



NDA 19-640/S-045

Eli Lilly and Company  
ATTENTION: Jeffrey T. Fayerman, Ph.D.  
Associate Director, US Regulatory Affairs  
Lilly Corporate Center  
Indianapolis, IN 46285

Dear Dr. Fayerman:

Please refer to your supplemental new drug application dated December 14, 2004, received December 15, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for **Humatrope (somatropin [rDNA origin] for injection)**, 6, 12, and 24 mg cartridges and 5 mg vials.

We acknowledge receipt of your submissions dated August 11 and 30, September 12, and October 6, 2005.

This supplemental new drug application provides for the addition to the package insert of new clinical information regarding the effects of Humatrope on bone.

The following text has been added as the fourth paragraph to the “Effects of Humatrope Treatment in Adults with Growth Hormone Deficiency” subsection of the **CLINICAL TRIALS** section of the labeling:

“Two studies evaluating the effect of Humatrope on bone mineralization were subsequently conducted. In a 2-year, randomized, double-blind, placebo-controlled trial, 67 patients with previously untreated adult-onset growth hormone (GH) deficiency received placebo or Humatrope treatment titrated to maintain serum IGF-I within the age-adjusted normal range. In men, but not women, lumbar spine bone mineral density (BMD) increased with Humatrope treatment compared to placebo with a treatment difference of approximately 4% ( $p=0.001$ ). There was no significant change in hip BMD with Humatrope treatment in men or women, when compared to placebo. In a 2-year, open-label, randomized trial, 149 patients with childhood-onset GH deficiency, who had completed pediatric GH therapy, had attained final height (height velocity  $< 1$  cm/yr) and were confirmed to be GH-deficient as young adults (commonly referred to as transition patients), received Humatrope 12.5  $\mu\text{g}/\text{kg}/\text{day}$ , Humatrope 25  $\mu\text{g}/\text{kg}/\text{day}$ , or were followed with no therapy. Patients who were randomized to treatment with Humatrope at 12.5  $\mu\text{g}/\text{kg}/\text{day}$  achieved a 2.9% greater increase from baseline than control in total body bone mineral content (BMC) ( $8.1 \pm 9.0\%$  vs.  $5.2 \pm 8.2\%$ ,  $p=0.02$ ), whereas patients treated with Humatrope at 25  $\mu\text{g}/\text{kg}/\text{day}$  had no significant change in BMC. These results include data from patients who received less than 2 years of treatment. A greater

treatment effect was observed for patients who completed 2 years of treatment. Increases in lumbar spine BMD and BMC were also statistically significant compared to control with the 12.5 µg/kg/day dose but not the 25 µg/kg/day dose. Hip BMD and BMC did not change significantly compared to control with either dose. The effect of GH treatment on BMC and BMD in transition patients at doses lower than 12.5 µg/kg/day was not studied. The effect of Humatrope on the occurrence of osteoporotic fractures has not been studied.”

We completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert).

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDAs*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved supplement NDA 19-640/S-045.**" Approval of this submission by FDA is not required before the labeling is used.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications  
Center for Drug Evaluation and Research  
Food and Drug Administration  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

If you issue a letter communicating important information about this drug product (i.e., a “Dear Health Care Professional” letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410  
FDA  
5600 Fishers Lane  
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

We also remind you that all regulatory mail for this division should be addressed as follows:

Division of Metabolism and Endocrinology Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

If you have any questions, call Enid Galliers, Chief, Project Management Staff, at 301-796-1211.

Sincerely,

*{See appended electronic signature page}*

David G. Orloff, MD  
Director  
Division of Metabolism and Endocrinology  
Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosure

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**This is a representation of an electronic record that was signed electronically and  
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/s/

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David Orloff  
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