with the relevant criteria outlined in the applicable Coverage Policy, including covered diagnosis and/or procedure code(s). Reimbursement is not allowed for services when billed for conditions or diagnoses that are not covered under this Coverage Policy (see "Coding Information" below). When billing, providers must use the most appropriate codes as of the effective date of the submission. Claims submitted for services that are not accompanied by covered code(s) under the applicable Coverage Policy will be denied as not covered. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

OVERVIEW

Synarel, a gonadotropin-releasing hormone (GnRH) agonist, is indicated for the following uses:[1]

- **Central precocious puberty**, treatment in children of both sexes.

- **Endometriosis management**, including pain relief and reduction of endometriotic lesions. Experience with Synarel for this indication is limited to women ≥ 18 years of age treated for 6 months.

GnRH agonists can also be used off-label for the treatment of **gender-dysphoric/gender-incongruent persons** to suppress physical changes of puberty and gonadal function.[2,3] Pubertal hormonal suppression should typically be initiated after the adolescent first exhibits physical changes of puberty (Tanner stages G2/B2). An advantage to using a GnRH analog is that the effects can be reversed; pubertal suppression can be discontinued if the individual no longer wishes to transition. Upon discontinuation of therapy, spontaneous pubertal development has been shown to resume. GnRH analogs can also be used in patients during late puberty to suppress the hypothalamic-pituitary-gonadal axis to allow for lower doses of cross-sex hormones.[4] In addition to use in adolescents, GnRH analog therapy is also used in adults, particularly male-to-female patients.[5]

Guidelines
GnRH agonists are the standard of care for the treatment of central precocious puberty.[6-8] The European Society for Paediatric Endocrinology and the Lawson Wilkins Pediatric Endocrine Society convened a consensus conference to review the use of GnRH agonists in pediatric patients with central precocious puberty (2009).[6] The panel noted that the available GnRH agonists (including nafarelin) are effective despite different routes of administration, dosing, and duration of action. In addition, the various GnRH agonists are well-tolerated in children and adolescents. An update by an International Consortium (2019) notes the lack of prospective comparative studies to establish differences in efficacy (if any) among the various GnRH agonists.[7] Discontinuation of GnRH agonist therapy should be individualized, based on the patient's readiness for resumption of puberty, recent growth rates, and shifts in height prediction.

The American College of Obstetricians and Gynecologists (ACOG) practice bulletin on the management of endometriosis (2010, reaffirmed 2018) notes that empiric treatment with a GnRH agonist is appropriate after an appropriate pretreatment evaluation (to exclude other causes of chronic pelvic pain) and failure of initial treatment with oral contraceptives and non-steroidal anti-inflammatory drugs.[9]

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POLICY STATEMENT
Prior Authorization is recommended for prescription benefit coverage of Synarel. All approvals are provided for 1 year in duration unless otherwise noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients with gender dysphoria as well as the monitoring required for adverse events and long-term efficacy, approval requires that the product be prescribed by or in consultation with a physician who specializes in the condition being treated.

Synarel is considered medically necessary when ONE of the following is met:

1. **Central Precocious Puberty .** Approve for 1 year if the patient meets ALL of the following (A, B, and C).
    A. Diagnosis is confirmed by ONE of the following (i or ii):
        i. Pubertal basal level of luteinizing hormone (LH) greater than or equal to 0.2 mIU/mL
        ii. Pubertal luteinizing hormone (LH) response to a GnRH stimulation test
    B. Onset of secondary sexual characteristics earlier than 8 years in females and 9 years in males

C. Preferred product criteria is met for the product as listed in the below table

2. **Endometriosis.** Approve for 6 months if the patient meets ALL of the following (A, B, and C):
   A. Patient is ≥ 18 years of age: AND
   B. Patient has tried ONE of the following, unless contraindicated (i, ii, or iii):
      i. A contraceptive; OR
         Note: Examples of contraceptives include combination oral contraceptives, levonorgestrel-releasing intrauterine systems [e.g., Mirena®, Liletta®]).
      ii. An oral progesterone (e.g., norethindrone tablets); OR
      iii. A depo-medroxyprogesterone injection.
         Note: An exception to the requirement for a trial of the above therapies can be made if the patient has previously used a gonadotropin-releasing hormone (GnRH) agonist (e.g., Lupron Depot) or antagonist (e.g., Orilissa) for endometriosis.
   C. Preferred product criteria is met for the product as listed in the below table

Other Uses with Supportive Evidence

3. **Gender-Dysphoric/Gender-Incongruent Persons; Persons Undergoing Gender Reassignment (Female-To-Male or Male-To-Female).** Approve the requested gonadotropin-releasing hormone agonist for 1 year if prescribed by or in consultation with an endocrinologist or a physician who specializes in the treatment of transgender patients.

Employer Plans:

Product	Criteria
Synarel (nafarelin acetate)	**ONE of the following:** 1. For endometriosis, patient meets **ONE** of the following (A or B): A. Patient has tried ONE of the following (i, ii, or iii): i. Lupron Depot (3.75 mg or 11.25 mg) [may require prior authorization] ii. Orilissa [may require prior authorization] iii. Myfembree [may require prior authorization] B. Patient has already been started on therapy with Synarel. 2. For a diagnosis of central precocious puberty, patient meets the following: A. Patient has tried ONE of the following (i, ii, or iii): i. Fensolvi [may require prior authorization] ii. Lupron Depot-Ped [may require prior authorization] iii. Triptodur [may require prior authorization]

Conditions Not Covered

Synarel for any other use is considered not medically necessary, including the following (this list may not be all inclusive; criteria will be updated as new published data are available):

1. **Peripheral Precocious Puberty (Also Known as Gonadotropin-Releasing Hormone-Independent Precocious Puberty)**. Children with peripheral precocious puberty do not respond to GnRH agonist therapy.[2] Treatment is directed at removing or blocking the production and/or response to the excess sex steroids, depending on the cause (e.g., surgically removing human chorionic gonadotropin-secreting tumors or using glucocorticoids to treat defects in adrenal steroidogenesis [such as classic congenital adrenal hyperplasia]).

References

1 Synarel® nasal spray [prescribing information]. New York, NY: Pfizer; November 2025.
2 Hembree WC, Cohen-Kettenis PT, Gooren L, et al. Endocrine treatment of gender-dysphoric/gender-incongruent persons: an Endocrine Society clinical practice guidelines. *J Clin Endocrinol Metab*. 2017;102:3869-3903.
3 World Professional Association for Transgender Health (WPATH). Standards of Care for the health of transgender and gender diverse people (version 8). Available at: Standards of Care for the Health of Transgender and Gender Diverse People, Version 8 (tandfonline.com). Accessed on January 9, 2026.
4 Rosenthal SM. Approach to the patient: transgender youth: endocrine considerations. *J Clin Endocrine Metab.* 2014;99:4379-4389.
5 Spack NP. Management of transgenderism. *JAMA*. 2013;309:478-484.
6 Carel JC, Eugster EA, Rogol A, et al. Consensus statement on the use of gonadotropin-releasing hormone analogs in children. *Pediatrics*. 2009;123(4):e752-762.
7 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.
8 Eugster EA. Treatment of central precocious puberty. *J Endo Soc*. 2019;3:965-972.
9 Management of Endometriosis. ACOG Practice Bulletin. Clinical Management Guidelines for Obstetrician-Gynecologists. Number 114, July 2010. (Reaffirmed 2022) *Obstetrics & Gynecology*. 2010;116(1):223-236.

Revision Details

Type of Revision	Summary of Changes	Date
Annual Revision	No criteria changes.	4/1/2025
Annual Revision	**Policy Title.** **Updated from** "Nafarelin Acetate" to "Gonadotropin Releasing Hormone Agonist – Synarel" **Central Precocious Puberty.** **Updated** pubertal basal LH from 0.3 to 0.2 mIU/mL **Endometriosis.** **Added** "Note: An exception to the requirement for a trial of the above therapies can be made if the patient has previously used a gonadotropin-releasing hormone (GnRH) agonist (e.g., Lupron Depot) or antagonist (e.g., Orilissa) for endometriosis." **Removed** "Documentation of failure, contraindication or intolerance to a gonadotropin-releasing hormone agonist (for example, Lupron	3/15/2026

	Depot) or antagonist (for example, Orilissa) for endometriosis **Gender-Dysphoric/Gender-Incongruent Persons; Persons Undergoing Gender Reassignment (Female-To-Male or Male-To-Female).** Added new criterion under Other Uses with Supportive Evidence for gender dysphoric/gender-incongruent persons; persons undergoing gender reassignment (female-to-male or male-to-female).	

The policy effective date is in force until updated or retired.