Drug and Biologic Coverage Policy

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Coverage Policy Number 8008

Histrelin Acetate Subcutaneous Implant

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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. 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.

Coverage Policy

This coverage policy addresses the use of Supprelin LA® (histrelin acetate subcutaneous implant). The use of Vantas (histrelin acetate subcutaneous implant) is addressed in a separate coverage policy. Please refer to the related coverage policy link above (Oncology Medications).

The use of histrelin acetate subcutaneous implant (Supprelin LA®, Vantas®) for the treatment of gender dysphoria is addressed in a separate coverage policy. Please refer to the related coverage policy link above (Treatment of Gender Dysphoria)

Histrelin acetate (Supprelin LA®) subcutaneous implant is considered medically necessary when ALL of the following criteria are met:

- Treatment of children with central precocious puberty (CPP) with onset of secondary sexual characteristics earlier than 8 years in females and 9 years in males
- Confirmation of diagnosis as defined by **ONE** of the following:
  - Pubertal basal level of luteinizing hormone (LH) greater than or equal to 0.3 mIU/ml
  - Pubertal luteinizing hormone (LH) response to GnRH stimulation testing

Initial authorization interval is once every 12 months.

Histrelin acetate (Supprelin LA®) subcutaneous implant is considered medically necessary for continued use when the following are met:

- Pretreatment clinical condition met the initial criteria
- Individual is younger than the appropriate time point for the onset of puberty (for example: 11 years for females and 12 years for males)

Reauthorization interval is once every 12 months.

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.

Histrelin acetate (Supprelin LA®) subcutaneous implant is considered experimental, investigational or unproven for ANY other use including the following:

- Concomitant use with recombinant growth hormone (GH) to prolong the pre-pubertal state

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

FDA Approved Indications

FDA Approved Indication

Supprelin LA® (histrelin acetate) subcutaneous implant is indicated for the treatment of children with central precocious puberty (CPP). Children with CPP (neurogenic or idiopathic) have an early onset of secondary sexual characteristics (earlier than 8 years of age in females and 9 years of age in males). They also show a significantly advanced bone age that can result in diminished adult height attainment.

Prior to initiation of treatment a clinical diagnosis of CPP should be confirmed by measurement of blood concentrations of total sex steroids, luteinizing hormone (LH) and follicle stimulating hormone (FSH) following stimulation with a GnRH analog, and assessment of bone age versus chronological age. Baseline evaluations should include height and weight measurements, diagnostic imaging of the brain (to rule out intracranial tumor), pelvic/testicular/adrenal ultrasound (to rule out steroid secreting tumors), human chorionic gonadotropin levels (to rule out a chorionic gonadotropin secreting tumor), and adrenal steroids to exclude congenital adrenal hyperplasia.

Recommended Dosing

FDA Recommended Dosing

The recommended dose of Supprelin LA® is one implant every 12 months. Each implant contains 50 mg histrelin acetate. The implant is inserted subcutaneously in the inner aspect of the upper arm and provides continuous release of histrelin (65 mcg/day) for 12 months of hormonal therapy. Supprelin LA® should be removed after 12 months of therapy (the implant has been designed to allow for a few additional weeks of histrelin acetate release, in order to allow flexibility of medical appointments). At the time an implant is removed, another implant may be inserted to continue therapy. Discontinuation of Supprelin LA® should be considered at the discretion of the physician and at the appropriate time point for the onset of puberty (approximately 11 years for females and 12 years for males).

Drug Availability

Supprelin LA® is available as a 50 mg histrelin acetate subcutaneous implant which delivers approximately 65 mcg histrelin acetate per day over 12 months.

General Background

Pharmacology

Like GnRH, Supprelin LA® initially stimulates the pituitary gland to release luteinizing hormone (LH) and follicle stimulating hormone (FSH). Continuous exposure to Supprelin LA® desensitizes the pituitary gland, decreasing LH and FSH release and gonadal steroid synthesis. Histrelin levels remain detectable and suppress gonadal steroid production for 12 months after implantation.

Histrelin is also available in the form of Vantas® (a subcutaneous implant) and is approved for use in advanced prostate cancer. Currently Supprelin LA® is not approved for use in advanced prostate cancer and Vantas® is not approved for use in CPP. Supprelin LA® releases at a rate of 65 mcg/day (the dosage required to be effective for CPP) while Vantas® releases at a rate of 50-60 mcg daily (the dosage required to be effective for advanced prostate cancer).

Professional Societies/Organizations

American Academy of Pediatrics

American Academy of Pediatrics (AAP) guidelines on the evaluation and referral of children with signs of early puberty recommends treatment with Gonadotropin Releasing Hormones (GnRH) agonists, such as leuprolide, may be administered either with an injection at monthly or 3-month intervals or with an annual subcutaneous histrelin implant. AAP recommends that therapy should be continued until the physician determines that continued pubertal suppression is no longer a benefit to the child. (Kaplowitz, 2016)

For suspected central precocious puberty, the diagnostic evaluation will normally include a bone age determination. Baseline laboratory testing may include the following: FSH, LH, and either estradiol or testosterone. An LH of greater than 0.3 IU/L is the most reliable screening test on a random sample of blood, however if it is less than 0.3 and CPP is suspected, a GnRH analog stimulation test may be necessary. (Kaplowitz, 2016)

European Society for Pediatric Endocrinology

The European Society for Pediatric 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). The panel used the operational definition of precocious puberty as puberty beginning prior to 8 years of age in girls and prior to 9 years of age in boys. The panel concluded that girls with onset of progressive central precocious puberty before 6 years of age will benefit the most from GnRH therapy in terms of height; decisions to treat girls with onset after the age of 6 years should be individualized. Treatment should be considered for all boys with progressive central precocious puberty who have compromised height potential. All of the available GnRH agonists (leuprolide, nafarelin, histrelin, triptorelin) are effective despite different routes of administration, dosing, and duration of action. Depot preparations are preferred because of reduced frequency of dosing and therefore, improved compliance. In general, the various GnRH agonists are well-tolerated in children and adolescents. The choice of a particular product is based on patient and physician preferences. Periodic monitoring of tanner stage, growth, and bone age is recommended. Discontinuation of therapy is dependent on several factors, including clinical variables (e.g., bone age, target height, growth velocity), synchronizing puberty with peers, and ameliorating psychological distress. (Carel, 2009)

The American Board of Internal Medicine's (ABIM) Foundation Choosing Wisely® Initiative:

No recommendations are available for histrelin acetate (Supprelin LA) subcutaneous implant.

Centers for Medicare & Medicaid Services - National Coverage Determinations (NCDs)

There are no CMS National Coverage Determinations for histrelin acetate (Supprelin LA®) subcutaneous implant.

Off Label Uses:

AHFS Drug Information 2019 Edition does not have a monograph for histrelin acetate (Supprelin LA®).

Experimental, Investigational, Unproven Uses

The literature on the final effect of the addition of GnRH agonists to GH in GH-deficient (GHD) children is limited. Studies did show positive results when leuprolide was given in combination with GH for precocious puberty, however, the need for further studies with larger groups of patients is warranted before safety and efficacy of use can be confirmed. (Pucarelli, 2000; Pucarelli, 2003)

Coding/ Billing Information

Note: 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
J9226	Histrelin implant (Supprelin LA), 50 mg

References

1. Carel JC, Eugster EA, Rogol A, et al. Consensus statement on the use of gonadotropin-releasing hormone analogs in children. *Pediatrics*. 2009 Apr;123(4):e752-62. doi: 10.1542/peds.2008-1783. Epub 2009 Mar 30.
2. Endo Pharmaceuticals Solutions Inc. Supprelin LA (histrelin acetate) subcutaneous implant [product information]. Malvern, PA: Endo Pharmaceuticals Solutions Inc.; May 2017.
3. Kaplowitz P, Bloch C. Evaluation and referral of children with signs of early puberty. Pediatrics. 2016;137(1):e20153732.
4. Pucarelli, I. et.al. Combined therapy with GnRH analog plus growth hormone in central precocious puberty. J Pediatric Endocrinology Metabolism. 2000 Jul;13 Suppl 1:811-20.
5. Pucarelli, I. et.al. Effects of combined gonadotropin-releasing hormone agonist and growth hormone therapy on adult height in precocious puberty: a further contribution. J Pediatric Endocrinology Metabolism. 2003 Sep;16(7):1005-10.