

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 219-640/S-032

Trade Name: Humatrope

Generic Name: [somatropin (rDNA origin) for injection]

Sponsor: Eli Lilly and Company

Approval Date: March 24, 2003

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APPROVAL LETTER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-640/S-032

Eli Lilly and Company
Attention: Jeffrey T. Fayerman, PhD
Sr. Regulatory Research Scientist, US Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Fayerman:

Please refer to your supplemental new drug application dated September 23, 2002, received September 24, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Humatrope [somatropin (rDNA origin) for injection].

This "Changes Being Effected" supplemental new drug application provides for the deletion of the criteria for biochemical diagnosis of adult growth hormone deficiency from the INDICATIONS AND USAGE section of the package insert.

We completed our review of this supplemental new drug application. It is approved, effective on the date of this letter, for use as recommended in the final printed labeling (FPL) submitted on September 23, 2002.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Monika Johnson, Regulatory Project Manager, at (301) 827-9087

Sincerely,

{See appended electronic signature page}

David G. Orloff, MD
Director
Division of Metabolic & Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

David Orloff

3/24/03 06:35:05 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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APPROVED LABELING

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HUMATROPE®
SOMATROPIN (rDNA ORIGIN) FOR INJECTION
VIALS
and
CARTRIDGES FOR USE WITH THE
HumatroPen™ INJECTION DEVICE

8

DESCRIPTION

9 Humatrope® (Somatropin, rDNA Origin, for Injection) is a polypeptide hormone of
10 recombinant DNA origin. Humatrope has 191 amino acid residues and a molecular weight of
11 about 22,125 daltons. The amino acid sequence of the product is identical to that of human
12 growth hormone of pituitary origin. Humatrope is synthesized in a strain of *Escherichia coli* that
13 has been modified by the addition of the gene for human growth hormone.

14 Humatrope is a sterile, white, lyophilized powder intended for subcutaneous or intramuscular
15 administration after reconstitution. Humatrope is a highly purified preparation. Phosphoric acid
16 and/or sodium hydroxide may have been added to adjust the pH. Reconstituted solutions have a
17 pH of approximately 7.5. This product is oxygen sensitive.

18 **VIAL** — Each vial of Humatrope contains 5 mg somatropin (15 IU or 225 nanomoles); 25 mg
19 mannitol; 5 mg glycine; and 1.13 mg dibasic sodium phosphate. Each vial is supplied in a
20 combination package with an accompanying 5-mL vial of diluting solution. The diluent contains
21 Water for Injection with 0.3% Metacresol as a preservative and 1.7% glycerin.

22 **CARTRIDGE** — The cartridges of somatropin contain either 6 mg (18 IU), 12 mg (36 IU), or
23 24 mg (72 IU) of somatropin. The 6, 12, and 24 mg cartridges contain respectively: mannitol 18,
24 36, and 72 mg; glycine 6, 12, and 24 mg; dibasic sodium phosphate 1.36, 2.72, and 5.43 mg.
25 Each cartridge is supplied in a combination package with an accompanying syringe containing
26 approximately 3 mL of diluting solution. The diluent contains Water for Injection;
27 0.3% Metacresol as a preservative; and 1.7%, 0.29%, and 0.29% glycerin in the 6, 12, and 24 mg
28 cartridges, respectively.

29

CLINICAL PHARMACOLOGY

30 **General**

31 *Linear Growth* — Humatrope stimulates linear growth in pediatric patients who lack adequate
32 normal endogenous growth hormone. In vitro, preclinical, and clinical testing have demonstrated
33 that Humatrope is therapeutically equivalent to human growth hormone of pituitary origin and
34 achieves equivalent pharmacokinetic profiles in normal adults. Treatment of growth
35 hormone-deficient pediatric patients and patients with Turner syndrome with Humatrope
36 produces increased growth rate and IGF-I (Insulin-like Growth Factor-I/Somatomedin-C)
37 concentrations similar to those seen after therapy with human growth hormone of pituitary
38 origin.

39 In addition, the following actions have been demonstrated for Humatrope and/or human
40 growth hormone of pituitary origin.

41 *A. Tissue Growth* — 1. Skeletal Growth: Humatrope stimulates skeletal growth in pediatric
42 patients with growth hormone deficiency. The measurable increase in body length after
43 administration of either Humatrope or human growth hormone of pituitary origin results from an
44 effect on the growth plates of long bones. Concentrations of IGF-I, which may play a role in
45 skeletal growth, are low in the serum of growth hormone-deficient pediatric patients but increase
46 during treatment with Humatrope. Elevations in mean serum alkaline phosphatase concentrations
47 are also seen. 2. Cell Growth: It has been shown that there are fewer skeletal muscle cells in

48 short-statured pediatric patients who lack endogenous growth hormone as compared with normal
49 pediatric populations. Treatment with human growth hormone of pituitary origin results in an
50 increase in both the number and size of muscle cells.

51 **B. Protein Metabolism** — Linear growth is facilitated in part by increased cellular protein
52 synthesis. Nitrogen retention, as demonstrated by decreased urinary nitrogen excretion and
53 serum urea nitrogen, follows the initiation of therapy with human growth hormone of pituitary
54 origin. Treatment with Humatrope results in a similar decrease in serum urea nitrogen.

55 **C. Carbohydrate Metabolism** — Pediatric patients with hypopituitarism sometimes experience
56 fasting hypoglycemia that is improved by treatment with Humatrope. Large doses of human
57 growth hormone may impair glucose tolerance. Untreated patients with Turner syndrome have
58 an increased incidence of glucose intolerance. Administration of human growth hormone to
59 normal adults or patients with Turner syndrome resulted in increases in mean serum fasting and
60 postprandial insulin levels although mean values remained in the normal range. In addition,
61 mean fasting and postprandial glucose and hemoglobin A_{1c} levels remained in the normal range.

62 **D. Lipid Metabolism** — In growth hormone-deficient patients, administration of human growth
63 hormone of pituitary origin has resulted in lipid mobilization, reduction in body fat stores, and
64 increased plasma fatty acids.

65 **E. Mineral Metabolism** — Retention of sodium, potassium, and phosphorus is induced by
66 human growth hormone of pituitary origin. Serum concentrations of inorganic phosphate
67 increased in patients with growth hormone deficiency after therapy with Humatrope or human
68 growth hormone of pituitary origin. Serum calcium is not significantly altered in patients treated
69 with either human growth hormone of pituitary origin or Humatrope.

70 **Pharmacokinetics**

71 **Absorption** — Humatrope has been studied following intramuscular, subcutaneous, and
72 intravenous administration in adult volunteers. The absolute bioavailability of somatotropin is 75%
73 and 63% after subcutaneous and intramuscular administration, respectively.

74 **Distribution** — The volume of distribution of somatotropin after intravenous injection is about
75 0.07 L/kg.

76 **Metabolism** — Extensive metabolism studies have not been conducted. The metabolic fate of
77 somatotropin involves classical protein catabolism in both the liver and kidneys. In renal cells, at
78 least a portion of the breakdown products of growth hormone is returned to the systemic
79 circulation. In normal volunteers, mean clearance is 0.14 L/hr/kg. The mean half-life of
80 intravenous somatotropin is 0.36 hours, whereas subcutaneously and intramuscularly administered
81 somatotropin have mean half-lives of 3.8 and 4.9 hours, respectively. The longer half-life observed
82 after subcutaneous or intramuscular administration is due to slow absorption from the injection
83 site.

84 **Excretion** — Urinary excretion of intact Humatrope has not been measured. Small amounts of
85 somatotropin have been detected in the urine of pediatric patients following replacement therapy.

86 **Special Populations**

87 **Geriatric** — The pharmacokinetics of Humatrope has not been studied in patients greater than
88 65 years of age.

89 **Pediatric** — The pharmacokinetics of Humatrope in pediatric patients is similar to adults.

90 **Gender** — No studies have been performed with Humatrope. The available literature indicates
91 that the pharmacokinetics of growth hormone is similar in both men and women.

92 **Race** — No data are available.

93 **Renal, Hepatic insufficiency** — No studies have been performed with Humatrope.

94

Table 1
Summary of Somatropin Parameters in the Normal Population

	C_{max} (ng/mL)	$t_{1/2}$ (hr)	$AUC_{0-\infty}$ (ng•hr/mL)	Cl _s (L/kg•hr)	$V\beta$ (L/kg)
0.02 mg (0.05 IU*)/kg					
iv					
MEAN	415	0.363	156	0.135	0.0703
SD	75	0.053	33	0.029	0.0173
0.1 mg (0.27 IU*)/kg					
im					
MEAN	53.2	4.93	495	0.215	1.55
SD	25.9	2.66	106	0.047	0.91
0.1 mg (0.27 IU*)/kg					
sc					
MEAN	63.3	3.81	585	0.179	0.957
SD	18.2	1.40	90	0.028	0.301

Abbreviations: C_{max} =maximum concentration; $t_{1/2}$ =half-life; $AUC_{0-\infty}$ =area under the curve; Cl_s=systemic clearance; $V\beta$ =volume distribution; iv=intravenous; SD=standard deviation; im=intramuscular; sc=subcutaneous.

* Based on previous International Standard of 2.7 IU=1 mg.

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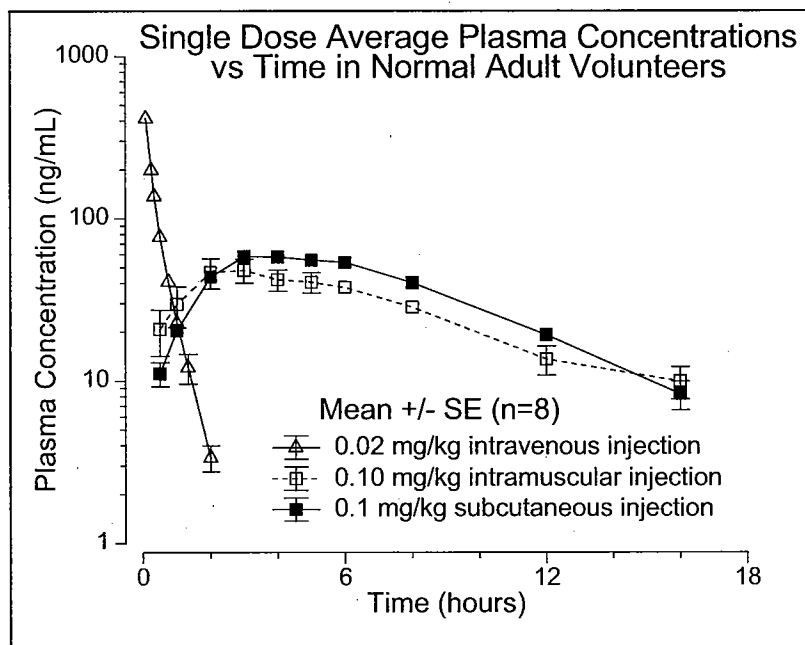


Figure 1

99
100
101

CLINICAL TRIALS

Effects of Humatrope Treatment in Adults with Growth Hormone Deficiency

Two multicenter trials in adult-onset growth hormone deficiency (n=98) and two studies in childhood-onset growth hormone deficiency (n=67) were designed to assess the effects of replacement therapy with Humatrope. The primary efficacy measures were body composition (lean body mass and fat mass), lipid parameters, and the Nottingham Health Profile. The Nottingham Health Profile is a general health-related quality of life questionnaire. These

107

108 four studies each included a 6-month randomized, blinded, placebo-controlled phase followed by
 109 12 months of open-label therapy for all patients. The Humatrope dosages for all studies were
 110 identical: 1 month of therapy at 0.00625 mg/kg/day followed by the proposed maintenance dose
 111 of 0.0125 mg/kg/day. Adult-onset patients and childhood-onset patients differed by diagnosis
 112 (organic vs. idiopathic pituitary disease), body size (normal vs. small for mean height and
 113 weight), and age (mean=44 vs. 29 years). Lean body mass was determined by bioelectrical
 114 impedance analysis (BIA), validated with potassium 40. Body fat was assessed by BIA and sum
 115 of skinfold thickness. Lipid subfractions were analyzed by standard assay methods in a central
 116 laboratory.

117 Humatrope-treated adult-onset patients, as compared to placebo, experienced an increase in
 118 lean body mass (2.59 vs. -0.22 kg, $p<0.001$) and a decrease in body fat (-3.27 vs. 0.56 kg,
 119 $p<0.001$). Similar changes were seen in childhood-onset growth hormone-deficient patients.
 120 These significant changes in lean body mass persisted throughout the 18-month period as
 121 compared to baseline for both groups, and for fat mass in the childhood-onset group. Total
 122 cholesterol decreased short-term (first 3 months) although the changes did not persist. However,
 123 the low HDL cholesterol levels observed at baseline (mean=30.1 mg/mL and 33.9 mg/mL in
 124 adult-onset and childhood-onset patients) normalized by the end of 18 months of therapy (a
 125 change of 13.7 and 11.1 mg/dL for the adult-onset and childhood-onset groups, $p<0.001$).
 126 Adult-onset patients reported significant improvements as compared to placebo in the following
 127 two of six possible health-related domains: physical mobility and social isolation (Table 2).
 128 Patients with childhood-onset disease failed to demonstrate improvements in Nottingham Health
 129 Profile outcomes.

130 Two additional studies on the effect of Humatrope on exercise capacity were also conducted.
 131 Improved physical function was documented by increased exercise capacity (VO_2 max, $p<0.005$)
 132 and work performance (Watts, $p<0.01$) (J Clin Endocrinol Metab 1995; 80:552-557).
 133

Table 2
Changes^a in Nottingham Health Profile Scores^b in Adult-Onset Growth Hormone-Deficient Patients

Outcome Measure	Placebo (6 Months)	Humatrope Therapy (6 Months)	Significance
Energy level	-11.4	-15.5	NS
Physical mobility	-3.1	-10.5	$p<0.01$
Social isolation	0.5	-4.7	$p<0.01$
Emotional reactions	-4.5	-5.4	NS
Sleep	-6.4	-3.7	NS
Pain	-2.8	-2.9	NS

134 ^a An improvement in score is indicated by a more negative change in the score.

135 ^b To account for multiple analyses, appropriate statistical methods were applied and the required level of
 136 significance is 0.01.

137 NS=not significant.
 138

139 **Effects of Growth Hormone Treatment in Patients with Turner Syndrome**

140 One long-term, randomized, open-label multicenter concurrently controlled study,
 141 two long-term, open-label multicenter, historically controlled studies and one long-term,
 142 randomized, dose-response study were conducted to evaluate the efficacy of growth hormone for
 143 the treatment of patients with short stature due to Turner syndrome.

144 In the randomized study, GDCT, comparing growth hormone-treated patients to a concurrent
 145 control group who received no growth hormone, the growth hormone-treated patients who

146 received a dose of 0.3 mg/kg/wk given 6 times per week from a mean age of 11.7 years for a
 147 mean duration of 4.7 years attained a mean near final height of 146.0 ± 6.2 cm (n=27,
 148 mean \pm SD) as compared to the control group who attained a near final height of 142.1 ± 4.8 cm
 149 (n=19). By analysis of covariance*, the effect of growth hormone therapy was a mean height
 150 increase of 5.4 cm (p=0.001).

151 In two of the studies (85-023 and 85-044), the effect of long-term growth hormone treatment
 152 (0.375 mg/kg/wk given either 3 times per week or daily) on adult height was determined by
 153 comparing adult heights in the treated patients with those of age-matched historical controls with
 154 Turner syndrome who never received any growth-promoting therapy. The greatest improvement
 155 in adult height was observed in patients who received early growth hormone treatment and
 156 estrogen after age 14 years. In Study 85-023, this resulted in a mean adult height gain of 7.4 cm
 157 (mean duration of GH therapy of 7.6 years) vs. matched historical controls by analysis of
 158 covariance.

159 In Study 85-044, patients treated with early growth hormone therapy were randomized to
 160 receive estrogen replacement therapy (conjugated estrogens, 0.3 mg escalating to 0.625 mg
 161 daily) at either age 12 or 15 years. Compared with matched historical controls, early GH therapy
 162 (mean duration of GH therapy 5.6 years) combined with estrogen replacement at age 12 years
 163 resulted in an adult height gain of 5.9 cm (n=26), whereas patients who initiated estrogen at age
 164 15 years (mean duration of GH therapy 6.1 years) had a mean adult height gain of 8.3 cm (n=29).
 165 Patients who initiated GH therapy after age 11 (mean age 12.7 years; mean duration of
 166 GH therapy 3.8 years) had a mean adult height gain of 5.0 cm (n=51).

167 In a randomized blinded dose-response study, GDCT, patients were treated from a mean age of
 168 11.1 years for a mean duration of 5.3 years with a weekly dose of either 0.27 mg/kg or
 169 0.36 mg/kg administered 3 or 6 times weekly. The mean near final height of patients receiving
 170 growth hormone was 148.7 ± 6.5 cm (n=31). When compared to historical control data, the mean
 171 gain in adult height was approximately 5 cm.

172 In some studies, Turner syndrome patients (n=181) treated to final adult height achieved
 173 statistically significant average height gains ranging from 5.0 to 8.3 cm.
 174

Table 3
Summary Table of Efficacy Results

Study/ Group	Study Design ^a	N at Adult Height	GH Age (yr)	Estrogen Age (yr)	GH Duration (yr)	Adult Height Gain (cm) ^b
GDCT	RCT	27	11.7	13	4.7	5.4
85-023	MHT	17	9.1	15.2	7.6	7.4
85-044:	A*	29	9.4	15	6.1	8.3
	B*	26	9.6	12.3	5.6	5.9
	C*	51	12.7	13.7	3.8	5
GDCI	RDT	31	11.1	8-13.5	5.3	~5 ^c

175 ^a RCT: randomized controlled trial; MHT: matched historical controlled trial; RDT: randomized dose-response trial.

176 ^b Analysis of covariance vs. controls.

177 ^c Compared with historical data.

178 * A: GH age <11 yr, estrogen age 15 yr.

179 B: GH age <11 yr, estrogen age 12 yr.

180 C: GH age >11 yr, estrogen at month 12.

181

* Analysis of covariance includes adjustments for baseline height relative to age and for mid-parental height.

182 **Effect of Humatrope Treatment in Pediatric Patients with Idiopathic Short Stature**

183 Two randomized, multicenter trials, 1 placebo-controlled and 1 dose-response, were conducted
 184 in pediatric patients with idiopathic short stature, also called non-growth hormone-deficient short
 185 stature. The diagnosis of idiopathic short stature was made after excluding other known causes of
 186 short stature, as well as growth hormone deficiency. Limited safety and efficacy data are
 187 available below the age of 7 years. No specific studies have been conducted in pediatric patients
 188 with familial short stature or who were born small for gestational age (SGA).

189 The placebo-controlled study enrolled 71 pediatric patients (55 males, 16 females) 9 to
 190 15 years old (mean age 12.38 ± 1.51 years), with short stature, 68 of whom received study drug.
 191 Patients were predominately Tanner I (45.1%) and Tanner II (46.5%) at baseline.

192 In this double-blind trial, patients received subcutaneous injections of either Humatrope
 193 0.222 mg/kg/wk or placebo. Study drug was given in divided doses 3 times per week until height
 194 velocity decreased to ≤ 1.5 cm/year ("final height"). Thirty-three subjects (22 Humatrope,
 195 11 placebo) had final height measurements after a mean treatment duration of 4.4 years (range
 196 0.11-9.08 years).

197 The Humatrope group achieved a mean final height Standard Deviation Score (SDS) of
 198 -1.8 (Table 4). Placebo-treated patients had a mean final height SDS of -2.3 (mean treatment
 199 difference = 0.51, $p=0.017$). Height gain across the duration of the study and final height SDS
 200 minus baseline predicted height SDS were also significantly greater in Humatrope-treated
 201 patients than in placebo-treated patients (Table 4 and 5). In addition, the number of patients who
 202 achieved a final height above the 5th percentile of the general population for age and sex was
 203 significantly greater in the Humatrope group than the placebo group (41% vs. 0%, $p<0.05$), as
 204 was the number of patients who gained at least 1 SDS unit in height across the duration of the
 205 study (50% vs. 0%, $p<0.05$).
 206

Table 4
Baseline Height Characteristics and Effect of Humatrope on Final Height^a

	Humatrope (n=22) Mean (SD)	Placebo (n=11) Mean (SD)	Treatment Effect Mean (95% CI)	p-value
Baseline height SDS	-2.7 (0.6)	-2.75 (0.6)		0.77
BPH SDS	-2.1 (0.7)	-2.3 (0.8)		0.53
Final height SDS ^b	-1.8 (0.8)	-2.3 (0.6)	0.51 (0.10, 0.92)	0.017
FH SDS - baseline height SDS	0.9 (0.7)	0.4 (0.2)	0.51 (0.04, 0.97)	0.034
FH SDS - BPH SDS	0.3 (0.6)	-0.1 (0.6)	0.46 (0.02, 0.89)	0.043

207 ^a For final height population.

208 ^b Between-group comparison was performed using analysis of covariance with baseline predicted height SDS as the
 209 covariant. Treatment effect is expressed as least squares mean (95% CI).

210 Abbreviations: FH=final height; SDS=standard deviation score; BPH=baseline predicted height; CI=confidence
 211 interval.
 212

213 The dose-response study included 239 pediatric patients (158 males, 81 females), 5 to 15 years
 214 old, (mean age 9.8 ± 2.3 years). Mean baseline characteristics included: a height SDS of
 215 -3.21 (± 0.70), a predicted adult height SDS of -2.63 (± 1.08), and a height velocity SDS of
 216 -1.09 (± 1.15). All but 3 patients were Tanner I. Patients were randomized to one of
 217 three Humatrope treatment groups: 0.24 mg/kg/wk; 0.24 mg/kg/wk for 1 year, followed by
 218 0.37 mg/kg/wk; and 0.37 mg/kg/wk.

219 The primary hypothesis of this study was that treatment with Humatrope would increase height
 220 velocity during the first 2 years of therapy in a dose-dependent manner. Additionally, after

221 completing the initial 2-year dose-response phase of the study, 50 patients were followed to final
222 height.

223 Patients receiving 0.37 mg/kg/wk had a significantly greater increase in mean height velocity
224 after 2 years of treatment than patients receiving 0.24 mg/kg/wk (4.04 vs. 3.27 cm/year,
225 $p=0.003$). The mean difference between final height and baseline predicted height was 7.2 cm for
226 patients receiving 0.37 mg/kg/wk and 5.4 cm for patients receiving 0.24 mg/kg/wk (Table 5).

227 While no patient had height above the 5th percentile in any dose group at baseline, 82% of the
228 patients receiving 0.37 mg/kg/wk and 47% of the patients receiving 0.24 mg/kg/wk achieved a
229 final height above the 5th percentile of the general population height standards ($p=NS$).

230

Table 5
Final Height Minus Baseline Predicted Height: Idiopathic Short Stature Trials

	Placebo-controlled Trial 3x per week dosing		Dose Response Trial 6x per week dosing		
	Placebo (n=10)	Humatrope 0.22 mg/kg (n=22)	Humatrope 0.24 mg/kg (n=13)	Humatrope 0.24/0.37 mg/kg (n=13)	Humatrope 0.37 mg/kg (n=13)
FH – Baseline PH					
Mean cm	-0.7	+2.2	+5.4	+6.7	+7.2
(95% CI)	(-3.6, 2.3)	(0.4, 3.9)	(2.8, 7.9)	(4.1, 9.2)	(4.6, 9.8)
Mean inches	-0.3	+0.8	+2.1	+2.6	+2.8
(95% CI)	(-1.4, 0.9)	(0.2, 1.5)	(1.1, 3.1)	(1.6, 3.6)	(1.8, 3.9)

231 Abbreviations: PH=predicted height; FH=final height; CI=confidence interval.

232

INDICATIONS AND USAGE

233

234 *Pediatric Patients* — Humatrope is indicated for the long-term treatment of pediatric patients
235 who have growth failure due to an inadequate secretion of normal endogenous growth hormone.

236 Humatrope is indicated for the treatment of short stature associated with Turner syndrome in
237 patients whose epiphyses are not closed.

238 Humatrope is indicated for the long-term treatment of idiopathic short stature, also called
239 non-growth hormone-deficient short stature, defined by height SDS ≤ -2.25 , and associated with
240 growth rates unlikely to permit attainment of adult height in the normal range, in pediatric
241 patients whose epiphyses are not closed and for whom diagnostic evaluation excludes other
242 causes associated with short stature that should be observed or treated by other means.

243 *Adult Patients* — Humatrope is indicated for replacement of endogenous growth hormone in
244 adults with growth hormone deficiency who meet either of the following two criteria:

245 1. **Adult Onset:** Patients who have growth hormone deficiency either alone, or with multiple
246 hormone deficiencies (hypopituitarism), as a result of pituitary disease, hypothalamic disease,
247 surgery, radiation therapy, or trauma;

248 **or**

249 2. **Childhood Onset:** Patients who were growth hormone-deficient during childhood who have
250 growth hormone deficiency confirmed as an adult before replacement therapy with Humatrope is
251 started.

252

CONTRAINDICATIONS

253 Humatrope should not be used for growth promotion in pediatric patients with closed
254 epiphyses.

255 Humatrope should not be used or should be discontinued when there is any evidence of active
256 malignancy. Anti-malignancy treatment must be complete with evidence of remission prior to
257 the institution of therapy.

258 Humatrope should **not** be reconstituted with the supplied Diluent for Humatrope for use by
259 patients with a known sensitivity to either Metacresol or glycerin.

260 Growth hormone should not be initiated to treat patients with acute critical illness due to
261 complications following open heart or abdominal surgery, multiple accidental trauma or to
262 patients having acute respiratory failure. Two placebo-controlled clinical trials in non-growth
263 hormone-deficient adult patients (n=522) with these conditions revealed a significant increase in
264 mortality (41.9% vs. 19.3%) among somatropin-treated patients (doses 5.3 to 8 mg/day)
265 compared to those receiving placebo (*see* WARNINGS).

266 Growth hormone is contraindicated in patients with Prader-Willi syndrome who are severely
267 obese or have severe respiratory impairment (*see* WARNINGS). Unless patients with
268 Prader-Willi syndrome also have a diagnosis of growth hormone deficiency, Humatrope is not
269 indicated for the long term treatment of pediatric patients who have growth failure due to
270 genetically confirmed Prader-Willi syndrome.

271

WARNINGS

272 If sensitivity to the diluent should occur, the **vials** may be reconstituted with Bacteriostatic
273 Water for Injection, USP or, Sterile Water for Injection, USP. When Humatrope is used with
274 Bacteriostatic Water (Benzyl Alcohol preserved), the solution should be kept refrigerated at
275 2° to 8°C (36° to 46°F) and used within 14 days. **Benzyl alcohol as a preservative in**
276 **Bacteriostatic Water for Injection, USP has been associated with toxicity in newborns.**
277 When administering Humatrope to newborns, use the Humatrope diluent provided or if the
278 patient is sensitive to the diluent, use Sterile Water for Injection, USP. When Humatrope is
279 reconstituted with Sterile Water for Injection, USP in this manner, use only one dose per
280 Humatrope vial and discard the unused portion. If the solution is not used immediately, it must
281 be refrigerated [2° to 8°C (36° to 46°F)] and used within 24 hours.

282 **Cartridges should be reconstituted only with the supplied diluent. Cartridges should not**
283 **be reconstituted with the Diluent for Humatrope provided with Humatrope Vials, or with**
284 **any other solution. Cartridges should not be used if the patient is allergic to Metacresol or**
285 **glycerin.**

286 See CONTRAINDICATIONS for information on increased mortality in patients with acute
287 critical illnesses in intensive care units due to complications following open heart or abdominal
288 surgery, multiple accidental trauma or with acute respiratory failure. The safety of continuing
289 growth hormone treatment in patients receiving replacement doses for approved indications who
290 concurrently develop these illnesses has not been established. Therefore, the potential benefit of
291 treatment continuation with growth hormone in patients having acute critical illnesses should be
292 weighed against the potential risk.

293 There have been reports of fatalities after initiating therapy with growth hormone in pediatric
294 patients with Prader-Willi syndrome who had one or more of the following risk factors: severe
295 obesity, history of upper airway obstruction or sleep apnea, or unidentified respiratory infection.
296 Male patients with one or more of these factors may be at greater risk than females. Patients with
297 Prader-Willi syndrome should be evaluated for signs of upper airway obstruction and sleep
298 apnea before initiation of treatment with growth hormone. If, during treatment with growth
299 hormone, patients show signs of upper airway obstruction (including onset of or increased
300 snoring) and/or new onset sleep apnea, treatment should be interrupted. All patients with
301 Prader-Willi syndrome treated with growth hormone should also have effective weight control
302 and be monitored for signs of respiratory infection, which should be diagnosed as early as
303 possible and treated aggressively (*see* CONTRAINDICATIONS). Unless patients with
304 Prader-Willi syndrome also have a diagnosis of growth hormone deficiency, Humatrope is not

305 indicated for the long term treatment of pediatric patients who have growth failure due to
306 genetically confirmed Prader-Willi syndrome.

307 PRECAUTIONS

308 *General* — Therapy with Humatrope should be directed by physicians who are experienced in
309 the diagnosis and management of patients with growth hormone deficiency, Turner syndrome,
310 idiopathic short stature, or adult patients with either childhood-onset or adult-onset growth
311 hormone deficiency.

312 Patients with preexisting tumors or with growth hormone deficiency secondary to an
313 intracranial lesion should be examined routinely for progression or recurrence of the underlying
314 disease process. In pediatric patients, clinical literature has demonstrated no relationship between
315 somatropin replacement therapy and CNS tumor recurrence. In adults, it is unknown whether
316 there is any relationship between somatropin replacement therapy and CNS tumor recurrence.

317 Patients should be monitored carefully for any malignant transformation of skin lesions.

318 For patients with diabetes mellitus, the insulin dose may require adjustment when somatropin
319 therapy is instituted. Because human growth hormone may induce a state of insulin resistance,
320 patients should be observed for evidence of glucose intolerance. Patients with diabetes or glucose
321 intolerance should be monitored closely during somatropin therapy.

322 In patients with hypopituitarism (multiple hormonal deficiencies) standard hormonal
323 replacement therapy should be monitored closely when somatropin therapy is administered.
324 Hypothyroidism may develop during treatment with somatropin and inadequate treatment of
325 hypothyroidism may prevent optimal response to somatropin.

326 *Pediatric Patients* (see General Precautions) — Pediatric patients with endocrine disorders,
327 including growth hormone deficiency, may develop slipped capital epiphyses more frequently.
328 Any pediatric patient with the onset of a limp during growth hormone therapy should be
329 evaluated.

330 Growth hormone has not been shown to increase the incidence of scoliosis. Progression of
331 scoliosis can occur in children who experience rapid growth. Because growth hormone increases
332 growth rate, patients with a history of scoliosis who are treated with growth hormone should be
333 monitored for progression of scoliosis. Skeletal abnormalities including scoliosis are commonly
334 seen in untreated Turner syndrome patients.

335 Patients with Turner syndrome should be evaluated carefully for otitis media and other ear
336 disorders since these patients have an increased risk of ear or hearing disorders (see Adverse
337 Reactions). Patients with Turner syndrome are at risk for cardiovascular disorders (e.g., stroke,
338 aortic aneurysm, hypertension) and these conditions should be monitored closely.

339 Patients with Turner syndrome have an inherently increased risk of developing autoimmune
340 thyroid disease. Therefore, patients should have periodic thyroid function tests and be treated as
341 indicated (see General Precautions).

342 Intracranial hypertension (IH) with papilledema, visual changes, headache, nausea and/or
343 vomiting has been reported in a small number of pediatric patients treated with growth hormone
344 products. Symptoms usually occurred within the first 8 weeks of the initiation of growth
345 hormone therapy. In all reported cases, IH-associated signs and symptoms resolved after
346 termination of therapy or a reduction of the growth hormone dose. Funduscopic examination of
347 patients is recommended at the initiation and periodically during the course of growth hormone
348 therapy. Patients with Turner syndrome may be at increased risk for development of IH.

349 *Adult Patients* (see General Precautions) — Patients with epiphyseal closure who were treated
350 with growth hormone replacement therapy in childhood should be re-evaluated according to the
351 criteria in INDICATIONS AND USAGE before continuation of somatropin therapy at the
352 reduced dose level recommended for growth hormone-deficient adults.

353 Experience with prolonged treatment in adults is limited.

354 *Geriatric Use* — The safety and effectiveness of Humatrope in patients aged 65 and over has
 355 not been evaluated in clinical studies. Elderly patients may be more sensitive to the action of
 356 Humatrope and may be more prone to develop adverse reactions.

357 *Drug Interactions* — Excessive glucocorticoid therapy may prevent optimal response to
 358 somatotropin. If glucocorticoid replacement therapy is required, the glucocorticoid dosage and
 359 compliance should be monitored carefully to avoid either adrenal insufficiency or inhibition of
 360 growth promoting effects.

361 Limited published data indicate that growth hormone (GH) treatment increases
 362 cytochrome P450 (CP450) mediated antipyrine clearance in man. These data suggest that
 363 GH administration may alter the clearance of compounds known to be metabolized by
 364 CP450 liver enzymes (e.g., corticosteroids, sex steroids, anticonvulsants, cyclosporin). Careful
 365 monitoring is advisable when GH is administered in combination with other drugs known to be
 366 metabolized by CP450 liver enzymes.

367 *Carcinogenesis, Mutagenesis, Impairment of Fertility* — Long-term animal studies for
 368 carcinogenicity and impairment of fertility with this human growth hormone (Humatrope) have
 369 not been performed. There has been no evidence to date of Humatrope-induced mutagenicity.

370 *Pregnancy — Pregnancy Category C* — Animal reproduction studies have not been conducted
 371 with Humatrope. It is not known whether Humatrope can cause fetal harm when administered to
 372 a pregnant woman or can affect reproductive capacity. Humatrope should be given to a pregnant
 373 woman only if clearly needed.

374 *Nursing Mothers* — There have been no studies conducted with Humatrope in nursing
 375 mothers. It is not known whether this drug is excreted in human milk. Because many drugs are
 376 excreted in human milk, caution should be exercised when Humatrope is administered to a
 377 nursing woman.

378 *Information for Patients* — Patients being treated with growth hormone and/or their parents
 379 should be informed of the potential risks and benefits associated with treatment. Instructions on
 380 appropriate use should be given, including a review of the contents of the patient information
 381 insert. This information is intended to aid in the safe and effective administration of the
 382 medication. It is not a disclosure of all possible adverse or intended effects.

383 Patients and/or parents should be thoroughly instructed in the importance of proper needle
 384 disposal. A puncture resistant container should be used for the disposal of used needles and/or
 385 syringes (consistent with applicable state requirements). Needles and syringes must not be reused
 386 (*see* Information for the Patient insert).

387 ADVERSE REACTIONS

388 Growth Hormone-Deficient Pediatric Patients

389 As with all protein pharmaceuticals, a small percentage of patients may develop antibodies to
 390 the protein. During the first 6 months of Humatrope therapy in 314 naive patients, only 1.6%
 391 developed specific antibodies to Humatrope (binding capacity ≥ 0.02 mg/L). None had antibody
 392 concentrations which exceeded 2 mg/L. Throughout 8 years of this same study, two patients
 393 (0.6%) had binding capacity > 2 mg/L. Neither patient demonstrated a decrease in growth
 394 velocity at or near the time of increased antibody production. It has been reported that growth
 395 attenuation from pituitary-derived growth hormone may occur when antibody concentrations are
 396 > 1.5 mg/L.

397 In addition to an evaluation of compliance with the treatment program and of thyroid status,
 398 testing for antibodies to human growth hormone should be carried out in any patient who fails to
 399 respond to therapy.

400 In studies with growth hormone-deficient pediatric patients, injection site pain was reported
 401 infrequently. A mild and transient edema, which appeared in 2.5% of patients, was observed
 402 early during the course of treatment.

403 Leukemia has been reported in a small number of pediatric patients who have been treated with
 404 growth hormone, including growth hormone of pituitary origin as well as of recombinant
 405 DNA origin (somatrem and somatropin). The relationship, if any, between leukemia and growth
 406 hormone therapy is uncertain.

407 **Turner Syndrome Patients**

408 In a randomized, concurrent controlled trial, there was a statistically significant increase in the
 409 occurrence of otitis media (43% vs. 26%), ear disorders (18% vs. 5%) and surgical procedures
 410 (45% vs. 27%) in patients receiving Humatrope compared with untreated control patients
 411 (Table 6). Other adverse events of special interest to Turner syndrome patients were not
 412 significantly different between treatment groups (Table 6). A similar increase in otitis media was
 413 observed in an 18-month placebo-controlled trial.
 414

Table 6
 Treatment-Emergent Events of Special Interest by Treatment Group in Turner Syndrome

Adverse Event	Overall	Treatment Group		Significance
		hGH ¹	Untreated ²	
Total Number of Patients	136	74	62	
Surgical procedure	50 (36.8%)	33 (44.6%)	17 (27.4%)	p≤0.05
Otitis media	48 (35.3%)	32 (43.2%)	16 (25.8%)	p≤0.05
Ear disorders	16 (11.8%)	13 (17.6%)	3 (4.8%)	p≤0.05
Bone disorder	13 (9.6%)	6 (8.1%)	7 (11.3%)	NS
Edema				
Conjunctival	1 (0.7%)	0	1 (1.6%)	NS
Non-specific	3 (2.2%)	2 (2.7%)	1 (1.6%)	NS
Facial	1 (0.7%)	1 (1.4%)	0	NS
Peripheral	6 (4.4%)	5 (6.8%)	1 (1.6%)	NS
Hyperglycemia	0	0	0	NS
Hypothyroidism	15 (11.0%)	10 (13.5%)	5 (8.1%)	NS
Increased nevi ³	10 (7.4%)	8 (10.8%)	2 (3.2%)	NS
Lymphedema	0	0	0	NS

415 ¹ Dose=0.3 mg/kg/wk.

416 ² Open-label study.

417 ³ Includes any nevi coded to the following preferred terms: melanosis, skin hypertrophy, or skin benign neoplasm.
 418 NS=not significant.
 419

420 **Patients with Idiopathic Short Stature**

421 In the placebo-controlled study, the adverse events associated with Humatrope therapy were
 422 similar to those observed in other pediatric populations treated with Humatrope (Table 7). Mean
 423 serum glucose level did not change during Humatrope treatment. Mean fasting serum insulin
 424 levels increased 10% in the Humatrope treatment group at the end of treatment relative to
 425 baseline values but remained within the normal reference range. For the same duration of
 426 treatment the mean fasting serum insulin levels decreased by 2% in the placebo group. The
 427 incidence of above-range values for glucose, insulin, and HbA_{1c} were similar in the growth
 428 hormone and placebo-treated groups. No patient developed diabetes mellitus. Consistent with the
 429 known mechanism of growth hormone action, Humatrope-treated patients had greater mean
 430 increases, relative to baseline, in serum insulin-like growth factor-I (IGF-I) than placebo-treated
 431 patients at each study observation. However, there was no significant difference between the
 432 Humatrope and placebo treatment groups in the proportion of patients who had at least

433 one serum IGF-I concentration more than 2.0 SD above the age- and gender-appropriate mean
 434 (Humatrope: 9 of 35 patients [26%]; placebo: 7 of 28 patients [25%]).
 435

Table 7
Nonserious Clinically Significant Treatment-Emergent Adverse Events by
Treatment Group in Idiopathic Short Stature

Adverse Event	Treatment Group	
	Humatrope	Placebo
Total Number of Patients	37	31
Scoliosis	7 (18.9%)	4 (12.9%)
Otitis media	6 (16.2%)	2 (6.5%)
Hyperlipidemia	3 (8.1%)	1 (3.2%)
Gynecomastia	2 (5.4%)	1 (3.2%)
Hypothyroidism	0	2 (6.5%)
Aching joints	0	1 (3.2%)
Hip pain	1 (2.7%)	0
Arthralgia	4 (10.8%)	1 (3.2%)
Arthrosis	4 (10.8%)	2 (6.5%)
Myalgia	9 (24.3%)	4 (12.9%)
Hypertension	1 (2.7%)	0

436
 437 The adverse events observed in the dose-response study (239 patients treated for 2 years) did
 438 not indicate a pattern suggestive of a growth hormone dose effect. Among Humatrope dose
 439 groups, mean fasting blood glucose, mean glycosylated hemoglobin, and the incidence of
 440 elevated fasting blood glucose concentrations were similar. One patient developed abnormalities
 441 of carbohydrate metabolism (glucose intolerance and high serum HbA_{1c}) on treatment.

442 *Adult Patients* — In clinical studies in which high doses of Humatrope were administered to
 443 healthy adult volunteers, the following events occurred infrequently: headache, localized muscle
 444 pain, weakness, mild hyperglycemia, and glucosuria.

445 In the first 6 months of controlled blinded trials during which patients received either
 446 Humatrope or placebo, adult-onset growth hormone-deficient adults who received Humatrope
 447 experienced a statistically significant increase in edema (Humatrope 17.3% vs. placebo 4.4%,
 448 $p=0.043$) and peripheral edema (11.5% vs. 0%, respectively, $p=0.017$). In patients with
 449 adult-onset growth hormone deficiency, edema, muscle pain, joint pain, and joint disorder were
 450 reported early in therapy and tended to be transient or responsive to dosage titration.

451 Two of 113 adult-onset patients developed carpal tunnel syndrome after beginning
 452 maintenance therapy without a low dose (0.00625 mg/kg/day) lead-in phase. Symptoms abated
 453 in these patients after dosage reduction.

454 All treatment-emergent adverse events with $\geq 5\%$ overall incidence during 12 or 18 months of
 455 replacement therapy with Humatrope are shown in Table 8 (adult-onset patients) and in Table 9
 456 (childhood-onset patients).

457 Adult patients treated with Humatrope who had been diagnosed with growth hormone
 458 deficiency in childhood reported side effects less frequently than those with adult-onset growth
 459 hormone deficiency.

460

Table 8
Treatment-Emergent Adverse Events with $\geq 5\%$ Overall Incidence in Adult-Onset Growth Hormone-Deficient Patients Treated with Humatrope for 18 Months as Compared with 6-Month Placebo and 12-Month Humatrope Exposure

Adverse Event	18 Months Exposure [Placebo (6 Months)/hGH (12 Months)] (N=46)		18 Months hGH Exposure (N=52)	
	n	%	n	%
Edema ^a	7	15.2	11	21.2
Arthralgia	7	15.2	9	17.3
Paresthesia	6	13.0	9	17.3
Myalgia	6	13.0	7	13.5
Pain	6	13.0	7	13.5
Rhinitis	5	10.9	7	13.5
Peripheral edema ^b	8	17.4	6	11.5
Back pain	5	10.9	5	9.6
Headache	5	10.9	4	7.7
Hypertension	2	4.3	4	7.7
Acne	0	0	3	5.8
Joint disorder	1	2.2	3	5.8
Surgical procedure	1	2.2	3	5.8
Flu syndrome	3	6.5	2	3.9

461 Abbreviations: hGH=Humatrope; N=number of patients receiving treatment in the period stated; n=number of
 462 patients reporting each treatment-emergent adverse event.

463 ^a p=0.04 as compared to placebo (6 months).

464 ^b p=0.02 as compared to placebo (6 months).

465

