



CIGNA MEDICAL COVERAGE POLICY

The following Coverage Policy applies to all health benefit plans administered by CIGNA Companies including plans formerly administered by Great-West Healthcare, which is now a part of CIGNA.

Effective Date 3/15/2011
Next Review Date 3/15/2012
Coverage Position Number 6116

Subject **Histrelin (Vantas™)**

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Hyperlink to Related Coverage Positions

Goserelin (Zoladex®)
Leuprolide (Lupron®, Lupron Depot®, Eligard®, Viadur®)
Triptorelin (Trelstar® Depot, Trelstar® LA)

INSTRUCTIONS FOR USE

Coverage Policies are intended to provide guidance in interpreting certain **standard** CIGNA HealthCare benefit plans. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement (GSA), 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 supercedes** 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. Proprietary information of CIGNA. Copyright ©2011 CIGNA

Coverage Policy

CIGNA covers histrelin (Vantas™) as medically necessary for ANY of the following indications:

- advanced prostate cancer
- localized prostate cancer with high risk of recurrence
- prostate cancer recurrence

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

FDA Approved Indications

Vantas is indicated in the palliative treatment of advanced prostate cancer.

FDA Recommended Dosing

The recommended dose of Vantas 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 (50 µg/day) for 12 months of hormonal therapy. Vantas should be removed after 12 months of therapy (the implant has been designed to allow for a few additional weeks of histrelin release, in order to allow flexibility of medical appointments). At the time an implant is removed, another implant may be inserted to continue therapy.

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

Histrelin implants are not radio-opaque and, therefore, will not be visible upon x-ray. Ultrasound and computed tomography (CT) scan may be used if the implant is difficult to locate by palpation.

Drug Availability

Vantas is supplied in a carton containing 2 inner cartons, one for the Vantas implant and one for the implantation kit.

General Background

Pharmacology

Histrelin is a synthetic analog of endogenous gonadotropin-releasing hormone (GnRH) or gonadorelin. GnRH regulates follicle-stimulating hormone (FSH) and luteinizing hormone (LH) synthesis and secretion by the anterior pituitary gland. In response to GnRH, FSH and LH synthesis initially increase, causing a transient increase in circulating levels of sex hormones. With continued administration for more than one to three weeks, the pituitary gland down-regulates and desensitizes GnRH receptors, reducing FSH and LH secretion. Although the physiologic effects are complicated, the end result of continuous GnRH use is chemical castration, or markedly reduced testosterone levels in males. In men, testosterone increases transiently during the first week after the initial dose and then falls to castrate levels after two to four weeks of continued therapy.

Histrelin is not active when administered orally. Peak serum concentrations of histrelin are usually attained at a median of 12 hours; the drug is delivered continuously at a rate of 50-60 mcg daily over 12 months. Approximately 70% of histrelin is bound to plasma proteins. No drug excretion study was conducted, but the drug does undergo metabolism with a terminal half-life of approximately four hours.

Guidelines

The National Comprehensive Cancer Network (NCCN) recommends Vantas for the treatment of prostate cancer as follows:

Grade 1

- Initial treatment for locally advanced (T3b-4) disease - short-term neoadjuvant/concomitant/adjuvant androgen deprivation therapy (ADT; 4-6 months) in combination with radiation therapy or long-term ADT (2-3 years)
- Initial treatment in combination with radiation therapy for clinically localized disease with high risk of recurrence. Short-term neoadjuvant/concomitant/adjuvant androgen deprivation therapy (ADT; 4-6 months) with radiation therapy may be recommended in selected patients with a single adverse high-risk factor (T3a disease, Gleason score 8 to 10, or prostate-specific antigen levels greater than 20 ng/mL)

Grade 2A

- Adjuvant treatment if pelvic lymph node dissection was performed and positive lymph nodes were found at initial prostatectomy
- For metastatic or recurrent disease - short-term neoadjuvant/concomitant/adjuvant androgen deprivation therapy (ADT; 4-6 months) in combination with radiation therapy for metastatic (any T, N1) disease at initial presentation or long-term ADT (2-3 years) for metastatic (any T, N1 or any T, any N, M1) disease at initial presentation or following prostatectomy in patients with distant metastases or following radiation therapy in patients with rising prostate-specific antigen levels or positive digital rectal examination who are not candidates for local therapy or in patients with distant metastases
- For postprostatectomy recurrence with or without radiation therapy in patients without distant metastases
- Initial short-term neoadjuvant/concomitant/adjuvant androgen deprivation therapy (4-6 months) in combination with radiation therapy with or without brachytherapy for clinically localized disease with intermediate risk of recurrence

- Neoadjuvant therapy in conjunction with brachytherapy in patients with a high-risk disease or a large prostate where neoadjuvant therapy can shrink the prostate to an acceptable size for brachytherapy
- Salvage therapy following radiation therapy in patients with rising prostate-specific antigen levels or positive digital rectal examination with a negative biopsy and no metastatic disease
- Single agent or in combination with antiandrogen for treatment of disseminated disease without neuroendocrine features. If there is relapse following initial treatment, discontinue antiandrogen. In patients who are at risk of developing symptoms associated with flare in testosterone levels with luteinizing hormone-releasing hormone (LHRH) agonist therapy alone, LHRH agonist should be give in combination with antiandrogen for at least 7 days

Clinical Efficacy

In an open-label, multicenter, single-arm study in 138 men with prostate cancer who received one 50 mg histrelin implant, medical castration (defined as serum total testosterone concentrations of 50 ng/dL or less) was achieved in 100% of 134 evaluable patients on day 28, and in 100% of 115 evaluable patients at week 52. Serum prostate specific antigen (PSA) concentrations, a secondary end-point in this study, decreased to within normal limits by week 24 in 103 of 111 evaluable patients (93%). Breakthrough, an increase in serum testosterone concentrations to 50 ng/dL or more following achievement of medical castration, was reported in four of 134 patients (approximately 3%); in two of these patients, the implant may have been expelled without the patient's knowledge (since it could neither be palpated nor visualized with ultrasound) and in one patient, lab error may have caused the aberrant value. After 52 weeks of therapy, a total of 113 patients underwent removal of the first implant and insertion of a second implant for another year of therapy. In 68 of these patients, serum testosterone concentrations were measured on day two or three and on day seven after insertion of the second implant to assess the "acute-on-chronic" phenomenon; no acute increase in serum testosterone was observed in any of the patients following insertion of the new implant. Medical castration was maintained in all patients throughout the second year of treatment.

Adverse Reactions / Contraindications

Common side effects reported in adults are those typical of hypogonadism. Hot flashes were the most common adverse event reported, occurring in approximately 65% of patients. The agent can cause erectile dysfunction, testicular atrophy, gynecomastia, and decreased libido. Other side-effects have included implant site reactions (e.g., bruising, pain/soreness/tenderness, and erythema), fatigue, and renal impairment. Long-term therapy (greater than six months) with GnRH agonists has a detrimental effect on bone mass, causing a reduction in bone mineral density. Although this effect is partially reversible, bone mineral density may remain below pretreatment values for more than one year after discontinuation.

Histrelin is contraindicated in women and in pediatric patients and was not studied in women or in children. Histrelin can cause fetal harm in pregnant women.

The signs and symptoms of prostate cancer may worsen during the first weeks of treatment because histrelin may initially cause a transient increase in serum testosterone levels. Patients may experience worsening of symptoms or onset of new symptoms, including neuropathy, bone pain, hematuria, or ureteral or bladder outlet obstruction. Cases of spinal cord compression have been reported, which may contribute to paralysis with or without fatal complications. Patients with metastatic vertebral lesions and/or with upper or lower urinary tract obstruction should be observed very closely during the first few weeks of treatment.

Coding/Billing Information

Note: This list of codes may not be all-inclusive.

Covered when medically necessary:

HCPSC Codes	Description
J9225	Histrelin implant (Vantas), 50 mg

ICD-9-CM	Description
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Diagnosis Codes	
185	Malignant neoplasm of prostate
V10.46	Personal history of malignant neoplasm of prostate

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