CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-538

SUMMARY REVIEW

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993-002

DIVISION DIRECTOR'S MEMO

NDA	21-538
Drug Name	Accretropin® Recombinant human growth hormone
Sponsor	Cangene Corporation
Indication	Treatment of short stature in pediatric GHD and Turner syndrome
Date of Submission	May 12, 2006 (CDER stamp date)
PDUFA Goal Date	March 10, 2007
Primary Medical Reviewer	Dragos Roman, M.D.

EXECUTIVE SUMMARY

This new drug application (NDA) is for the immediate-release recombinant human growth hormone (rhGH), Accretropin®. The applicant is seeking its approval for the treatment of short stature in patients with GH deficiency (GHD) or Turner syndrome (TS). There are currently 8 immediate-release rhGH products marketed in the U.S. All but one have an indication for pediatric GHD and three (Nutropin®, Humatrope®, and Genotropin®) have indications for TS.

Like the other marketed rhGH products, Accretropin contains the entire 191 amino acid sequence of native GH manufactured via recombinant DNA technology using an E.coli expression system. Its route of administration is also by daily subcutaneous injections, six times per week.

The clinical efficacy and safety of Accretropin was characterized in two studies described below. Multiple assessments of linear growth in pre-pubertal patients with GHD or TS all support the conclusion that Accretropin is effective with a safety profile that is similar to other approved rhGH products. Anti-GH antibodies develop in a higher percentage of study patients than has been observed with other products; however, no evidence of attenuation in growth was noted with this finding.

The only outstanding issues identified in this application have been with microbiology. Consequently, the overall recommendation for this review cycle will be approvable.

CLINICAL STUDIES

Three clinical studies were submitted to this NDA. Study GA-002 was a Phase 1 bioequivalence (BE) study comparing Accretropin® to Humatrope®. Study GA-005/5A and GA-007/7A were both open-label, historical-control, single-arm clinical studies evaluating the safety and effectiveness of Accretropin on improving linear growth in children with severe short stature secondary to GHD or TS, respectively. These two studies included extension phases out to 36 months.

Dr. Wei Qiu reviewed Study GA-002 in her Clinical Pharmacology Review. This was a single-dose, double-blind, randomized, 2-way crossover study comparing the bioavailability of hGH and levels of IGF-1, IGFBP-3, and glucose after administration of Accretropin 4 mg and Humatrope 4 mg in 24 healthy male volunteers. The washout period between hGH administrations was 7 days. Study volunteers' endogenous GH levels were suppressed with somatostatin, administered intravenously for 42 hrs. Test rhGH products were administered 25 hrs after the somatostatin infusion was initiated. The study was conducted under fed conditions. Accretropin and Humatrope were found to be bioequivalent based on the Accretropin to Humatrope ratios of the AUC_{0-24} and Cmax of hGH. The means (90% CI) for both these variables were 94.23 (88.7-100.10) and 103.84 (95.73-112.63), respectively. Pharmacodynamic measures of IGF-1, IGFBP-3, and glucose concentrations were also similar between the two products. This NDA was submitted as a 505(b)(1) application with clinical trials conducted by the applicant in support of the proposed indications. The results of Study GA-002 would be inadequate to support other indications approved for Humatrope under a 505(b)(2) application as the comparison used an earlier formulation of Accretropin that contains ——— phenol than the to-be-marketed formulation.

Dr. Roman has extensively reviewed and summarized the results of the two clinical studies. With notable exception for the study population, single vs multicenter, and doses used, the two studies employed very similar designs. Conventional measures of linear growth were used for efficacy determination in both studies and included height velocity (cm/year), height velocity standard deviation score (SDS), and height SDS. Because pre-trial height data were not collected in a manner consistent with Good Clinical Practice or per protocol, the accuracy of the calculated pre-treatment (or baseline) height velocity is somewhat questionable. As such, comparisons of on-treatment HV data to baseline HV were considered supportive evidence of efficacy. For each specific short-stature study population, appropriate reference populations were used as historical comparators.

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Pediatric GHD

At standard doses of 0.18 to 0.30 mg/kg/week divided equally into 6 daily sc injections, Accretropin demonstrated improvements in linear growth in prepubertal patients with GHD. Forty-four patients were enrolled in this study, efficacy data were available in 42 patients at 6 months and 25 patients completed the extension period out to 36 months. On-treatment HV and HV SDS reflected expected improvements in linear growth with rhGH. Comparisons of annualized height velocity for Accretropin-treated patients to age- and gender-matched population of normally growing children locally (Polish and Hungary) and internationally (British) showed significantly higher mean HV at different time points of assessment associated with Accretropin treatment.

Mean height velocity (cm/yr) at 1 year increased more than double relative to baseline HV (8.8 ± 2.3 vs 4.1 ± 1.2). Mean HV at years 2 and 3 were also increased over baseline although the greatest change is observed in the first year after therapy is initiated. Other assessments of linear growth summarized in Dr. Roman's review show parallel findings of effectiveness. Pharmacologic assessments of IGF-1 and IGFBP-3 levels also demonstrated the expected increase with rhGH therapy.

A notable finding for both safety and efficacy was the development of anti-GH antibodies in up to 50% of patients. Dr. Roman has thoroughly reviewed the relevance of this finding on efficacy by comparing HV between antibody-positive and antibody-negative patients at 6, 12, 24, and 36 months. No attenuation in efficacy was observed.

Dr. Roman has also summarized a table provided by the applicant which compared efficacy in pediatric GHD across all approved GH products and contrasted those findings with Accretropin (see Table 36 in his review). The studies employed different doses but still showed that the change in HV after one year of treatment with Accretropin compared to Baseline is comparable to data observed with other approved products. While this comparison is not necessary for a finding of effectiveness for Accretropin, it is

reassuring and adds to the totality of evidence provided by the applicant in this NDA with data derived from its own clinical studies.

Turner Syndrome
Accretropin dosed at 0.36 mg/kg/week, divided equally into daily sc injections, improved linear growth in prepubertal females with Turner syndrome. Thirty-seven patients enrolled in this single-center study; all completed the initial 6 month study period and 36 completed the extension period out to 36 months. Similar to the findings in pediatric GHD, Turner patients had on-treatment increases in HV and HV SDS with the most pronounced effect observed within the first year of therapy but continued efficacy observed at Years 2 and 3.

Historical comparisons to the same reference populations used in the assessment of pediatric GHD showed significant increases in annualized HV from baseline to Months 6 and 12 and between Months 12 and 24 associated with Accretropin treatment. The applicant also presented comparative data to local HV growth standard for untreated TS patients. This analysis showed significant increases in annualized HV at all time points including from Month 24 to 36.

As in Study GA-005, a higher than usual rate of anti-GH antibodies was observed in TS patients than with other approved products. Up to 35% of patients developed such Abs; however, analyses by antibody-positive versus antibody-negative subgroups showed no attenuation in efficacy at Month 6, 12, 24, or 36.

The applicant also provided a table summarizing efficacy in TS patients treated with other rhGH products. Accretropin's efficacy was within the expected range of these other products; however, this comparative analysis is not necessary for the purposes of approval of this NDA.

In both clinical studies, Dr. Roman noted that the safety profile was similar to other approved rhGH products. The only notable difference was a higher immunogenicity profile. He has extensively discussed this finding, including discussions with Dr. Yang regarding manufacturing process and impurity profiles, and no reasonable explanation for this difference can be offered. Despite this difference, he has found no evidence that the higher rate of developing anti-GH antibodies alters the safety profile of this product. Of relevance, the anti-GH antibody binding activity was below 1 to 2 mg/L, a threshold value for which development of neutralizing antibodies to GH has not been described with other rhGH therapies.

One death was reported in this NDA in the pediatric GHD study. This involved a 15 year-old body who had cardiomyopathy secondary to fatty degeneration. Dr. Roman has reviewed the literature for GH use and this finding has not been reported in any postmarketing surveillance studies.

PHARMACOLOGY/TOXICOLOGY
From a PharmTox perspective, this application can be approved.

CMC
From a CMC standpoint, this application can be approved. The microbiology review has identified several deficiencies in their review dated March 3, 2007 and has recommended an approvable action.

CONSULTS
DSI Audits
Over recommendation of inspections of one site in Study GA005 and of the single center for Study 007 was acceptable.

DMETS/DDMAC
No objections were raised to the proposed tradename, Accretropin.

OTHER REGULATORY ISSUES

No Phase 4 commitments requested. A waiver for pediatric studies of children below 2 years of age will be granted.

Dr. Roman recommends that the applicant conduct postmarketing surveillance studies similar to those conducted by other manufacturers. This is not a requirement; however, I concur that we should strongly encourage the company to initiate this study to better inform us of the long-term safety profile for Accretropin. This is particularly important given the difference in immunogenicity profile compare to other approved rhGH products.

RECOMMENDATIONS

From a clinical perspective, this application can be approved. However, microbiology deficiencies need to be addressed therefore an approvable action will be taken on this review cycle.

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/s/

Mary Parks
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MEDICAL OFFICER