CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-732

Medical Review(s)

NDA 21-732

Medical Team Leader's Memorandum: NDA Review

Date submitted:	December 8, 2003
Date received CDER:	December 12, 2003
Date received Div Doc Room:	December 16, 2003
Date TL's memo completed:	October 12, 2004
Drug:	Vantas™ (histrelin acetate implant)
Dose and route:	subcutaneous implant containing 50mg histrelin
Sponsor:	Valera Pharmaceuticals Cranbury, New Jersey
Indication:	Palliative treatment of advanced prostate cancer

1. Executive summary:
The purpose of this team leader's memo is to provide the Division Director with my overall recommendation for regulatory action on this NDA. Labeling negotiations have been successfully completed and the final recommendation from the Office of Compliance is "acceptable". Therefore, I recommend **approval** of this NDA.

2. Clinical background:
Currently, the standard of care for the palliative treatment of advanced prostate cancer is medical or surgical castration. This is because most adenocarcinomas of the prostate are initially sensitive to the action of testosterone and lowering serum testosterone concentrations to "castrate" levels will result in at least temporary regression of tumor and symptomatic relief. Today, most patients in this situation opt for medical castration with analogues of naturally occurring luteinizing hormone releasing hormone (LHRH), rather than orchiectomy or estrogens. LHRH analogues are widely available as depot injectable formulations (e.g. Lupron, Zoladex, Eligard, Trelstar, etc). They work by initially stimulating receptors in the pituitary (LHRH agonism), but eventually the chronic agonistic action results in a "down-regulation" or "desensitization" of these receptors with resultant decreases in serum LH and in serum testosterone.

Most of the currently approved products for this indication are available as intramuscular and subcutaneous depot injections. For example, Lupron (leuprolide) is an intramuscular injection that is available as monthly, 3-month, and 4-month depots. Zoladex (goserelin) is a biodegradable subcutaneous inplant available as monthly, 3-month and 4-month depots. Eligard (leuprolide) is a subcutaneous injection available as monthly, 3-month and 4-month depots. The approved product most closely related to Vantas is a 12-month, *non-biodegradable* subcutaneous implant known as Viadur (ALZA Corporation). Viadur is a miniaturized osmotic pump system, made partly of titanium, and contains the drug leuprolide. Viadur is inserted under the skin of the upper arm via a small incision and it must be removed (and replaced) after 12 months. It was approved in 1998. The fundamental benefit of Viadur is that it provides systemic leuprolide for a full 12 months without the need for repeated depot drug injection.

Valera Pharmaceuticals now submits the NDA for Vantas, another 12-month implant containing an LHRH analogue and intended for the palliative treatment of advanced prostate cancer. Like Viadur, Vantas must be inserted via a small incision into the subcutaneous tissues of the medial upper arm. Like Viadur, it is intended for a 12-month treatment period followed by removal. If appropriate, a fresh implant can be inserted. Vantas differs from Viadur in two basic ways; it contains a different LHRH analogue (histrelin) and it is different structurally. Vantas contains

histrelin not leuroplide. Histrelin was approved by FDA in 1991 under NDA 19-836 (Shire Pharmaceuticals) as the drug product "Supprelin". At that time, histrelin was indicated only for the treatment of children with central precocious puberty. Further, Vantas is described by sponsor as a "unique delivery system". It is a non-biodegradable, flexible, reservoir that contains no metals and allows for diffusion of histrelin through its thin *hydrogel* walls (hydroxyethyl methacrylate).

3. Regulatory history:
On October 2, 1992, Roberts Pharmaceuticals opened original IND#40,772 for histrelin acetate for the palliative treatment of advanced prostate cancer.

On July 14, 1999, the Division held an End-of- Phase 2 meeting with Roberts and provided input on their proposed Phase 3 pivotal trials (Studies 301 and 302). Both were designed as randomized, open-label, comparative efficacy and safety trials - Study 301 was versus Lupron and Study 302 versus Zoladex.

> On *April 21, 2000*, the first patient was enrolled in pivotal Study 301. On *May 25, 2000*, the first patient was enrolled in Study 302.
>
> On *April 28, 2000*, the ownership of the IND was transferred from Roberts Pharmaceuticals to Shire Laboratories.
>
> On *April 26, 2001*, the ownership of the IND was transferred again; this time from Shire Laboratories to Hydro Med Sciences (now known as "Valera Pharmaceuticals").

On December 19, 2001, the Division held a Type C Guidance meeting with Hydro Med Sciences to discuss proposed revisions to the ongoing Phase 3 Studies 301 and 302. Hydro Med Sciences proposed to terminate enrollment into Study 302 and to continue Study 301 without the comparator arm but with an increased enrollment for Vantas. The Division agreed with these changes to the Phase 3 program.

> On *January 31, 2002*, Hydro Med Sciences submitted formal protocol amendments to Studies 301 and 302 consistent with discussions at the December 2001 Guidance meeting. Study 302 was closed to further enrollment. Study 301 was revised to terminate the comparator arm and to increase overall enrollment for Vantas.

On August 12, 2003, the Division held a Pre-NDA meeting with Hydro Med Sciences.

> On *August 27, 2003*, the last patient completed the single pivotal trial, Study 301.

On December 12, 2003, NDA 21-732 was submitted.

4. Clinical Efficacy and Safety
The sponsor submitted the results from the one "pivotal", Phase 3, non-randomized, open-label, efficacy and safety study (Study 301) conducted in 138 patients at 27 sites in the U.S. and Canada for up to 60 weeks.

This single Phase 3 pivotal study was supported by results from the following investigations:

1) The Study 301 Extension phase - in at least 21 patients.

2) BAR-002-0591A-USA, a Phase 2 dose-ranging trial - in 42 patients at 3 sites in New York, Austria and Israel.
3) Study 302, the prematurely terminated comparative study of Vantas versus Zoladex 10.8mg - in a total of 59 patients for up to 52 weeks of treatment.

[*Reviewer's Note: Again, the reader is reminded that Study 302 was prematurely terminated by agreement with DRUDP during the December 19, 2001 Guidance meeting.*]

4.1. Clinical Efficacy

Efficacy results were submitted for the pivotal study (Study 301) and the supporting studies; but the most substantial evidence for efficacy comes from the pivotal study. The other sources provide consistent and supporting efficacy results.

In ***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 rest had an elevated or rising serum PSA after definitive therapy for localized disease. The median patient age was 75 years (range 53-92). Thirty-two patients were black, 99 were Caucasian, and 7 were Hispanic. 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 $\leq$50 ng/dL by Week 4 and through Week 52. 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.

Attainment of castrate levels of serum testosterone

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 concentration 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. Serum testosterone concentrations remained below the castrate level in all patients in this subset for the entire treatment period (see Figure 1 below).

Reviewer's comment: Serum LH data from these 17 patients confirms the pharmacodynamic effect of Vantas.

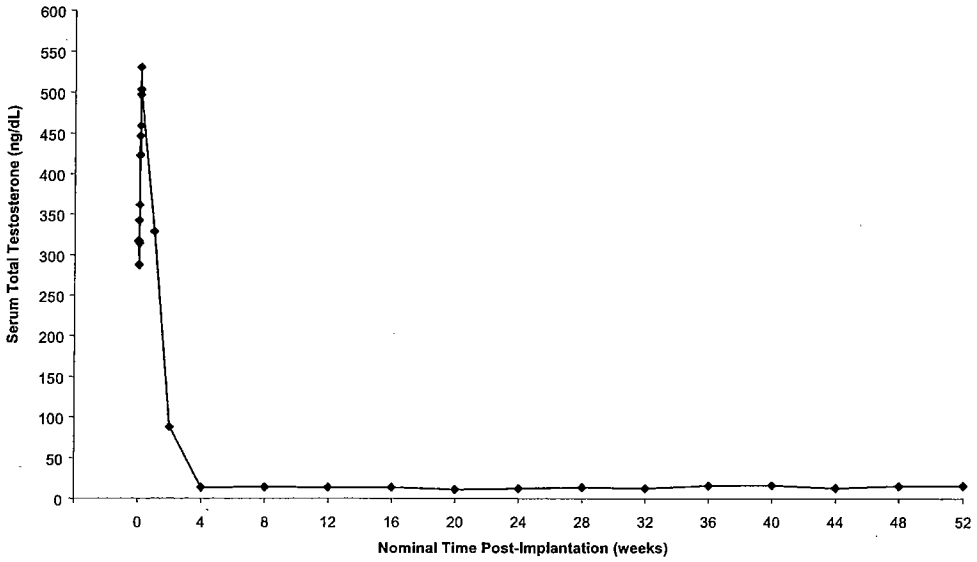

***Figure 1**: Mean Serum Total Testosterone Concentrations for all pK Patients, n=17. (Note that in this group, sampling began minutes after insertion of Vantas.)*

In the overall treatment group (n=138), mean serum testosterone was 388.3ng/dL at Baseline. At the time of first assessment of testosterone (which was not until Day 7[Week 1]), the mean serum testosterone concentration was 382.8ng/dL, slightly lower than the baseline mean. At Week 2, mean serum testosterone was 92.2ng/dL. At Week 4 it was 15ng/dL. At Week 52, the mean testosterone concentration was 14.3ng/dL (see Figure 2).

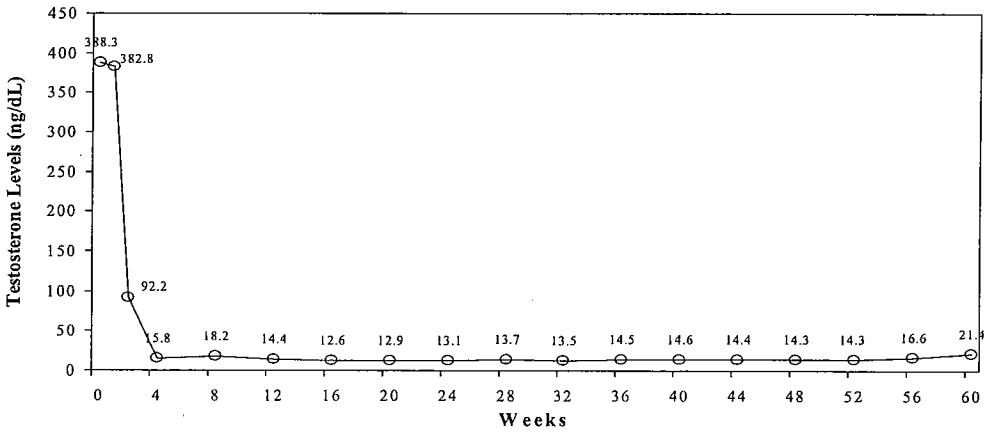

***Figure 2**: Mean serum testosterone concentration-time curve for all 138 patients in Study 301. Of note, first blood draw was not until Day 7 (Week 1) in this overall group; therefore, the mean biochemical "surge"(which occurs on Day 2 and may be seen clearly in Figure 1) is not seen in Figure 2.*

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 (≤50ng/dL) in all 134 evaluable patients on Day 28. This represents **100%** success in attaining medical castration by Day 28 in the evaluable cohort. All three patients with missing values at Day 28 were castrate by the time of their next visit (Day 56).

Maintenance of castrate levels of serum testosterone
Once serum testosterone concentrations at or below castrate level (≤50ng/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 noted to be 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. It was believed that the implant might 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. Again, it was believed that the implant might 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. In this "observed cases" cohort at Week 52, all patients had a serum testosterone ≤50ng/dL. In those 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.

Acute-on-chronic phenomenon
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.

Other efficacy endpoints
Serum prostate specific antigen (PSA) was monitored as a secondary endpoint in the pivotal study. 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 the 111 evaluable patients (93%). Baseline WHO Performance Status and "level of pain" (based upon a 5-point Likert scale) were noted to change very minimally over the course of the trial in the evaluable cohort of 111 patients. Finally, the only notable findings in the exploratory "FACT-P" disease-specific quality-of-life questionnaire were a modest increase in fatigue ("lack of energy") and decrease in sexual function ("decrease in satisfaction with sex life") over the course of the trial.

Reviewer's comment: The results of the pivotal study 301 are strongly supportive of efficacy.

As described above (see "Regulatory history"), enrollment into ***Study 302*** was prematurely terminated by prior agreement with the Division and it was intended as a "supportive" study for this NDA. Prior to stopping enrollment, 59 patients had been randomized and 58 had received study medication. This was a randomized, open-label, multicenter study comparing Vantas to Zoladex 10.8mg for 52 weeks. Thirty-three (33) patients received a single Vantas implant and 25 patients received Zoladex 10.8mg every 12 weeks. Of those who received Vantas, 8 patients discontinued prior to reaching Week 52. Reasons given were: death (n=4), disease progression (n=2), implant expulsion (n=1), and patient request with no specific reason given (n=1).

Two patients discontinued prior to the Day 28 blood draw - both were deaths. (In one of these two patients, a castrate serum testosterone concentration was reported after insertion of the implant but before death.) Three other patients had no available serum testosterone concentration for Day 28. Of the 28 patients who had a serum testosterone concentration on Day 28, 26 patients (**93%**) were below castrate level. The two patients who did not attain this goal by Day 28 had serum testosterone concentrations of 76.3ng/dL and 58.4ng/dL. Repeat assay for the latter patient actually revealed a serum testosterone below castrate level (44.7ng/dL). In the former patient and in all without a value for Day 28, serum testosterone concentration was ≤50ng/dL at the next scheduled visit (Week 8). Once castration was attained, only **one patient** in the Vantas group had a "breakthrough" testosterone of >50ng/dL; that was Patient 10-010, who had a serum testosterone value of 64.6ng/dL at Week 16. A total of 22 Vantas patients had a serum testosterone concentration at Week 52. The reasons for the decreased number of evaluable patients from Week 8 to Week 52 were six additional premature discontinuations (as above) and three additional patients without a serum testosterone value for the Week 52 visit. Of those patients who withdrew prematurely, all had castrate serum testosterone concentrations up to and including the visit prior to their withdrawal.

Reviewer's comment: The efficacy results from Study 302 support those from Study 301.

Finally, ***Study BAR-002-0591A-USA*** was a non-randomized, open-label, Phase 2, parallel-group design, dose-ranging trial in 42 patients, conducted at 3 sites (Rockefeller Institute, New York; Salzburg, Austria; and Jerusalem, Israel). Patients received 1 (n=14), 2 (n=20), or 4 (n=8) Vantas implants with an intended duration of treatment of 4 months. Serial blood measurements were made for testosterone, LH and histrelin. The study was designed for all implants to be removed at Month 4 and replaced at the discretion of the sponsor, but the study was later amended to allow investigators discretion to leave the implant in place for up to 12 months. In addition, investigators were allowed discretion to prescribe an antiandrogen during the initial period of the trial.

Reviewer's comment: The study is sufficient as a dose-finding trial but has limitations that preclude drawing confirmatory efficacy conclusions. For example: premature discontinuation of 15 of 41 patients, discretionary use of an antiandrogen, discretionary implant removal and replacement at Month 4 versus continued in situ treatment, and proscribed use of another LHRH agonist in some patients (n=7) at the Rockefeller Institute who received leuprolide "in the final stages of their participation and their efficacy data during those times was excluded from the efficacy analysis." Nevertheless, the study still is considered acceptable for purposes of dose justification.

A total of 15 patients prematurely discontinued from the study for the following reasons: death (n=8; 5 at the Austrian site), disease progression (n=3, all at the Israeli site), lost to follow-up (n=3; all at the Austrian site), and patient request with no specific reason given (n=1). One patient was excluded from the efficacy analysis because his serum testosterone concentration was castrate at baseline (≤ 2nmol/L). Of 41 evaluable patients, all had efficacy data at the end of Month 1. All Patients were castrate at Month 1 except three (**93%**). These were: 1 patient in the single implant group and 2 patients in the two-implant group. All three of these were castrate by Month 4. There was no difference between groups in attaining castration by Month 1. At Month 4, there was efficacy data for 39 patients – of these, **2 patients** were not castrate: 1 in one implant group and 1 in four-implant group. Again, there was no difference in response between groups at Month 4. The original implant was left in situ for one year in 22 patients (8 patients with one implant, 13 with two implants, none with 4 implants). In all these, serum testosterone remained below 2nmol/L for the entire treatment period.

> **Reviewer's comment**: After one year, the data is somewhat difficult to interpret, as some patients had removal and replacements and others had their implants left in situ. Still, there is no apparent difference between 1 and 2 implants in the small group with 1 continuous year of treatment, and there was no difference between groups at Month 4.

4.2. Clinical Safety

4.2.2. Extent of Exposure

In the Phase 3 study 301 and the supportive study 302, a total of 171 patient received Vantas. At the time of submission of the original NDA, 134 patients had been exposed to treatment for ≥1 year (actually for at least 60 weeks). In Study 301, 138 patients received one implant and 113 patients underwent removal of the first implant after 12 months and insertion of a new implant (the "Extension Phase" of Study 301). Some patients have received a third or a fourth implant on an every 12-month schedule, with the maximum exposure being up to 4 continuous years of exposure. Short-term safety information (4 months) is available from patients treated with 2 or 4 implants at the same time, and one year of safety information is available in a small number of patients treated with 2 implants at the same time.

> **Reviewer's comment**: This overall exposure is sufficient for a new formulation of a well-understood LHRH analogue for the palliative treatment of advanced prostate cancer.

4.2.3. Exposure with Implantation Trochar #3

Vantas is inserted into the subcutaneous tissue using an implantation tool and specific instructions. This is important because certain safety results (implant expulsion/extrusion) appear to vary by the specific device and specific methodology used for implant insertion. The to-be-marketing implantation tool is heretofore referred to as "trochar #3" and its use was initiated in April 2003. Exposure with trochar #3 comprises a total of 84 patients with 55, 57, 61 and 74 of these patients having 12months, 9months, 6months and 3months of exposure, respectively. No implant expulsions were reported in this group of patients. This result contrasts with results for previous inplantation tools (trochar #2 and manual insertion), wherein a total of 8 implants were expelled, 7 of these expulsions occurred in association with the use of trochar #2 , [ ] tuberculin syringe). Sponsor believes that these results indicate the importance of a well-designed insertion tool, a standardized insertion technique, and clearly illustrated instructions to ensure that the placement of the implant is adequate.

> **Reviewer's comment**: The exposure with trochar #3 is considered adequate and supportive of safety. We are in agreement with sponsor on this issue.

The major safety issues with Vantas are: the overall adverse events (many consistent with medical castration itself), local insertion site reactions, expulsions/extrusions of the implant, and difficulty palpating/locating the implant. In addition, it is appropriate to analyze the reasons for premature discontinuation. Each of these issues is discussed herein:

4.2.4. Deaths and Serious Adverse Events

In the original NDA, a total of 14 deaths were reported in Studies 301 and 302 combined. In the pivotal 301 and its extension, a total of 8 deaths were reported out of 138 patients. The reasons for death were as follows: MI (n=2), stroke and MI (n=1), progression of prostate cancer (n=1), progression of colon cancer (n=1), suicide (n=1), CHF/pneumonia (n=1), anoxic encephalopthy (n=1). Similar etiologies were listed for the 6 deaths reported in Study 302. No death was attributed to study drug.

In the original NDA, a total of 32 additional patients reported serious adverse events (not including deaths) in Studies 301 and 302. A total of 29 of these occurred in Study 301 and its extension, and 3 SAEs occurred in Study 302. Listings of these events revealed serious medical conditions and episodes common to old age and extensive co-morbidity (e.g. MI, CVA, lacunar infarct, atrial fibrillation, bronchitis, coronary artery disease, hip injury, colon cancer, throat cancer, pulmonary embolism, urinary retention, hematuria, and others). No serious adverse event was reported to be drug-related.

> **Reviewer's comment**: There were no drug-related deaths or serious adverse events

4.2.5. Premature discontinuations

A total of 18 patients discontinued prematurely from pivotal Study 301. Six patients died and twelve others discontinued before Week 52, for: disease progression (n=5), implant expulsion (n=3), hospice placement (n=2), and patient request/no reason given (n=2). None of these patients discontinued due to an adverse event.

At the Week 52 visit, 6 patients refused a second implant. No specific reasons were given for this refusal. In one of these six patients, the implant was not palpated and was not recovered. In a seventh patient, the patient was being admitted to a long-term care facility due to falls and a hip injury and the decision was made not to explant nor re-implant in this patient. Finally, in an eighth patient, a second implant was inserted, but this patient returned 15 days later to ask that it be removed – it was removed and he was terminated from the trial. He offered no reason for his request.

> **Reviewer's comment**: It is possible that in some patients who refused a second implant, the reason was unstated adverse events, such as hot flashes or fatigue.

In the Study 301 Extension Phase, as of an August 12, 2004 cut-off date, an additional 32 patients were reported as premature discontinuations. As per the Division's request, the sponsor provided narratives for these 32 patients on September 24, 2004. The clinical review team assessed each and every narrative.

The clinical review team broke these out as follows: rising PSA (n=7), site closure (n=6), death (n=5), moved away from site (n=3), objective disease progression (n=2), advancing age/co-morbidity (n=2), "hot flashes" (n=2), "concerned over PSA" (n=1), "too time-consuming" (n=1), physician concerned about loss of bone density (n=1), patient never returned/unreachable (n=1), and old lot used/implant removed (n=1).

Reviewer's comments:

1. The single site closure was due to retirement of a urologist and no replacement available.
2. The incidence of adverse events leading to discontinuation was very low.
3. The reasons for discontinuation were often due to age, general infirmity, co-morbidity, and prostate cancer progression.

4.2.6. Overall/systemic adverse events

The overall and systemic adverse events reported in the pivotal and supportive trial of Vantas were those typically reported in trials of LHRH analogues for the palliative treatment of advanced prostate cancer. Table 1 presents a list of "possibly" or "probably" related systemic adverse events occurring in at least 2% of patients treatment with Vantas in Studies 301 and 302 combined. Experience from the Study 301 Extension phase is also included.

Table 1: Incidence (%) of Possibly or Probably Related Systemic Adverse Events Reported by ≥ 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%)

* Denotes an expected pharmacological consequences of testosterone suppression.

** Five of the 8 patients with an adverse event reported as "renal impairment" had a single occurrence of mild renal impairment (defined as creatinine clearance ≥ 30 < 60 mL/min), which returned to a normal range by the next visit.

Hot flashes were the most commonly reported adverse event (reported by 65.5 % of all patients). In terms of severity, 2.3% of patients reported severe hot flashes, 25.4 % of patients reported moderate hot flashes, 37.7% reported mild hot flashes, and the remainder reported no hot flashes.

There were many systemic adverse events reported at incidences of <2%. None of these were particularly notable.

Reviewer's comment: The overall and systemic adverse events were consistent with those for other LHRH analogues for this indication.

4.2.7. Local insertion site reactions

Careful examination of the local insertion site was part of the procedures in the pivotal Study 301. 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 of these were associated with the initial insertion (or removal and insertion) of a new implant, and began and resolved within the first two weeks following implant insertion. Local site reactions

persisted in only 4 patients (2.8%). An additional 4 patients (2.8%) developed reactions at the insertion site *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 Study 301, 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 the initial insertion

> **Reviewer's comment:** Local insertion site reactions were not particularly concerning.

4.2.8. Expulsions/Extrusions

In the first 12 months after initial insertion of the implant, an implant extruded through the incision site in eight (8) of 171 patients in the pivotal and supportive study combined (see Section 4.2.3 above). Expulsion of the implant appears to be related to the technique of insertion, the implantation tool, and the post-procedure patient instructions.

There was one implant expulsion in *Study 302* – in this case, an "infection" was noted at the insertion site 69 days after implantation with Device #2 - the implant was spontaneously extruded on Day 109.

There were seven expulsions in *Study 301*. In two of these, the implant was noted to be "missing" only after recognition of a rising serum testosterone. These two patients (#03-005 and #37-012) have already been described in detail in the Clinical Efficacy section and are not repeated here

> **Reviewer's comment**: Since extrusion is possible without the patient's appreciation of the event, it is important that patients and physicians are made aware of this possibility. This has been made very clear in the both the PI and PPI. Routine standard-of-care patient care (with followup) should also help to lessen this risk.

In the other five patients from Study 301 who reported expulsions, all were implanted using device #2. In one patient, the implant was extruding on Day 15 and the patient "pushed it back" – a wound infection and expulsion soon ensued. In one case, the implant extruded on Day 208, possibly as a consequence of radiation therapy to the area and skin friability. In one case, the implant extruded on Day 37, seven days after the patient noted erythema at the site. In one case, the patient "picked off a scab" on Day 46 and the implant extruded. Finally, in one case, the implant was partially exposed on Day 70 following vigorous exercise.

> **Reviewer's comment**: The lack of expulsions with the new implantation device (plus the clarified insertion procedures and improved patient instructions) leads the reviewer to believe that the incidence of expulsions ought to be fairly low with the to-be-approved product.

4.2.9. Difficulty locating/palpating the implant

There were eight patients in Study 301 and its Extension Phase in whom the implant was never recovered. Two of these were previously described in both the Clinical Efficacy and Clinical

Safety/Expulsions sections (Patients #03-005 and #37-012). Both patients had rising serum testosterone concentrations that signaled expulsion of the implant.

Of the remaining 6 patients (three in Study 301 and three in the Extension Phase) all maintained castrate serum T concentrations but still the implant was not palpable and was never located. All except one – Patient 301E-06-008 – were implanted using device #2. In one patient (#301E-07-002), a 15-minute in-office exploration of the implant site was not successful. In one patient (#10-003), an ultrasound was reported as being "not definitive". In one patient (#06-009), the investigator stated that obesity and paraplegia limited palpation and ultrasonography wasn't done. In one patient (#301E-06-008), ultrasound and CT scan were ordered but were cancelled due to patient's travel limitations. Overall, of these 6 patients, 4 were simply re-implanted without finding the old implant. Of the other two patients, one refused a second implant, and the other terminated when the local investigative site closed and there was no other nearby site.

In Study 302, there were two additional non-located implants (total of eight + the 2 assumed expulsions). In one of these patients, the implant had been inserted manually into the abdominal wall. Neither palpation nor ultrasound was successful. A new implant was inserted in the arm without removing the old one from the abdomen. In the other patient, device #2 was used to place the implant in the left arm. The implant was neither palpated nor visualized with ultrasound. Another implant was inserted without removing the old one.

When the Division inquired as to the utility of ultrasound and/or CT in localizing a non-palpable implant, the sponsor responded with several items:

1. Sponsor was able to find one patient in whom a linear 7MHz ultrasound probe was able to locate a non-palpable implant (Patient 301-21-001). The site was marked and the implant was easily removed. The office equipment at the primary urologist's office was not adequate in detecting this implant but the radiologist's equipment was clearly successful.
2. Ultrasonography was conducted at one site in a radiology suite in 6 patients in whom the implant *WAS* palpable. These images all showed the implant in the subcutaneous tissues with clarity. The implant looked like a "straw" consisting of two very straight, 3cm, parallel lines.
3. CT scan without contrast was conducted at one site in a radiology suite in 6 patients in whom the implant *WAS* palpable. The skin site was marked prior to CT. Again, the CT scan showed the implant in the subcutaneous tissues with clarity. However, the density of the implant was similar to subcutaneous vessels and muscle. No contrast was given. No other modality was tested (e.g. MRI).

Reviewer's comments:

1. The issue of potential difficulty in locating an implant was described in detail in the PI and PPI. Physicians and patients will be aware about this possibility.
2. If the implant is in the subcutaneous tissues, ultrasound and/or CT should be able to detect it.
3. If the implant is in the muscular tissue, neither ultrasound nor non-contrast CT has been shown to have utility in detecting it. Contrast CT and MRI were not studied.
4. Because almost all the data on the clinical utility of imaging for the implant comes from patients in whom the implant *WAS* palpable, the sponsor has committed to conduct a post-marketing study in 10 patients in whom the implant is *NON*-palpable. An "algorithm" will be used in an attempt to detect and mark the site of the implant. (e.g. ultrasound first, then CT, then MRI). This surveillance study should provide the Agency with some useful information as to the utility of imaging techniques in the detection of Vantas implants that are *non*-palpable.

5. Finally, our Pharm/Tox reviewers believe that leaving the implant in situ for an indefinite period of time poses little or no risk to patients who are being treated for advanced prostate cancer in terms of direct tissue toxicity or mutagenecity. Vantas is contraindicated in children and in women.
6. Overall, the clinical review team does not believe that this issue should preclude approval. At this time, we believe that the issue has been sufficiently resolved to allow approval with clear labeling and a Phase 4 commitment for further study of the issue.

5. Clinically Relevant Issues From Other Disciplines

5.1. Chemistry, Manufacturing and Controls (CMC)

In her final memo dated October 8, 2004, Dr. Tran stated:

> "From the Chemistry perspective, NDA 21-732 is recommended for approval."

The memo indicates that all chemistry issues have been resolved including: a recommendation of "acceptable" from Office of Compliance, acceptable final insert and package labeling, acceptable packaging, and an acceptable trademark logo.

In her final review dated September 23, 2004, Dr. Tran had indicated that most CMC review issues had been resolved as of that date, including: sterility assurance (by Microbiology), the implantation tool (by CDRH), the safety of specified impurities and residual raw materials (by Pharmacology/Toxicology), and the elution rate (by Clinical Pharmacology). Other more specific Chemistry review issues that were also resolved by sponsor's NDA amendments included: impurity and drug release criteria, information on solvents and reagents, information on development of the hydrogel including optimizing hydration and storage, and other issues.

5.2. Pharmacology/Toxicology

In his final review dated September 13, 2004, Dr. Raheja stated:

> "Pharmacology recommends approval for NDA 21-732 for the treatment of advnaced prostate cancer."

Dr. Raheja's review indicates that he based his approval on new studies submitted by Valera and on reference to the previous NDA approved for histrelin subcutaneous injection for the treatment of central precocious puberty. Specific findings of note in Dr. Raheja's include:

1. Qne of the excipients in the formulation (in the reservoir itself) is a new entity – trimethylolpropanetrimethylacrylate or *TMPTMA*. The sponsor conducted a battery of genotoxicity and toxicity studies for this compound and Pharm/Tox found these to be sufficient and acceptable in support of safety, for example:
   a. Extracts of the reservoir were not genotoxic.
   b. Extracts of the reservoir were associated with no significant adverse effects in toxicology studies.
2. There are – impurities from the synthesis of histrelin. [ ] of these are easily detectable using the drug substance assay. The [ ] has not been detected at levels above [ ]
3. Studies from the previously approved NDA (19-836) were not reviewed by Dr. Raheja, only those done specifically for the present formulation.

4. Studies in dogs showed that "pre-hydration" of reservoirs was critical to effect a rapid release of histrelin upon subcutaneous insertion into animals.
5. Studies in dogs revealed full recovery of testicular function at 90 days after termination of the treatment.
6. In various studies, extracts of the reservoir were found to be non-pyrogenic, non-hemolytic, non-irritating, and had only a weak potential as an allergan.

5.3. Clinical Pharmacology and Biopharmaceutics

In her final review dated October 7, 2004, Dr. Apparaju stated:

> "The submitted data is acceptable from a Clinical Pharmacology and Biopharmaceutics perspective."

Specific issues of note from Dr. Apparaju's review include:

1. The sponsor has adequately characterized the pharmacokinetics of histrelin as released from the Vantas implant. Intensive pK sampling in 17 patients in the Phase 3 trial reveals that histrelin is released promptly upon subcutaneous implantation (e.g. 5 minutes) and is released from the reservoir for 52 weeks in a slow and controlled manner. Histrelin concentrations following a first implant and a second implant (52 weeks later) are comparable.
2. The impact of renal insufficiency on pK has been adequately characterized. Renal impairment patients had slightly higher Cmax and AUC which was not believed to be clinically relevant
3. Race and age appeared to have no significant impact on histrelin pharmacokinetics.
4. The final dissolution testing method and agreed-upon specifications (August 19, 2004) are acceptable; however, the proposed in-vitro/in-vivo correlation was not acceptable. This was conveyed to sponsor in a regulatory letter.
5. Histrelin concentrations (Cavg and AUC) increased in proportion to dose (1 versus 2 versus 4 implants). However, one Vantas implant was as effective as 2 or 4 implants in suppressing serum T.
6. The Cmax for histrelin occurred approximately 12 hours after implant insertion and this preceded an acute rise in serum LH and the Tmax for serum testosterone (at approximately 48 hours).
7. Histrelin is a nonapeptide derived from the basic structure of LHRH by [redacted]

[redacted]

8. Vantas is a 3cm by 3.5mm cylindrical shaped implant. The core of the reservoir contains 4 hard pellets of histrelin. At the end of 4 weeks of hydration storage, the pellets become a "aqueous slurry" and the walls of the reservoir are fully saturated with drug solution.
9. Of the 50mg of histrelin in the implant, 20mg is released during the 12-month treatment period, at a rate of approximately 50-60 micrograms per day.
10. The clinical and to-be-marketed formulations were identical.
11. Serum histrelin, testosterone and LH were quantified using validated analytical techniques.

5.4. Microbiology

In his final memo dated September 21, 2004, Dr. McVey reiterates the Microbiology final approval recommendation for this NDA and states that now there are **no** formal Phase 4 commitments being requested by Microbiology. (*Therefore, the previous Phase 4 Micro commitments discussed in his September 14 review were formally withdrawn*).

In his final review dated September 14, 2004, Dr. McVey stated:

> "The application is recommended for approval from a product quality microbiology perspective. *Phase 4 commitments are provided.*"

The Phase 4 commitment recommended at that time was: ' [ ]' In the September 21 memo, Dr. McVey indicated that these data were requested as a Phase 4 commitment to "confirm that the process is in a state of control". However, he explains in this same memo that: "If the process is under control (which is likely), no additional action is needed. If it is not under control, a supplement should be submitted by the applicant. No follow-up by the microbiology reviewer will be needed." Therefore his memo concludes that no formal Phase 4 commitment is necessary.

> **Reviewer's comment**: Microbiology no longer recommends a Phase 4 commitment for microbiology and is approving this NDA without reservation. Therefore, no Phase 4 Micro commitment is necessary in the action letter.

Other issues of note in the Micro review are:

1. The implant is sterilized by [ ] A contract sterilizer [ ] will be doing the sterility test and will use a validated test method.
2. Dr. McVey notes that final sterilization of the implant is important, as multiple steps of manual assembly make it possible to incorporate microorganisms inside the implant. He states that: "Once placed into 5mL vials [ ]
3. Sterilization of the simple trochar device is deferred to the review of CDRH.
4. The remainder of the review discusses the sponsor's responses to the August 19, 2004 deficiency letter. According to Dr. McVey, all issues were successfully resolved by sponsor. The response to each issue was deemed "acceptable". Three issues of note in this review are:
   a. Sponsor will be doing a [ ] bioburden test on every lot.
   b. Time between assembly and sterilization will be [ ]
   c. As stated above, [ ] will be doing the sterility test. The sterility testing protocol and the test validation are acceptable.
   d. A limit on total endotoxin for the reservoir and for the drug substance was set (This is particularly important in the event of severing the reservoir while inserting or removing it). Validation of the endotoxin limit testing protocol will occur prior to marketing, and this was acceptable to our Microbiology and Chemistry review teams.

5.5. Center for Devices and Radiological Health (CDRH)

In her final review, dated "August 19, 2004" and entered into DFS on September 17, 2004 by Ms. Nita Crisostomo, Viola Hibbard of CDRH states:

> "The information from Valera Pharmaceuticals was forwarded from CDER to CDRH (August 23, 2004) to answer the request for additional information and clarification of the July 22, 2004 correspondence. The sponsor has adequately addressed the question."

In the August 19th memo, Ms. Hibbard explains this particular issue, as follows:

1. The trochar implantation device will be [ ] sterilized and this is acceptable to her.

2. Pyrogen testing of the device will, in fact, be done. The method for this testing will be provided. This was also acceptable to Ms. Hibbard.

In her June 29th review, Ms. Hibbard provides details on the to-be-marketed implantation tool, as well as on the sponsor's answers to her 5 major review issues, as follows:

1. A *description of the finished device* was requested and was submitted. Response was adequate.
2. *Biocompatibility information* for the parts of the device that contact blood or tissue was requested and was submitted. Response was acceptable.
3. Information regarding method of *sterilization and pyrogen testing* of the device was requested. This information was eventually submitted and responses were acceptable (as described in the August 19th memo).
4. *Labeling* for the final finished device should be provided. Our chemists concurred to all labeling, including package labeling for the implantation kit.
5. Additional information in regard to *device functionality* was requested (information from both the bench and from the clinic) and was submitted. The response to bench testing was acceptable to CDRH. However, Ms. Hibbard raised some concerns in regard to the "clinical experience" for functionality. She stated that the device was used in clinical trials in a total of 66 patients, and of these, 4 devices "had functionality problems", as follows:

    a. One comment was: "Trocar not great"
    b. One comment was: "Implant became lodged in the trocar and broke."
    c. One comment was: "Difficulty in loading the implant and plastic coating was sheared off."
    d. One comment was: "Implant would not release from trochar because implant had sheared on edge".

    Reviewer's comments:

    1. The total number of patients who have received an implant using trochar #3 was actually 84 patients (not 66 patients). A total of 55 of these have reached 12 months treatment duration. There have been no expulsions in this group and only 1 case of difficulty palpating the implant. Thus, evidence from clinical trials indicates that trochar#3 actually improves two important safety concerns (expulsions and difficulty locating) compared to the previous implantation methods.
    2. Still, this reviewer acknowledges the concerns raised by the latter three comments. These cases appear to share some features: First, coating was either sheared off the implant or the implant was damaged. Second, the implant was difficult to load or would not release as a consequence of damage to it. The sponsor believes that the reason for this problem is due to poor inplantation technique: either the implant was mishandled upon loading (for example, the body of the implant was grasped with a mosquito clamp or the implant was inadvertently sliced by the implantation tool bevel) or the cannula/needle was prematurely slid forward while in the process of dropping the implant into the subcutaneous space. The sponsor has inserted highlighted text and photographs into the appropriate section of the label showing how to avoid mishandling the implant while loading it and also advising NOT to slide the green retraction button forward while releasing the implant (which may slice the implant). I believe these statements and photos in the labeling are appropriate and acceptable. In my opinion, these few cases do not reflect a fundamental flaw in the trocar or in the implant. I agree with sponsor that it is a matter of less than strict attention to surgical detail during the insertion procedure. The sponsor has stated

their intent to educate prescribers in regard to the insertion technique (including post-marketing use of educational videotapes) and I believe such education efforts are likely to further reduce the incidence of damage to the implant during insertion.

5.6. Division of Drug Marketing, Advertising and Communications (DDMAC)

On July 7, 2004, Corinne Kulick of DDMAC provided comments on the proposed physician package insert. Her review was taken into consideration during labeling negotiations. Each comment and recommendation was carefully considered by both the clinical review team and by the appropriate discipline reviewer, and many recommendations were enacted.

5.7 Division of Surveillance, Research and Communication Support (DSRCS)

On June 8, 2004, Jeanine Best of DSRCS provided comments on the proposed patient package insert. Her review was taken into consideration during labeling negotiations. All DSRCS recommendations were enacted by the Division and all were accepted by the sponsor.

5.8. Division of Medication Errors and Technical Support (DMETS)

Two consults were completed by the DMETS, as led by Denise Toyer and Carol Holquist. In the first consult, dated July 7, 2004, DMETS stated:

> "DMETS does not recommend the use of the proprietary name, Vantas."

In conducting their review, DMETS did the following: they conducted an extensive search and review of available databases for potential look-alike and sound-alike tradenames (with follow-up panel discussion) and they did three separate "prescription analysis studies" involving health care professionals within FDA. In these three studies, a total of 124 health care professionals were involved in an attempt to "simulate the prescription ordering process". An inpatient order and an outpatient prescription were written, and these were optically scanned and delivered to a random sample of these participants. Also, an outpatient verbal order was recorded on voicemail and again delivered to a random sample of participants.

The search for sound-alikes and look-alikes revealed two major concerns to DMETS:

1. Vantas can sound and look similar to *Lantus* when pronounced or scripted. Lantus is a long-acting insulin product and indicated for the treatment of diabetes. The two drugs must be refrigerated, are delivered by subcutaneous route, and share overlapping numerals for dose (50mg and 50 units). DMETS felt with these similarities, there was an "increased potential for medication errors due to name confusion" between the two products.
2. Vantas can look similar to *Zantac* when scripted. Zantac is a histamine antagonist indicated for ulcers, esophagitis, and GERD. The two share the same dosage strength (50mg). DMETS also felt that there was also "an increased potential for medication errors due to name confusion" between this product and Vantas.

The prescription studies revealed that all outpatient written prescriptions were accurate and virtually all inpatient written scripts were accurate ("Vanta" in one case, and "Vamtas" in another). For the verbal prescription, two persons interpreted the script as "Vantin", a currently marketed, parenteral cephalosporin antibiotic.

After being informed of the DMETS review, sponsor submitted two more potential tradenames: [ ]. In their second consult, dated September 22, 2004, DMETS stated the following:

> "DMETS does not recommend the use of the proprietary name, [ ]. However DMETS has no objections to the name, [ ]."

In providing a reason for not recommending [ ], DMETS gave the opinion that [ ] may look similar to [ ] when scripted. [ ] is indicated for hypertension and heart failure. DMETS felt that 50mg could look similar to 80mg, an approved dose for [ ]. In addition, DMETS was concerned that the similarity in the first three letters [ ] could result in a "computer screen entry" error, leading to a potential in-hospital medication error.

Reviewer's comments:

1. Sponsor could not accept the tradename [ ] since they ultimately identified that it had already been patented.
2. The Division considered all the DMETS recommendations very carefully and held internal meetings to discuss the best possible pathway for the resolution of this tradename issue. Ultimately, we believe that the tradename Vantas is acceptable, and not likely to be associated with medication errors. We believe that there are special circumstances that surround the use of the histrelin implant that will reduce the potential for medication errrors. First (and most importantly), Vantas is a surgically placed, one-time, non-biodegradable, 12-month subcutaneous implant. Usually, the procedure will be done in a urologist's, surgeon's or oncologist's office. Each "kit" will be used for a single patient. There is likely to be close scrutiny of the patient and the kit for this surgical procedure.
3. Further, the Division notes that in the 3 controlled presecription recognition trials, not a single respondent would have dispensed Lantus, the look-alike, sound-alike product that was of most concern to DMETS.

Finally, in their original consult, DMETS made several recommendations for the container and carton labeling and these were all carefully considered and enacted by our Chemistry review team and sponsor as deemed appropriate.

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/s/

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NDA 21-732

Date submitted: December 12, 2003
Date received: December 12, 2003
MOR draft completed: September 28, 2004
MOR final completed: October 8, 2004

Medical Officer's Review of Original NDA

Sponsor:	Valera Pharmaceuticals Cranbury, NJ 08512
Drug product:	Generic: histrelin acetate 50 mg Trade: Vantas™ 50 mg
Route of administration:	Subdermal
Dosage form:	Implant
Strength:	50 mg per implant
Dosing Regimen:	One implant every 12 months
Proposed indication:	Palliative treatment of advanced prostate cancer
Related NDAs:	For the indication: "palliative treatment of advanced prostate cancer" NDA 20-517/S-005 (TAP Pharmaceuticals "Lupron Depot") NDA 21-343 (Atrix Labs. "Eligard") NDA 21-088 (Alza Corp. "Viadur")

Harry Handelsman, DO
Medical Officer

Mark Hirsch, MD
Clinical Team Leader

Executive Summary:

I. Recommendations

In the opinion of this reviewer, from a clinical perspective, the safety and efficacy of histrelin implant 50 mg has been established by data from the pivotal multicenter study #301 and its extension study, as well as by supporting data from 2 additional trials. This product should be approved for the indication "palliative treatment of advanced prostate cancer". A specific phase IV commitment is recommended: to conduct sonogram and CT examinations for 10 patients in whom implants cannot be found by palpation. Early safety concerns surrounding the issue of implant expulsions have been satisfactorily resolved by the introduction and testing of trochar # 3, which will be the "to be marketed" implant device.

II. Summary of Clinical Findings

II.A. Brief overview of the clinical program.

Orchiectomy or the administration of estrogens had, in the recent past, been the primary mode of treatment for advanced prostate cancer. More recently, LH-RH agonists are offered as an alternative to these primary treatments when they are either not indicated or unacceptable to the patient.

Histrelin acetate, as a synthetic analog of the naturally occurring gonadotropic releasing hormone LH-RH, is being proposed as a 50 mg subcutaneous implant administered every 12 months.

In support of NDA 21,732, the sponsor submitted a single, pivotal, open-label clinical study of histrelin 50 mg in 138 patients with prostate cancer, and a pharmacokinetic study in subset of 17 patients. In addition, supportive data were derived from an extension of the pivotal trial and from 2 additional studies.

***Reviewer's comment**: This reviewer believes that in view of the fact that extensive data on both safety and efficacy are available for essentially the same product (Supprelin), marketed since 1991, but not using this unique delivery system, for the treatment of central precocious puberty, and other data from a similar class of marketed products (e.g. Lupron and Eligard), submitted data from only one clinical trial are regarded as being sufficient for this NDA.*

II. B Efficacy

The primary efficacy endpoint for this clinical trial was the reduction from baseline levels of testosterone, ≥ 150 ng/dL to castrate levels (≤50 ng/dL) by Study Week 4 and maintenance of the reduced levels for the 52 week course of treatment.

***Reviewer's comment**: This reviewer believes that the results of this clinical trial, (# 301) demonstrated that doses of histrelin 50 mg subdermal implant administered at 52-week intervals to patients with advanced prostate cancer, could reliably achieve the primary*

efficacy endpoint; that is, attaining and maintaining castrate levels of total serum testosterone (T).

II. C Safety

The majority of data regarding clinical adverse events (AE's) were derived from the single, open-label trial in 138 patients who were exposed to 1or more doses of histrelin. There were no reported deaths associated with the administration of this product. The most common AE was hot flashes/sweats, seen in 65% of the patients. Fatigue was reported in 10% of patients and injection site reactions in 6%. Other treatment related AE's reported in ≤5% of patients included testicular pain or atrophy, constipation, gynecomastia, weight increase, headache, insomnia, decreased libido, and erectile dysfunction.

***Reviewer's Comment**: The AE profile consisted mainly of mild to moderate events normally seen with this class of drugs. There were no overriding safety issues that would preclude approval of this NDA.*

II.D Dosing, Regimen, and Administration Issues

The dosage strength used in this clinical trial was 50 mg of the histrelin product administered as a single subcutaneous implant every 12 months. A phase-2 study revealed no additional benefit of 2 or 4 implants over a single implant. The sponsor believes that the 50 mg dose had the best balance between efficacy and safety in achieving the desired testosterone suppression.

II. E Use in Special Populations

Gender:Histrelin 50 mg is indicated in the palliative treatment of advanced prostate cancer and should not be used in women. No studies in females were conducted.
Pediatric: Safety and effectiveness of histrelin have not been established in pediatric patients. A full waiver for pediatric labeling was requested by the sponsor, and such a waiver is considered appropriate.
Elderly: The inclusion criteria for the study population in the treatment protocol included patients age 45 and older (89.9% were ≥ age 65).
Race/Ethnicity: There is no evidence of the effect of race/ethnicity on the pharmacokinetics of this product as tested in 7 Hispanic, 30 Black and 77 Caucasian subjects.
Renal/Hepatic Insufficiency: No changes in drug dosing are warranted in these patient subpopulations.

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Clinical Review

1. Introduction and Background

1.1. Proposed trade name of drug, class, proposed indication, dose and regimen.

Histrelin is a synthetic analog of the naturally occurring gonadotropic releasing hormone LH-RH, being proposed as palliative treatment for advanced prostate cancer. It is classified as a GnRH agonist and administered once every 12 months as a subcutaneous implant. The tradename for the drug product is Vantas™.

1.2. State of armamentarium for indication.

Orchiectomy or the administration of estrogens had been the primary mode of treatment for advanced prostate cancer, and GnRH agonists, with varying durations of action, are offered as an alternative to these primary treatments when they are either not indicated or unacceptable to the patient. A GnRH antagonist is available for selected patients with advanced symptomatic prostate cancer where orchiectomy is refused and other treatments are not appropriate.

1.3. Milestones in product development.

IND 40,772 was originally filed on October 9, 1992. Subsequent to the initial submission, the IND has undergone several sponsorship changes. An "end of phase-2 meeting" was held on July 14, 1999; a type C teleconference was held on December 19, 2001; and a Pre-NDA meeting was held on August 12, 2003. The original NDA 21,732 was submitted on December 12, 2003.

1.4. Foreign marketing history.

Vantas 50 mg has not been marketed outside of the United States.

1.5. Important issues with pharmacologically related agents.

A transient rise in serum T (testosterone) levels during the first week of treatment may cause a worsening of symptoms or the occurrence of additional signs and symptoms of prostate cancer. Additional adverse events reported in at least 5% of patients include hot flashes, fatigue, vasodilation, nausea, weight gain, myalgia, decreased libido, urinary frequency, erectile dysfunction, asthenia, and pain on injection. Vantas, in contrast to other agonists in its class, appears to exhibit an earlier, and perhaps a more transient surge in serum T.

2. Significant findings from Chemistry, Pharmacology, Toxicology, and Statistics.

There are no outstanding issues related to chemistry, pharmacology, toxicology, or statistics.

3. Human Pharmacokinetics and Pharmacodynamics

A subset of 17 subjects in 3 categories were included for both pharmacokinetic (PK) and pharmacodynamic studies of histrelin 50 mg implanted on day 0 of cycle 1. Five subjects had normal renal/hepatic function, 10 had renal impairment, and 2 had hepatic impairment. In cycle 1, histrelin C_{max} was 0.294, 0.337 and 0.323 ng/mL respectively; $T_{max(hr)}$ was 12 (12-24), 12 (6-6078), and 677.75 (12-1344) respectively; and the histrelin $AUC_{(ng\text{-}hr/mL)}$ was 12.8 (4.35), 15.2 (2.71), and 10.0 (2.20) respectively.

As requested by the Division, the sponsor conducted an additional PK study (completed September, 2003) in 6 healthy male volunteers. A dose of 500 µg of histrelin was administered as a SC bolus and serum was collected pre-dose and at 5, 10, 15, 20, 30, 45, min and at 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, and 36 hr post-dose. The mean histrelin C_{max} (± SD) was 13.50 ± 3.00 ng/mL. T_{max} was 1.00 hr with a range of 0.75-2.03 hr. Histrelin $AUC_{0\text{-}t}$ (± SD) was 50.85 ± 12.63 ng.hr/mL. The distribution of histrelin was found to be similar to other GnRH agonists, with a mean half life of 4 hr.

Drug-drug interaction studies have not been conducted.

Pharmacodynamics:

As a LH-RH agonist, histrelin acts ultimately as a potent inhibitor of gonadotropin secretion. Following an initial increase of luteinizing hormone (LH) and follicle stimulating hormone (FSH), and an associated transient increase of serum T from baseline, continuous administration of drug resulted in castrate levels of testosterone (< 50 ng/dL), in all 17 evaluable PK subjects, from day 28 through the end of the 52-week study.

4. Description of Clinical Data and Sources.

The following materials from the NDA were reviewed: 1) Description and analysis of the pivotal single Phase-3 clinical study in the treatment of prostate cancer. 2) Integrated summary of safety. 3) Integrated summary of efficacy. 4) Documentation of statistical methods. 5) Adverse events data. 6) Additional data from supportive study #302, extension study #301, and study BAR-002-0591A USA.

5. Clinical Review Methods.

The single Phase-3 clinical trial #301, its interim extension study, and the supportive study #302 were reviewed in detail. Reviews of the Integrated Summaries of Safety and Efficacy were conducted. In addition, a dose-ranging study (BAR-002-0591A USA) was reviewed.

Documentation related to financial disclosure was reviewed and was acceptable. According to the DSI, there was no apparent reason to conduct site inspections and none were conducted.

6. Integrated Review of Efficacy.

6.1 Introduction

Evidence of efficacy comes from identical protocols in a pivotal study data set involving 138 subjects at 27 sites in the US and Canada, 2 supportive studies involving 33 subjects and 42 subjects each, at multiple study sites, and an extension of the pivotal study involving a total of 104 subjects.

6.2 General Approach

The focus of the efficacy review is the pivotal phase-3 trial, #301, which began enrollment in April, 2000 and completed the last subject in August, 2003.

6.3 Brief Review of Clinical Trial #301

Study Design:

This was a phase-3, multicenter, randomized, open-label, safety and efficacy study of histrelin acetate, 50 mg implant, surgically placed into the subcutaneous tissues of the inner aspect of the upper arm of 138 subjects with advanced prostate cancer.

Objectives. The objective of the trial and the primary efficacy endpoint was achieving a reduction of baseline testosterone levels to castrate levels (≤50 ng/mL) by week 4 and maintaining those levels through week 52. Safety was evaluated by clinical laboratory tests, physical examinations, ECGs, and reported adverse events.

Inclusion Criteria:

The subjects enrolled (ages 45 or older) in this open-label, multi-center study had either histologically confirmed stage III or IV prostate cancer or were an apparent failure of initial definitive therapy indicated by an elevated or rising PSA. The study entry criterion for serum testosterone was a screening serum total testosterone ≥150 ng/dL. Normal laboratory values were required, and informed consent was obtained.

Subjects were otherwise expected to be in good health, with a WHO Performance Scale of 0-3, have a clinical indication for androgen suppressive therapy, and have a minimum life expectancy of 1 year.

Reviewer's Comment: *It is worth noting that despite an adequate performance status, a substantial number of trial subjects were over age 75, with some approaching age 90, which appeared to contribute (in part) to the total of 18 premature discontinuations in study 301.*

Exclusion Criteria:

- Bilateral orchiectomy.
- Prior androgen-ablative or systemic corticosteroid therapy within 1 year of trial.
- Second malignancy within 5 years, except superficial bladder or non-melanomatous skin cancer.
- Spinal cord compression.
- Vertebral metastases that would be a risk for treatment related cord compression
- Brain metastasis confirmed by CT scan.
- Hypersensitivity to study medication.
- AST or ALT >3 x ULN.
- Illnesses that might interfere with return visits.
- Subject not suitable for study, or a participant in another study within 30 days of screening.

The protocol included pre-treatment laboratory samples for CBC, chemistry, urinalysis, and serum T. At selected study sites for PK/PD in a total of 17 subjects, serum T, LH and histrelin were obtained prior to and after implant insertion at 5, 15, 30, and 45 minutes, and 1, 2, 4, 6, 8, 12, 24, 48, and 96 hours post-insertion and at subsequent visits to determine PK parameters.

Implant insertion occurred on Day 1, and subjects were evaluated at Weeks 1 and 2 and then monthly from Weeks 4-60 to evaluate T, PSA, AE's, disease progression, and urine and serum histrelin in a renal/hepatic impairment subgroup. Subjects were offered a second implant at Week 52, and an Acute-on-Chronic subgroup of 68 subjects had blood samples taken prior to and 48 and 72 hours post-implant and at Weeks 53, 56, and 60 to determine the dynamics of suppression.

Safety for all subjects was evaluated by physical examinations, clinical laboratory tests, ECG's, and monitoring for AE's throughout the study.

Efficacy Results

The intent-to-treat (ITT) population included 111 subjects, 75% white, 21% black, and 4% Hispanic. 88% were over age 65, and 53% had PSA ≥ 5ng/mL. Thirty-nine subjects had 1 or more missing T values. Three subjects experienced implant expulsions.

At Week 4, 100% of subjects attained chemical castration which, according to sponsor, was maintained in not less than 99% (CI 96.5%-100%) of subjects. At week 52, 100% of evaluable subjects had chemical castration. The lowest binomial confidence interval observed over the 13 visits was 95.4%.

There were 4 subjects with reported T levels above castration: Two subjects had undergone an unnoticed expulsion. One subject had consistent castrate T levels except one reading of 3340 ng/dL, regarded as a laboratory error. One subject had a breakthrough reading of 63.1 ng/dL.

The completer population (n=72), defined as those subjects without any missing T value samplings, included 3 subjects who had an expulsion, were given a second implant, and completed the study.

LH values, as another surrogate marker of efficacy, were significantly reduced from baseline mean of 8.5 mlU/mL to values of 1.0, 1.0, and 1.1 at 24, 48 and 60 weeks respectively.

The Acute-On-Chronic (AOC) population was the 68 subjects who reached 52 weeks and received a second implant in order to determine if there was an acute rise in T measured at 48-72 hours and at 7 days. There was no short term increase in either T or LH levels, and their suppression was maintained.

PSA level was another efficacy indicator, and less than 10% of the ITT population had PSA levels ≥ 5 ng/dL after 16 weeks post-implant. PSA response status is shown in Table 1.

Table 1. Summary of PSA Response Status, Efficacy Evaluable Subjects N=111

	Week 24	Week 60
PSA Complete Response	103 (92.8%)	87 (78.4%)
PSA Stable	6 (5.4%)	11 (9.9%)
PSA Progression	2 (1.8%)	12 (10.8%)

For the evaluation of these implants for continued efficacy and safety, 21 subjects were enrolled in an extension phase of study #301. At the time of the data cut-off in June 2003, 18 subjects completed their 2nd year of treatment, and 4 subjects completed their 3rd year of treatment and received a 4th implant. Castrate levels of T were maintained in all subjects, and the safety profile was similar to that seen in the first year of treatment.

As of the data cut on August 12, 2004, 65 subjects were implanted using trochar # 3 (after its introduction on April 2, 2003). Nine subjects discontinued prior to 52 weeks, 47 subjects were reimplanted using trochar # 3, and 17 discontinued through the following 52 weeks. In this group, there were no expulsions. There were 39 subjects implanted with alternate methods, and 10 of these subjects discontinued prior to 52 weeks, and 15 discontinued of these discontinued through the following 52 weeks.

As of September17, 2004, the total number of subjects inserted with trochar #3 was 84, and of these, 55 patients had ≥12 months exposure.

Brief Review of Supportive Study #302

The 33 subjects who received the 50 mg histrelin implant had essentially the same baseline characteristics as in study #301 In this randomized study, the efficacy of this implant was compared with the efficacy of Zoladex depot formulation (10.8 mg) administered every 3 months subcutaneouly in 25 subjects. Both agents were shown to be equally efficacious in achieving castrate T levels at 4 weeks and maintaining such levels through week 52. There was no consistent association or pattern of AE's related to either drug. Only 1subject had an implant expulsion, although 2 additional subjects experienced implant displacement so that it could not be located.

Brief Review of Study BAR-002- 0591A USA

Study Design

This was an open-label, parallel-group, dose-ranging multicenter study in subjects with advanced prostate cancer, who were candidates for hormonal therapy. Forty-two subjects received 1, 2, or 4 subdermal implants, each containing 50 mg histrelin. Fourteen subjects received 1 implant, 20 received 2 implants, and 8 subjects received 4 implants. The implants remained in place for 4-12 months or longer. Serial blood samples were analysed for T, LH, FSH, PSA and histrelin. AE's and selected laboratory values were noted.

Objectives

The primary objective was to evaluate the long-term safety and efficacy of these implants. The secondary objectives were to identify the dose required to adequately suppress T levels and to measure histrelin levels when castrate levels of T were achieved.

Inclusion Criteria

Subjects aged 50 or older with documented advanced prostate cancer, otherwise in good health, were eligible for study.

Exclusion Criteria

Subjects were to be excluded if they had any prior hormonal suppressive therapy.

Efficacy Results

According to sponsor, all 42 subjects achieved castrate levels of T at 1 month and maintained such levels for as long as the implant remained in situ. Overall, 95 % of subjects maintained the implants for 1 year, 76 % for 2 years, and 64 % for 3 years.

Safety Results

The safety profile in this study for the implants inserted for up to 50 months in some subjects appeared unremarkably typical for this class of agents. The majority of AE's were judged to be mild or moderate in severity. The most commonly reported AE's were hot flashes (48 %), asthenia (26 %), pain (19 %), and dizziness (17 %).

Brief Review of Study 301 (Interim Extension).

Study Design

Subjects initially enrolled in study 301 who had completed 1 year and demonstrated both a clinical and PSA response, and had received a 2nd implant were eligible to enroll in this extension study for continued assessment of safety and efficacy for an additional 21-30 months with the old implant removed and a new implant inserted every 12 months.

Efficacy Results

All 104 subjects who achieved castrate levels of T with their initial implant and who proceeded into the extension phase of the trial, continued to maintain castrate levels of serum T. A review of the explanations for the 32 discontinued subjects, requested by the Division and provided by the sponsor on September 17, 2004, concluded that these discontinuations were satisfactorily explained by such issues as progression of disease, death, moves away from study site, and unwillingness to continue due to AE's (hot flashes).

6.4 Efficacy Conclusions

The results of these trials confirm that Vantas, a hydrogel reservoir implant containing histrelin 50 mg, is effective in achieving suppression of T to castrate levels by 4 weeks and

maintaining such levels over 52 weeks during each implant. PSA and LH levels showed the same pattern of response.

Reviewer's Comment: *As expected from prior data using this drug, and other agents of this class, the primary efficacy endpoint was reliably achieved in all subjects in whom the implant was not expelled.*

7. Integrated Review of Safety

7.1 Brief Statement of Findings

Safety variables assessed were clinical and reported AE's, with particular attention to the implant insertion site, vital signs measurements, clinical laboratory results, physical examination results, and ECG's collected at per-protocol defined times throughout the study.

Because a novel formulation was employed in this study, insertion site reactions, and expulsion were the major safety concerns. Nineteen subjects had site reactions. 12/19 were reported from 3 study sites. Reaction site descriptions are listed individually in Table 2.

Table 2. Insertion Site Reactions

Insertion Technique	Day of Reaction (post insertion)	Reaction Description
Device 2	15	Implant expulsion, mild infection
Manual	2	Mild tenderness, bruising
Device 2	--	None with 2nd implant
Device 2	4	Mild erythema
Device 2	--	None with 2nd implant
Device 2	1	Mild bruising
Device 2	55	Moderate soreness
Device 2	2	Moderate bruising
Device 2	1	Moderate bruising
Device 2	2	Mild bruising
Device 3	1	Mild bruising
Device 2	--	No problem
Device 3	1	Mild bruising
Device 2	--	No problem
Device 3	7	Mild bruising
Device 2	1	Moderate swelling
Device 2	--	No problem
Device 3	1	Mild pain
Other device	--	No problem

Device 3	2	Mild bruising
Other device	--	No problem
Device 3	2	Mild bruising
Device 2	2	Mild erythema
Device 3	--	No problem with 2nd implant
Device 2	303	Mild pain
Manual	--	No problem with 2nd implant
Device 2	67	Mild erythema, expulsion
Manual	--	No problem with 2nd implant
Manual	--	No problem with 3rd implant
Manual	69	Mild erythema, scabbing
Manual	--	No problem with 2nd implant
Device 2	1	Mild soreness

Fifty eight of the 110 subjects who received a 2nd implant after week 52, had their implant inserted with Device 3.

Reviewer's Comments: *Most insertion site AE's were in the category of mild bruising and local pain, and most of these were associated with Device 2, which relied somewhat on the investigator's surgical technique. (Device 3, which included a standardized and consistent technique, was not available until April 2003). Review of the patient narratives regarding these AE's indicated that almost all resolved without treatment.*

Implant expulsions occurred in 7/138 subjects (5.1%), all with device 2. Two subjects elected to forego a re-implant, an additional subject was not re-implanted at sponsor's discretion, and the remaining 4 received a 2nd implant without further complications.

Almost all subjects (98.6%) experienced at least 1 AE during the study. All body systems were involved, and the mean number of AE's per subject was 7.4.

Among the AE's deemed to be related to study drug and commonly associated with LHRH agonists as a class, were hot flushes reported in 90/138 subjects (65.2%), fatigue, decrease in libido, erectile dysfunction, gynecomastia/breast pain, and testicular atrophy, each reported in approximately 5% of subjects.

Other AE's reported to be related to study drug were anemia, constipation, fatigue, hepatic disorder, random elevations of some blood chemistry values, dizziness, depression, insomnia, irritability, and increased urinary frequency.

Thirteen subjects were listed as having "hepatic impairment" as an AE. 7/13 had single reports of elevations for AST and/or ALT. Three had elevations on 2 separate occasions, and an additional 4 had elevations on 4 or more visits. Most abnormal values returned to normal on follow-up. None had abnormal bilirubin elevations or clinical evidence of hepatic impairment.

Fifty-five subjects were listed as having "renal impairment" (creatinine clearance < 60 mL/min) as an AE. 15/55 had single occurrences, 8 had this twice, 5 had it 3 times, 4 had it 4 times, 3 subjects had it 5 times, and 20 subjects had abnormal values observed at 6 or more visits. Most subjects had concomitant elevations of creatinine and BUN at the same visits, but only 6 subjects had BUN > 20% or more above the ULN.

Reviewer's Comments: *Considering this patient population, with its range of co-morbid conditions and the amount of concomitant medications consumed, it can reasonably be expected that random anomalous laboratory values will be encountered. There does not appear to be any pattern of AE's suggesting concern over hepatic or renal toxicities.*

Other chemical laboratory values remained unchanged throughout the study.

Initially, hemoglobin and hematocrit remained unchanged. However, from week 8 to end of study, the decrease in these parameters was statistically significant. Likewise, RBC's, platelets, and basophils were initially unchanged but slowly and significantly declined throughout the study. WBC's remained unchanged throughout the study.

Reviewer's Comment: *The statistically significant reductions in the hematological parameters were not clinically meaningful, and all of the laboratory values remained within normal limits.*

No clinically significant changes from baseline were noted in heart or respiratory rate, blood pressure, temperature, weight, ECG, or bone scan abnormalities.

A total of 34/138 subjects (24.6%) were reported with serious SE's. None of these AE's were attributed to study drug and, according to sponsor, were most likely associated with age or pre-existing medical conditions of subjects.

Although no subjects withdrew from study due to AE's, 7/138 subjects died on study and 1 additional subject died within 30 days of study discontinuation. None of the deaths were classified as related to study drug. Descriptions of subjects who withdrew from study due to these serious AE's are seen in Table 3.

Table 3. Subjects Who Withdrew Due to Serious AE's

Study Site	Age	Adverse Event(s)	Drug Relationship	Outcome
04	75	Anoxic encephalopathy	None	Death
04	74	Myocardial infarction	Unlikely	Death
07	66	Anaplastic astrocytoma	None	Resolved
10	87	CHF and pneumonia	None	Death

16	88	Myocardial infarction	Unlikely	Death
28	83	Colon cancer progression	None	Death
28	77	CVA and myocardial infarction	None	Death
30	70	Suicide	None	Death

In response to Division's concerns regarding potential difficulty in removing the implant in some subjects, and of greater concern, the inability to locate the implant in 8 subjects, the sponsor agreed to make labeling changes addressing these issues. These changes included: recommendations that subjects contact their physician should they believe that the implant has been expelled and in addition, to return for periodic follow-up to check on the status of the implant. Further, the label also advises that ultrasound or CT may aid in locating the implant. In support of this statement, the sponsor provided sonograms indicating successful identification of the implant in 6 subjects, and CT scans indicating successful identification of the implant in 6 subjects.

Reviewer's Comment: *The sponsor has indeed provided some evidence of the utility of ultrasound and CT in locating this device in some patients, but evidence of the utility of these modalities in locating implants that are impalpable has, as yet, not been demonstrated. Ultrasound and CT were capable of detecting an implant in the subcutaneous tissues. With this background, the Division has requested, and the sponsor has agreed to conduct a phase-4 study of the utility of these modalities in 10 consecutive subjects in whom the device cannot be palpated.*

7.1 Materials Utilized in the Review.

Efficacy and AE data were principally derived from clinical studies 301, 302 and BAR 002 involving 138, 42, and 33 subjects respectively. In addition, there were 104 subjects enrolled in an extension phase of study 301(still ongoing) from which some safety and efficacy data are available.

7.2 Extent of Exposure.

In all studies, subjects received a 50 mg histrelin implant. In study 301, of the 138 subjects, 73 % had duration of treatment > 12 months, with a mean of 357 days. In study 302, the extent of exposure was 52 weeks, and in study BAR 002, the mean duration of exposure was 29 months (range, 3-38 months).

7.3 Deaths

> There were 21 deaths reported in the combined study population of 224 (9.4 %). None of the deaths were attributed to study drug or device. The most common causes of death were progressive prostate cancer, myocardial infarction, CHF, and pneumonia. Other causes included CVA, kidney failure, other malignancies, and 1 suicide.

Reviewer's Comment: *I have reviewed the narrative summaries of all the reported deaths and agree with the assessments of the investigators that these deaths were unrelated to study drug or device.*

8. Dosing, Regimen and Administration Issues.

The dose used in the pivotal study and supporting trials was derived from the phase-2 study BAR 002 that provided evidence that 2 or more implants conferred no additional benefit over a single implant. Therefore, Vantas 50 mg appeared to have the best balance between safety and efficacy in attaining and maintaining castrate levels of T for the duration of implant placement.

9. Use in Special Populations.

Gender: Histrelin 50 mg implant is indicated in the palliative treatment of advanced prostate cancer and should not be used in women.
Pediatric: Safety and effectiveness of histrelin have not been established in pediatric patients.. A full waiver for pediatric labeling was requested by the sponsor, and this is considered appropriate.
Elderly: Approximately 90 % of subjects studied in clinical trials were age 65 and older.
Race/Ethnicity: The effect of race/ethnicity on the pharmacokinetics of this product has not been studied.
Renal/Hepatic Insufficiency: No changes in drug dosing are warranted in such patients.

10.0 Conclusions, Recommendations, and Labeling.

10.1 Conclusions Regarding Safety and Efficacy.

It can be concluded that the safety and efficacy of Vantas has been established for the palliative treatment of advanced prostate cancer.

10.2 Recommendations on Approvability.

From a clinical perspective, Vantas should be approved for the indication "palliative treatment of advanced prostate cancer".

10.3 Labeling.

Review of the draft package insert indicated, that for clinical parameters, this product is essentially the same as that seen with other currently marketed LH-RH agonists (Viadur®, Elilgard®, and Lupron®) proposed for the same clinical indication. The sponsor and Division have come to agreement on all labeling issues, including the issues of implant expulsion and implants that were not located.

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/s/

Harry Handelsman
10/8/04 03:20:59 PM
MEDICAL OFFICER

Mark S. Hirsch
10/8/04 03:27:01 PM
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I concur.

NDA 21-732
Vantas™ histrelin implant
Valera Pharmaceuticals

Safety Update

Review of the Safety Updates is incorporated in the Medical Officer's Review dated October 8, 2004.