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Review of a Request for Orphan Drug Designation

Designation Number: [redacted]

Date Received by FDA:	September 9, 2005
Date Received by Reviewer:	October 18, 2005
Date Review Completed:	November 8, 2005

Product: Generic name: histrelin acetate implant
Trade name: to be determined

Sponsor: Valera Pharmaceuticals
8 Clarke Drive
Cranbury, NJ 08612

Contact Person: William B. Gray, M.S.
Senior Director, Regulatory Affairs
Telephone (609) 235-3206

Frank Sasinowski, Esq.
Kurt Karst, Esq.
Valera's Regulatory Counsel
Hyman, Phelps & McNamara, P.C.
Telephone (202) 737-5600

Manufacturer: Bachem Holding AG
4416 Bubendorf, Switzerland

Regulatory Status: Histrelin acetate implant (VANTAS) was approved for the palliative treatment of prostate cancer on October 12, 2004 under NDA 21-732. The sponsor filed IND [redacted] on December 30, 2003 to investigate histrelin acetate implant in the treatment of central precocious puberty (CPP).

Proposed Indication: Treatment of central precocious puberty.

Disease Background: Central precocious puberty is a condition in which puberty starts before age 9 years in boys and age 6-7 in girls[1]. Normal pubertal development is caused by the increasing pulsatile activity of the hypothalamic gonadotropin-releasing hormone (GnRH) pulse generator which leads to the release of luteinizing hormone (LH) and follicle stimulating hormone (FSH) from the pituitary[2]. Increased LH levels stimulate production of estrogen, progesterone and testosterone that lead to the physical changes of puberty and mediate the pubertal growth spurt. Increased FSH levels cause enlargement of the gonads in both sexes and eventually promote follicular maturation in girls and spermatogenesis in boys, which in turn stimulates a child's sex hormone production, sexual development, and physical growth. In CPP, there is an early maturation of the

entire hypothalamic-pituitary-gonadal (HPG) axis that leads to earlier than normal pubertal body changes.

The primary causes of CPP are idiopathic or neurogenic. Neurogenic causes of CPP include central nervous system (CNS) tumors, CNS malformations, CNS infections, radiation therapy, chemotherapy and trauma. However, most cases of CPP occur without any known cause.

Central precocious puberty is diagnosed with a detailed physical examination that may include x-rays of the bone and wrist to determine if bone development is older than the child's chronological age; blood tests to determine hormone levels; a pelvic and adrenal ultrasound to look for abnormalities of the ovaries, tests or adrenal glands; and imaging studies such as MRI or CAT scans to check for abnormalities of the pituitary or the hypothalamus[3].

Children with CPP may be treated with long-acting GnRH analogs such as leuprolide (Lupron®) or nafarelin (Synarel®) to inhibit gonadotropin and sex steroid secretion, and suppress the manifestations of puberty. These drugs can be administered until the chronological age of normal puberty is reached. Suppression of gonadotropins until appropriate chronological age may allow continued skeletal maturation prior to epiphysial closure, leading to improved final adult height; however, some studies have found that GnRH analog therapy may not provide any improved height benefit in girls with pubertal onset after age 6 years[1]. Treatment may also be used to address the psychological issues presented with physical maturation prior to mental maturation.

Population Estimate: The incidence of CPP is approximately 1:5000-10,000 children[2]. The most recent decennial census conducted by the US Census Bureau in 2000 estimates a population under age 9 of 39,725,303[4]. Based on this population figure and the incidence of CPP, the sponsor estimates the prevalence of CPP in the United States to be between 3,973 and 7,945.

Rationale for Use: Histrelin acetate is a synthetic nonapeptide analogue of the naturally occurring GnRH hormone. The histrelin acetate implant is a sterile non-biodegradable, diffusion-controlled reservoir drug delivery system designed to deliver histrelin continuously for 12 months upon subcutaneous implantation in the inner aspect of the upper arm.

The sponsor has completed a phase I/II study of 50 mg histrelin acetate subcutaneous implants in 11 girls age 4 to 11 years with CPP over an 18 month period[5]. Each subject had advanced pre-treatment bone age relative to chronological age and elevated estradiol levels ($\geq$ 20 pg/ml or 73 pmol/ml). Seven patients received 1 implant and 4 patients received 2 implants, depending on body weight and ease of surgical insertion. Efficacy was evaluated by serial assessment of hormone concentrations (estradiol, FSH, LH), GnRH stimulation testing, and objective measurements including Tanner staging, wrist bone age x-rays, transabdominal pelvic ultrasounds, height and body weight, and quality of life questionnaires. Patients were evaluated at months 1, 3, 6, 9, 12, 15 and 18. At the 9 month visit, subjects were divided into two parallel tracks in which the original

implant(s) was replaced with one new implant or the original implant was left in place for the remainder of the study period. Preliminary results from this study indicate that the histrelin acetate implant delivers steady concentrations of histrelin acetate, which maintained suppression of gonadotropins for at least 12 months. Following insertion of 1 or 2 histrelin acetate implants, 10 subjects had estradiol serum concentrations that were at prepubertal levels (i.e. $\leq$ 73 pmol/L) at each evaluation through month 12. One subject withdrew from the study at month 9 when a local wound infection occurred at the site where an implant had been replaced. All subjects continued to have no response to GnRH stimulation through month 9 for those who had the implant replaced at this time and through month 12 in those in which the implant remained. Preliminary assessments of pubertal characteristics, as measured by the Tanner Scale and bone-age x-rays, indicated continued suppression of puberty in all subjects. Seven of the 11 subject (64%) reported adverse events during the first 12 months of the study. All adverse events were mild in intensity.

An open-label phase III study to evaluate the safety and efficacy of histrelin acetate subcutaneous implant in subjects with CPP was initiated in September 2004 and is currently ongoing. Thirty-six subjects have been enrolled in this trial. Subjects are divided into two groups: (1) pre-treated subjects who have received treatment for CPP for at least 6 months prior to study entry; and (2) naïve subjects. Efficacy parameters in this study include clinical and biochemical responses observed at months 1, 3, 6, 9, and 12. To date, one subject has been followed for 9 months, ten subjects have been followed for 6 months, and all 36 subjects have been followed for 3 months. No serious adverse events have occurred to date.

Prior Orphan Approvals for Histrelin: Histrelin (Supprelin®), sponsored by Roberts Pharmaceuticals, was approved as an orphan drug for the use in the treatment of CPP on December 24, 1991 (NDA 19-836). Therefore, the orphan drug exclusivity for this product expired on December 24, 1998. The sponsor of this present application indicates that Supprelin® has not been marketed since 1997 due to commercial reasons.

The sponsor points out that FDA states in the preamble to the final orphan drug regulations that "[o]rphan-drug designation can be granted to new sponsors of drugs currently protected by orphan drug exclusive marketing if such sponsors provide a plausible scientific rationale in an application submitted pursuant to 316.20 that studies to be conducted on the drug may result in a finding of clinical superiority over the marketed drug." The sponsor indicates they do not believe it is necessary to provide a rationale for clinical superiority since Supprelin® is not currently protected by orphan drug exclusivity or marketed, but they never-the-less provide the argument that the histrelin implant may be clinically superior to Supprelin® on the basis that it may provide a major contribution to patient care.

The sponsor also points out that FDA indicates in the preamble to its final orphan drug regulations that "convenient treatment location; duration of treatment; patient comfort; improvements in drug efficiency; advances in the ease and comfort of drug administration; longer periods between doses; and potential for self administration. . .

might sometimes be legitimately considered to bear on whether a drug makes a major contribution to patient care. However, this determination will have to be made on a case-by-case basis." The sponsor refers to one case in which FDA has designated an orphan drug based on demonstration of major contribution to patient care. In 1998, a reformulated octreotide product was found to be clinically superior to a previously approved subcutaneous octreotide product because patients could be managed with one injection per month with the reformulated product instead of 60 to 90 injections per month with the subcutaneous product. The sponsor indicates that the histrelin implant will provide therapeutic blood levels for a period of 12 months with a single subcutaneous implant compared to daily subcutaneous injections for Supprelin®[3]. The sponsor states that the histrelin implant product should avoid the pain and inconvenience associated with daily subcutaneous injections resulting in improved patient compliance and better therapeutic outcomes.

Discussion and Conclusions: The sponsor has provided adequate scientific rationale to support orphan drug designation for histrelin implant in the treatment of CPP. Central precocious puberty is a condition in which there is an early maturation of the entire HPG axis that leads to earlier than normal pubertal body changes (before age 9 years in boys and age 6-7 in girls). This condition may be may be treated with long-acting GnRH analogs. Histrelin implant is a sterile non-biodegradable, diffusion-controlled reservoir drug delivery system designed to deliver this GnRH analog continuously for 12 months upon subcutaneous implantation in the inner aspect of the upper arm. The sponsor has completed a phase I/II study of 50 mg histrelin acetate subcutaneous implants in 11 girls age 4 to 11 years with CPP over an 18 month period, and has a phase III open label study in children with CPP currently ongoing.

The sponsor has provided adequate population data to show that the prevalence of CPP is well less than the 200,000 threshold for orphan drug designation but the figure provided is not current and may underestimate the number of children with CPP. To estimate the prevalence of CPP, the sponsor uses the incidence for CPP (1:5,000-10,000) and the population of children age less than 9 years in 2000. This results in an estimate of 3,973 to 7,945. However, the final orphan drug regulations define prevalence as the number of persons in the United States who have been diagnosed as having the disease or condition at the time of the request for orphan designation. The sponsor has used a population figure that is 5 years old. Further, the sponsor uses an estimate of children aged less than 9 years, but the children with CPP studied in the phase I/II study were age 4 to 11 years, and the inclusion criteria for the study was age 2 to 13 years[5]. Table 1-RES from the United States Census Bureau provides estimates of the United States population by selected age groups for July 1, 2004[6]. On this date, it is estimated that there were 56.4 million children age 13 years and younger in the United States. Using this number and the incidence for CPP provides a maximum estimate of 11,280, which should account for all children currently with CPP in the United States.

The sponsor has provided an adequate hypothesis of why their histrelin product may be clinically superior to Supprelin®. To show that a same drug is clinically superior to an existing product, a sponsor needs to provide a reasonable hypothesis that the subsequent

drug has greater effectiveness, is safer in a substantial portion of the target population, or provides a major contribution to patient care. The sponsor indicates that a single histrelin subcutaneous implant could provide therapeutic blood levels for a period of 1 year versus 365 daily injections of Supprelin®. This provides a reasonable hypothesis for a major contribution to patient care since it offers a measure of therapeutic superiority that can not be otherwise demonstrated as safer or more effective.

Recommendation: It is recommended that histrelin implant be designated for use in the treatment of central precocious puberty. The prevalence of patients with CPP in the United States is not higher than 11,280.

Erica K. McNeilly, R.Ph.
Reviewing Pharmacist

Concur: _____ for Date: 11/14/05
Marlene E. Haffner, MD, MPH
RADM, USPHS
Director, Office of Orphan Products Development, HF-35

CC: HF-35 dsg file
HF-35 chron