

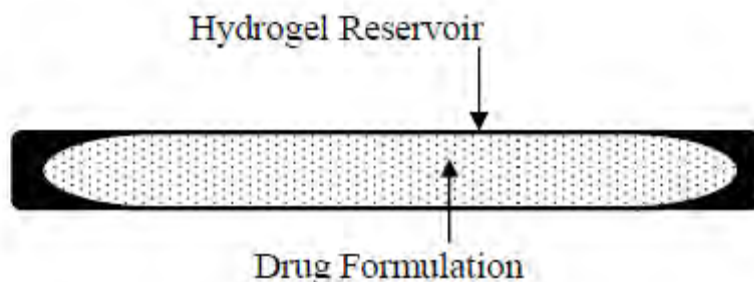
Vantas™ (histrelin implant)

DESCRIPTION

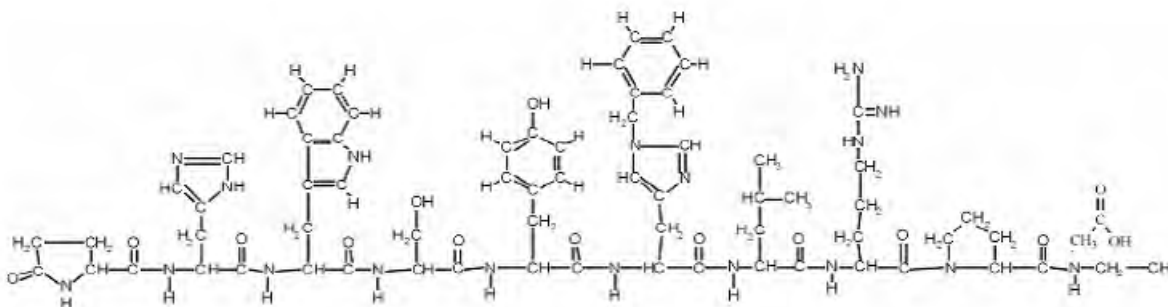
Vantas™ (histrelin implant) is a sterile non-biodegradable, diffusion-controlled reservoir drug delivery system designed to deliver histrelin continuously for 12 months upon subcutaneous implantation. The Vantas implant contains 50 mg of histrelin acetate. Histrelin acetate is a synthetic nonapeptide analogue of the naturally occurring gonadotropin releasing hormone (GnRH) or luteinizing hormone releasing hormone (LH-RH). The sterile Vantas implantation device (provided with the implant) is used to insert the implant subcutaneously in the inner aspect of the upper arm. After 12 months, the implant must be removed. At the time the implant is removed, another implant may be inserted to continue therapy.

The sterile Vantas™ implant consists of a 50-mg histrelin acetate drug core inside a nonbiodegradable, 3 cm by 3.5 mm cylindrically shaped hydrogel reservoir (Figure A). The drug core also contains the inactive ingredient stearic acid NF. The hydrogel reservoir is a hydrophilic polymer cartridge composed of 2-hydroxyethyl methacrylate, 2-hydroxypropyl methacrylate, trimethylolpropane trimethacrylate, benzoin methyl ether, Perkadox-16, and Triton X-100. The hydrated implant is packaged in a glass vial containing 2.0 mL of 1.8% NaCl solution. The implant is primed for release of the drug upon insertion.

Figure A. Vantas Histrelin Implant diagram (not to scale)



Histrelin acetate is chemically described as 5-oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-Nt-benzyl-D-histidyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide acetate (salt) $[C_{66}H_{86}N_{18}O_{12} \cdot (1.7-2.8 \text{ moles}) CH_3COOH, (0.6-7.0 \text{ moles}) H_2O]$, with the molecular weight of 1443.70 (or 1323.50 as histrelin base). Histrelin acetate has the following structural formula



CLINICAL PHARMACOLOGY

Histrelin acetate, an LH-RH agonist, acts as a potent inhibitor of gonadotropin secretion when given continuously in therapeutic doses. Both animal and human studies indicate that following an initial stimulatory phase, chronic, subcutaneous administration of histrelin acetate desensitizes responsiveness of the pituitary gonadotropin which, in turn, causes a reduction in testicular steroidogenesis.

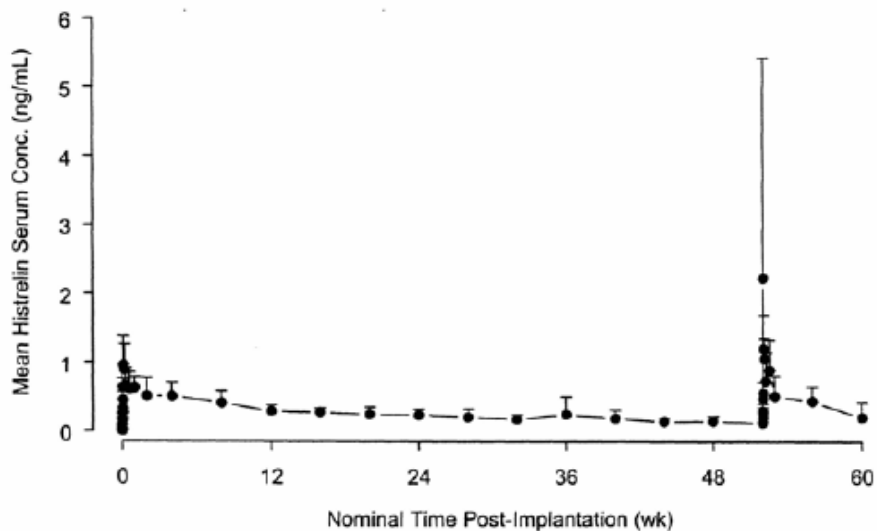
In humans, administration of histrelin acetate results in an initial increase in circulating levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), leading to a transient increase in concentration of gonadal steroids (testosterone and dihydrotestosterone in males). However, continuous administration of histrelin acetate results in decreased levels of LH and FSH. In males, testosterone is reduced to castrate levels. These decreases occur within 2 to 4 weeks after initiation of treatment.

The Vantas Implant is designed to provide continuous subcutaneous release of histrelin acetate at a nominal rate of 50-60 micrograms per day over 12 months. Histrelin acetate is not active when given orally.

PHARMACOKINETICS

Absorption: Following subcutaneous insertion of one Vantas (histrelin implant) 50 mg implant in advanced prostate cancer patients (n = 17), peak serum concentrations of 1.10 ± 0.375 ng/mL (mean \pm SD) occurred at a median of 12 hours. Continuous subcutaneous release was evident, as serum levels were sustained throughout the 52 week dosing period (see Figure 1). The mean serum histrelin concentration at the end of the 52 week treatment duration was 0.13 ± 0.065 ng/ml. When histrelin serum concentrations were measured following a second implant inserted after 52 weeks, the observed serum concentrations over 8 weeks following the second implant were comparable to the same period following the first implant. The average rate of subcutaneous drug release from 41 implants assayed for residual drug content was 56.7 ± 7.71 μ g/day over the 52 week dosing period. The relative bioavailability for the Vantas implant in prostate cancer patients with normal renal and hepatic function compared to a subcutaneous bolus dose in healthy male volunteers was 92%. Serum histrelin concentrations were proportional to dose after one, two or four 50 mg Vantas implants (50, 100 or 200 mg as histrelin acetate) in 42 prostate cancer patients.

Figure 1: *Mean Serum Histrelin Concentration Versus Time Profile for 17 Patients Following Insertion of First and Second Vantas implants. (Note that only four patients underwent intensive pK sampling during the first 96 hours following the second implant.)*



Distribution: The apparent volume of distribution of histrelin following a subcutaneous bolus dose (500 µg) in healthy volunteers was 58.4 ± 7.86 L. The fraction of drug unbound in plasma measured in vitro was $29.5\% \pm 8.9\%$ (mean \pm SD).

Metabolism: An *in vitro* drug metabolism study using human hepatocytes identified a single histrelin metabolite resulting from C-terminal dealkylation. Peptide fragments resulting from hydrolysis are also likely metabolites. Following a subcutaneous bolus dose in healthy volunteers the apparent clearance of histrelin was 179 ± 37.8 mL/min (mean \pm SD) and the terminal half-life was 3.92 ± 1.01 hr (mean \pm SD). The apparent clearance following a 50 mg (as histrelin acetate) Vantas implant in 17 prostate cancer patients was 174 ± 56.5 mL/min (mean \pm SD).

Excretion: No drug excretion study was conducted with Vantas 50 mg implants.

Special Populations:

Geriatrics: The majority (89.9%) of the 138 patients studied in the pivotal clinical trial were age 65 and over.

Pediatrics: The safety and efficacy of Vantas in pediatric patients has not been established (see CONTRAINDICATIONS).

Race: When serum histrelin concentrations were compared for 7 Hispanic, 30 Black and 77 Caucasian patients, average serum histrelin concentrations were similar.

Renal Insufficiency: When average serum histrelin concentrations were compared between 42 prostate cancer patients with mild to severe renal impairment (CLcr: 15-60 ml/min) and 92 patients with no renal or hepatic impairment, levels were approximately 50% higher in those patients with renal impairment (0.392 ng/ml versus 0.264 ng/ml). These changes in exposure as a result of renal impairment are not considered to be clinically relevant. Therefore, no changes in drug dosing are warranted for these patient subpopulations.

Hepatic insufficiency: The influence of hepatic insufficiency on histrelin pharmacokinetics has not been adequately studied.

Drug-Drug Interactions: No pharmacokinetic-based drug-drug interaction studies were conducted with Vantas.

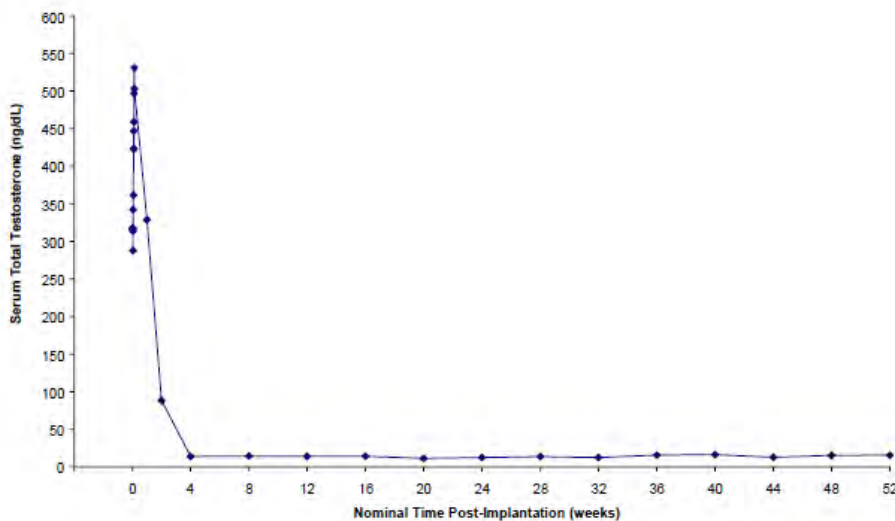
CLINICAL STUDIES

In one open-label, multicenter, Phase 3 study (Study 301), 138 patients with prostate cancer were treated with a single Vantas implant and were evaluated for at least 60 weeks. Of these, 37 patients had Jewett stage C disease, 29 had stage D disease, and the remaining 72 patients had an elevated or rising serum PSA after definitive therapy for localized disease. Serum testosterone levels were assessed as the primary efficacy endpoint to evaluate both achievement and maintenance of castrate testosterone suppression, with treatment success being defined as a serum testosterone level ≤ 50 ng/dL. At Week 52, the study included the option for removal and insertion of a new implant, with evaluation for an additional 52 weeks (the “extension phase”).

A total of 120 patients completed the initial 52-week treatment period. Reasons for discontinuation were: death (n=6), disease progression (n=5), implant expulsion (n=3), hospice placement (n=2), and patient request/no specific reason given (n=2). Of the 120 patients who successfully completed 52 weeks of treatment, 111 were evaluable for efficacy. A total of 113 patients underwent removal of the first implant and insertion of a second implant for another year of therapy.

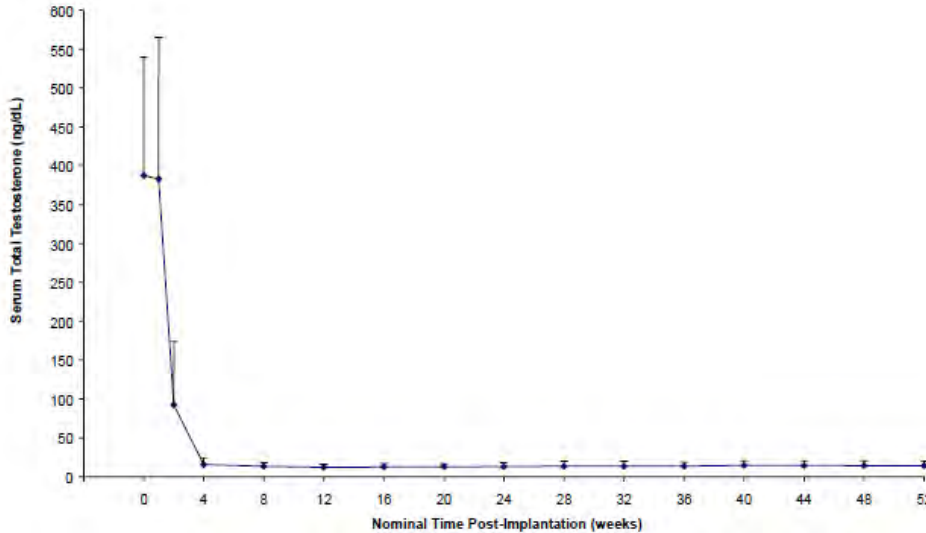
In a subset of 17 patients, serum testosterone concentrations were measured within the first week following initial implantation. In these 17 patients, mean serum testosterone concentrations increased from 376.4ng/dL at Baseline to 530.5ng/dL on Day 2, then decreased to below baseline by Week 2, and to below the 50ng/dL castrate threshold by Week 4 (see Figure 2). Serum testosterone concentrations remained below the castrate level in this subset for the entire treatment period.

Figure 2: Mean Serum Total Testosterone Concentrations for all pK Patients, n=17. (Note that in this group, sampling began minutes after insertion of Vantas.)



In the overall treatment group (n=138), mean serum testosterone was 388.3ng/dL at Baseline. At the time of first assessment of testosterone (at the end of Week 1), the mean serum testosterone concentration was 382.8ng/dL. At Week 2, mean serum testosterone was 92.2ng/dL. At Week 4 it was 15ng/dL. At Week 52, the final mean testosterone concentration was 14.3ng/dL (see Figure 3).

Figure 3. Mean Serum Total Testosterone Concentrations (+SD) for All Patients (n=138) Who Received One Implant. (Note that in this group, sampling began at the end of Week 1.)



Of 138 patients who received an implant, one discontinued prior to Day 28 when the implant was expelled on Day 15. Three others did not have an efficacy measurement for the Day 28 visit. Otherwise serum testosterone was suppressed to below the castrate level (≤ 50 ng/dL) in all 134 evaluable patients (100%) on Day 28. All three patients with missing values at Day 28 were castrate by the time of their next visit (Day 56).

Once serum testosterone concentrations at or below castrate level (≤ 50 ng/dL) were achieved, a total of 4 patients (3%) demonstrated breakthrough during the study. In one patient, a serum testosterone of 63ng/dL was reported at Week 44. In another patient, a serum testosterone of 3340ng/dL was reported at Week 40. This aberrant value was possibly related to lab error. In two patients, serum testosterone rose above castrate level and the implant could neither be palpated nor visualized with ultrasound. In the first patient, serum testosterone was 669ng/dL at Week 8 and 311ng/dL at Week 12. This patient reported strenuous exertion after insertion of the implant and a large scab forming at the insertion site. The implant may have been expelled without the patient's appreciation of the event. The other patient developed erythema at the insertion site at Week 22 and was treated with oral antibiotics. At Week 26, the implant was not palpable and was not visualized with ultrasound. At Week 34, the serum testosterone rose to 135ng/dL. The implant may have been expelled without the patient's appreciation of the event. A new implant was inserted.

Of 120 patients who completed 52 weeks of treatment, a total of 115 patients had a serum testosterone measurement at Week 52. Of these, all had serum testosterone ≤ 50 ng/dL. In patients

without a Week 52 value, castrate levels were achieved by Day 28, were maintained up to Week 52, and remained below the castrate threshold after Week 52.

In all 18 patients who prematurely discontinued prior to Week 52 – except one (implant expulsion on Day 15) –castrate levels of serum testosterone were achieved by Day 28 and were maintained up to and including the time of withdrawal.

A total of 113 patients had a new implant inserted for a second year of therapy following removal of the first implant. Of this group, 68 patients had measurement of serum testosterone on Day 2 or Day 3 and on Day 7 after insertion of the second implant in order to assess for the “acute-on-chronic” phenomenon. No acute increase in serum testosterone was seen in any patient in this group following insertion of the new implant.

Serum prostate specific antigen (PSA) was monitored as a secondary endpoint. Serum PSA decreased from baseline in all patients after they began treatment with Vantas. Serum PSA decreased to within normal limits by Week 24 in 103 of 111 evaluable patients (93%). Prior to conducting the pivotal Study 301, a Phase 2, dose-ranging study was performed in 42 patients with advanced prostate cancer. Efficacy was assessed by serum testosterone levels as the primary efficacy endpoint. Patients received 1, 2 or 4 implants. The use of 2 or 4 implants did not confer any additional benefit in suppression of testosterone beyond that produced by the single implant.

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

1. Vantas is contraindicated in patients with hypersensitivity to GnRH, GnRH agonist analogs, or any of the components in Vantas. Anaphylactic reactions to synthetic LH-RH or LH-RH agonist analogs have been reported in the literature.²
2. Vantas is contraindicated in women and in pediatric patients and was not studied in women or in children. Moreover, histrelin acetate can cause fetal harm when administered to a pregnant woman.

WARNINGS

Vantas, like other LH-RH agonists, causes a transient increase in serum concentrations of testosterone during the first week of treatment. Patients may experience worsening of symptoms or onset of new symptoms, including bone pain, neuropathy, hematuria, or ureteral or bladder outlet obstruction (see **PRECAUTIONS**). Cases of ureteral obstruction and spinal cord compression, which may contribute to paralysis with or without fatal complications, have been reported with LH-RH agonists. If spinal cord compression or renal impairment develops, standard treatment of these complications should be instituted.

PRECAUTIONS

General: Patients with metastatic vertebral lesions and/or with urinary tract obstruction should be closely observed during the first few weeks of therapy (see **WARNINGS**). Implant insertion is a surgical procedure. Careful adherence to the recommended Insertion and Removal Procedures (see **DOSAGE & ADMINISTRATION**) is advised to minimize the potential for

complications and for implant expulsion. In addition, patients should be instructed to refrain from wetting the arm for 24 hours and from heavy lifting or strenuous exertion of the inserted arm for 7 days after implant insertion.

In all clinical trials combined, an implant was not recovered in 8 patients. For two of these (see CLINICAL PHARMACOLOGY; Clinical Studies), serum testosterone rose above castrate level and the implant was neither palpable nor visualized with ultrasound. These two implants were believed to have been extruded without appreciation by the patients. In the other six, serum testosterone remained below the castrate level, but the implant was not palpable. No further diagnostic tests were conducted. One of these patients underwent in-clinic surgical exploration that did not locate the implant. Based upon these findings, it is important to know that Vantas is **not** radio-opaque and therefore will **not** be visible through X-ray. However, in the instance where the implant is difficult to locate by palpation, ultrasound and CT scan may be used.

Information for Patients: An information leaflet for patients is included with the product and should be given to the patient.

Laboratory tests: Response to Vantas should be monitored by measuring serum concentrations of testosterone and prostate-specific antigen periodically, especially if the anticipated clinical or biochemical response to treatment has not been achieved.

Results of testosterone determinations are dependent on assay methodology. It is advisable to be aware of the type and precision of the assay methodology to make appropriate clinical and therapeutic decisions.

Drug Interactions: See PHARMACOKINETICS.

Drug/Laboratory Test Interactions: Therapy with histrelin results in suppression of the pituitary-gonadal system. Results of diagnostic tests of pituitary gonadotropic and gonadal functions conducted during and after histrelin therapy may be affected.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenicity studies were conducted in rats for 2 years at doses of 5, 25 or 150 mcg/kg/day (up to 15 times the human dose) and in mice for 18 months at doses of 20, 200, or 2000 mcg/kg/day (up to 200 times the human dose). As seen with other LH-RH agonists, histrelin acetate injection administration was associated with an increase in tumors of hormonally responsive tissues. There was a significant increase in pituitary adenomas in rats. There was an increase in pancreatic islet-cell adenomas in treated female rats and a non-dose-related increase in testicular Leydig-cell tumors (highest incidence in the low-dose group). In mice, there was significant increase in mammary-gland adenocarcinomas in all treated females. In addition, there were increases in stomach papillomas in male rats given high doses, and an increase in histiocytic sarcomas in female mice at the highest dose.

Mutagenicity studies have not been performed with histrelin acetate. Saline extracts of implants with and without histrelin were negative in a battery of genotoxicity studies. Fertility studies have been conducted in rats and monkeys given subcutaneous daily doses of histrelin acetate up to 180 mcg/kg for 6 months and full reversibility of fertility suppression was demonstrated. The

development and reproductive performance of offspring from parents treated with histrelin acetate has not been investigated.

Pregnancy, Teratogenic Effects: Pregnancy Category X (see **CONTRAINDICATIONS**). Major fetal abnormalities were observed in rabbits but not in rats after administration of histrelin acetate throughout gestation. There were increased fetal mortality and decreased fetal weights in rats and rabbits. The effects on fetal mortality are expected consequences of the alterations in hormonal levels brought about by this drug. The possibility exists that spontaneous abortion may occur.

Pediatric Use: Vantas is contraindicated in pediatric patients and was not studied in children.

Hyperglycemia and diabetes: Hyperglycemia and an increased risk of developing diabetes have been reported in men receiving GnRH agonists. Hyperglycemia may represent development of diabetes mellitus or worsening of glycemic control in patients with diabetes. Monitor blood glucose and/or glycosylated hemoglobin (HbA1c) periodically in patients receiving a GnRH agonist and manage with current practice for treatment of hyperglycemia or diabetes.

Cardiovascular disease: Increased risk of developing myocardial infarction, sudden cardiac death and stroke has been reported in association with use of GnRH agonists in men. The risk appears low based on the reported odds ratios, and should be evaluated carefully along with cardiovascular risk factors when determining a treatment for patients with prostate cancer. Patients receiving a GnRH agonist should be monitored for symptoms and signs suggestive of development of cardiovascular disease and be managed according to current clinical practice.

ADVERSE REACTIONS:

The safety of Vantas was evaluated in 171 patients with prostate cancer treated for up to 36 months in two clinical trials. The pivotal study (study 301) consisted of 138 patients, while a separate supportive study (study 302) consisted of 33 patients.

Vantas, like other LH-RH analogs, caused a transient increase in serum testosterone concentrations during the first week of treatment. Therefore, potential exacerbations of signs and symptoms of the disease during the first few weeks of treatment are of concern in patients with vertebral metastases and/or urinary obstruction or hematuria. If these conditions are aggravated, it may lead to neurological problems such as weakness and/or paresthesia of the lower limbs or worsening of urinary symptoms (see **WARNINGS and PRECAUTIONS**).

In the first 12 months after initial insertion of the implant(s), an implant extruded through the incision site in eight of 171 patients in the clinical trials (see Insertion and Removal Procedures for correct implant placement).

In the pivotal study (Study 301) a detailed evaluation for implant site reactions was conducted. Out of the 138 patients in the study, 19 patients (13.8%) experienced local or insertion site reactions. All these local site reactions were reported as mild in severity. The majority were associated with initial insertion or removal and insertion of a new implant, and began and resolved within the first two weeks following implant insertion. Reactions persisted in 4 (2.8%)

patients. An additional 4 (2.8%) patients developed application-site reactions after the first two weeks following insertion.

Local reactions after implant insertion included bruising (7.2% of patients) and pain/soreness/tenderness (3.6% of patients). Other, less frequently reported, reactions included erythema (2.8% of patients) and swelling (0.7% of patients). In this study, two patients had events described as local infections/inflammations, one that resolved after treatment with oral antibiotics and the other without treatment.

Local reactions following insertion of a subsequent implant were comparable to those seen after initial insertion.

The following possibly or probably related systemic adverse events occurred during clinical trials of up to 24 months of treatment with Vantas, and were reported in $\geq 2\%$ of patients (Table 1).

Table 1: Incidence (%) of Possibly or Probably Related Systemic Adverse Events Reported by $\geq 2\%$ of Patients Treated with Vantas for up to 24 Months

Body System	Adverse Event	Number (%)	
Vascular Disorders	Hot flashes*	112	(65.5%)
General Disorders	Fatigue	17	(9.9%)
	Weight increased	4	(2.3%)
Skin and Appendage Disorders	Implant site reaction	10	(5.8%)
Reproductive System and Breast Disorders	Erectile dysfunction *	6	(3.5%)
	Gynecomastia *	7	(4.1%)
	Testicular atrophy *	9	(5.3%)
Psychiatric Disorders	Insomnia	5	(2.9%)
	Libido decreased *	4	(2.3%)
Renal and Urinary Disorders	Renal impairment**	8	(4.7%)
Gastrointestinal Disorders	Constipation	6	(3.5%)
Nervous System Disorders	Headache	5	(2.9%)

* Expected pharmacological consequences of testosterone suppression.

** 5 of the 8 patients had a single occurrence of mild renal impairment (defined as creatinine clearance $\geq 30 < 60$ mL/min), which returned to a normal range by the next visit.

Hot flashes were the most common adverse event reported (65.5 % of patients). In terms of severity, 2.3% of patients reported severe hot flashes, 25.4 % of patients reported moderate hot flashes and 37.7% reported mild hot flashes. In addition, the following possibly or probably related systemic adverse events were reported by $<2\%$ of patients using Vantas in clinical studies.

Blood and Lymphatic System Disorders: Anemia

Cardiac Disorders: Palpitations, ventricular extrasystoles

Gastrointestinal Disorders: Abdominal discomfort, nausea

General Disorders: Feeling cold, lethargy, malaise, edema peripheral, pain, pain exacerbated, weakness, weight decreased

Hepatobiliary Disorders: Hepatic disorder

Injury, Poisoning and Procedural Complications: Stent occlusion

Laboratory Investigations: Aspartate aminotransferase increased, blood glucose increased, blood lactate dehydrogenase increased, blood testosterone increased, creatinine clearance decreased, prostatic acid phosphatase increased

Metabolism and Nutrition Disorders: Appetite increased, fluid retention, food craving, hypercalcemia, hypercholesterolemia

Musculoskeletal and Connective Tissue Disorders: Arthralgia, back pain, back pain aggravated, bone pain, muscle twitching, myalgia, neck pain, pain in limb

Nervous System Disorders: Dizziness, tremor

Psychiatric Disorders: Depression, irritability

Renal and Urinary Disorders: Calculus renal, dysuria, hematuria aggravated, renal failure aggravated, urinary frequency, urinary frequency aggravated, urinary retention

Reproductive System and Breast Disorders: Breast pain, breast tenderness, genital pruritus male, gynecomastia aggravated, sexual dysfunction

Respiratory, Thoracic and Mediastinal Disorders: Dyspnea exertional

Skin and Subcutaneous Tissue Disorders: Contusion, hypotrichosis, night sweats, pruritus, sweating increased

Vascular Disorders: Flushing, hematoma

Changes in Bone Density: Decreased bone density has been reported in the medical literature in men who have had orchiectomy or who have been treated with an LH-RH agonist analog. It can be anticipated that long periods of medical castration in men will have effects on bone density.

OVERDOSAGE

Histrelin acetate injection of up to 200 mcg/kg (rats, rabbits), or 2000 mcg/kg (mice) resulted in no systemic toxicity. This represents 20 to 200 times the maximal recommended human dose of 10 mcg/kg/day. Adverse event profiles were similar in patients receiving one, two or four Vantas implants.

DOSAGE AND ADMINISTRATION

The recommended dose of Vantas is one implant for 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 for 12 months of hormonal therapy. Vantas must be removed after 12 months of therapy. At the time an implant is removed, another implant may be inserted to continue therapy (see Insertion and Removal Procedures).

Insertion and Removal Procedures

The Vantas implant is supplied in a sterile vial within an opaque plastic bag, which in turn is in a carton. **The implant should be kept refrigerated (2-8° C / 36-46° F) until the day of the procedure.** A kit, containing all the supplies necessary to insert and/or explant the implant is provided with the implant. The kit itself does not require refrigeration.

It is important to use aseptic techniques to minimize any chance of infection. Sterile gloves are required for the insertion procedure and subsequent removal of the implant.

The implant is inserted using the procedure outlined below:

Identifying the Insertion Site

The patient should be on his back, with the arm least used (e.g., left arm for a right-handed person) flexed so the physician has ready access to the inner aspect of the upper arm. Prop the arm with pillows so the patient can easily hold that position. The optimum site for insertion is approximately half way between the shoulder and the elbow and in the crease between the bicep and triceps.

Contents of the Sterile Kit

The sterile kit contains:

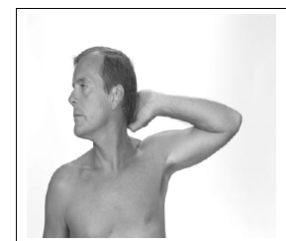
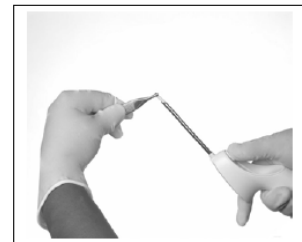
- 1 #11 disposable scalpel
- 1 syringe
- 1 25 gauge 1.5" needle
- 1 S/S mosquito clamp
- 1 package betadine swabs
- 1 package alcohol swabs
- 1 fenestrated drape
- 1 sachet antiseptic ointment
- 1 package gauze sponges 4"
- 1 package surgical closure strips
- 1 vicryl sutures – coated
- 1 package elastoplast
- 1 ampule lidocaine HCl 1% w/epinephrine
- 1 implant insertion tool in sterile bag



Loading the Insertion Tool

Load the insertion tool prior to prepping the insertion field and insertion. Remove the insertion tool from its sterile bag. The tool is

shipped with the cannula fully extended. Verify this by inspecting the position of the green retraction button. The button should be all the way forward, towards the cannula, away from the handle.



Remove the metal band from the vial, remove the rubber stopper and use the mosquito clamp to grasp either tip of the implant. **AVOID GRABBING OR CLAMPING THE MIDDLE OF THE IMPLANT TO PREVENT DISTORTION OF THE IMPLANT.**

Insert the implant into the insertion tool. It will seat in cannula so that just the tip is visible at the bottom of the bevel.

Inserting the Implant

1. Swab the insertion area with the betadine swabs, then lay the fenestrated drape over the insertion site (*for clarity of illustration, the accompanying photos do not show the drape*).



Anesthetic

2. Determine that the patient has no lidocaine/epinephrine allergies. Inject a few cc's of the anesthetic, starting at the planned incision site, then infiltrating up to the length of the implant, 32 mm, in a fan like fashion.



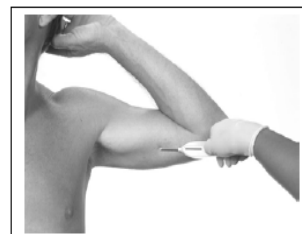
Incision

3. Using the scalpel, make a 2-3 mm incision immediately subcutaneous and perpendicular to the shoulder.



Insertion

4. Grasp the insertion tool by its handle, as shown.
5. Insert the tip of the insertion tool into the incision with the bevel up and advance the tool subcutaneously along the path of the anesthetic, up to the inscribed line on the cannula. To ensure subcutaneous placement, the implanter should visibly raise the skin at all times during insertion. Be sure that the implanter doesn't enter muscle tissue



6. Hold the insertion tool in place as you move your thumb to the green retraction button. Press the button down to release the locking mechanism, then draw the button back to the back stop, all the while holding the tool in place. The cannula will withdraw from the incision, leaving the implant in the dermis. Withdraw the implanter from the incision. Release of the implant can be checked by palpation.

NOTE: Do not try to push the tool in deeper once the retraction process has started to avoid severing the implant. If you wish to re-start the process, withdraw the tool, grasp the implant by the tip to extract it, reset the retraction button to its most forward position, reload the implant and start again.



After placement, sterile gauze may be used to apply pressure briefly to the insertion site to ensure hemostasis.

Closing the Incision

7. To close the incision, use one to two sutures (optional), knots facing inside the incision. Apply a light coating of antibiotic ointment directly onto the incision. Close with two surgical strips. Apply one or two of the 4" gauze pads over the incision and secure with elastoplast.

Patient Instructions- Aftercare

Give the patient the Patient Summary Information. Instruct the patient to refrain from wetting the arm with the implant for 24 hours. The pressure bandage can be removed at that time. The patient should not remove the surgical strips; rather, the strips should be allowed to fall off on their own after several days. Patients should refrain from heavy lifting and strenuous physical activity of the inserted arm for 7 days to allow the incision to fully close.

Removal Procedure and New Implant Insertion

The Vantas implant must be removed after 12 months of therapy. The techniques and instruments required are the same as found in the Vantas kit for implantation (see kit contents). If a new Vantas implant will be inserted, the new kit sent with the new implant will provide all necessary instruments and anesthesia/antiseptics. Otherwise, assemble all the necessary implements prior to the procedure.

Locating the Implant

The implant may be located by palpating the area near the incision from the prior year. Generally, the implant is readily palpated. Press the distal end of the implant to determine the proximal tip's location relative to the old incision.

In the event the implant is difficult to locate, ultrasound can be used. If ultrasound fails to locate the implant, other imaging techniques such as CT or MRI may be used to locate it.

Preparing the Site

1. Patient position and site preparation are the same as for the initial insertion. Swab the area above and around the implant with the betadine swabs. Drape the area with a fenestrated drape.



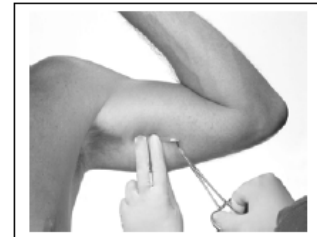
Anesthetic

2. After determining the absence of known allergies to the anesthetic agent, press down on the implant tip furthest from the old incision to determine the location of the tip closest to the incision. Inject a small amount of lidocaine/epinephrine at the tip near the incision, then advance the needle along the length, but beneath the implant, steadily injecting a small amount of anesthetic along the way. The anesthetic will raise up the implant within the dermis. If you are inserting a new implant, you have the option of either putting the new one in the same “pocket” as the removed one, or using the same incision, insert the new implant in the opposite direction. If placing the implant in the opposite direction, apply anesthetic along the length of the path for the new implant prior to explantation.



Incision/Explantation

3. Using the #11 scalpel, make a 2-3 mm incision near the tip and about 1-2 mm deep. Generally, the tip of the implant will be visible through a thin pseudo- capsule of tissue. If not, push down on the distal tip of the implant and massage it forward towards the incision. Carefully “nick” the pseudo capsule to reveal the polymer tip.



4. Grasp the tip with the mosquito clamp and extract the implant.

5. Dispose of the implant in a proper manner, treating it like any other bio-waste.

IF INSERTING A NEW IMPLANT - PROCEED ACCORDING TO “LOADING THE INSERTION TOOL”, "INSERTION" AND "CLOSING THE INCISION” SECTIONS. The new implant may be placed through the same incision site. Alternatively, the contralateral arm may be used.

6. Provide the patient the patient instructions-aftercare card found in the kit.

HOW SUPPLIED

Vantas (NDC 67979-500-01) is supplied in a carton containing 2 inner cartons, one for the Vantas implant and one for the Vantas implantation kit:

The Vantas implant carton contains a cold pack for refrigerated shipment and a small carton containing an amber plastic pouch. Inside the pouch is a glass vial with a teflon-coated stopper and an aluminum seal, containing the implant immersed in 2 mL of 1.8% sterile sodium chloride.

Upon receipt, refrigerate the small carton containing the amber plastic pouch and glass vial (with the implant inside) until the day of insertion.

Store the implant refrigerated, 2-8 °C (36-46 °F), in the unopened glass vial with the 1.8% sterile sodium chloride solution, overwrapped in the amber plastic pouch and carton. Protect from light. Do not freeze.

The Vantas implantation kit carton contains one each of the following (individually wrapped in sterile packaging): Vantas implantation device, #11 scalpel, syringe, 25g 1.1/2” needle, mosquito hemostat, Betadine swabs, alcohol swab, fenestrated drape, Neosporin, gauze sponges, adhesive skin closures, vicryl sutures (coated), elastoplast, and lidocaine HCl 1% with epinephrine.

A physician insert with insertion and removal instructions and patient instructions are provided in the carton.

Rx Only

For more information, call 1-800-462-3636 or visit www.vantasimplant.com

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Manufactured by
Endo Pharmaceuticals Solutions Inc.
Chadds Ford, PA 19317



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