

IDENTIFIER

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

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DESCRIPTION

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

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

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

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

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CLINICAL PHARMACOLOGY

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General

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

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

44 **A. Tissue Growth** — 1. Skeletal Growth: Humatrope stimulates skeletal growth in pediatric
45 patients with growth hormone deficiency. The measurable increase in body length after
46 administration of either Humatrope or human growth hormone of pituitary origin results from an
47 effect on the growth plates of long bones. Concentrations of IGF-I, which may play a role in
skeletal growth, are low in the serum of growth hormone-deficient pediatric patients but increase
during treatment with Humatrope. Elevations in mean serum alkaline phosphatase concentrations
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 somatropin is 75%
73 and 63% after subcutaneous and intramuscular administration, respectively.

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

76 **Metabolism** — Extensive metabolism studies have not been conducted. The metabolic fate of
77 somatropin 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 somatropin is 0.36 hours, whereas subcutaneously and intramuscularly administered
81 somatropin 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 somatropin 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.

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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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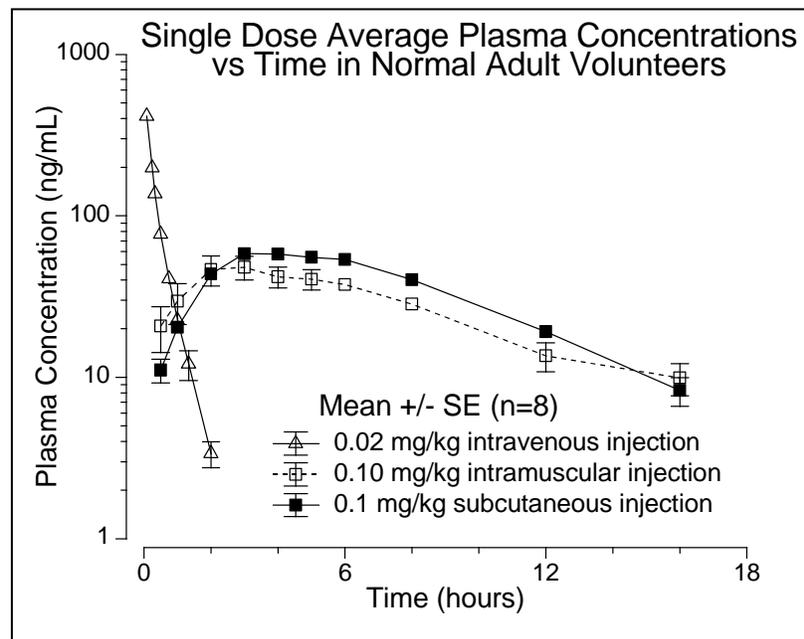


Figure 1

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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

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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 Two studies evaluating the effect of Humatrope on bone mineralization were subsequently
134 conducted. In a 2-year, randomized, double-blind, placebo-controlled trial, 67 patients with
135 previously untreated adult-onset growth hormone (GH) deficiency received placebo or
136 Humatrope treatment titrated to maintain serum IGF-I within the age-adjusted normal range. In
137 men, but not women, lumbar spine bone mineral density (BMD) increased with Humatrope
138 treatment compared to placebo with a treatment difference of approximately 4% ($p=0.001$).
139 There was no significant change in hip BMD with Humatrope treatment in men or women, when
140 compared to placebo. In a 2-year, open-label, randomized trial, 149 patients with
141 childhood-onset GH deficiency, who had completed pediatric GH therapy, had attained final
142 height (height velocity < 1 cm/yr) and were confirmed to be GH-deficient as young adults
143 (commonly referred to as transition patients), received Humatrope 12.5 μ g/kg/day, Humatrope
144 25 μ g/kg/day, or were followed with no therapy. Patients who were randomized to treatment
145 with Humatrope at 12.5 μ g/kg/day achieved a 2.9% greater increase from baseline than control
146 in total body bone mineral content (BMC) ($8.1 \pm 9.0\%$ vs. $5.2 \pm 8.2\%$, $p=0.02$), whereas patients
147 treated with Humatrope at 25 μ g/kg/day had no significant change in BMC. These results include
148 data from patients who received less than 2 years of treatment. A greater treatment effect was
149 observed for patients who completed 2 years of treatment. Increases in lumbar spine BMD and
150 BMC were also statistically significant compared to control with the 12.5 μ g/kg/day dose but not
151 the 25 μ g/kg/day dose. Hip BMD and BMC did not change significantly compared to control
152 with either dose. The effect of GH treatment on BMC and BMD in transition patients at doses
153 lower than 12.5 μ g/kg/day was not studied. The effect of Humatrope on the occurrence of
154 osteoporotic fractures has not been studied.

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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

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

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

159 NS=not significant.

160

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

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

166 In the randomized study, GDCT, comparing growth hormone-treated patients to a concurrent
 167 control group who received no growth hormone, the growth hormone-treated patients who
 168 received a dose of 0.3 mg/kg/wk given 6 times per week from a mean age of 11.7 years for a
 169 mean duration of 4.7 years attained a mean near final height of 146.0 ± 6.2 cm (n=27,
 170 mean ± SD) as compared to the control group who attained a near final height of 142.1 ± 4.8 cm
 171 (n=19). By analysis of covariance*, the effect of growth hormone therapy was a mean height
 172 increase of 5.4 cm (p=0.001).

173 In two of the studies (85-023 and 85-044), the effect of long-term growth hormone treatment
 174 (0.375 mg/kg/wk given either 3 times per week or daily) on adult height was determined by
 175 comparing adult heights in the treated patients with those of age-matched historical controls with
 176 Turner syndrome who never received any growth-promoting therapy. The greatest improvement
 177 in adult height was observed in patients who received early growth hormone treatment and
 178 estrogen after age 14 years. In Study 85-023, this resulted in a mean adult height gain of 7.4 cm
 179 (mean duration of GH therapy of 7.6 years) vs. matched historical controls by analysis of
 180 covariance.

181 In Study 85-044, patients treated with early growth hormone therapy were randomized to
 182 receive estrogen replacement therapy (conjugated estrogens, 0.3 mg escalating to 0.625 mg
 183 daily) at either age 12 or 15 years. Compared with matched historical controls, early GH therapy
 184 (mean duration of GH therapy 5.6 years) combined with estrogen replacement at age 12 years
 185 resulted in an adult height gain of 5.9 cm (n=26), whereas patients who initiated estrogen at age
 186 15 years (mean duration of GH therapy 6.1 years) had a mean adult height gain of 8.3 cm (n=29).
 187 Patients who initiated GH therapy after age 11 (mean age 12.7 years; mean duration of
 188 GH therapy 3.8 years) had a mean adult height gain of 5.0 cm (n=51).

189 In a randomized blinded dose-response study, GDCl, patients were treated from a mean age of
 190 11.1 years for a mean duration of 5.3 years with a weekly dose of either 0.27 mg/kg or

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

191 0.36 mg/kg administered 3 or 6 times weekly. The mean near final height of patients receiving
 192 growth hormone was 148.7 ± 6.5 cm (n=31). When compared to historical control data, the mean
 193 gain in adult height was approximately 5 cm.

194 In some studies, Turner syndrome patients (n=181) treated to final adult height achieved
 195 statistically significant average height gains ranging from 5.0 to 8.3 cm.
 196

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

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

198 ^b Analysis of covariance vs. controls.

199 ^c Compared with historical data.

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

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

202 C: GH age >11 yr, estrogen at month 12.
 203

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

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

211 The placebo-controlled study enrolled 71 pediatric patients (55 males, 16 females) 9 to
 212 15 years old (mean age 12.38 ± 1.51 years), with short stature, 68 of whom received study drug.
 213 Patients were predominately Tanner I (45.1%) and Tanner II (46.5%) at baseline.

214 In this double-blind trial, patients received subcutaneous injections of either Humatrope
 215 0.222 mg/kg/wk or placebo. Study drug was given in divided doses 3 times per week until height
 216 velocity decreased to ≤ 1.5 cm/year (“final height”). Thirty-three subjects (22 Humatrope,
 217 11 placebo) had final height measurements after a mean treatment duration of 4.4 years (range
 218 0.11-9.08 years).

219 The Humatrope group achieved a mean final height Standard Deviation Score (SDS) of
 220 -1.8 (Table 4). Placebo-treated patients had a mean final height SDS of -2.3 (mean treatment
 221 difference = 0.51, $p=0.017$). Height gain across the duration of the study and final height SDS
 222 minus baseline predicted height SDS were also significantly greater in Humatrope-treated
 223 patients than in placebo-treated patients (Table 4 and 5). In addition, the number of patients who
 224 achieved a final height above the 5th percentile of the general population for age and sex was
 225 significantly greater in the Humatrope group than the placebo group (41% vs. 0%, $p<0.05$), as
 226 was the number of patients who gained at least 1 SDS unit in height across the duration of the
 227 study (50% vs. 0%, $p<0.05$).
 228

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

^a For final height population.

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

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

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

The primary hypothesis of this study was that treatment with Humatrope would increase height velocity during the first 2 years of therapy in a dose-dependent manner. Additionally, after completing the initial 2-year dose-response phase of the study, 50 patients were followed to final height.

Patients receiving 0.37 mg/kg/wk had a significantly greater increase in mean height velocity after 2 years of treatment than patients receiving 0.24 mg/kg/wk (4.04 vs. 3.27 cm/year, $p=0.003$). The mean difference between final height and baseline predicted height was 7.2 cm for patients receiving 0.37 mg/kg/wk and 5.4 cm for patients receiving 0.24 mg/kg/wk (Table 5). While no patient had height above the 5th percentile in any dose group at baseline, 82% of the patients receiving 0.37 mg/kg/wk and 47% of the patients receiving 0.24 mg/kg/wk achieved a final height above the 5th percentile of the general population height standards ($p=NS$).

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 (95% CI)	-0.7 (-3.6, 2.3)	+2.2 (0.4, 3.9)	+5.4 (2.8, 7.9)	+6.7 (4.1, 9.2)	+7.2 (4.6, 9.8)
Mean inches (95% CI)	-0.3 (-1.4, 0.9)	+0.8 (0.2, 1.5)	+2.1 (1.1, 3.1)	+2.6 (1.6, 3.6)	+2.8 (1.8, 3.9)

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

INDICATIONS AND USAGE

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

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

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

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

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

270 **or**

271 2. Childhood Onset: Patients who were growth hormone-deficient during childhood who have
272 growth hormone deficiency confirmed as an adult before replacement therapy with Humatrope is
273 started.

CONTRAINDICATIONS

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275 Humatrope should not be used for growth promotion in pediatric patients with closed
276 epiphyses.

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

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

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

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

293

WARNINGS

294 If sensitivity to the diluent should occur, the **vials** may be reconstituted with Bacteriostatic
295 Water for Injection, USP or, Sterile Water for Injection, USP. When Humatrope is used with
296 Bacteriostatic Water (Benzyl Alcohol preserved), the solution should be kept refrigerated at
297 2° to 8°C (36° to 46°F) and used within 14 days. **Benzyl alcohol as a preservative in**
298 **Bacteriostatic Water for Injection, USP has been associated with toxicity in newborns.**
299 When administering Humatrope to newborns, use the Humatrope diluent provided or if the
300 patient is sensitive to the diluent, use Sterile Water for Injection, USP. When Humatrope is
301 reconstituted with Sterile Water for Injection, USP in this manner, use only one dose per
302 Humatrope vial and discard the unused portion. If the solution is not used immediately, it must
303 be refrigerated [2° to 8°C (36° to 46°F)] and used within 24 hours.

304 **Cartridges should be reconstituted only with the supplied diluent. Cartridges should not**
305 **be reconstituted with the Diluent for Humatrope provided with Humatrope Vials, or with**
306 **any other solution. Cartridges should not be used if the patient is allergic to Metacresol or**
307 **glycerin.**

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

315 There have been reports of fatalities after initiating therapy with growth hormone in pediatric
316 patients with Prader-Willi syndrome who had one or more of the following risk factors: severe
317 obesity, history of upper airway obstruction or sleep apnea, or unidentified respiratory infection.
318 Male patients with one or more of these factors may be at greater risk than females. Patients with
319 Prader-Willi syndrome should be evaluated for signs of upper airway obstruction and sleep
320 apnea before initiation of treatment with growth hormone. If, during treatment with growth
321 hormone, patients show signs of upper airway obstruction (including onset of or increased
322 snoring) and/or new onset sleep apnea, treatment should be interrupted. All patients with
323 Prader-Willi syndrome treated with growth hormone should also have effective weight control
324 and be monitored for signs of respiratory infection, which should be diagnosed as early as
325 possible and treated aggressively (*see* CONTRAINDICATIONS). Unless patients with
326 Prader-Willi syndrome also have a diagnosis of growth hormone deficiency, Humatrope is not
327 indicated for the long term treatment of pediatric patients who have growth failure due to
328 genetically confirmed Prader-Willi syndrome.

329 **PRECAUTIONS**

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

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

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

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

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

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

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

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

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

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

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

375 Experience with prolonged treatment in adults is limited.

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

379 *Drug Interactions* — Excessive glucocorticoid therapy may prevent optimal response to
380 somatropin. If glucocorticoid replacement therapy is required, the glucocorticoid dosage and
381 compliance should be monitored carefully to avoid either adrenal insufficiency or inhibition of
382 growth promoting effects.

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

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

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

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

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

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

409 **ADVERSE REACTIONS**

410 **Growth Hormone-Deficient Pediatric Patients**

411 As with all protein pharmaceuticals, a small percentage of patients may develop antibodies to
 412 the protein. During the first 6 months of Humatrope therapy in 314 naive patients, only 1.6%
 413 developed specific antibodies to Humatrope (binding capacity ≥ 0.02 mg/L). None had antibody
 414 concentrations which exceeded 2 mg/L. Throughout 8 years of this same study, two patients
 415 (0.6%) had binding capacity > 2 mg/L. Neither patient demonstrated a decrease in growth
 416 velocity at or near the time of increased antibody production. It has been reported that growth
 417 attenuation from pituitary-derived growth hormone may occur when antibody concentrations are
 418 > 1.5 mg/L.

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

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

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

429 **Turner Syndrome Patients**

430 In a randomized, concurrent controlled trial, there was a statistically significant increase in the
 431 occurrence of otitis media (43% vs. 26%), ear disorders (18% vs. 5%) and surgical procedures
 432 (45% vs. 27%) in patients receiving Humatrope compared with untreated control patients
 433 (Table 6). Other adverse events of special interest to Turner syndrome patients were not
 434 significantly different between treatment groups (Table 6). A similar increase in otitis media was
 435 observed in an 18-month placebo-controlled trial.

436

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 \leq 0.05
Otitis media	48 (35.3%)	32 (43.2%)	16 (25.8%)	p \leq 0.05
Ear disorders	16 (11.8%)	13 (17.6%)	3 (4.8%)	p \leq 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

437 ¹ Dose=0.3 mg/kg/wk.

438 ² Open-label study.

439 ³ Includes any nevi coded to the following preferred terms: melanosis, skin hypertrophy, or skin benign neoplasm.

440 NS=not significant.

441

442 Patients with Idiopathic Short Stature

443 In the placebo-controlled study, the adverse events associated with Humatrope therapy were
 444 similar to those observed in other pediatric populations treated with Humatrope (Table 7). Mean
 445 serum glucose level did not change during Humatrope treatment. Mean fasting serum insulin
 446 levels increased 10% in the Humatrope treatment group at the end of treatment relative to
 447 baseline values but remained within the normal reference range. For the same duration of
 448 treatment the mean fasting serum insulin levels decreased by 2% in the placebo group. The
 449 incidence of above-range values for glucose, insulin, and HbA_{1c} were similar in the growth
 450 hormone and placebo-treated groups. No patient developed diabetes mellitus. Consistent with the
 451 known mechanism of growth hormone action, Humatrope-treated patients had greater mean
 452 increases, relative to baseline, in serum insulin-like growth factor-I (IGF-I) than placebo-treated
 453 patients at each study observation. However, there was no significant difference between the
 454 Humatrope and placebo treatment groups in the proportion of patients who had at least
 455 one serum IGF-I concentration more than 2.0 SD above the age- and gender-appropriate mean
 456 (Humatrope: 9 of 35 patients [26%]; placebo: 7 of 28 patients [25%]).

457

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

458

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

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

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

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

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

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

482

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

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

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

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

487

Table 9
Treatment-Emergent Adverse Events with $\geq 5\%$ Overall Incidence in Childhood-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=35)		18 Months hGH Exposure (N=32)	
	n	%	n	%
Flu syndrome	8	22.9	5	15.6
AST increased ^a	2	5.7	4	12.5
Headache	4	11.4	3	9.4
Asthenia	1	2.9	2	6.3
Cough increased	0	0	2	6.3
Edema	3	8.6	2	6.3
Hypesthesia	0	0	2	6.3
Myalgia	2	5.7	2	6.3
Pain	3	8.6	2	6.3
Rhinitis	2	5.7	2	6.3
ALT increased	2	5.7	2	6.3
Respiratory disorder	2	5.7	1	3.1
Gastritis	2	5.7	0	0
Pharyngitis	5	14.3	1	3.1

488 Abbreviations: hGH=Humatrope; N=number of patients receiving treatment in the period stated; n=number of
489 patients reporting each treatment-emergent adverse event; ALT=alanine amino transferase, formerly SGPT;
490 AST=aspartate amino transferase, formerly SGOT.
491 ^a p=0.03 as compared to placebo (6 months).
492

493 Other adverse drug events that have been reported in growth hormone-treated patients include
494 the following:

- 495 1) Metabolic: Infrequent, mild and transient peripheral or generalized edema.
- 496 2) Musculoskeletal: Rare carpal tunnel syndrome.
- 497 3) Skin: Rare increased growth of pre-existing nevi. Patients should be monitored carefully
498 for malignant transformation.
- 499 4) Endocrine: Rare gynecomastia. Rare pancreatitis.

500 OVERDOSAGE

501 Acute overdosage could lead initially to hypoglycemia and subsequently to hyperglycemia.
502 Long-term overdosage could result in signs and symptoms of gigantism/acromegaly consistent
503 with the known effects of excess human growth hormone. (See recommended and maximal
504 dosage instructions given below.)

505 DOSAGE AND ADMINISTRATION

506 Pediatric Patients

507 The Humatrope dosage and administration schedule should be individualized for each patient.
508 Therapy should not be continued if epiphyseal fusion has occurred. Response to growth hormone
509 therapy tends to decrease with time. However, failure to increase growth rate, particularly during
510 the first year of therapy, should prompt close assessment of compliance and evaluation of other
511 causes of growth failure such as hypothyroidism, under-nutrition and advanced bone age.

512 *Growth hormone-deficient pediatric patients* — The recommended weekly dosage is
513 0.18 mg/kg (0.54 IU/kg) of body weight. The maximal replacement weekly dosage is

514 0.3 mg/kg (0.90 IU/kg) of body weight. It should be divided into equal doses given either on
515 3 alternate days, 6 times per week or daily. The subcutaneous route of administration is
516 preferable; intramuscular injection is also acceptable. The dosage and administration schedule
517 for Humatrope should be individualized for each patient.

518 *Turner Syndrome* — A weekly dosage of up to 0.375 mg/kg (1.125 IU/kg) of body weight
519 administered by subcutaneous injection is recommended. It should be divided into equal doses
520 given either daily or on 3 alternate days.

521 *Patients with idiopathic short stature* — A weekly dosage of up to 0.37 mg/kg of body weight
522 administered by subcutaneous injection is recommended. It should be divided into equal doses
523 given 6 to 7 times per week.

524 **Adult Patients**

525 *Growth hormone-deficient adult patients* — The recommended dosage at the start of therapy is
526 not more than 0.006 mg/kg/day (0.018 IU/kg/day) given as a daily subcutaneous injection. The
527 dose may be increased according to individual patient requirements to a maximum of
528 0.0125 mg/kg/day (0.0375 IU/kg/day).

529 During therapy, dosage should be titrated if required by the occurrence of side effects or to
530 maintain the IGF-I response below the upper limit of normal IGF-I levels, matched for age and
531 sex. To minimize the occurrence of adverse events in patients with increasing age or excessive
532 body weight, dose reductions may be necessary.

533 **Reconstitution**

534 **Vial** — Each 5-mg vial of Humatrope should be reconstituted with 1.5 to 5 mL of Diluent for
535 Humatrope. The diluent should be injected into the vial of Humatrope by aiming the stream of
536 liquid against the glass wall. Following reconstitution, the vial should be swirled with a
537 GENTLE rotary motion until the contents are completely dissolved. **DO NOT SHAKE**. The
538 resulting solution should be inspected for clarity. It should be clear. If the solution is cloudy or
539 contains particulate matter, the contents **MUST NOT** be injected.

540 Before and after injection, the septum of the vial should be wiped with rubbing alcohol or an
541 alcoholic antiseptic solution to prevent contamination of the contents by repeated needle
542 insertions. Sterile disposable syringes and needles should be used for administration of
543 Humatrope. The volume of the syringe should be small enough so that the prescribed dose can be
544 withdrawn from the vial with reasonable accuracy.

545 **Cartridge** — Each cartridge of Humatrope should only be reconstituted using the diluent
546 syringe and the diluent connector which accompany the cartridge **and should not be**
547 **reconstituted with the Diluent for Humatrope provided with Humatrope Vials.** (See
548 **WARNINGS** section.) **See the HumatroPen™ User Guide for comprehensive directions on**
549 **Humatrope cartridge reconstitution.**

550 The reconstituted solution should be inspected for clarity. It should be clear. If the solution is
551 cloudy or contains particulate matter, the contents **MUST NOT** be injected.

552 The HumatroPen allows the somatropin dosage volume to be dialed in increments of 0.048 mL
553 per click of dosage knob, and the maximum dosage volume that can be injected is 0.576 mL
554 (based on a 12-click maximum). (See Table 10 for additional information.)
555

Table 10
Concentration of Reconstituted Humatrope Solutions, Incremental Dosage and
Maximum Injectable Dose for Each Cartridge

Cartridge	Somatropin Concentration	Dose Per Click of Dosage Knob	Maximum Injectable Dose
6 mg	2.08 mg/mL	0.1 mg	1.2 mg
12 mg	4.17 mg/mL	0.2 mg	2.4 mg
24 mg	8.33 mg/mL	0.4 mg	4.8 mg

556

557 This cartridge has been designed for use only with the HumatroPen. A sterile disposable needle
 558 should be used for each administration of Humatrope.

559

STABILITY AND STORAGE

Vials

561 *Before Reconstitution* — Vials of Humatrope and Diluent for Humatrope are stable when
 562 refrigerated [2° to 8°C (36° to 46°F)]. Avoid freezing Diluent for Humatrope. Expiration dates
 563 are stated on the labels.

564 *After Reconstitution* — Vials of Humatrope are stable for up to 14 days when reconstituted
 565 with Diluent for Humatrope or Bacteriostatic Water for Injection, USP and stored in a
 566 refrigerator at 2° to 8°C (36° to 46°F). Avoid freezing the reconstituted vial of Humatrope.

567 *After Reconstitution with Sterile Water, USP* — Use only one dose per Humatrope vial and
 568 discard the unused portion. If the solution is not used immediately, it must be refrigerated
 569 [2° to 8°C (36° to 46°F)] and used within 24 hours.

Cartridges

571 *Before Reconstitution* — Cartridges of Humatrope and Diluent for Humatrope are stable when
 572 refrigerated [2° to 8°C (36° to 46°F)]. Avoid freezing Diluent for Humatrope. Expiration dates
 573 are stated on the labels.

574 *After Reconstitution* — Cartridges of Humatrope are stable for up to 28 days when
 575 reconstituted with Diluent for Humatrope and stored in a refrigerator at 2° to 8°C (36° to 46°F).
 576 Store the HumatroPen without the needle attached. Avoid freezing the reconstituted cartridge of
 577 Humatrope.

578

HOW SUPPLIED

Vials

580 5 mg (No. 7335) — (6s) NDC 0002-7335-16, and 5-mL vials of Diluent for Humatrope
 581 (No. 7336)

Cartridges

583 Cartridge Kit (MS8089) NDC 0002-8089-01
 584 6 mg cartridge (VL7554), and prefilled syringe of Diluent for Humatrope (VL7557)

585
 586 Cartridge Kit (MS8090) NDC 0002-8090-01
 587 12 mg cartridge (VL7555), and prefilled syringe of Diluent for Humatrope (VL7558)

588
 589 Cartridge Kit (MS8091) NDC 0002-8091-01
 590 24 mg cartridge (VL7556), and prefilled syringe of Diluent for Humatrope (VL7558)

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