

Division Director Memo

NDA #	20-280/Supplement 060
Applicant	Pfizer
Drug Product	Genotropin® (recombinant human growth hormone)
Indication	Idiopathic Short Stature

Background

Pfizer has submitted this efficacy supplement to expand the indication for Genotropin®, recombinant human growth hormone (rhGH), for use in pediatric patients with idiopathic short stature (ISS). Currently, of the 10 FDA-approved rhGH products, only two have an indication for ISS. Humatrope® was approved in 2003 and Nutropin® was approved in 2004 for this indication. For both of these products, the applicants provided evidence that their rhGH increased final height compared to placebo (Humatrope) or no treatment (Nutropin).

Pfizer has provided data from two clinical trials in support of the ISS indication. Study TRN 88-080 (or 080) was considered the pivotal study and was a randomized, open-label, multicenter study which enrolled 177 patients with short stature but who were NOT growth hormone deficient. There were three different study arms in this trial: Genotropin 0.033 mg/kg/day, Genotropin 0.067 mg/kg/day, and an observational or untreated control arm. In addition, patients who were pre-pubertal after a one-year observation were randomized into each of these three different arms whereas patients who reached puberty were randomized to the 0.067 mg/kg/day or untreated control arm. Patients were followed until they reached final height. Study CTN 89-050 (or 050) was a 3-year, randomized, open-label multicenter study which enrolled 37 patients with familial short stature. These patients were randomized to receive either Genotropin 0.047 mg/kg or observation (an untreated control arm). Unlike Study 080, this trial did not follow patients until they reached final height. Instead an atypical primary endpoint for short stature trials was employed which compared the effect of Genotropin versus non-treatment on height for bone age. However, more standard efficacy measures of linear growth (height SDS and growth velocity) were secondary endpoint measures. In addition, all the patients evaluated in Study 050 were prepubertal.

Dr. Roman and Ms. Mele have each thoroughly discussed the study design and efficacy findings in their respective clinical and statistical reviews. In addition, Dr. Roman has conducted a safety review and has not identified any unusual side effect or adverse event profile related to GH use in the pediatric population that has not already been discussed in the labels of these products or in published literature. Consequently, my memo serves to highlight the Division's decisional memo to approve this supplement and summarize any critical scientific or regulatory issues. Please review Dr. Roman's review dated May 1, 2008, and Ms. Mele's review dated April 18, 2008, for the complete FDA review of this application. Since Genotropin is an approved product for other short stature indications and ISS did not require any further evaluation from clinical pharmacology or pharmacology/toxicology, this supplement does not contain any such discipline reviews. CMC did have to provide a review for a claim of categorical exclusion to the environmental assessment requirements. Dr. Julia Pinto's review dated April 28, 2008 has addressed this supplement can be approved from a CMC perspective.

Key Clinical/Statistical Findings

In both clinical studies, Genotropin in a dose range of 0.033 to 0.067 mg/kg/day, demonstrated significant effects on linear growth compared to no treatment in patients with ISS. The statistical analysis plan (written by Pfizer after they acquired the trial data and were unblinded to the data) proposed the combination of both Genotropin dose groups to compare to the untreated group. However, Ms. Mele further evaluated the efficacy findings by subgroups (dose, gender, pubertal status). A more notable effect on linear growth is observed with the higher dose, 0.067 mg/kg/day, particularly in pre-pubertal patients. The effect of Genotropin on linear growth is not significant in the pubertal population, more likely reflecting the contribution of puberty to epiphyseal closure and missed opportunity for improving final height.

The applicant had initially proposed a single dose regimen of 0.067 mg/kg/day for ISS; however, it was agreed that since all doses evaluated demonstrated efficacy over no-treatment, a range of recommended doses should be stated in the label to not encourage one single high dose regimen of GH in the treatment of ISS.

Also during labeling discussions, there were two areas requiring lengthy negotiations. One of these pertained to the inclusion of small for gestational age (SGA) patients in the description of clinical trial and study results. The second was the definition of ISS under the INDICATIONS section. With respect to the first issue, since the subgroup analysis with and without SGA patients did not impact the overall efficacy (or safety) findings, it was agreed that a descriptive presentation of how the trial was designed and implemented would be most appropriate since identification of SGA/ISS was not a predefined aspect of Study 080.

Regarding the second issue, the applicant proposed to define ISS under the INDICATIONS section based on a height SDS ≤ 2.0 , a cut-point that would have distinguished this label from Humatrope and Nutropin which uses a height SDS ≤ 2.25 . The applicant argued that the proposed definition reflected the inclusion criteria for identifying short stature patients in these two trials. The division argued and the firm accepted that the same language be maintained across all ISS labels for the following reason. The original language put forward by Humatrope was based on concerns that approval of GH for a non-GH deficient short stature condition would result in misuse of the product in a large patient population. By limiting the indication to those who have more severe short stature, the risk-benefit and economic considerations would likely be more favorable. FDA maintains that this rationale should be upheld and noted that such a definition would not preclude a physician from prescribing it for SDS ≤ 2.0 , if he/she felt the published literature supported initiation of therapy in this population. Specific to Pfizer's argument about labeling based on the studied population, FDA pointed out that the study was not initially designed to identify ISS patients and that ISS patients were identified after Pfizer acquired the data. Furthermore, it is not atypical for use of broad inclusion criteria for a clinical study to bolster patient numbers but that the final decision on target population must take into consideration the risk-benefit calculus.

Regulatory Issues

Dr. Roman has thoroughly covered all regulatory/administrative issues in his excellent review (pediatric, financial disclosure, DSI audits, data integrity). The only regulatory issue that requires discussion in my memo is the applicant's proposal for marketing, distribution, and promotion with this new expanded indication.

The approval letters for Humatrope and Nutropin discusses plans proposed by both these companies to limit promotion (no DTC advertisement), to have a limited sales force, education programs, and controlled distribution. As stated above, these applications were approved in 2003 and 2004, before the 2007 re-authorization of PDUFA (or FDAAA – FDA Amendments Act). Under FDAAA, certain approvals might be subject to a Risk Evaluation Mitigation Strategy (REMS). This might include some of the proposals put forward by Pfizer that are in line with previous commitments made by Humatrope and Nutropin. As such, this application was not approved on its PDUFA goal date and consultation with Office of Regulatory Policy and Office of Chief Counsel were necessary to determine if Genotropin’s approval for the ISS indication would require a REMS.

On June 11, 2008, the review division was notified by the Safety Requirements Team that the Office of Chief Counsel has cleared the approval of Genotropin for this ISS indication without a requirement for a REMS.

Recommendation

I concur with the clinical and statistical reviewers that this application can be approved for the new indication, idiopathic short stature.

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Mary Parks
6/12/2008 10:31:41 AM
MEDICAL OFFICER