Drug Coverage Policy

Effective Date.....5/1/2024
Coverage Policy Number IP0108
Policy Title.....Leuprolide

Gonadotropin-Releasing Hormone Agonists - Central Precocious Puberty – Leuprolide

- Fensolvi® (leuprolide acetate subcutaneous injection, extended-release – Tolmar)
- Lupron Depot-Ped® (leuprolide acetate depot intramuscular injection – AbbVie)

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 and have discretion in making individual coverage determinations. 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.

Medical Necessity Criteria

The use of leuprolide for oncology and infertility indications are addressed in separate coverage policies. Please refer to the related coverage policy links above (Oncology Medications, Infertility Injectables).

Coverage for treatment of gender dysphoria varies across plans. Coverage of drugs for hormonal therapy, as well as whether the drug is covered as a medical or a pharmacy benefit, varies across plans. Refer to the customer's benefit plan document for coverage details. In addition, coverage for treatment of gender dysphoria, including gender reassignment surgery and related services may be governed by state and/or federal mandates.[11]

Fensolvi, Lupron Depot-Ped are considered medically necessary when ONE of the following criteria are met:

1. **Central Precocious Puberty (CPP).** Individual meets **ALL** of the following criteria:
    A. Onset of secondary sexual characteristics earlier than 8 years in females and 9 years in males
    B. Diagnosis is confirmed by documentation of **ONE** of the following:
        i. Pubertal basal level of luteinizing hormone (LH) greater than or equal to 0.3 mIU/mL
        ii. Pubertal luteinizing hormone (LH) response to a GnRH stimulation test

    Dosing. ONE of the following dosing regimens for Fensolvi or Lupron Depot-Ped:
    (1) Fensolvi: Up to one injection (45 mg) given subcutaneously once every 6 months
    (2) Lupron Depot-Ped: **ONE** of the following:
        a. 1-month depot and weight less than or equal to 25 kg: Up to one 1-month depot (7.5 mg) given intramuscularly (IM) once every month
        b. 1-month depot and weight is greater than 25 kg up to 37.5 kg: Up to one 1-month depot (11.25 mg) given IM once every month
        c. 1-month depot and weight is greater than 37.5 kg: Up to one 1-month (15 mg) given IM once every month
        d. 3-month depot: Up to one 3-month (11.25 mg or 30 mg) given IM once every 3 months
        e. 6-month depot: Up to one 6-month depot (45 mg) given IM once every 6 months

2. **Gender-Dysphoric/Gender-Incongruent Persons; Person Undergoing Gender Reassignment (Female-to-Male or Male-to-Female).** Medication is prescribed by, or in consultation with, an endocrinologist or a physician who specializes in the treatment of transgender individuals.

    Dosing. ONE of the following dosing regimens for Fensolvi or Lupron Depot-Ped:
    (1) Fensolvi: Up to one injection (45 mg) given subcutaneously once every 6 months
    (2) Lupron Depot-Ped: **ONE** of the following:
        a. 1-month depot: Up to one 1-month depot (7.5 mg, 11.25 mg, or 15 mg) given intramuscularly (IM) once every month
        b. 3-month depot: Up to one 3-month depot (11.25 mg or 30 mg) given IM once every 3 months (12 weeks)
        c. 6-month depot: Up to one 6-month depot (45 mg) given IM once every 6 months (24 weeks)

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Receipt of sample product does not satisfy any criteria requirements for coverage.

Reauthorization Criteria

Continuation of Fensolvi, Lupron Depot-Ped is considered medically necessary for **ALL** covered diagnoses when the above medical necessity criteria are met AND there is documentation of beneficial response.

Authorization Duration

Initial approval duration: up to 12 months
Reauthorization approval duration: up to 12 months

Conditions Not Covered

Any other use is considered experimental, investigational, or unproven, including the following (this list may not be all inclusive):

1. **Peripheral Precocious Puberty (Also Known As GnRH-Independent Precocious Puberty)**. Children with peripheral precocious puberty do not respond to GnRH agonist therapy.[4] 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]).

Coding Information

1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

HCPCS Codes	Description
J1950	Leuprolide acetate (for depot suspension), per 3.75 mg
J1951	Injection, leuprolide acetate for depot suspension (Fensolvi), 0.25 mg

Background

OVERVIEW
Fensolvi, Lupron Depot-Ped, and Triptodur are gonadotropin-releasing hormone (GnRH) agonists indicated for the treatment of pediatric patients with central precocious puberty.[1-3]

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.[7,8] Pubertal hormonal suppression should typically be initiated after the adolescent first exhibits physical changes of puberty (Tanner stages G2/B2). Long-acting GnRH analogs are the currently preferred treatment option. 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.[9] In addition to use in adolescents, GnRH analog therapy is also used in adults, particularly male-to-female patients.[10]

Dosing Information
Fensolvi is administered by a subcutaneous injection and both Lupron Depot-Ped and Triptodur are administered by intramuscular injection.[1-3] Fensolvi is administered once every 6 months, Lupron Depot-Ped is administered once a month, once every 3 months (12 weeks), or once every 6 months (24 weeks), and Triptodur is administered once every 24 weeks. There are no specific dosing recommendations for off-label use of Fensolvi, Lupron Depot-Ped, or Triptodur. Therefore, the FDA-approved dosing in the product labeling for approved uses has been cited for off-label uses. Treatment decisions, including duration of therapy, are individualized with careful consideration of the risks and benefit of the selected regimen.

Guidelines
The standard of care for central precocious puberty is GnRH agonists.4-6 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).[4] The panel noted that the available GnRH agonists (including leuprolide and triptorelin) 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.[5] The Consortium does not prefer one GnRH agonist over another. 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.

References

1. Lupron Depot-Ped® [prescribing information]. North Chicago, IL; AbbVie; April 2023.
2. Triptodur™ [prescribing information]. Woburn, MA: Azurity; December 2022.
3. Fensolvi® [prescribing information]. Fort Collins, CO: Tolmar; April 2023.
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):e752-62.
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.
6. Eugster EA. Treatment of central precocious puberty. *J Endo Soc*. 2019;3:965-972.
7. 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.
8. World Professional Association for Transgender Health (WPATH). Standards of Care for the health of transgender and gender diverse people (version 8). Available at: https://www.wpath.org/publications/soc. Accessed on November 6, 2023.
9. Rosenthal SM. Approach to the patient: transgender youth: endocrine considerations. *J Clin Endocrine Metab*. 2014;99:4379-4389.
10. Spack NP. Management of transgenderism. *JAMA*. 2013;309:478-484.
11. American Academy of Pediatrics (AAP). Ensuring Comprehensive care and support for transgender and gender diverse children and adolescents. Policy statement. Pediatrics. Volume 142(4): October 2018.

Revision Details

Type of Revision	Summary of Changes	Date
Annual Revision	• No criteria change • Updated title of coverage policy • Added dosing for diagnosis, *Gender-Dysphoric/Gender-Incongruent Persons; Person Undergoing Gender Reassignment*	5/1/2024

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