PA 1646 AMP

HUMATROPE®
SOMATROPIN (rDNA ORIGIN) FOR INJECTION
VIALS and CARTRIDGES

DESCRIPTION

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

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

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

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

CLINICAL PHARMACOLOGY

General

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

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

A. *Tissue Growth* — 1. Skeletal Growth: Humatrope stimulates skeletal growth in pediatric patients with growth hormone deficiency. The measurable increase in body length after administration of either Humatrope or human growth hormone of pituitary origin results from an 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 short-statured pediatric patients who lack endogenous growth hormone as compared with normal pediatric populations. Treatment with human growth hormone of pituitary origin results in an increase in both the number and size of muscle cells.

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

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

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

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

Pharmacokinetics

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

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

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

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

Special Populations

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

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

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

Race — No data are available.

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

Table 1
Summary of Somatropin Parameters in the Normal Population

	C_{max} (ng/mL)	$t_{1/2}$ (hr)	$AUC_{0-\infty}$ (ng•hr/mL)	Cls (L/kg•hr)	Vβ (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; Cls=systemic clearance; Vβ=volume distribution; iv=intravenous; SD=standard deviation; im=intramuscular; sc=subcutaneous.
* Based on previous International Standard of 2.7 IU=1 mg.

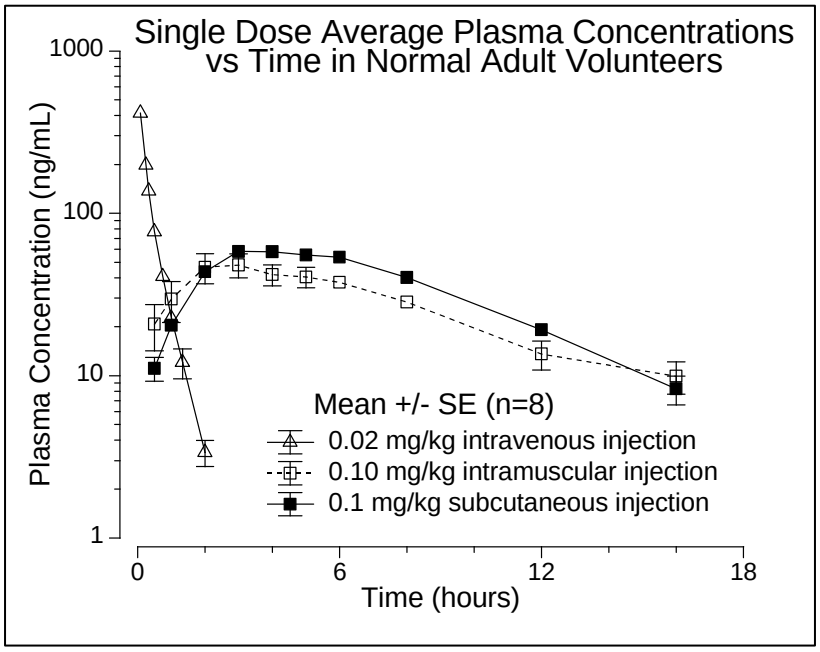


Figure 1

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

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

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

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

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

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

[a] An improvement in score is indicated by a more negative change in the score.
[b] To account for multiple analyses, appropriate statistical methods were applied and the required level of significance is 0.01.
NS=not significant.

Effects of Growth Hormone Treatment in Patients with Turner Syndrome

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

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

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

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

In a randomized blinded dose-response study, GDCI, patients were treated from a mean age of 11.1 years for a mean duration of 5.3 years with a weekly dose of either 0.27 mg/kg or 0.36 mg/kg administered 3 or 6 times weekly. The mean near final height of patients receiving

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

growth hormone was 148.7 ± 6.5 cm (n=31). When compared to historical control data, the mean gain in adult height was approximately 5 cm.

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

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***	**MHT**	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]

[a] RCT: randomized controlled trial; MHT: matched historical controlled trial; RDT: randomized dose-response trial.
[b] Analysis of covariance vs. controls.
[c] Compared with historical data.
* A: GH age <11 yr, estrogen age 15 yr.
B: GH age <11 yr, estrogen age 12 yr.
C: GH age >11 yr, estrogen at month 12.

Effect of Humatrope Treatment in Pediatric Patients with Idiopathic Short Stature

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

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

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

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

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 (±0.70), a predicted adult height SDS of -2.63 (±1.08), and a height velocity SDS of -1.09 (±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**	-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)

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

INDICATIONS AND USAGE

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

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

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

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

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

or

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

CONTRAINDICATIONS

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

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

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

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

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

WARNINGS

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

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

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

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

PRECAUTIONS

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

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

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

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

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

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

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

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

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

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

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

Experience with prolonged treatment in adults is limited.

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

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

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

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

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

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

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

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

ADVERSE REACTIONS

Growth Hormone-Deficient Pediatric Patients

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

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

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

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

Turner Syndrome Patients

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

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

Adverse Event	Overall	Treatment Group hGH[1]	Untreated[2]	Significance
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

[1] Dose=0.3 mg/kg/wk.
[2] Open-label study.
[3] Includes any nevi coded to the following preferred terms: melanosis, skin hypertrophy, or skin benign neoplasm.
NS=not significant.

Patients with Idiopathic Short Stature

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

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

	Treatment Group	
Adverse Event	**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

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

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

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

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

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

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

Table 8
Treatment-Emergent Adverse Events with ≥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

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

[a] p=0.04 as compared to placebo (6 months).

[b] p=0.02 as compared to placebo (6 months).

Table 9
Treatment-Emergent Adverse Events with ≥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

Abbreviations: hGH=Humatrope; N=number of patients receiving treatment in the period stated; n=number of patients reporting each treatment-emergent adverse event; ALT=alanine amino transferase, formerly SGPT; AST=aspartate amino transferase, formerly SGOT.

[a] p=0.03 as compared to placebo (6 months).

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

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

OVERDOSAGE

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

DOSAGE AND ADMINISTRATION

Pediatric Patients

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

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

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

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

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

Adult Patients

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

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

Reconstitution

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

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

Cartridge — Each cartridge of Humatrope should only be reconstituted using the diluent syringe that accompanies the cartridge **and should not be reconstituted with the Diluent for Humatrope provided with Humatrope Vials.** (*See* WARNINGS section.) ***See*** **Information for the Patient for comprehensive directions on Humatrope cartridge reconstitution.**

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

The somatropin concentrations for the reconstituted Humatrope cartridges are as follows: 2.08 mg/mL for the 6 mg cartridge; 4.17 mg/mL for the 12 mg cartridge; and 8.33 mg/mL for the 24 mg cartridge.

This cartridge has been designed for use only with the Humatrope injection device. A sterile disposable needle should be used for each injection of Humatrope.

STABILITY AND STORAGE

Vials

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

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

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

Cartridges

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

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

HOW SUPPLIED

Vials

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

Cartridges

Cartridge Kit (MS8147) NDC 0002-8147-01
6 mg cartridge (VL7554), and prefilled syringe of Diluent for Humatrope (VL7618)

Cartridge Kit (MS8148) NDC 0002-8148-01
12 mg cartridge (VL7555), and prefilled syringe of Diluent for Humatrope (VL7619)

Cartridge Kit (MS8149) NDC 0002-8149-01
24 mg cartridge (VL7556), and prefilled syringe of Diluent for Humatrope (VL7619)

Literature revised October 13, 2005

Eli Lilly and Company, Indianapolis, IN 46285, USA

www.humatrope.com

PA 1646 AMP PRINTED IN USA

PA 9330 FSAMP

INFORMATION AND PATIENT INSTRUCTIONS

HUMATROPE®

Somatropin (rDNA origin) for Injection CARTRIDGES

Lilly

HUMATROPE CARTRIDGES ARE ONLY TO BE USED WITH HUMATROPEN® OR HUMATROPEN® 3 INJECTION DEVICES.

Important Things to Know

It is important to learn the names of the parts of the Humatrope Cartridge Kit and how these parts work before injecting yourself or your child. Make sure you have been properly trained by your nurse, pharmacist or doctor before you mix the drug (add the diluent liquid to the dry Humatrope powder) or inject it. Wash your hands and be careful to follow the instructions given to you by your nurse, pharmacist or doctor. After mixing, throw away the diluent syringe in a puncture-resistant container such as the type your nurse, pharmacist or doctor has told you to use.

Storage

Humatrope must be kept refrigerated (36° to 46°F [2° to 8°C]) before and after it is mixed. **Do not freeze.** Once Humatrope has been mixed and is in liquid form, it must be used within 28 days. Throw away any mixed Humatrope left over after 28 days. Before giving an injection, check the date on the cartridge. **Do not** use the cartridge if it has expired.

WARNING

HUMATROPE CARTRIDGES SHOULD NOT BE USED IF THE PATIENT IS ALLERGIC TO METACRESOL OR GLYCERIN.

Contents

- one cartridge with 6, 12, or 24 mg of dried Humatrope
- one prefilled syringe with diluent (the liquid used to mix the dried Humatrope)

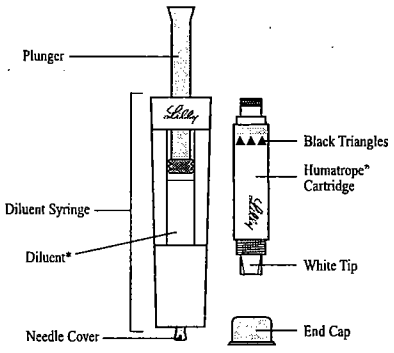
NOTE: There are three kinds of Humatrope cartridges that have different amounts of Humatrope (6, 12, or 24 mg). Make sure that you have the cartridge that your doctor prescribed.

Mixing the Humatrope in the Cartridge

Use only the prefilled diluent syringe to mix the Humatrope in the cartridge. DO NOT use the diluent that comes in the Humatrope vial box, or any other liquid.

Reconstitution Instructions

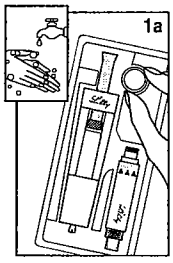
Parts



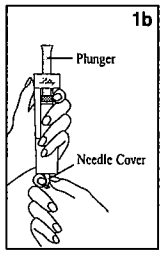
Use only this kit to prepare the Humatrope cartridge.

*Note: The liquid is colorless.
It is shown here as blue for illustration purposes only.

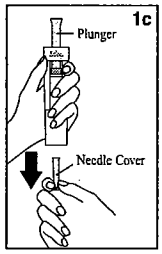
Preparing Your New Cartridge



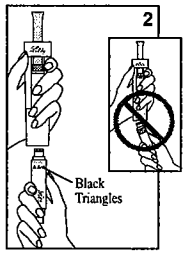
Remove ALL contents from the tray.
Note: This product is designed for left or right handed use so you may use whichever hand is most comfortable for you.



Grasp the gray Needle Cover, at the bottom of the Diluent Syringe.

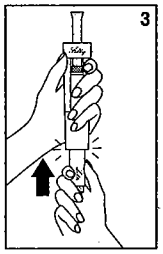


Remove the Needle Cover and discard. DO NOT depress the Plunger yet. It is okay if a drop of fluid is lost. It is not necessary to release air from the Diluent Syringe.

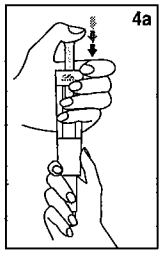


Hold the cartridge, with the Black Triangles up toward the Diluent Syringe. Align the cartridge and Diluent Syringe in a straight line. DO NOT insert the cartridge at an angle.

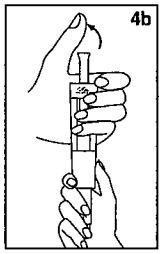
LILLY FRANCE - Fegersheim PRINTED PACKAGING DEVELOPMENT	ITEM CODE PA9330FSAMP	PREVIOUS ITEM CODE —	1/3 BLACK 2/3 CYAN 3/3 PMS 485	FINISHED PRODUCT CODE MS8147 / MS8148 / MS8149	Approved by: NAME: Signature: DATE:	Created by:
RESPONSIBLE — Lilly	SIZE (mm) 176 x 250	SICK CODE 629 / FILE N° 05C062		☒ Trade 001AM ☐ Hospital ☐ sample	Approved by: NAME: Signature: DATE:	Checked by: Date:
	NB OF PAGES 1/2	PROOF N°: 2 DATE: 06 December 2005				



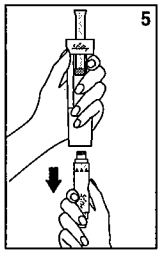
PUSH the cartridge STRAIGHT in until it stops AND the Black Triangles ARE COVERED.
You may hear or feel a click.
DO NOT twist the cartridge.



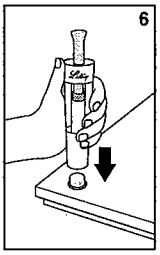
Hold the Diluent Syringe and the cartridge together with TWO HANDS. Push and release the Plunger 2 or 3 times until the Diluent is in the cartridge.



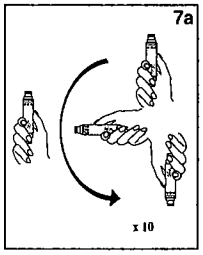
Remove your thumb from the Plunger and check that the Diluent Syringe is empty [it is normal for small drops of Diluent to remain in the Diluent Syringe].



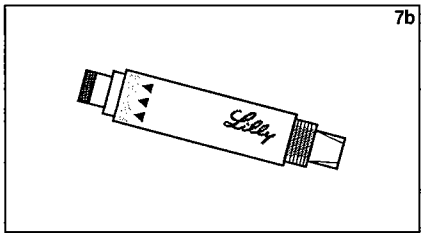
With your thumb OFF the plunger, pull the cartridge away from the Diluent Syringe.



Place the End Cap on a hard, flat surface. Push the Diluent Syringe onto the End Cap and immediately discard the Diluent Syringe as instructed by your healthcare professional.



Mix the cartridge by gently inverting 10 times and let it sit for 3 minutes,
DO NOT SHAKE.



Inspect the solution. The Humatrope solution should be clear.
If the solution is clear, your cartridge is now prepared and ready to be attached to your pen injection device (see the User Manual for your pen injection device).
If the solution is cloudy or contains particles, gently invert the cartridge 10 additional times. Let the cartridge sit for 5 more minutes. If the solution remains cloudy or contains particles, DO NOT USE THE CARTRIDGE.
Contact your healthcare professional or Lilly.
If you have questions about preparing your Humatrope cartridge, you should contact your Humatrope provider or your healthcare professional.

Injections can be given in the following areas:
- Abdomen (above, below, or either side of the navel)
- Front of the upper thighs
- Upper, outer buttocks
- Back of the arms above the elbow and below the shoulder

Discuss use of the pen injection device, the right places to inject, and site rotation with your nurse or doctor.

Literature revised August 1, 2005

Manufactured by Lilly France S.A.S.
F-67640 Fegersheim, France
for Eli Lilly and Company
Indianapolis, IN 46285, USA

www.humatrope.com

PA 9330 FSAMP

LILLY FRANCE - Fegersheim PRINTED PACKAGING DEVELOPMENT	ITEM CODE PA9330FSAMP	PREVIOUS ITEM CODE —		1/3 BLACK 2/3 PMS 485	FINISHED PRODUCT CODE MS8147 / MS8148 / MS8149	Approved by: NAME: Signature: DATE:	Created by:
RESPONSIBLE —	SIZE (mm) 176 x 250	SICK CODE 629	FILE N° 05C062		[X] Trade 001AM [ ] Hospital [ ] sample	Approved by: NAME: Signature: DATE:	Checked by: Date:
Lilly	NB OF PAGES 2/2	PROOF N°: 2 DATE: 06 December 2005					

PA 1646 AMP

HUMATROPE®
SOMATROPIN (rDNA ORIGIN) FOR INJECTION
VIALS and CARTRIDGES

DESCRIPTION

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

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

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

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

CLINICAL PHARMACOLOGY

General

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

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

A. *Tissue Growth* — 1. Skeletal Growth: Humatrope stimulates skeletal growth in pediatric patients with growth hormone deficiency. The measurable increase in body length after administration of either Humatrope or human growth hormone of pituitary origin results from an 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 short-statured pediatric patients who lack endogenous growth hormone as compared with normal pediatric populations. Treatment with human growth hormone of pituitary origin results in an increase in both the number and size of muscle cells.

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

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

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

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

Pharmacokinetics

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

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

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

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

Special Populations

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

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

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

Race — No data are available.

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

Table 1
Summary of Somatropin Parameters in the Normal Population

	C_{max} (ng/mL)	$t_{1/2}$ (hr)	$AUC_{0-\infty}$ (ng•hr/mL)	Cls (L/kg•hr)	Vβ (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; Cls=systemic clearance; Vβ=volume distribution; iv=intravenous; SD=standard deviation; im=intramuscular; sc=subcutaneous.
* Based on previous International Standard of 2.7 IU=1 mg.

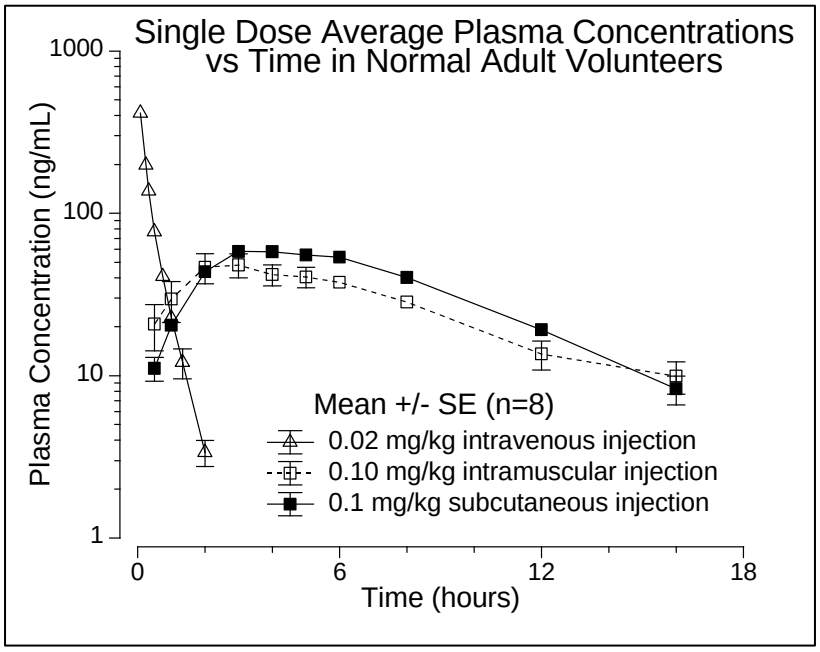


Figure 1

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

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

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

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

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

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

[a] An improvement in score is indicated by a more negative change in the score.
[b] To account for multiple analyses, appropriate statistical methods were applied and the required level of significance is 0.01.
NS=not significant.

Effects of Growth Hormone Treatment in Patients with Turner Syndrome

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

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

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

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

In a randomized blinded dose-response study, GDCI, patients were treated from a mean age of 11.1 years for a mean duration of 5.3 years with a weekly dose of either 0.27 mg/kg or 0.36 mg/kg administered 3 or 6 times weekly. The mean near final height of patients receiving

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

growth hormone was 148.7 ± 6.5 cm (n=31). When compared to historical control data, the mean gain in adult height was approximately 5 cm.

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

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***	**MHT**	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]

[a] RCT: randomized controlled trial; MHT: matched historical controlled trial; RDT: randomized dose-response trial.
[b] Analysis of covariance vs. controls.
[c] Compared with historical data.
* A: GH age <11 yr, estrogen age 15 yr.
B: GH age <11 yr, estrogen age 12 yr.
C: GH age >11 yr, estrogen at month 12.

Effect of Humatrope Treatment in Pediatric Patients with Idiopathic Short Stature

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

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

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

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

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 (±0.70), a predicted adult height SDS of -2.63 (±1.08), and a height velocity SDS of -1.09 (±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**	-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)

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

INDICATIONS AND USAGE

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

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

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

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

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

or

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

CONTRAINDICATIONS

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

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

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

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

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

WARNINGS

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

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

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

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

PRECAUTIONS

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

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

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

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

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

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

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

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

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

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

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

Experience with prolonged treatment in adults is limited.

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

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

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

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

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

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

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

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

ADVERSE REACTIONS

Growth Hormone-Deficient Pediatric Patients

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

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

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

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

Turner Syndrome Patients

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

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

Adverse Event	Overall	Treatment Group hGH[1]	Untreated[2]	Significance
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

[1] Dose=0.3 mg/kg/wk.
[2] Open-label study.
[3] Includes any nevi coded to the following preferred terms: melanosis, skin hypertrophy, or skin benign neoplasm.
NS=not significant.

Patients with Idiopathic Short Stature

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

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

	Treatment Group	
Adverse Event	**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

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

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

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

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

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

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

Table 8
Treatment-Emergent Adverse Events with ≥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

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

[a] p=0.04 as compared to placebo (6 months).

[b] p=0.02 as compared to placebo (6 months).

Table 9
Treatment-Emergent Adverse Events with ≥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

Abbreviations: hGH=Humatrope; N=number of patients receiving treatment in the period stated; n=number of patients reporting each treatment-emergent adverse event; ALT=alanine amino transferase, formerly SGPT; AST=aspartate amino transferase, formerly SGOT.

[a] p=0.03 as compared to placebo (6 months).

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

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

OVERDOSAGE

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

DOSAGE AND ADMINISTRATION

Pediatric Patients

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

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

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

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

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

Adult Patients

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

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

Reconstitution

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

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

Cartridge — Each cartridge of Humatrope should only be reconstituted using the diluent syringe that accompanies the cartridge **and should not be reconstituted with the Diluent for Humatrope provided with Humatrope Vials.** (*See* WARNINGS section.) ***See*** **Information for the Patient for comprehensive directions on Humatrope cartridge reconstitution.**

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

The somatropin concentrations for the reconstituted Humatrope cartridges are as follows: 2.08 mg/mL for the 6 mg cartridge; 4.17 mg/mL for the 12 mg cartridge; and 8.33 mg/mL for the 24 mg cartridge.

This cartridge has been designed for use only with the Humatrope injection device. A sterile disposable needle should be used for each injection of Humatrope.

STABILITY AND STORAGE

Vials

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

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

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

Cartridges

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

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

HOW SUPPLIED

Vials

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

Cartridges

Cartridge Kit (MS8147) NDC 0002-8147-01
6 mg cartridge (VL7554), and prefilled syringe of Diluent for Humatrope (VL7618)

Cartridge Kit (MS8148) NDC 0002-8148-01
12 mg cartridge (VL7555), and prefilled syringe of Diluent for Humatrope (VL7619)

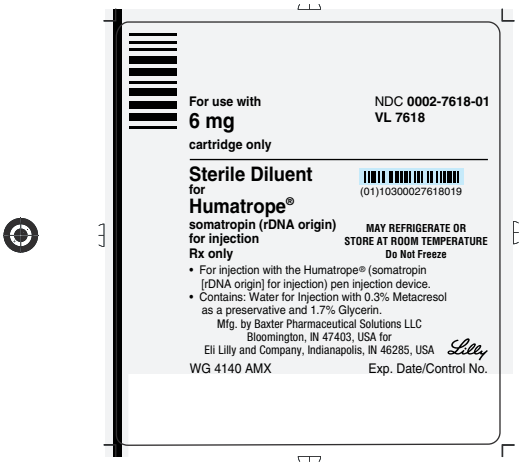
Cartridge Kit (MS8149) NDC 0002-8149-01
24 mg cartridge (VL7556), and prefilled syringe of Diluent for Humatrope (VL7619)

Literature revised October 13, 2005

Eli Lilly and Company, Indianapolis, IN 46285, USA

www.humatrope.com

PA 1646 AMP PRINTED IN USA



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Die No.: D-1290
KC Drawing No: N/A
View: Printed Side Up

BKGD ID

D-1290-LB02
Approved by: Roger W. Wetzel
Date: 3-7-05

LILLY APPROVALS

Graphics Operator:	Date:
Proofreader:	Date:
Label Editor or Label Editor Asst:	Date:
Printing Quality Control:	Date:

(b)(4)

VENDOR APPROVALS

Production Order Number:
Item Number: Scanner Code:
OK FOR PRODUCTION (copy only) Client Services: Date:
FINAL OK Production Engineering: Date:

(b)(4)

COLOR ID

Item Code: WG 4140 AMX
Colors:

BLACK	WG 4140 AMX
1055 WHITE	D-1290-LB02
COATING	D-1290-LE02

ENGINEER'S APPROVAL

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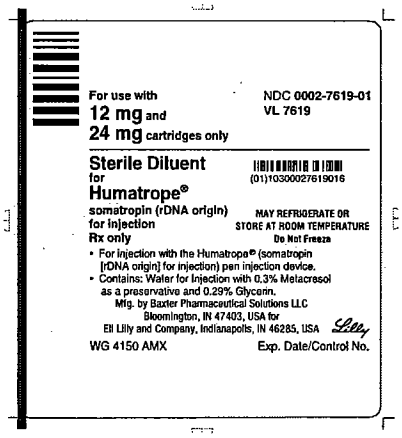
Finishing Line No.: Baxter Pharmaceuticals
Approved by: Tonjalee Miller
Date: 09-05-03



DIE ID	
	Die No.: D-1290
	KC Drawing No: N/A
	View: Printed Side Up

BKGD ID	
	D-1290-LB02
	Approved by:
	Date: 3-7-05

LILLY APPROVALS		
	Graphics Operator:	Date:
	Proofreader:	Date:
	Label Editor or Label Editor Asst:	Date:
	Printing Quality Control:	Date:

VENDOR APPROVALS		
	Production Order Number:	
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	FINAL OK	Production Engineering: Date:

COLOR ID		
	Item Code: WG 4150 AMX	
	Colors:	
	BLACK	WG 4150 AMX
	COATING	D-1290-LE02

ENGINEER'S APPROVAL	
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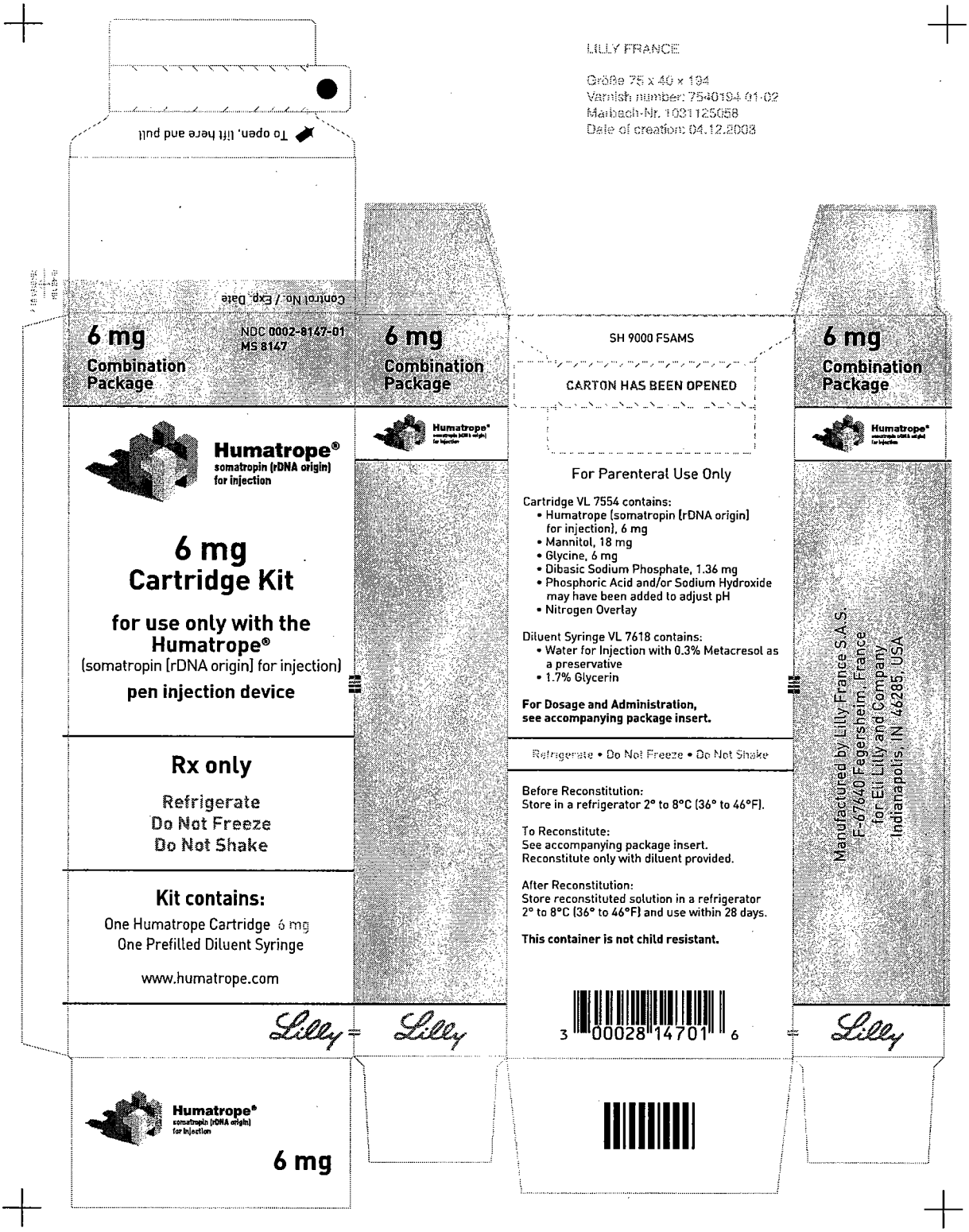
	Finishing Line No.: Baxter Pharmaceuticals
	Approved by:
	Date: 09-05-03



LILLY FRANCE

Größe 75 x 40 x 194
Varnish number: 7540194 01-02
Marbach-Nr. 1031125058
Date of creation: 04.12.2008

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RESPONSIBLE	SIZE (mm) 75 x 40 x 194	SICK CODE 3821 / FILE N° 05C001	1/4 CYAN	☒ Trade 001AM		
Lilly	NB OF PAGES 1/1	PROOF N°: 2 DATE: 17 February 2005	1/4 MAGENTA	☐ Hospital ☐ Sample	Approved by: NAME: Signature: DATE:	Checked by: Date:

LILLY FRANCE

Größe 75 x 40 x 194
Varnish number: 7540194-01-02
Marbach-Nr. 1021125058
Date of creation: 04.12.2003

To open, lift here and pull

Batch No. / Exp. Date

12 mg
Combination Package

NDC 0002-8148-01
MS 8148

Humatrope®
somatropin [rDNA origin]
for injection

12 mg
Cartridge Kit

for use only with the Humatrope®
(somatropin [rDNA origin] for injection)
pen injection device

Rx only

Refrigerate
Do Not Freeze
Do Not Shake

Kit contains:

One Humatrope Cartridge 12 mg
One Prefilled Diluent Syringe

www.humatrope.com

Lilly

12 mg
Combination Package

Humatrope®
somatropin [rDNA origin]
for injection

Lilly

SH 9010 FSAMS

CARTON HAS BEEN OPENED

For Parenteral Use Only

Cartridge VL 7555 contains:
- Humatrope (somatropin [rDNA origin] for injection), 12 mg
- Mannitol, 36 mg
- Glycine, 12 mg
- Dibasic Sodium Phosphate, 2.72 mg
- Phosphoric Acid and/or Sodium Hydroxide may have been added to adjust pH
- Nitrogen Overlay

Diluent Syringe VL 7619 contains:
- Water for Injection with 0.3% Metacresol as a preservative
- 0.29% Glycerin

For Dosage and Administration, see accompanying package insert.

Refrigerate • Do Not Freeze • Do Not Shake

Before Reconstitution:
Store in a refrigerator 2° to 8°C (36° to 46°F).

To Reconstitute:
See accompanying package insert.
Reconstitute only with diluent provided.

After Reconstitution:
Store reconstituted solution in a refrigerator 2° to 8°C (36° to 46°F) and use within 28 days.

This container is not child resistant.

3 00028 14801 3

12 mg
Combination Package

Humatrope®
somatropin [rDNA origin]
for injection

Lilly

Manufactured by Lilly France S.A.S.
F-67640 Fegersheim, France
for Eli Lilly and Company
Indianapolis, IN 46285, USA

Humatrope®
somatropin [rDNA origin]
for injection

12 mg

LILLY FRANCE - Fegersheim PRINTED PACKAGING DEVELOPMENT	ITEM CODE SH9010FSAMS	PREVIOUS ITEM CODE (TO BE DESTROYED)	1/4 BLACK	FINISHED PRODUCT CODE MS8148	Approved by: NAME: Signature: DATE:	Created by: /
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Lilly	NB OF PAGES 1/1	PROOF N°: 1 DATE: 17 February 2005	3/4 MAGENTA	☐ Hospital ☐ Sample	Approved by: NAME: Signature: DATE:	Checked by: Date:

LILLY FRANCE

Größe 75 x 40 x 194
Varnish number: 7540194 01 02
Marbach-Nr. 1021125058
Date of creation: 04.12.2003

To open, lift here and pull

Control No. / Exp. Date

24 mg
Combination Package

NDC 0002-8149-01
MS 8149

Humatrope®
somatropin (rDNA origin)
for injection

24 mg Cartridge Kit

for use only with the Humatrope®
(somatropin [rDNA origin] for injection)
pen injection device

Rx only

Refrigerate
Do Not Freeze
Do Not Shake

Kit contains:

One Humatrope Cartridge 24 mg
One Prefilled Diluent Syringe

www.humatrope.com

Lilly

24 mg
Combination Package

Humatrope®
somatropin (rDNA origin)
for injection

SH 9020 FSAMS

CARTON HAS BEEN OPENED

For Parenteral Use Only

Cartridge VL 7556 contains:
- Humatrope (somatropin [rDNA origin] for injection), 24 mg
- Mannitol, 72 mg
- Glycine, 24 mg
- Dibasic Sodium Phosphate, 5.43 mg
- Phosphoric Acid and/or Sodium Hydroxide may have been added to adjust pH
- Nitrogen Overlay

Diluent Syringe VL 7619 contains:
- Water for Injection with 0.3% Metacresol as a preservative
- 0.29% Glycerin

For Dosage and Administration, see accompanying package insert.

Refrigerate • Do Not Freeze • Do Not Shake

Before Reconstitution:
Store in a refrigerator 2° to 8°C (36° to 46°F).

To Reconstitute:
See accompanying package insert.
Reconstitute only with diluent provided.

After Reconstitution:
Store reconstituted solution in a refrigerator 2° to 8°C (36° to 46°F) and use within 28 days.

This container is not child resistant.

3 00028 14901 0

24 mg
Combination Package

Humatrope®
somatropin (rDNA origin)
for injection

Lilly

Manufactured by Lilly France S.A.S.
F-67640 Fegersheim, France
for Eli Lilly and Company
Indianapolis, IN 46285, USA

Humatrope®
somatropin (rDNA origin)
for injection

24 mg

LILLY FRANCE - Fegersheim PRINTED PACKAGING DEVELOPMENT	ITEM CODE SH9020FSAMS	PREVIOUS ITEM CODE (TO BE DESTROYED)	1/4 BLACK	FINISHED PRODUCT CODE MS8149	Approved by: NAME: Signature: DATE:	Created by:
RESPONSIBLE	SIZE (mm) 75 x 40 x 194	SICK CODE 3828 / FILE N° 05C001	2/4 CYAN	☒ Trade 001AM	Approved by: NAME: Signature: DATE:	Checked by:
Lilly	NB OF PAGES 1/1	PROOF N°: 1 DATE: 17 February 2005	3/4 MAGENTA	☐ Hospital ☐ Sample		Date:

Humatrope®
somatropin (rDNA origin)
for injection

Model MS8050

HumatroPen®

Injection Device For Use With Humatrope® Cartridges

If you have questions, call 1-800-847-6988

Lilly

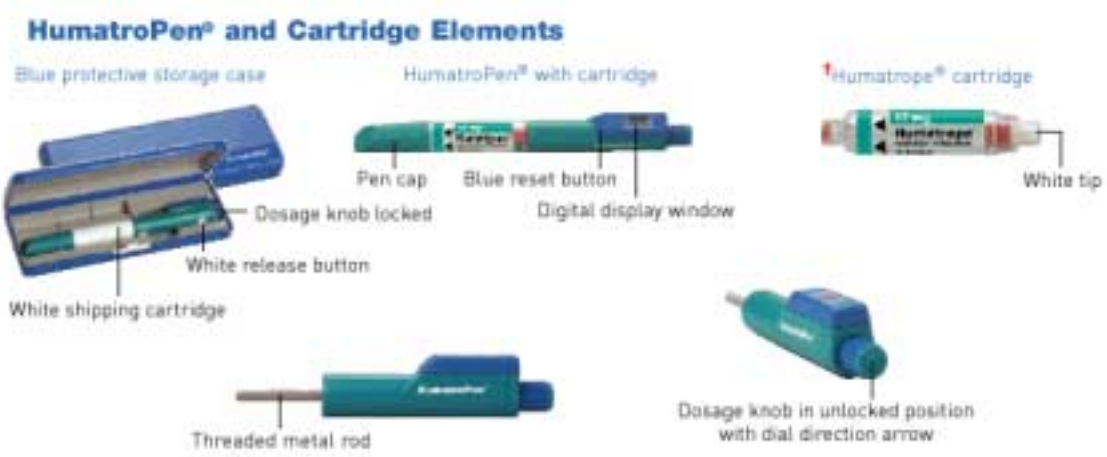
HumatroPen® Package
(When first opened)

Blue protective storage case

HumatroPen® Injection Device and storage case

HumatroPen® User Guide

a Please fold out to reference the diagrams for the **HumatroPen®** Injection Device.



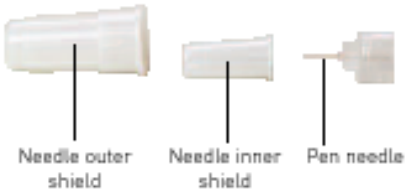
b † *Sold separately by prescription as part of the Humatrope® Cartridge Kit.*

Accessories Sold Separately

Additional supplies you will need before using the HumatroPen® (all sold separately) are:

Humatrope® Cartridge Kit (6, 12, or 24 mg quantity) as prescribed by your healthcare professional.

Alcohol swab



c **Becton, Dickinson and Company pen needles are suitable for use with the HumatroPen®.**

Contents
PA 9184 FSAMP

Humatrope®
somatropin (rDNA origin)
for injection

Introducing the **HumatroPen®**
Injection Device

Introduction

This booklet is the User Guide for the HumatroPen® Injection Device. **Before using the HumatroPen, please read this User Guide thoroughly.** Keep this important guide for future reference. Your healthcare professional has told you the Humatrope® dose that you or your child should receive. **DO NOT change this dose unless directed by your healthcare professional.** If you have any questions about the HumatroPen Injection Device, please call Eli Lilly and Company at 1-800-847-6988 or visit www.humatrope.com.

WARNING: DO NOT USE THE HUMATROPEN INJECTION DEVICE AND HUMATROPE CARTRIDGES IF YOU ARE ALLERGIC TO METACRESOL OR GLYCERIN.

Humatrope®
somatropin (rDNA origin)
for injection

Important Notes

The HumatroPen is not recommended for use by blind or visually impaired individuals without the assistance of a sighted individual trained in its use.

Maintenance and Care of the HumatroPen

- The pen requires no maintenance.
- Soiled parts can be cleaned with a damp cloth. Do not use alcohol or other cleaning agents.
- Protect the pen and case from moisture especially when transporting in a cooler.
- For the cleaning of the HumatroPen Injection Device, the body of the HumatroPen may be wiped with a cloth slightly dampened with water. **DO NOT IMMERSE THE HUMATROPEN IN WATER.**
- The case is not watertight and will not protect the pen if immersed.
- Do not soak or immerse the pen in liquid.
- Do not apply oil or other lubricant.

Storage of the HumatroPen

- All Humatrope cartridges and diluent must be refrigerated at temperatures between +2° and +8°C (36° and 46°F). DO NOT FREEZE. A prepared cartridge can be left on a pen for 28 days in the refrigerator. If any reconstituted product remains after 28 days, it should be discarded.

- While traveling, daily room temperature exposure should not exceed 30 minutes.

- Use a new needle for each injection. Do not store the pen with needle attached. This could cause liquid to leak, air bubbles to form, or growth hormone crystals to clog the needle.

- Pen should be stored with dosage knob in locked position.

- Discomfort may be noticed at the injection site if Humatrope is given cold. Let Humatrope stand at room temperature for 10 minutes before injecting.

Humatrope®
somatropin (rDNA origin)
for injection

Terms and Definitions
It may be helpful to refer to the fold-out diagrams on the inside front cover of this booklet, page X, as you review these terms.

Dosage knob - The cylindrical knob extending from the end of the HumatroPen that turns to dial the dosage setting of Humatrope. The arrow marked on the flat end of the dosage knob indicates the direction in which the knob is turned to dial the dose.

Dosage knob click - The slight sharp noise that is heard and the snap felt when the dosage knob is turned.

Dosage setting - The numbers that appear in the digital display window and correspond to the number of dosage knob clicks. The dosage setting you dial should be calculated by your healthcare professional to correspond to the prescribed Humatrope dose. The chart on page XX illustrates the relationship between the Humatrope dose and the HumatroPen dosage setting.

Humatrope cartridge - A sealed container of Humatrope powder that attaches to the HumatroPen. Humatrope is mixed directly in the cartridge and stored there. Cartridges are available in three (3) Humatrope quantities: 6 mg, 12 mg, and 24 mg.

Reconstitution - The mixing of diluent (liquid) with the Humatrope powder in order to make it injectable. Reconstituted Humatrope must be refrigerated and used within 28 days.

Release button - The white button on the opposite side of the HumatroPen from the digital display window. Pressing the white release button unlocks the dosage knob.

Reset button - The blue ridged button on the slanted area near the digital display window. The blue reset button allows you to dial the dosage knob backward. Note that when the dosage knob is turned backward, no clicking sound is heard.

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† *Humatrope Cartridges sold separately by prescription as part of the Humatrope Cartridge Kit.*

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Features

The HumatroPen Injection Device system is:

- **Convenient** - One (1) injection device that can be used with any one of three (3) Humatrope cartridges (6 mg, 12 mg, and 24 mg).
- **Versatile** - Your healthcare professional can adjust the dose in either 0.1, 0.2, or 0.4 mg increments depending on the strength of reconstituted Humatrope in the cartridge.
- **Stable** - Once reconstituted, refrigerated Humatrope in cartridges can be used for up to 28 days.
- **"Sense"-able** - ***See, Hear, and Feel,*** as you dial the dosage setting that corresponds to the prescribed Humatrope dose.

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Steps for Using the HumatroPen Injection Device

Follow these steps for using the HumatroPen. Refer to the fold-out diagrams on the inside front cover, page X, as you go through these steps.

1. Getting Started

- Wash your hands before you start.

- Before first-time use, remove the pen cap and unscrew the white shipping cartridge from the HumatroPen. Dispose of the white shipping cartridge.

- Firmly press the white release button on the HumatroPen to unlock the dosage knob. The numbers "00" will appear in the digital display window.

- Press and hold in the blue reset button and turn the dosage knob counterclockwise (in the direction opposite to the arrow on the end of the dosage knob) until the metal rod is fully retracted and stops.

  NOTE: *Do not use excessive force while turning the dosage knob. If the dosage knob does not turn, it is already in the correct position.*

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- You will see either "00" or "--" in the digital display window.
- If the display shows “00” in the digital display window, then proceed to the next page.

- If the display shows “--” in the digital display window, then press down the dosage knob until it locks in place. Press the white release button. The dosage knob will unlock, and the numbers “00” will reappear in the digital display window.

  NOTE: *The digital display will automatically shut off in two (2) minutes. The display can be reactivated by pressing down the dosage knob until it locks in place. Then press the white release button, and “00” will reappear.*

Follow the mixing (reconstitution) directions as described in your Humatrope Cartridge Kit.

- If a cartridge **is** already attached to your pen: go to "Attaching the Pen Needle" on page X.

OR

- If a cartridge **is not** already attached to your pen: place a **reconstituted** cartridge on the pen by screwing the cartridge counterclockwise (in the direction opposite the arrow on the end of the dose knob) into the pen. Go to "Attaching the Pen Needle" on page X.

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2. Attaching the Pen Needle

- Wipe the rubber seal on the Humatrope cartridge with an alcohol swab.

- Remove the tab from the needle outer shield but do not remove the needle. Holding the HumatroPen upright and away from your face, screw the needle shield onto the Humatrope cartridge until snug.
- Remove the needle outer shield but do not discard.

3. Priming the HumatroPen Injection Device

The HumatroPen must be primed before setting or injecting **the first dose** from each **new** cartridge. After priming the HumatroPen with a new cartridge, it is **not** necessary to prime the HumatroPen again between doses. This is only necessary when you remove or replace the cartridge.

- Hold the HumatroPen with the pen needle pointing upright and away from your face. Pull off and discard the needle inner shield.

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- Push in the dosage knob at the end of the HumatroPen until it locks in place. A small stream of solution and air bubbles may come out of the tip of the pen needle.

- Continuing to hold the HumatroPen with the pen needle upright, unlock the dosage knob by firmly pressing the white release button. You should see, hear, and feel the dosage knob unlock.

- Turn the dosage knob clockwise, in the direction of the arrow marked on its end, until "01" appears in the digital display window and a click is heard as the number locks in place. Holding the HumatroPen upright, push the dosage knob in until it locks in place. “01” will remain in the digital display window until the white release button is pressed. Then press the white release button. Repeat this procedure until Humatrope solution appears at the pen needle tip. Once the solution appears at the pen needle tip—the injection device is primed.
  ***NOTE*:** *It is normal for a small air bubble to remain in the cartridge.*

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4. Dialing the Prescribed Dose

- With your healthcare professional, determine the HumatroPen dosage setting (number of dosage knob clicks) that corresponds to the prescribed dose of Humatrope.

- To dial the dose, press the white release button. The numbers "00" should reappear in the digital display window. The dosage knob is now unlocked. Do not depress the dosage knob while setting the dose. This will cause the solution to be released from the HumatroPen prior to injection, making the dose inaccurate.

- Turn the dosage knob in the direction of the arrow until the dosage setting corresponding to the prescribed dose appears in the digital display window. You will hear and feel a click as the numbers are dialed.

  NOTE: *The HumatroPen will dial to a maximum dosage setting of 12 (twelve clicks of the dosage knob).*

- If the dosage knob will not dial the prescribed dosage setting, the cartridge may be nearly empty and may not contain enough Humatrope solution for a complete dose. Talk with your healthcare professional at the start of therapy about how to deal with this.

  NOTE: *If you turn the dosage knob past the correct number of clicks, press and hold in the blue reset button and dial the dosage knob counterclockwise (in the direction opposite to the arrow) until the correct number appears in the digital display window. If you dial back past "00", refer to Troubleshooting Tip #7.*

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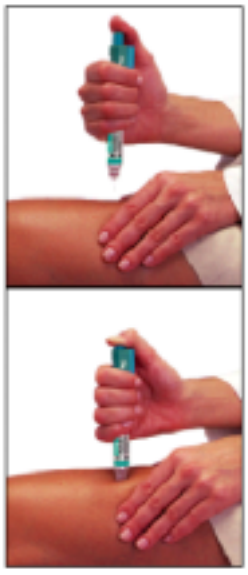
5. Preparing the Injection Site

- Choose an appropriate site for injection as instructed by your healthcare professional. Using an alcohol swab, apply firm pressure to the injection site and rub outward in increasingly larger circles. Do not retrace your steps. Let the alcohol dry a few seconds before injecting.

NOTE: *Humatrope should be injected subcutaneously (under the skin). Rotate injection sites daily. See the Injection Site Chart on pages XX-XX and talk to your healthcare professional about injection site rotation.*



6. Injecting the Humatrope Dose

- Gently pinch up a large area of skin. Quickly push the pen needle into the skin, as instructed by your healthcare professional.
- Inject the dose of Humatrope by slowly pushing the dosage knob in until it locks in place, then slowly count to five (5). Let go of the pinched-up area of skin. Then pull the pen needle straight out.
- After injection, the dosage setting will stay in the digital display window. The display will turn off after two (2) minutes.

NOTE: *It is normal for a small drop of Humatrope solution to form on the pen needle tip after removing it from the skin. It is also quite common to see a small drop of Humatrope solution or blood on the skin at the injection site. Simply apply pressure to the site.*

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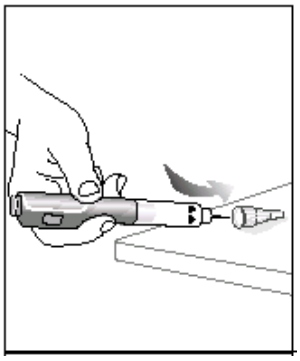

- Carefully replace the needle outer shield as instructed by your healthcare professional.

- Remove the capped needle by turning counterclockwise and throw it away as instructed by your healthcare professional.

- Recap the HumatroPen, leaving the cartridge in place. Make sure the dosage knob is locked in place. If it is not, push the dosage knob in until you feel it lock in place.

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- Store the HumatroPen with attached Humatrope cartridge in the blue protective storage case in the refrigerator until the time of the next injection. **DO NOT FREEZE.**

- At the time of the next injection from the same cartridge, reinspect the solution for clarity as described in your Humatrope Cartridge Kit. Making sure the cartridge remains snug, attach a new (sterile) pen needle as described in Step 2, on page XX. To dial and inject the dose, proceed from Step 4, on page XX.

Replacing a Cartridge

When a Humatrope cartridge needs to be replaced:

- Wash your hands.
- Remove the pen cap.
- Unscrew the empty cartridge from the HumatroPen.
- Dispose of the cartridge as directed by your healthcare professional.
- Check that the threaded metal rod is completely wound back into the HumatroPen. To rewind the threaded metal rod, press and hold in the blue reset button, and turn the dosage knob counterclockwise (in the direction opposite to the arrow on the end of the dosage knob) until it stops.
  NOTE: *Do not use excessive force when turning the dosage knob. If the dosage knob does not turn, it is already in the correct position.*
- Return to the top of page XX, and follow all of the remaining *Steps for Using the HumatroPen Injection Device.*

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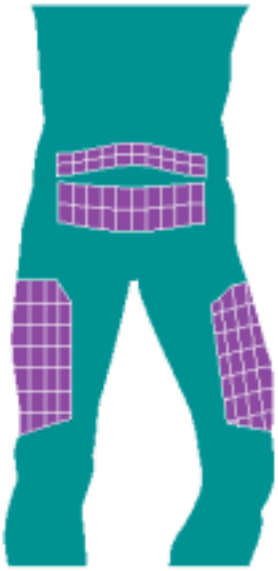
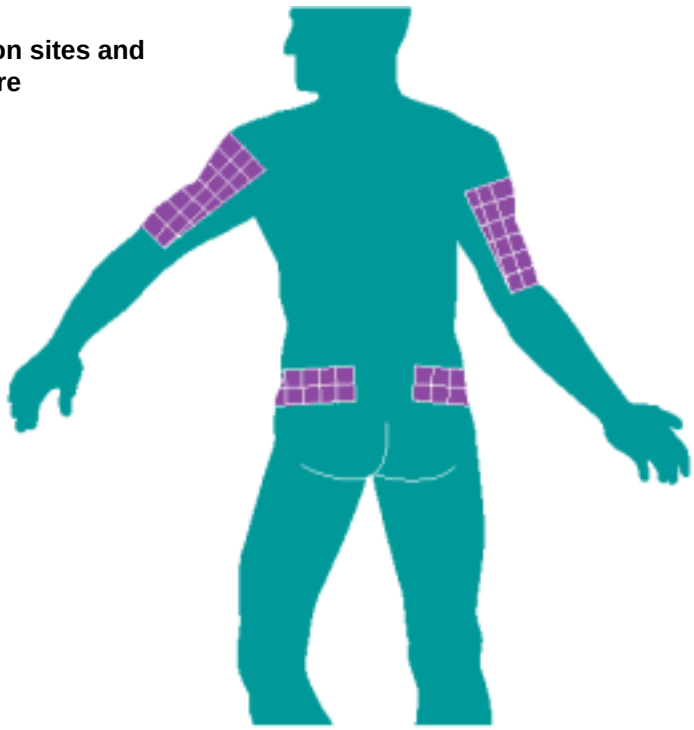
Cleaning the HumatroPen Injection Device
The body of the HumatroPen may be wiped with a cloth slightly dampened with water only. **DO NOT IMMERSE THE HUMATROPEN IN WATER.**

Injection Site Chart
Injections can be given in the following areas:
- Abdomen (above, below, or either side of the navel)
- Front of the upper thighs
- Upper, outer buttocks
- Back of the arms above the elbow and below the shoulder

Discuss the appropriate injection sites and site rotation with your healthcare professional.

Discuss the appropriate injection sites and site rotation with your healthcare professional.





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Determining the Humatrope Dose

Your healthcare professional should discuss the prescribed dose and the appropriate dosage setting with you. The following conversion chart illustrates the relationship between the prescribed dose and the dosage setting (number of clicks) on your HumatroPen. If you have any questions, ask your healthcare professional.

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Conversion Chart

After Reconstitution

Clicks	Volume (mL)	6 mg Cartridge Dose (mg)	12 mg Cartridge Dose (mg)	24 mg Cartridge Dose (mg)
1	0.05	0.1	0.2	0.4
2	0.10	0.2	0.4	0.8
3	0.15	0.3	0.6	1.2
4	0.20	0.4	0.8	1.6
5	0.25	0.5	1.0	2.0
6	0.30	0.6	1.2	2.4
7	0.35	0.7	1.4	2.8
8	0.40	0.8	1.6	3.2
9	0.45	0.9	1.8	3.6
10	0.50	1.0	2.0	4.0
11	0.55	1.1	2.2	4.4
12	0.60	1.2	2.4	4.8

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Commonly Asked Questions

How should I store the Humatrope cartridges and the HumatroPen?

Cartridges-Humatrope must be kept refrigerated (36° to 46°F or 2° to 8°C) before and after reconstitution. **DO NOT FREEZE.** Store the HumatroPen with the Humatrope cartridge attached in the refrigerator until time of the next injection. Reconstituted Humatrope must be used within 28 days. Discard any remaining Humatrope after 28 days. Check the date on the cartridge. **Do not** use the cartridge if it has expired.

HumatroPen-Store the HumatroPen with the dosage knob locked in the depressed position. Store the HumatroPen with the Humatrope cartridge attached in the blue protective storage case in the refrigerator until the time of the next injection. **Do not store the HumatroPen with the pen needle attached because this could cause a safety hazard. DO NOT FREEZE.**

When should I attach a new pen needle to the HumatroPen?

Use a new pen needle for each injection. Do not attach a pen needle until you are ready to use the HumatroPen. **Pen needles are to be used one (1) time only and then discarded properly.**

What is the lifetime of the HumatroPen?

The HumatroPen should last approximately two (2) years from the first use. However, the lifetime may vary by a few months. When the pen is about to expire, "≡" will appear in the digital display window. Please call Eli Lilly and Company at 1-800-847-6988 for assistance. The digital display window will show "≡ ≡" when the pen has expired and should no longer be used.

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How will I know if my HumatroPen battery is low?

When "bt" (see adjacent photo) appears in the digital display window, this indicates that the HumatroPen has a low battery. It is time to replace the injection device immediately. Call Eli Lilly and Company at 1-800-847-6988 for assistance.

Troubleshooting Tips
It may be helpful to refer to the fold-out diagrams on the inside front cover, page X, as you review these tips.

1. Problem: The Humatrope cartridge and HumatroPen injection device will not screw together.
Action: The threaded metal rod in the injection device may not be completely wound back.

- Check to make sure the dosage knob is unlocked by pressing the white release button.
- Turn the injection device so the dosage knob on the end is facing you.
- Press and hold down the blue reset button and turn the dosage knob counterclockwise (in the direction opposite the arrow on the end of the dosage knob).
- **Make sure you turn the dosage knob until it stops.** This will retract the threaded metal rod in the injection device.
- Screw the white-tipped end of the cartridge onto the HumatroPen, as described on page XX.

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2. Problem: Humatrope solution is not clear after mixing.
Action: Gently invert the HumatroPen up and down ten (10) times. **DO NOT SHAKE.** Then let the HumatroPen sit for at least three (3) minutes. If the Humatrope solution remains cloudy or contains particles, then gently invert the HumatroPen up and down ten (10) more times. Let the HumatroPen sit for five (5) more minutes. **The Humatrope solution should then be clear. If the solution remains cloudy or contains particles, the contents MUST NOT be injected.** Call your healthcare professional or Humatrope provider.

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3. Problem: The small white plastic piece in the end of the cartridge moves when the dosage knob is unlocked.
Action: This is normal. The white plastic piece may move freely inside the cartridge.

4. Problem: Dosage knob is unlocked and display turns off **before** dose is dialed.
Action: The display will turn off after two (2) minutes to save battery life. The display can be reactivated by pressing down the dosage knob until it locks in place. Press the white release button. The dosage knob will be unlocked, and the numbers "00" will appear in the digital display window.

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5. Problem: Dosage knob is unlocked and display turns off **after** dose is dialed.
Action: The display will turn off after two (2) minutes to save battery life. If you are unsure of the dosage setting, press and hold in the blue reset button and slowly turn the dosage knob counterclockwise (in the direction opposite to the arrow on the end of the dosage knob) until the digital display turns back on. Then release the reset button and turn the dosage knob clockwise, in the same direction of the arrow, until you reach the prescribed dose. Proceed with the injection.

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6. Problem: You have over-dialed the dose.
Action: Press and hold in the blue reset button and turn the dosage knob counterclockwise (in the direction opposite to the arrow on the end of the dosage knob) until the correct dosage setting appears in the digital display window.

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7. Problem: You have dialed back past "00".
Action: DO NOT PUSH IN THE DOSAGE KNOB. Two dashes "--" will appear in the digital display window. Dial the dosage knob forward again in the direction of the arrow. The "00" should reappear in the digital display window. Follow the steps to dial the number of dosage knob clicks that corresponds to the prescribed dose as described on pages XX-XX.

8. Problem: Full dose cannot be dialed.
Action: The Humatrope cartridge does not contain a full dose. Follow the procedure recommended by your healthcare professional at the start of therapy.

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9. Problem: After the Humatrope cartridge is changed, the dosage knob is stuck and will not turn.
Action: Please call Eli Lilly and Company at 1-800-847-6988 for instructions on replacing the HumatroPen.

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10. Problem: Dosage knob is dialed beyond the maximum dose — dosage setting of 12 (twelve).
Action: The dose is still accurate up to the dosage setting of 12. However, the additional drug dose beyond the maximum dose of 12 will be wasted. (Humatrope solution will flow out from the pen needle tip as you dial past 12.) To dial back, see Troubleshooting Tip #6, on page XX.

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11. Problem: After insertion of the needle through the skin, the dosage knob will not depress.
Action: First withdraw the needle from the skin. Check to make sure the pen needle is screwed on tightly. If the needle is tight, then the problem could be a clogged pen needle. Replace the pen needle.

12. Problem: Following an injection, Humatrope solution continues to drip out of the pen needle.
Action: Air bubbles may be present in the cartridge. Before dialing the next dose, follow Step 3, *Priming the HumatroPen Injection Device*, on pages XX-XX. See also Step 6, *Injecting the Humatrope Dose*, on page XX.

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13. Problem: A click sound is not heard when the dosage knob is depressed.
Action: The sound level of the HumatroPen dosage knob varies depending on dose size, speed of pressing dosage knob, and the injection device itself. As long as the knob locks in place, the HumatroPen is working properly.

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14. Problem: Display shows "≡" instead of "00".
Action: The expected life of the HumatroPen is about to expire. The display will work for approximately another four (4) weeks before it shuts off automatically. The mechanical parts of the pen will remain functional. Please call Eli Lilly and Company at 1-800-847-6988 for instructions on replacing the HumatroPen.

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15. Problem: Flashing "--" or "00" appears in the digital display window.
Action: You may have dialed too quickly or slowly. A flashing "--" or "00" indicates that a counting error may have occurred. DO NOT INJECT. Point the pen away from your face, depress the dosage knob until a click is heard as the number locks in place, and continue preparing your dose by following Step 4, *Dialing the Prescribed Dose*, on pages XX-XX.

16. Problem: With a Humatrope cartridge attached to the HumatroPen, the dosage knob does not fully extend when the white release button is pressed.
Action: Loosen the cartridge by turning the cartridge ¼ turn in a clockwise direction (in the same direction as the arrow on the end of the dosage knob). The dosage knob should now fully extend. Retighten the cartridge. Turn the dosage knob in the direction of the arrow marked on its end until "01" appears in the digital display window. Push in the dosage knob until it locks in place. Press the white release button. Before dialing the next dose, follow Step 3, *Priming the HumatroPen Injection Device*, on pages XX-XX. If the dosage knob still does not fully extend, please call Eli Lilly and Company at 1-800-847-6988 for instructions on replacing the HumatroPen.

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17. Problem: How can I check that the medication comes out of my pen when I push the dosage knob?
Action: If you suspect that your pen may have been damaged, you can check that your pen is delivering the medication by performing the steps below.

1. Hold pen with needle pointing upright and away from your face.
2. Remove needle container and needle cap.
3. Depress the dosage knob until it locks in place.
4. You should hear or feel a click when the dosage knob is fully depressed.
5. A drop of liquid may appear at the tip of the needle.
6. Unlock the dosage knob by pressing the white release button.
7. Turn the dosage knob as indicated by direction of the arrow on the end of the dosage knob until "01" appears in the digital display window and a click is heard or felt.
8. Depress the dosage knob until it locks in place.
9. The check is complete when liquid is seen at the tip of the needle.
10. If liquid does not appear repeat Steps 6, 7, and 8 above until at least a drop of liquid is seen.
11. If liquid does not appear after repeating the procedure several times, please call Eli Lilly and Company at 1-800-847-6988 for instructions on replacing the HumatroPen.

Replacement of the HumatroPen

Eli Lilly and Company (“Lilly”) will replace this HumatroPen for the HumatroPen user without charge at any time, if the pen is damaged or stops working properly, or if the low battery indicator (“bt”) or the expiration indicator ("≡") is displayed in the digital display window of the pen.

To return the HumatroPen for replacement, please call 1-800-847-6988 toll-free for instructions.

If you are concerned that the HumatroPen may not be working properly, please call 1-800-847-6988 toll-free for assistance.

Lilly’s replacement of the HumatroPen for the HumatroPen user without charge is the user’s only remedy for any claim relating to the HumatroPen. Lilly is not liable for incidental or consequential damages.

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Manufactured for Eli Lilly and Company
Pharmaceutical Delivery Systems
Indianapolis, IN 46285, USA

Packaged by Lilly France S.A.S.
F-67640 Fegersheim, France

Made in Switzerland

www.lilly.com
1-800-847-6988
www.humatrope.com

June 2005

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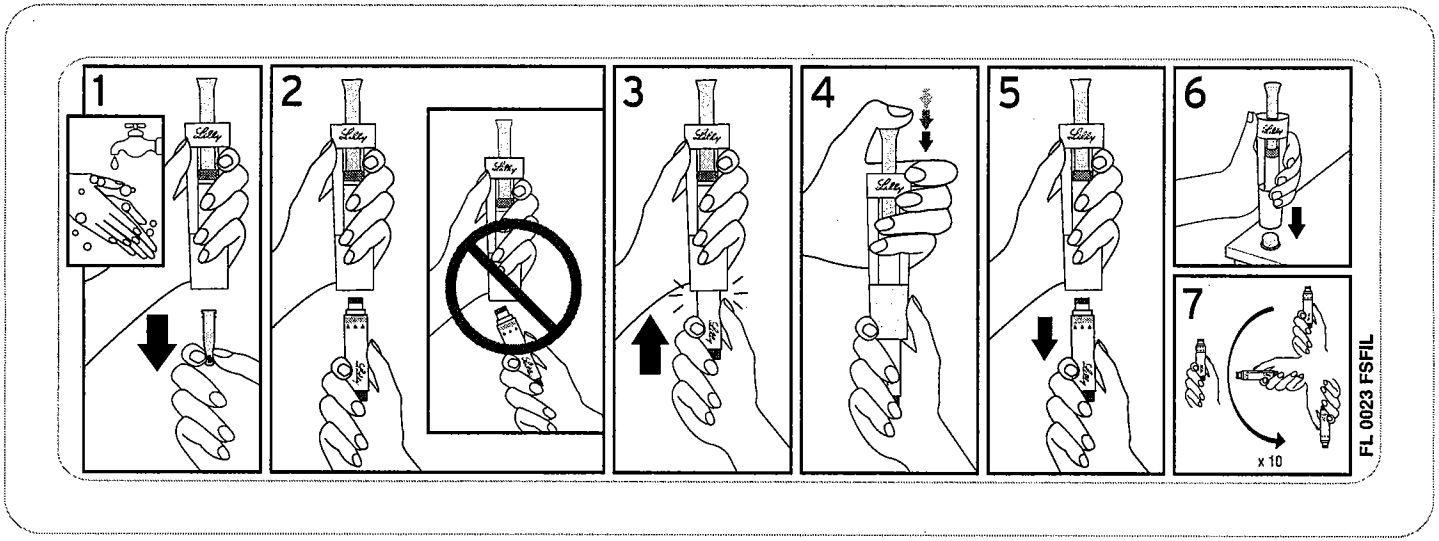

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Lilly	NB OF PAGES 1/1	PROOF N°: 4 DATE: 06 July 2004	3/3 CYAN	☐ Hospital / ☐ Sample	Approved by: NAME: Signature: DATE:	Checked by: Date:


(01)10300027554010
6 mg
NDC 0002-7554-01
VL7554
Humatrope®
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for injection
Rx only
Refrigerate • Do Not Freeze • Do Not Shake
6 mg cartridge
for use with the Humatrope®
[somatropin [rDNA origin] for injection]
pen injection device
Manufactured by Lilly France S.A.S., F-67640 Fegersheim, France
for Eli Lilly and Company, Indianapolis, IN 46285, USA
YL 0530 FSAMX
Control No. / Exp. Date
Lilly


(01)10300027555017
12 mg
NDC 0002-7555-01
VL7555
Humatrope®
somatropin (rDNA origin)
for injection
Rx only
Refrigerate • Do Not Freeze • Do Not Shake
12 mg cartridge
for use with the Humatrope®
[somatropin [rDNA origin] for injection]
pen injection device
Manufactured by Lilly France S.A.S., F-67640 Fegersheim, France
for Eli Lilly and Company, Indianapolis, IN 46285, USA
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Rx only
Refrigerate • Do Not Freeze • Do Not Shake
24 mg cartridge
for use with the Humatrope®
[somatropin [rDNA origin] for injection]
pen injection device
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for Eli Lilly and Company, Indianapolis, IN 46285, USA
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Control No. / Exp. Date
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