

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Vantas 50 mg implant.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each implant contains approximately 50 mg histrelin acetate corresponding to 41 mg histrelin.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Implant.

The implant is in the form of a small, thin flexible tube. The histrelin acetate core is placed in a non-biodegradable 34.5 mm x 3.15 mm cylindrically shaped hydrogel reservoir.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Palliative treatment of advanced prostate cancer.

4.2 Posology and method of administration

The recommended dose of Vantas is one implant for 12 months. An average of 50 µg histrelin acetate is delivered daily. The implant is inserted subcutaneously in the inner aspect of the upper arm.

Response to Vantas therapy should be monitored by clinical parameters and by measuring prostate-specific antigen (PSA) serum levels. Clinical studies have shown that serum testosterone concentrations may increase during the first week of treatment (testosterone flare-up). Testosterone concentrations then decreased and reached castrate levels (≤ 50 ng/dL) by Week 4. Once attained, castrate level was maintained as long as Vantas therapy continued. If a patient's clinical response appears to be sub-optimal, then it would be advisable to confirm that patient's serum testosterone concentration is at castrate level.

The implant must be removed after 12 months of treatment. At the time the implant is removed a new implant may be inserted in order to continue the treatment. Please see insertion and removal procedures below.

Pediatric population

Vantas is contraindicated for use in children under 18 years old as the safety and efficacy of Vantas have not been established in this population. No data is available.

Hepatic impairment and Renal impairment

Vantas has not been studied adequately in patients with impaired liver function.

In patients with mild to moderate renal impairment (CLcr: 15-60 ml/min), no adjustments in drug dosing are warranted.

Vantas has not been studied in prostate cancer patients with severe renal impairment.

4.3 Contraindications

Vantas is contraindicated in patients with hypersensitivity to histrelin or to any of the excipients listed in section 6.1, GnRH, GnRH-agonists/- analogues, or stearic acid. Anaphylactic reactions to synthetic LHRH or LHRH-agonists/- analogues, have also been reported. Use in women and children is contraindicated.

4.4 Special warnings and precautions for use

Reactions to the treatment with Vantas should be monitored by regular measurement of serum concentrations of testosterone and prostate-specific antigen, especially if the anticipated clinical or biochemical response to treatment has not been achieved. (*See section 4.2.*).

Histrelin, causes a transient increase in serum concentrations of testosterone during the first week of treatment. Patients may experience a worsening of symptoms or onset of new symptoms, including joint pain, bone pain, neuropathy, haematuria, or ureteral or bladder outlet obstruction. Cases of ureteral obstruction and spinal cord compression, which may lead to paralysis with or without fatal complications, have been reported in connection with LHRH-agonists. Patients with metastatic vertebral lesions and/or urinary tract obstruction should be closely observed during the first few weeks of therapy. These patients should be considered for prophylactic treatment with anti-androgens. If spinal cord compression or renal impairment occurs, the standard treatment for these complications should be initiated.

The results of the testosterone determinations are dependent on the method of analysis. It is advisable to be aware of the type and precision of the assay methodology to ensure the correct clinical and therapeutic decisions.

Long-term androgen deprivation either by bilateral orchiectomy or administration of GnRH analogues is associated with increased risk of bone loss and may lead to osteoporosis and increased risk of bone fracture. In addition, patients may experience metabolic changes (e.g. glucose intolerance or worsening of existing diabetes) or an increased risk of cardiovascular events. Patients at high risk for metabolic or cardiovascular diseases should be carefully assessed before commencing treatment and adequately monitored during androgen deprivation therapy.

Androgen deprivation therapy may prolong the QT interval. In patients with a history of or risk factors for QT prolongation and in patients receiving concomitant medicinal products that might prolong the QT interval (see section 4.5) physicians should assess the benefit risk ratio including the potential for Torsade de pointes prior to initiating Vantas.

Vantas should be used with caution in patients with abnormal hepatic function in order to ascertain applicability of Vantas in such patients, as Vantas has not been studied adequately in patients with impaired liver function.

There is an increased risk of incident depression (which may be severe) in patients undergoing treatment with GnRH agonists, such as histrelin. Patients should be informed accordingly and treated as appropriate if symptoms occur.

Insertion of an implant is a surgical procedure. Only Vantas implantation device can be used for insertion of the implant. Careful adherence to the recommended procedures for insertion and removal is recommended in order to reduce the risk of complications and implant expulsion (see section 6.6).

In cases where the implant is difficult to locate by palpation, ultrasound or CT scan may be used.

Children and women have not been studied.

The container of this medicinal product contains latex rubber. May cause severe allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

No pharmacokinetic-based drug-drug interaction studies have been performed with Vantas.

Treatment with histrelin results in suppression of the pituitary-gonadal system. Results of diagnostic tests of pituitary/gonadotropic and gonadal functions conducted during or after histrelin treatment may be affected.

Since androgen deprivation treatment may prolong the QT interval, the concomitant use of Vantas with medicinal products known to prolong the QT interval or medicinal products able to induce Torsade de pointes such as class IA (e.g. quinidine, disopyramide) or class III (e.g. amiodarone, sotalol, dofetilide, ibutilide) antiarrhythmic medicinal products, methadone, moxifloxacin, antipsychotics, etc. should be carefully evaluated (see section 4.4).

4.6 Fertility, pregnancy and lactation

Preclinical studies have shown that histrelin decreases fertility in animals due to its pharmacological effect. However, fertility returns to normal after cessation of treatment. (See section 5.3.).

Due to its indication, Vantas has not been studied in pregnant or breast-feeding women and is not for use in women.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

The safety of Vantas was evaluated in 171 patients with prostate cancer treated for up to 36 months in two clinical trials. Vantas, like other LHRH-analogues, caused a transient increase in serum testosterone concentrations during the first week of treatment. Therefore, potential exacerbations of the signs and symptoms of the disease during the first few weeks of treatment are a factor in patients with vertebral metastases and/or urinary obstruction or hematuria. If these conditions are aggravated, it may lead to neurological problem such as weakness and/or paraesthesia of the lower limbs or worsening of urinary tract symptoms (see section 4.4).

In the first 12 months after insertion of the implant(s), an implant extruded through the incision site in eight out of 171 patients in the clinical trials. In a pivotal study, a detailed evaluation of implant site reactions was also conducted. Insertion site reactions were very common and were experienced by 13.8 % of the patients in the study. All these local site reactions were reported as mild in severity. The majority of these reactions were associated with initial insertion or removal/insertion of a new implant and began and resolved within the first two weeks following implant insertion. Reactions persisted in 2.8 % of the patients, and an additional 2.8 % developed insertion-site reactions after the first two weeks following implantation.

Of 138 patients in a pivotal study, 2 patients developed a local skin infection and inflammation. The one instance 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 after up to 24 months treatment with Vantas or are ADRs based on post-marketing reports or ADRs which are class-effects of LHRH-agonists.. The reported undesirable effects during Vantas treatment are presented in Table 1 below according to the organ systems and frequency.

Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000), not known (cannot be estimated from the available data)
Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1: The incidence of possible or probably related undesirable effects reported by patients treated with Vantas up to 24 months.

Organ group	Very common	Common	Uncommon	Rare	Not known
Infections and infestations				Skin infection	
Blood and lymphatic system disorders			Anaemia		
Metabolism and nutrition disorders			Fluid retention, hypercalcemia,		Glucose intolerance ³ ,

			hypercholesterolaemia, food cravings, increased appetite		worsening of existing diabetes ³
Psychiatric disorders		Mood changes, depression, decreased libido, insomnia			
Nervous system disorders		Dizziness, headache	Tremor, lethargy		
Cardiac disorders			Palpitations, ventricular extrasystoles		Cardiovascular disease ³ , QT- prolongation ³ (see sections 4.4 and 4.5)
Vascular disorders	Hot flushes ¹	Blushing	Haematoma		
Respiratory, thoracic and mediastinal disorders		Exercise induced dyspnoea			
Gastrointestinal disorders		Constipation	Abdominal discomfort, nausea		
Hepatobiliary disorders		Hepatic disorder			
Skin and subcutaneous tissue disorders		Hypertrichosis	Night sweats, pruritus, hyperhidrosis		Rash ⁴
Musculoskelatal and connective tissue disorders		Arthralgia, pain in the extremities	Back pain, muscle spasm, muscle infiltration, neck pain		Osteoporosis ³
Renal and urinary disorders		Pollakisuria, impaired renal function ² , urinary retention	Renal failure, nephrolithiasis, dysuria, haematuria		
Reproductive system and breast disorders		Erectile dysfunction ¹ , testicular atrophy ¹ , gynecomastia ¹	Sexual dysfunction, breast pain, breast tenderness, genital pruritus (males)		
General disorders and administration site conditions		Injury at the application site, erythema at the application site, asthenia, fatigue, reaction at the application site, pain, tenderness	Peripheral edema, pain (exacerbated), swelling, pain (non specific), malaise, feelings of cold, irritability	Application site inflammation	
Investigations		Weight gain, elevated blood glucose	Elevated aspartate- aminotransferase, elevated blood lactate dehydrogenase, elevated blood testosterone, lowered creatinine		

			clearance, elevated acid phosphatase in the prostate, weight loss		
Injury, poisoning and procedural complications			Ureteral stent occlusion, bruising		

- 1. Anticipated pharmacological reaction to inhibition of testosterone
- 2. 5 of 8 patients experienced a single instance of mildly impaired renal function (defined as creatinine clearance ≥ 30 ml/min and < 60 ml/min), which resolved to the normal range by the next medical consultation.
- 3. Class-effect of LHRH-agonists
- 4. Based on post-marketing data

Long-term androgen deprivation either by bilateral orchiectomy or administration of GnRH analogues is associated with increased risk of bone loss and may lead to osteoporosis and increased risk of bone fracture. In addition, patients may experience metabolic changes (e.g. glucose intolerance or worsening of existing diabetes) or an increased risk of cardiovascular events.

Reporting of suspected adverse reaction
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRa Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie
Email: medsafety@hpra.ie.

4.9 Overdose

Not relevant.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Gonadotropin-releasing hormones. ATC code: L02AE05.

Histrelin is a synthetic analogue of a naturally occurring LHRH. After implantation of Vantas, histrelin is diffused into the tissue, resulting in inhibition of pituitary LH secretion leading to a fall in serum testosterone concentrations in males. The effect is reversible on discontinuation of therapy. Initially, Vantas like other LHRH agonists may transiently increase serum testosterone concentration.

By one month after the implantation, testosterone concentrations have fallen to within castrate range (≤ 50 ng/dL) and remain suppressed while Vantas is present. This inhibition leads to prostate tumour regression and symptomatic improvement in the majority of patients.

The implant is inserted subcutaneously and remains in place for 12 months whilst the drug is released through the hydrogel reservoir. The mean daily release over the 12-month period is approximately 50 μ g histrelin acetate with higher histrelin plasma concentration in the beginning of the dosing period and lower concentration towards the end, but maintaining castration level of testosterone.

The implant's hydrogel reservoir determines the diffusion rate in the water-based environment. Hydrogel is not dissolved, but is similar to living tissue in composition, which contributes to its biocompatibility as it lessens the mechanical irritation of surrounding cells and tissue. It also displays low surface tension in vivo, which lessens the tendency for proteins to be absorbed and gather on the surface. This is important for the prevention of thrombosis and other biological rejection processes.

5.2 Pharmacokinetic properties

Absorption:

Following subcutaneous insertion of one Vantas 50 mg implant in patients with advanced prostate cancer ($n = 17$), peak serum concentrations of 1.10 ± 0.375 ng/ml (mean value \pm SD) occurred at a median of 12 hours. Continuous subcutaneous release was evident as serum levels were sustained throughout the entire 52-week dosing period. The mean serum histrelin concentration at the end of the 52-week treatment period 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 insertion of the second implant were comparable to the level in 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.

Distribution:

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

Biotransformation:

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 value \pm SD), and the terminal half-life was 3.92 ± 1.01 hr (mean value \pm SD). The apparent clearance following insertion of a 50 mg (as histrelin acetate) Vantas implant in 17 prostate cancer patients was 174 ± 56.5 ml/min (mean value \pm SD).

Elimination:

No drug excretion study has been conducted with Vantas 50 mg implants.

Luteinizing hormone (LH) returned to normal level 1 to 6 weeks after extraction of the implant. The testosterone level also returned to normal level within 2 weeks of the increase in LH-level, which indicated that the inhibition is reversible.

Special populations:

Geriatrics

The majority (89.9 %) of the 138 patients studied in the primary clinical trial were 65 years or older.

Paediatrics

Safety and efficacy for Vantas in paediatric patients have not been established (see section 4.2).

Race

When serum histrelin concentrations were compared for 7 Latin-American, 30 Black and 77 Caucasian patients, average histrelin concentrations were similar.

Renal impairment:

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

Hepatic insufficiency

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

5.3 Preclinical safety data

No signs of overt toxicity were seen in repeated dose toxicity studies and the effects were related mainly to the pharmacological properties of histrelin. Carcinogenicity studies in rats at doses up to 30 times and in mice at doses up to 230 times the human dose revealed, as seen with other LHRH agonists, an increase in tumours of hormonally responsive tissues (testes, pancreas, mammary and pituitary glands). In addition, there was an increase in histiocytic sarcomas in female mice at the highest dose.

Mutagenicity studies performed with saline extracts of implants with and without histrelin were negative in a battery of genotoxicity studies.

Local tolerance studies showed that Vantas is a mild irritant and becomes encapsulated over time. Mineralization occurred in rats, rabbits and dogs, but not in monkeys.

Administration of histrelin in laboratory animals was associated with atrophy of reproductive organs and reduced fertility. This is due to the pharmacological effect and full reversibility was demonstrated after cessation of administration.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The drug core contains stearic acid.

The acrylic copolymer shell consists of:

- 2-hydroxyethyl methacrylate
- 2-hydroxypropyl methacrylate
- trimethylolpropan trimethacrylate

The storage solution of the implant consists of:

sodium chloride
water for injections

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Implant:

Store in a refrigerator (2° C - 8° C). Do not freeze.

Store in the original package in order to protect from light.

Implantation device:

The implantation device supplied is sterile in its pouch. Do not store above 25° C.

Do not refrigerate or freeze. Store in the original package in order to protect from light.

6.5 Nature and contents of container

The implant is contained in a type I glass vial and supplied with a Teflon-coated stopper (chlorobutyl isoprene rubber) and an aluminium seal. The stopper contains latex rubber. The implant is stored in 2ml of 1.8 % sterile sodium chloride solution.

Vantas is supplied in a carton with an amber plastic bag, which contains the glass vial with the implant.

The sterile implantation device is supplied in a self-sealing Tyvek-bag for sterilization, which is placed in a carton.

6.6 Special precautions for disposal and other handling

Vantas implantation device is for single use only.

Packaging and any unused product or waste material should be disposed of in accordance with local requirements.

Insertion procedure

It is important that aseptic technique be used in order to minimize the risk of infection. Sterile gloves are required for insertion and removal of the implant.

Identification of the insertion site

The patient should lie on his back with the arm that is least used (i.e. the left arm in 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 in the crease between the biceps and triceps muscle.

Preparation of the implantation device

Prepare the implantation device before preparation of the insertion site and prior to insertion. Remove the implantation device from its sterile bag. The device is supplied with the cannula fully extended. Verify this by inspecting the position of the green retraction button. The button should be all the way forwards, toward the cannula, and away from the handle.

Remove the metal band from the glass vial, remove the rubber stopper and use a mosquito clamp to grasp either tip of the implant. Avoid grasping or clamping the middle of the implant to prevent distortion of the implant.

Insert the implant into the implantation device. The implant will lie in the cannula in such a way that just the tip is visible at the bottom of the bevel.

Inserting the implant

Swab the insertion site with povidone-iodine and place a fenestrated drape over the site.

Anesthetic

Ensure that the patient is not allergic to lidocaine/adrenaline. Inject a few ml of the anesthetic, starting at the planned incision site and then infiltrating up to the length of the implant, 32 mm, in a fan-like fashion.

Incision

Using a scalpel make a 2-3 mm shallow skin incision on in the inner aspect of the upper arm perpendicular to length of the biceps.

Insertion

Grasp the implantation device by its handle.

Insert the tip of the device into the incision with the bevel upward, and advance the device subcutaneously along the path of the anaesthetic up to the inscribed line on the cannula. To ensure subcutaneous placement, the implantation

device should visibly raise the skin at all times during insertion. Make sure that the implantation device does not enter muscle tissue.

Hold the device in place at the same time as you move your thumb toward the green retraction button. Press the button down to release the locking mechanism, then draw the button back to the back-stop whilst holding the device in place. The cannula is withdrawn from the incision leaving the implant in the dermis. Withdraw the implantation device from the incision. The freed implant can be checked by palpation.

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

Closing the incision

Close the incision using one or two sutures (optional) with the knots facing inside the incision. Apply a thin layer of antibiotic ointment directly onto the incision. Close the incision with two surgical steri-strips. Apply a gauze dressing over the incision and secure it with a bandage.

Removal procedure and insertion of new implant

The Vantas implant must be removed after 12 months of treatment.

Locating the implant

The implant can be located by palpating the area near the incision of the previous year. The implant is normally readily palpated. Press on the distal end of the implant to determine the proximal tip location relative to the old incision.

If the implant is difficult to locate, ultrasound may be used. If the implant cannot be located by ultrasound, other imaging techniques such as CT or MRI may be used to locate it.

Preparation of the insertion site

Patient position and preparation of the implantation site are the same as for the initial implantation. Swab the area above and around the implant with povidone-iodine. Drape the area with a fenestrated drape.

Anesthetic

First determine that the patient is not allergic to lidocaine/adrenaline then press down on the tip of the implant furthest from the original incision. Inject a small amount of lidocaine/adrenaline at the tip near the incision, then advance the cannula along the length, but beneath the implant, steadily injecting a small amount of anesthetic into the skin. The anesthetic will raise up the implant within the dermis. If a new implant is to be inserted, you have the option of placing the implant in the same "pocket" as the removed one, or of using the same incision and inserting the implant in the opposite direction. If you place the implant in the opposite direction, inject the anesthetic along the length of the new implant prior to explantation.

Incision/explantation

Use a scalpel to make a 2-3 mm incision near the tip and approximately 1-2 mm deep. Generally, the tip of the implant will be visible through a thin pseudo-capsule of tissue. If the implant is not visible, press 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.

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

If inserting a new implant, proceed as per the initial instructions. The new implant may be placed through the same incision site. Alternatively, the opposite arm may be used.

Patient instructions – aftercare

Give the patient the information leaflet. Instruct the patient to avoid wetting the arm containing the implant for 24 hours. The pressure bandage can be removed after 24 hours. The patient must not remove the surgical steri-strips. These strips should be allowed to fall off by themselves after several days. Patients should avoid lifting heavy objects and participating in strenuous physical activity involving the treated arm for 7 days to allow the incision to fully close.

7 MARKETING AUTHORISATION HOLDER

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FI-02200
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8 MARKETING AUTHORISATION NUMBER

PA 1327/014/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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