CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-058

SUMMARY REVIEW

DIVISION DIRECTOR'S MEMO

NDA#:	22-058
Drug name:	Supprelin LA® (histrelin implant) – GnRH analogue
Applicant:	Valera
Indication:	Treatment of Central Precocious Puberty
Submission Date:	June 30, 2006
PDUFA Goal Date:	May 3, 2007
Primary Medical Reviewer:	Dragos Roman, M.D.

BACKGROUND

This NDA proposes a new indication for the currently marketed gonadotropin releasing hormone (GnRH) analog, histrelin acetate, for the treatment of central precocious puberty (CPP). Precocious puberty is often identified when sexual development is observed before the age of 8 years in girls and 9 years in boys. CPP results from early activation of GnRH neurons that then stimulate episodic gonadotropin (LH and FSH) secretion to levels that initiate pubertal development. A variety of CNS disorders or insults including inflammation, structural defects, tumor, trauma, or chemotherapy may contribute to the development of CPP; however, in many cases, no cause is identified (idiopathic). Acceleration of sexual development includes early thelarche and menarche in girls, increased testicular and penile growth in boys, appearance of pubic hair, accelerated linear growth, and possible reduced final height. Other consequences of precocious puberty include detrimental psychological impact and social stigmatization.

GnRH agonists are structurally similar to endogenous GnRH; however, modification to the native amino acid sequence results in a greater binding affinity for the GnRH receptor. The use of GnRH agonists results in an initial stimulation of gonadotropin release and possible acceleration of sexual development or exacerbation of clinical presentations, but this is soon followed by antagonism of gonadotropin release as continued occupation of the GnRH receptors on pituitary gonadotropes by the analogue down-regulates receptor response resulting in a reduction in LH and FSH levels to pre-pubertal levels. Currently available GnRH agonists approved for CPP include nafarelin acetate (Synarel) and leuprolide acetate (Lupron).

Histrelin acetate was approved in 1991 for CPP as a daily subcutaneous injection but this formulation was discontinued with the availability of formulations with more convenient dosing. In October 2004, the applicant received an approval for Vantus® implant (NDA 21-732), a drug-device that contained histrelin acetate 50 mg, for the palliative treatment of prostate cancer. The implant requires surgical implantation subcutaneously into the inner aspect of the upper arm and releases histrelin acetate at a rate of 55 mcg per day. The device in this NDA is similar to the one approved under NDA 21-732 with the exception that this implant has been modified to allow a higher amount of histrelin acetate released (65 mcg daily). The

recommended duration of implant is 12 months, after which time the implant is to be removed or replaced if continued gonadotropin suppression is necessary. The remainder of this memo will refer to this drug product as histrelin acetate implant.

Valera Pharmaceuticals Inc., submitted the results of two clinical trials reviewed by Dr. Dragos Roman in his clinical review of this NDA. Both studies demonstrate that histrelin acetate implant is effective in suppressing gonadotropin levels. In addition, other hormonal assessments and measures of sexual development and linear growth support the conclusion that histrelin acetate implant will suppress gonadotropin release sufficiently to delay pubertal progression. The most common adverse events reported were related to the implant insertion and site reactions. Other safety concerns primarily reflect the pharmacologic action of a GnRH agonist. Overall, the safety findings were not unexpected or of a clinically significant magnitude to offset the efficacy findings. Dr. Roman recommends approval and I concur with his conclusion. This memo will only present an overview of the program and recommendations from other disciplines involved in the review of this NDA.

CLINICAL EFFICACY AND SAFETY

(Please see Dr. Roman's review for details of the pivotal studies)
The two clinical studies were open-label, uncontrolled studies. Study-02-CPP-HIS-300 (or Study 300) was a multi-center, 12-month study evaluating 36 patients (20 treatment-naïve and 16 previously treated) and Study 01-02-001 (or Study 001) was a single-center, 18-month study in 11 girls previously treated with another GnRH agonist. The mean age was higher in the pre-treated patients (8.9 and 8.6 yrs in Study 300 and 001, respectively) compared to treatment-naïve patients (mean age 7.2 years). Histrelin implant 50 mg was used in both studies with Study 001 evaluating the insertion of two implants in four patients in a non-randomized fashion. The small number of patients treated with two implants and the non-randomized fashion in which treatment assigned present limitations to conclusions on dose-response. The applicant is not proposing the insertion of two implants for the treatment of CPP and labeling will not provide data to encourage such use. Only 3 male patients were studied and all had received prior GnRH therapy.

Both studies demonstrated that 50-mg histrelin acetate administered over the course of approximately 12 months was effective at either lowering LH levels to prepubertal levels in patients naïve to therapy or maintaining suppressed LH levels in those switching from another GnRH agonist to histrelin acetate implant. Graphic illustrations of LH and FSH response to histrelin acetate treatment are displayed in Figures 2.2.1.1 and 2.2.1.2 for Study 001 and Figures 2.9.2 (pre-treated population) and 2.9.3 (treatment naïve) for Study 300 in Dr. Roman's review. Correlating with these changes was the observation that gonadal steroid levels were suppressed with all female patients displaying estradiol levels in the suppressed range. Testosterone levels in the three male patients remained suppressed throughout treatment with histrelin acetate implant.

Dr. Roman has summarized other secondary measures of efficacy. The absence of a control group and standardized assessments for certain measures (e.g., ovarian ultrasound readings) presented limitations to overall conclusions regarding these secondary measures. However, overall the findings supported the results of LH/FSH and sex steroid hormone levels.

There were no deaths in these two clinical trials and only two serious AEs were reported including amblyopia and a benign pituitary tumor. The latter was considered possibly related to drug treatment; however, the patient had received another GnRH agonist for 7 years prior to receiving treatment with histrelin acetate implant. There was one discontinuation secondary to a wound infection at the site of insertion followed by implant extrusion. The most common adverse event reported was related to implant insertion: 61.1% of patients in Study 300 and 18.2% of patient in Study 001 reported such adverse events. Dr. Roman has summarized some of the narratives regarding implant/insertion-related AEs. He recommends that collection of these adverse events reported in the post-marketing setting and their

reported in periodic safety update reports. I concur with his Phase 4 request. Furthermore, the label instructions for implant insertion should not deviate from that of the approved device, Vantus®, as there is more experience with that drug-device product.

Other adverse events were mild or may represent age-appropriate complaints/symptoms. The absence of a control group severely limits the interpretation of these reports but the non-serious nature of the events provides some reassurance about the clinical significance of these findings. Several AEs may be attributed to GnRH agonist activity including ovulatory/menstrual disturbances. As noted earlier, the initial effect of GnRH agonist may result in a surge in LH/FSH secretion with acceleration/exacerbation of secondary sexual characteristics. The patient/parents should be counseled accordingly if the patient is naïve to GnRH agonist therapy.

Overall, the efficacy of Supprelin LA appears similar to other GnRH agonists approved for CPP and the safety profile reflects the pharmacologic activity or the method of drug administration. Much of these safety concerns can be labeled and user education and experience with implant insertion may likely reduce the adverse events related to implant insertion.

CLINICAL PHARMACOLOGY

No drug-drug interactions were conducted for this NDA. Pharmacokinetic assessments were obtained in the two clinical studies and summarized in Dr. Roman's review. No approvability issues were identified.

PHARMACOLOGY/TOXICOLOGY

Both Drs. Antonipillai and Davis-Bruno recommend approval of this NDA. No additional studies are requested.

CHEMISTRY, MANUFACTURING AND CONTROL

The drug substance is histrelin acetate, a synthetic nonapeptide of the naturally occurring GnRH or LHRH which is a decapeptide. [redacted] b(4)

This is a drug-device combination product. The implant is non-biodegradable and consists of 4 drug pellets which contains a total of 50 mg histrelin acetate [redacted] inside a cylindrical hydrogel reservoir measuring 35 mm x 3.1 mm. b(4)

The drug product is packaged for surgical implantation and is sterilized by [redacted] b(4)
Once implanted in the inner aspect of the upper arm, it is calculated that histrelin acetate is released at approximately 65 mcg/day over 12 months. The applicant has another similarly marketed drug-device combination product which also contains histrelin acetate. This product, Vantas®, is approved for advanced prostate cancer.

Both the chemistry and microbiology reviewers are recommending approval of this NDA.

CONSULTS

DMETS

The proposed tradename is Supprelin LA. An objection was initially raised by DMETS to the modifier "LA" as the daily subcutaneous injection was not marketed and the need for a long-acting distinction appeared superfluous. However, the applicant provided a rebuttal which included its plan to re-introduce a short-acting formulation of histrelin acetate for diagnostic purposes. As no other look-alike/sound-alike names were identified, the Division does not object to allowing the proposed tradename, Supprelin LA, to be approved. This has been discussed with DMETS and there is concurrence with this decision.

CDRH
The CDRH consulted noted that this is the same device approved under NDA 21-732 (Vantus®) for palliative treatment of prostate cancer. Recommendations by the CDRH reviewer were limited to labeling, including a possible updated consult to address user education to address problems with insertion noted in the clinical trials. As part of labeling recommendations, the applicant was informed to use the similar instructions to the approved Vantus® label.

DDMAC
No objections raised to the proposed tradename. Labeling recommendations were made and incorporated in labeling negotiations with the company.

LABELING
The applicant has submitted labeling in the Physician Labeling Rule (PLR) format. A Patient Prescriber Information leaflet has also been submitted with this application. Pending labeling negotiations that are acceptable to both the applicant and the agency, this application should be approved.

RECOMMENDATIONS
Approval pending labeling negotiations.

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/s/

Mary Parks
4/30/2007 12:01:55 PM
MEDICAL OFFICER