PRODUCT MONOGRAPH

Pr HUMATROPE®

(somatropin for injection)

Biosynthetic Human Growth Hormone of
Recombinant DNA Origin

5 mg vial
6, 12, 24 mg cartridges

Sterile Lyophilized Powder
and Diluent

Lilly Standard

Growth Stimulant

3650 Danforth Avenue
Toronto, Ontario
M1N 2E8
1-888-545-5972
www.lilly.ca

Date of Authorization:
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Control No.: 123086

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HUMATROPE®

Somatropin

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Non-medicinal Ingredients*
Subcutaneous	Sterile lyophilized powder in: Vial: 5 mg Cartridges: 6 mg 12 mg 24 mg	Supplied with diluent that contains metacresol and glycerin.

*For a complete listing, see DOSAGE FORMS, COMPOSITION and PACKAGING section.

DESCRIPTION

HUMATROPE (somatropin for injection) is a polypeptide hormone of recombinant DNA origin. The amino acid sequence is identical to that of human growth hormone of pituitary origin. HUMATROPE is synthesized in a strain of *E. coli* which has been modified by the addition of the gene for human growth hormone.

INDICATIONS AND CLINICAL USE

Pediatric Patients:

Growth Hormone Deficiency:
HUMATROPE (somatropin for injection) is indicated for the long-term treatment of pediatric patients who have growth failure due to an inadequate secretion of normal endogenous growth hormone and whose epiphyses are not closed.

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

Patients with Idiopathic Short Stature (ISS):
HUMATROPE is indicated for the long-term treatment of idiopathic short stature defined by:

- normal birth weight,

- careful diagnostic evaluation that excludes other known causes of short stature that should be either observed or treated by other means,
- height at least 2.25 standard deviation scores (SDS) below the mean for age and sex,
- height velocity below the 25th percentile for bone age and sex over 12 months of observation and unlikely to permit attainment of adult height in the expected range.

HUMATROPE treatment for idiopathic short stature should be prescribed only for those patients whose epiphyses are not closed and should be managed by physicians who have sufficient knowledge of idiopathic short stature and the efficacy/safety profile of HUMATROPE.

Patients with Short stature Homeobox-containing gene (SHOX) deficiency:
HUMATROPE is indicated for the treatment of short stature or growth failure in children with *SHOX* (short stature homeobox-containing gene) deficiency whose epiphyses are not closed.

Small for Gestational Age (SGA):
HUMATROPE is indicated for the treatment of growth failure in children born small for gestational age (birth weight and/or length below -2 SD) and who fail to achieve catch-up growth by 2 to 4 years or later (see CLINICAL TRIALS, Effect of Humatrope on Pediatric Patients Born Small for Gestational Age).

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 must have somatotropin deficiency syndrome, either alone or associated 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 as a result of congenital, genetic, acquired, or idiopathic causes.

Confirmation of the diagnosis of adult growth hormone deficiency in both groups by appropriate growth hormone stimulation test is usually required. However, confirmatory growth hormone stimulation testing may not be required in patients with congenital/genetic growth hormone deficiency or multiple pituitary hormone deficiencies due to organic disease.

CONTRAINDICATIONS

Somatropin 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 (see WARNINGS AND PRECAUTIONS, General).

Somatropin is contraindicated in patients with Prader-Willi syndrome who are severely obese or have severe respiratory impairment (see WARNINGS AND PRECAUTIONS, General,

Congenital Disorders). HUMATROPE (somatropin for injection) is not indicated for the long-term treatment of pediatric patients who have growth failure due to genetically confirmed Prader-Willi syndrome.

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 used in patients with active intracranial tumour (see WARNINGS AND PRECAUTIONS).

For patients with a known sensitivity to either metacresol or glycerin, HUMATROPE should not be reconstituted with the supplied diluent for HUMATROPE (see WARNINGS AND PRECAUTIONS, Sensitivity/Resistance; DOSAGE AND ADMINISTRATION, Reconstitution and Specific Precautions).

WARNINGS AND PRECAUTIONS

General

HUMATROPE (somatropin for injection) therapy should be directed by physicians experienced in the diagnosis and management of patients with growth hormone deficiency, Turner syndrome, idiopathic short stature, SHOX deficiency, children born small for gestational age, or adult patients with either childhood-onset or adult-onset growth hormone deficiency.

If home use is determined to be desirable by the physician, instructions on appropriate use should be given, including a review of the INFORMATION FOR THE CONSUMER.

It is recommended that insulin-like growth factor-I (IGF-I) concentrations be monitored regularly and maintained within the normal range for age and sex.

Pharmacologic glucocorticoid therapy and supraphysiologic glucocorticoid treatment may attenuate the growth promoting effects of somatropin in children. Therefore, glucocorticoid replacement dosing should be carefully adjusted in children receiving concomitant somatropin and glucocorticoid treatments to avoid both hypoadrenalism and an inhibitory effect on growth (see DRUG INTERATIONS, Drug-Drug Interactions).

HUMATROPE should be administered by subcutaneous injection, with regular rotation of injection sites to prevent lipoatrophy.

Acute critical illnesses: In 2 placebo-controlled trials in non-growth hormone deficient adults (N=522), a significant increase in mortality was reported among somatropin-treated patients with acute critical illnesses in intensive care units due to complications following open heart surgery

or abdominal surgery, multiple accidental trauma or acute respiratory failure (41.9%), compared with those receiving placebo (19.3%). Doses of 5.3 to 8.0 mg/day were given (see CONTRAINDICATIONS). The safety of continuing somatropin 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 somatropin in patients having acute critical illnesses should be weighed against the potential risk.

Pre-existing tumours or growth hormone deficiency secondary to an intracranial tumour: Patients with pre-existing tumours or with growth hormone deficiency secondary to an intracranial tumour should be examined routinely for progression or recurrence of the underlying disease process.

- In pediatric patients, clinical literature has demonstrated no relationship between somatropin therapy and CNS tumour recurrence.
- In adults, it is unknown whether there is any relationship between somatropin therapy and CNS tumour recurrence.

Carcinogenesis and Mutagenesis

Long-term animal studies for carcinogenicity with this human growth hormone (HUMATROPE) have not been performed. There has been no evidence to date of HUMATROPE-induced mutagenicity. Patients developing neoplasia should be reported to the Health Products and Food Branch (HPFB) by the treating physician.

Leukemia has been reported in a small number of children 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 somatropin therapy continues to be uncertain.

In childhood cancer survivors, an increased risk of a second neoplasm (benign and malignant) has been reported in patients treated with somatropin. Intracranial tumours, in particular meningiomas in patients treated with radiation to the head for their first neoplasm, were the most common of these second neoplasms. However, in childhood cancer survivors, no increased risk of primary cancer recurrence has been reported with somatropin treatment.

Congenital Disorders

Prader-Willi Syndrome (see CONTRAINDICATIONS)**:** There have been reports of sleep apnea and fatalities after initiating therapy with somatropin 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 somatropin. If during treatment with somatropin patients show signs of upper airway obstruction (including onset of or increased

snoring) and /or new onset of sleep apnea treatment should be interrupted. All patients with Prader-Willi syndrome treated with somatropin 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.

Turner Syndrome (see WARNINGS AND PRECAUTIONS, General):
Skeletal abnormalities including scoliosis are commonly seen in untreated Turner syndrome patients.

Patients with Turner syndrome may be at increased risk for development of intracranial hypertension.

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 Endocrine and Metabolism).

Endocrine and Metabolism (*see* WARNINGS AND PRECAUTIONS, General):
Treatment with somatropin may decrease insulin sensitivity, particularly at higher doses in patients with risk factors for diabetes mellitus, such as obesity, Turner syndrome, or a family history of diabetes mellitus, and patients with impaired glucose tolerance or pre-existing diabetes mellitus. As a result, previously undiagnosed impaired glucose tolerance and overt diabetes mellitus may be unmasked during somatropin treatment. Therefore, patients who receive somatropin should be monitored for evidence of abnormal glucose metabolism and/or diabetes mellitus. New-onset type 2 diabetes mellitus has been reported in children and adults receiving somatropin.

Patients who have pre-existing or treatment-emergent diabetes mellitus and who receive concomitant somatropin may require adjustment of their doses of insulin and/or other anti-hyperglycemic agents.

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. Because inadequate treatment of hypothyroidism may prevent optimal response to somatropin, thyroid function should be

monitored regularly during somatropin treatment.

Ophthalmologic
See Special Populations, Pediatric patients.

Peri-Operative Considerations
See General, Acute critical illnesses.

Renal
Somatropin should be discontinued at the time of the renal transplantation until one year post-transplant.

Before instituting treatment with somatropin for growth retardation secondary to chronic renal insufficiency, patients should be followed for one year to verify growth disturbance.

Sensitivity/Resistance
Sensitivity to diluent (metacresol or glycerin): If patients are sensitive to the metacresol or if sensitivity to the diluent develops, the drug should be reconstituted with Water for Injection, USP (see DOSAGE AND ADMINISTRATION, Reconstitution and Specific Precautions).

Resistance: As with all protein pharmaceuticals, a small percentage of patients may develop antibodies to the protein (see ADVERSE REACTIONS, Growth Hormone Deficient Pediatric Patients).

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

Special Populations

Pediatric Patients (see INDICATIONS AND CLINICAL USE)

Patients with endocrine disorders, including growth hormone deficiency, may develop slipped capital femoral epiphyses more frequently. Any pediatric patient with onset of a limp during somatropin therapy should be evaluated.

Somatropin has not been shown to increase the incidence of scoliosis. Progression of scoliosis can occur in pediatric patients who experience rapid growth. Because growth hormone increases growth rate, patients with a history of scoliosis who are treated with somatropin should be monitored for progression of scoliosis.

Intracranial hypertension (IH) with papilledema, visual changes, headache, nausea and/or vomiting has been reported in a small number of patients treated with growth hormone products. Symptoms usually occurred within the first eight (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.

Idiopathic Short Stature: HUMATROPE treatment for idiopathic short stature should be prescribed only for those patients whose epiphyses are not closed and should be managed by physicians who have sufficient knowledge of idiopathic short stature and the efficacy/safety profile of HUMATROPE.

Second neoplasms in survivors of childhood cancer: In childhood cancer survivors, an increased risk of a second neoplasm (benign and malignant) has been reported in patients treated with somatropin. Intracranial tumours, in particular meningiomas in patients treated with radiation to the head for their first neoplasm, were the most common of these second neoplasms. However, in childhood cancer survivors, no increased risk of primary cancer recurrence has been reported with somatropin treatment.

Pancreatitis in children: Children treated with somatropin may have an increased risk of developing pancreatitis compared to adults treated with somatropin. Although rare, pancreatitis should be considered in somatropin-treated children who develop abdominal pain.

Adult Patients: Patients with ephiphyseal closure who were treated with somatropin therapy in childhood should be re-evaluated according to the criteria in INDICATIONS AND CLINICAL USE before continuation of somatropin therapy at the reduced dose level required for growth hormone-deficient adults.

Experience with prolonged treatment in adults is limited. Adverse events such as peripheral edema, myalgia, arthralgia, and paresthesiae were reported during post-marketing studies (see under ADVERSE REACTIONS). In addition, an assessment of clinical trial data, post-marketing data, and spontaneous reports found that carpal tunnel syndrome occurs more frequently in patients over 40 years of age, and in almost half of these cases the recommended maximum dose had been exceeded. In the majority of cases, the condition was resolved with a decrease in dosage, interruption of treatment, discontinuation of treatment or spontaneously. The maximum recommended dosage should not be exceeded.

Pregnant women: Animal reproduction studies and animal studies for impairment of fertility with HUMATROPE have not been performed. HUMATROPE should be given to a pregnant woman only if clearly needed. It is not known whether HUMATROPE can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity.

Nursing women: 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.

Geriatrics (≥ 65 years of age): The safety and effectiveness of HUMATROPE in patients aged ≥ 65 years have not been evaluated in clinical studies. Geriatric patients may be more sensitive to somatropin, and therefore may be more prone to adverse reactions. A lower starting dose and smaller dose increments should be considered for older patients.

Obese patients: Obese individuals are more likely to manifest adverse effects when treated with a weight-based regimen (see DOSAGE AND ADMINISTRATION).

Monitoring and Laboratory Tests
See General, Congenital Disorders, and Endocrine and Metabolism.

Serum concentrations of inorganic phosphorus, alkaline phosphatase, parathyroid hormone and IGF-I may increase during somatropin therapy. It is recommended that IGF-I concentrations be monitored regularly and maintained within the normal range. When these concentrations are higher than the normal range, a dose reduction should be considered.

ADVERSE REACTIONS

Adverse Drug Reaction Overview
The data presented below reflect the findings from clinical trials and post-marketing experience of treatment with HUMATROPE .

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Table 1
Adverse Reactions from All Clinical Trial Sources by Body System

Body System	Adverse Reactions	Frequency
Body as a whole	Injection site reaction	≥1% and <10%
	Hypersensitivity to diluent	≥1% and <10%
	Localized muscle pain	≥0.01% and <0.1% (pediatric) ≥1% and <10% (adults)
	Benign intracranial hypertension	≤0.1%
Endocrine	Hypothyroidism	≥10%
Metabolic	Edema	≥1% and <10% (pediatric); ≥10% (adults)
	Hyperglycemia	<1% (pediatric); ≥1% and <10% (adults)
Musculoskeletal	Arthralgia	≥10% (adults)
Nervous	Carpal Tunnel Syndrome	≥1% and <10% (adults)
	Paresthesias	≥1% and <10% (adults)

Growth Hormone-Deficient Pediatric Patients: As with all protein pharmaceuticals, a small percentage of patients may develop antibodies to the protein. During the first six months of HUMATROPE (somatropin for injection) 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, 2 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 somatropin should be carried out in any patient who fails to respond to therapy (see WARNINGS AND PRECAUTIONS, Sensitivity/Resistance).

In studies with growth hormone-deficient pediatric patients, injection site pain was reported infrequently. Mild and transient edema, (either localized or generalized) was observed in 2.5% of patients 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, and recombinant somatrem and somatropin. The relationship, if any, between leukemia and growth hormone is uncertain.

Healthy adult volunteers: 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.

Adult patients: In the first 6 months of controlled, blinded trials, adult-onset growth hormone deficient patients experienced a statistically significant increase in edema (HUMATROPE 17.3% vs placebo 4.4%, (p=0.043) and peripheral edema relative to patients receiving placebo (11.5% vs. 0% respectively, (p=0.017).

In patients with adult-onset somatotropin deficiency, edema, muscle pain, and joint pain and disorder were reported early in therapy and tended to be transient or responsive to dosage titration.

Two out 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.

In growth hormone-deficient adults, treatment-emergent adverse events reported after 18 months of therapy which are possibly related to replacement therapy but were not statistically significant during the first 6 months, include: carpal tunnel syndrome, edema, arthralgia, paresthesia, hypesthesia, myalgia, peripheral edema, back pain, headache and joint disorder.

Adult patients treated with somatropin, following diagnosis of growth hormone deficiency in childhood, reported side effects less frequently than those with adult onset growth hormone deficiency.

Turner Syndrome: Patients with Turner syndrome have an increased risk of ear or hearing disorders. In a randomized, concurrent controlled clinical trial, there was a statistically significant increase, as compared to untreated controls, in otitis media, (43% vs 26%) ear disorders (18% vs 5%) and surgical procedures (45% vs 27%) in patients receiving HUMATROPE (see WARNINGS AND PRECAUTIONS, Congenital Disorders).

Patients with Idiopathic Short Stature: In the placebo-controlled study, there were no significant differences between the HUMATROPE-treated and placebo-treated groups for any of the nonserious clinically significant treatment-emergent adverse events (See Table 2). 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 occurrence of above-range values for glucose, insulin, and HbA_{1c} were similar in the HUMATROPE and placebo-treated groups. No patient developed diabetes mellitus. Consistent with the known mechanism of growth hormone action, HUMATROPE-treated patients (0.222 mg/kg/week) 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%]). There is no available information regarding IGF-I levels at the recommended dose of 0.37 mg/kg/week.

Table 2
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%)
Arthosis	4 (10.8%)	2 (6.5%)
Myalgia	9 (24.3%)	4 (12.9%)
Hypertension	1 (2.7%)	0

* Coding of adverse events was performed using the Medical Dictionary for Regulatory Activities (MedDRA).

The adverse events observed in the dose-response study (239 patients treated for 2 years) did not indicate a pattern suggestive of a somatropin dose effect. Among HUMATROPE dose groups, mean fasting blood glucose, mean glycosylated hemoglobin, and the occurrence rates of elevated fasting blood glucose concentrations were similar. One patient developed abnormalities of carbohydrate metabolism (glucose intolerance and slightly elevated HbA_{1c}) on treatment, which resolved when treatment was discontinued.

Five patients discontinued from the clinical trials because of adverse events. One patient discontinued from the placebo-controlled study following diagnosis of Stage 3B Hodgkin disease after 19 weeks of HUMATROPE treatment. It was subsequently determined on the basis of clinical, radiographic and laboratory findings that subclinical Hodgkin disease was likely present at study entry. One placebo-treated patient discontinued the study after an accidental injury. One patient in the dose-response study discontinued following diagnosis of a desmoplastic small round cell tumour after 6.4 years of HUMATROPE treatment and died 4 years later. It was subsequently determined that the tumour had an abnormal karyotype typically associated with this type of tumour. Neither case of neoplasia in the ISS studies was considered causally related to HUMATROPE exposure. Two additional patients discontinued from the dose-response study due to adverse events: one patient discontinued after diagnosis of a slipped capital femoral epiphysis following trauma; one patient was withdrawn from the study due to decreased glucose tolerance. Both events have been previously reported in patients receiving somatropin.

The impact of ethnicity was not evaluated in the clinical trials for idiopathic short stature.

Patients with SHOX Deficiency: Clinically significant adverse events (adverse events previously observed in association with growth hormone treatment in general) were assessed prospectively during the 2-year randomized, open-label study; those observed are presented in Table 3. In both treatment groups, the mean fasting plasma glucose concentration at the end of the first year was similar to the baseline value and remained in the normal range. No patient developed diabetes mellitus or had an above normal value for fasting plasma glucose at the end of one-year of treatment. During the 2 year study period, the proportion of patients who had at least one IGF-I concentration greater than 2.0 SD above the age- and gender-appropriate mean was 10 of 27 [37.0%] for the HUMATROPE-treated group vs. 0 of 24 patients [0.0%] for the untreated group. The proportion of patients who had at least one IGFBP-3 concentration greater than 2.0 SD above the age and gender appropriate mean was 16 of 27 [59.3%] for the HUMATROPE treated group vs. 7 of 24 [29.2%] for the untreated group. There were no discontinuations due to adverse events in this study. No serious adverse events were reported for subjects with SHOX Deficiency.

Table 3
Clinically Significant Treatment-Emergent Adverse Events[a,b] by Treatment Group and Patients with SHOX Deficiency

Adverse Event	Treatment Group	
	Untreated	HUMATROPE
Total Number of Patients	25	27
Patients with at least one event	2	5
Arthralgia	2 (8.0%)	3 (11.1%)
Gynecomastia[c]	0 (0.0%)	1 (8.3%)
Excessive number of cutaneous nevi	0 (0.0%)	2 (7.4%)
Scoliosis	0 (0.0%)	1 (3.7%)

[a] All events were non-serious.
[b] Events are included only if reported for a greater number of HUMATROPE-treated than Untreated patients.
[c] Percentage calculated for males only (1/12).

Patients Born Small for Gestational Age: The safety of Humatrope treatment in children born small for gestational age was assessed in 2 clinical trials (Study GDGB and Study 0908) and one observational study (Study GDFC) (see CLINICAL TRIALS, Effects of Humatrope on Pediatric Patients Born Small for Gestational Age).

In Study GDGB, 4 patients discontinued due to adverse events, 3 from the FHD group (1 patient each for impaired fasting glucose, mood alteration and pain in extremity) and 1 patient from the IAD group (focal glomerulosclerosis).

Adverse events possibly or probably related to HUMATROPE are provided in Table 4. The most frequently reported of these adverse drug reactions was headache, for which there was a suggestion of a modest dose-response (FHD, 9%; IAD, 3%). There were no clear cut cases of new-onset diabetes mellitus, no children treated for hyperglycemia, and no children whose

fasting blood glucose exceeded 7 mmol/L at any time during the study. However, 6 children (4 in the FHD group and 2 in the IAD group whose dose was increased from 0.035 mg/kg/day to 0.067 mg/kg/day [one at Month 3 and one at Year 1]) manifested impaired fasting glucose at Year 2. Two of these six children had impaired fasting glucose during the study as well, and one of them was required to discontinue Humatrope at Month 15 as a consequence.

A modestly dose-dependent increase in mean serum IGF-I SDS concentrations within the reference range was observed; of note, at study completion, 22% of these children had serum IGF-I values more than 2 standard deviations above the mean for age and sex. Eight children in the FHD group and 2 in the IAD group required dose reduction due to high IGF-I or IGFBP-3.

Table 4 represents adverse drug reactions reported at a frequency of ≥1% in Study GDGB, listed in descending order of frequency within system organ class.

Table 4
Adverse Drug Reactions* with Frequency ≥ 1% in Study GDGB

System Organ Class	Preferred Term	FHD (N=99) n (%)	IAD (N=94) n (%)	Total (N=193) n (%)
Ear and labyrinth disorders	Vertigo	1 (1)	1 (1)	2 (1)
Endocrine disorders	Hypothyroidism	2 (2)	2 (2)	4 (2)
General disorders and administration site conditions	Fatigue	2 (2)	1 (1)	3 (2)
	Injection site pain	2 (2)	1 (1)	3 (2)
	Edema	0 (0)	2 (2)	2 (1)
Investigations	Blood insulin increased	4 (4)	3 (3)	7 (4)
	Low density lipoprotein decreased	3 (3)	1 (1)	4 (2)
Musculoskeletal and connective tissue disorders	Pain in extremity	3 (3)	6 (6)	9 (5)
	Arthralgia	1 (1)	2 (2)	3 (2)
	Limb deformity	2 (2)	0 (0)	2 (1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Melanocytic naevus	2 (2)	0 (0)	2 (1)
Nervous system disorders	Headache	9 (9)	3 (3)	12 (6)
	Psychomotor hyperactivity	1 (1)	3 (3)	4 (2)
Psychiatric disorders	Aggression	1 (1)	1 (1)	2 (1)
Respiratory, thoracic and mediastinal disorders	Adenoidal hypertrophy	0 (0)	3 (3)	3 (2)

N=total number in treatment group; n=number for whom event was reported; FHD=fixed high dosage (0.067 mg/kg/day); IAD=individually-adjusted dosage (0.035 to 0.067 mg/kg/day).
*Terms designated by investigator as related to study drug in at least one patient.

In Study 0908, treatment-emergent adverse events (TEAEs) were reported for 30/35 (86%) of study participants. Because of the size of this study, all events were reported at a frequency of >1%. The most frequently reported non-serious TEAEs were typical childhood illnesses, such as nasopharyngitis (29%) and bronchitis, gastroenteritis, influenza and vomiting (14% for each event). Gynecomastia was reported for 13% of males. In addition, the following events were each reported for 11% of study patients: arthralgia, headache, injection site pain, pyrexia; the following events were reported for 9% of patients: asthenia, cough, eczema, pharyngitis, pharyngolaryngeal pain, rhinitis; the following events were reported for 6% of patients: appendicitis, ear infection, hyperthermia, hypothyroidism, joint sprain, lymphadenopathy, tracheitis, tracheobronchitis. No patient was reported to have discontinued the study because of an adverse event.

In the observational study GDFC, non-serious TEAEs were reported for 76 of 379 (20%) children with a study entry diagnosis of short stature due to small for gestational age birth, who were naïve to treatment at study entry and had at least one post-baseline visit. The majority of these events were typical childhood illnesses or injuries unlikely to have been related to Humatrope treatment.

Less Common Clinical Trial Adverse Drug Reactions (<1%)
The following list provides the adverse events reported with a frequency of <1% in studies GDGB and GDFC that were designated by the investigators as possibly-related to the study drug, or for which no designation was made: abnormal behaviour, back pain, blood thyroid stimulating hormone increased, cardiovascular disorder, carpal tunnel syndrome, contusion, eyelid edema, epiphysiolysis (slipped capital femoral epiphysis), hyperinsulinemia, hypertension, impaired fasting glucose, injection site bruising, injection site hematoma, injection site induration, injection site pain, injection site vesicles, mood altered, muscle mass, nervousness, periorbital edema, precocious puberty, puberty, tonsillar hypertrophy, type 2 diabetes mellitus, and visual disturbance. In study 0908, there were no events reported with a frequency of <1%, due to study size (n=35).

Post-Market Adverse Drug Reactions
In addition to the Clinical Trial Adverse Reactions listed in Table 1, the Adverse Reactions shown in Table 5 have been noted in post-marketing studies.

Table 5
Adverse Reactions from Post-Marketing Studies by Body System

Body System	Adverse Reactions	Frequency
Respiratory	Dyspnea Sleep Apnea	≥1% and <10% (adults) ≥1% and <10% (adults)
Vascular	Hypertension	≥1% and <10% (adults)
Metabolic	Type 2 Diabetes Mellitus	≥0.1% and <1% (pediatric)*

*adult cases of Type 2 diabetes mellitus were reported spontaneously

DRUG INTERACTIONS

Drug-Drug Interactions

Potential drug interactions are tabulated below (Table 6).

Table 6
Established or Potential Drug-Drug Interactions with HUMATROPE (somatropin for injection)

Therapeutic Class	Effects	Clinical comments
Glucocorticoids	Inhibition of 11ß-hydroxysteroid dehydrogenase type 1 (11ßHSD-1). Somatropin inhibits the liver enzyme 11β-HSD-1 which is required for conversion of administered cortisone and prednisone to their active metabolites, cortisol and prednisolone, respectively.	In patients treated with somatropin, previously undiagnosed secondary hypoadrenalism may be unmasked and may require glucocorticoid replacement therapy. If glucocorticoid replacement therapy is required for newly-diagnosed or preexisting hypoadrenalism, dosage and compliance should be monitored carefully to avoid either inhibition of growth promoting effects or adrenal insufficiency; increases in maintenance or stress doses of glucocorticoids may be required after initiation of somatropin.
Cytochrome P450 Metabolized Drugs	Somatropin can increase cytochrome P450 (CYP) liver enzyme activity in humans and may result in reduced plasma concentrations and decreased effectiveness of drugs metabolized by CYP3A such as sex steroids (for example, estrogen or oral contraceptives), cyclosporine and some anticonvulsants.	Limited published data indicate that somatropin treatment increases cytochrome P450 (CP450)-mediated antipyrine clearance in humans. Careful monitoring is advised when somatropin is administered in combination with drugs metabolized by CP450 liver enzymes.
Insulin and Anti-hyperglycemic Agents	Patients with diabetes mellitus who receive concomitant somatropin may require adjustment of their doses of insulin and/or other anti-hyperglycemic agents.	Because somatropin may induce a state of insulin resistance, patients who receive somatropin should be monitored for evidence of abnormal glucose metabolism and/or diabetes mellitus. New-onset type 2 diabetes mellitus has been reported in children and adults receiving somatropin.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established

Drug-Laboratory Interactions
For interactions between HUMATROPE and laboratory tests, see WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests subsection.

DOSAGE AND ADMINISTRATION

Dosing Considerations
Adult Patients: Patients with epiphyseal closure who were treated with somatropin therapy in childhood should be re-evaluated according to the criteria in INDICATIONS AND CLINICAL USE before continuation of somatropin therapy at the reduced dose level required for growth hormone-deficient adults. A lower starting dose may be necessary in older and obese patients.

***Estrogen-replete women*:** Estrogen-replete women may need higher doses than men. Oral estrogen administration may increase the dose requirements in women.

Recommended Dose and Dosage Adjustment

The dosage and administration schedule for HUMATROPE (somatropin for injection) should be individualized for each patient (see Table 7). Clinicians should carefully monitor the growth response in all children, and adjust the somatropin dose as necessary.

Table 7
Recommended Dose and Administration Schedule for HUMATROPE

Indication	Recommended dose (mg/kg body weight)	Route	Comments
GH-deficient pediatric patients	0.18 mg/kg/week Maximum: 0.3 mg/kg/week	SC	Divide into equal doses given on: • 3 alternate days OR • 6 times/week OR • daily
GH-deficient adult patients	Initiate at not more than 0.006 mg/kg/day Maximum: 0.0125 mg/kg/day	SC	Should be titrated • based on adverse effects (increasing age or excessive body weight may require dose reductions) • to maintain IGF-I<ULN matched for age and sex
Patients with Turner syndrome	Up to 0.375 mg/kg/week	SC	Divide into equal doses given: • daily OR • on 3 alternate days
Patients with idiopathic short stature	0.37 mg/kg/week	SC	Divided into equal doses given 6 to 7 times per week
Patients with SHOX deficiency	0.35 mg/kg/week	SC	Divided into equal doses given 6 to 7 times per week
Patients born small for gestational age**	Up to 0.47 mg/kg/week	SC	Divided into equal doses given 6 to 7 times per week

** It is recommended that treatment be initiated with larger doses of somatropin (e.g., 0.067 mg/kg/day), especially in very short children (i.e., height SDS ≤3) and/or older pubertal children. A reduction in dosage (e.g. to 0.035 mg/kg/day) should be considered if substantial catch-up growth is observed during the first few years of therapy.

In younger SGA children (approximately <4 years of age) with less severe short stature (i.e., baseline height SDS values between -2 and -3), consideration should be given to initiating treatment with a lower dose (e.g., 0.035 mg/kg/day), then titrating the dose as needed.

It is recommended that IGF-I concentrations be monitored regularly and maintained within the normal range for age and sex. When these concentrations are higher than the normal range, a dose reduction should be considered.

Administration

HUMATROPE should be administered subcutaneously and the injection site should be rotated to minimize the risk of lipoatrophy.

HUMATROPE treatment for improvement of linear growth in childhood should be administered to pediatric patients whose epiphyses have not closed. For patients whose height velocity in the first year of treatment does not improve by at least 50% above the pre-treatment height velocity, consideration should be given to the following:

- Is the patient receiving the correct dosage and frequency of the medication?
- Is the growth disorder diagnosis correct?
- Does the patient have a coexistent condition that may impair growth (such as hypothyroidism, a gastrointestinal disorder or severe psychological disturbance)?
- Is the patient receiving adequate nutrition?
- Is the patient receiving a concomitant medication that may impair response to GH (such as systemic corticosteroids or stimulant medications)?

If no underlying reason for a suboptimal response to HUMATROPE treatment can be found, discontinuation of treatment should be considered.

In pediatric patients receiving HUMATROPE for improvement of linear growth, consideration should be given to discontinuation of treatment when growth is nearly complete, as evidenced by:

- Height velocity less than 2.0 cm per year,
- Bone age of 14 years or greater in girls or 16 years or greater in boys.

Reconstitution and Specific Precautions

If home use is prescribed, a puncture resistant container for the disposal of used needles and syringes should be recommended to the patient. Patients and/or caregivers should be thoroughly instructed in the importance of proper needle disposal and cautioned against the reuse of needles and syringes.

HUMATROPE Vials

Reconstitute each vial of HUMATROPE with 1.5 to 5 mL of diluent for HUMATROPE. Inject the diluent for HUMATROPE (metacresol and glycerin solution) into the vial of HUMATROPE aiming the stream of liquid against the glass wall. Following reconstitution, swirl the vial with a GENTLE ROTARY motion until the contents are completely dissolved. DO NOT SHAKE. The resulting solution should be clear, without particulate matter. If the solution is cloudy or contains particulate matter, the contents MUST NOT be injected.

Before and after injections, the septum of the vial should be wiped with rubbing alcohol or another alcoholic antiseptic solution to prevent contamination of the contents by repeated needle insertions. HUMATROPE should be administered using sterile, disposable syringes and needles. The syringes should be of small enough volume that the prescribed dose can be drawn from the vial with reasonable accuracy. The needle should be of sufficient length (usually 1 inch or more) to ensure that the injection reaches the muscular layer for intramuscular injections.

If sensitivity to the diluent should occur, HUMATROPE vials may be reconstituted with Sterile Water for Injection, USP. When reconstituting with water, use only once and discard the unused portion. The vial should be used immediately after reconstitution. Although not recommended, the solution can be stored refrigerated (2º to 8ºC) but must be used within 24 hours.

HUMATROPE Cartridges

Each HUMATROPE cartridge (for use with the HumatroPen™) should be reconstituted using the accompanying diluent syringe. To reconstitute, attach the cartridge to the pre-filled diluent

syringe and then inject the entire contents of the pre-filled diluent syringe into the cartridge. The diluent needle aims the stream of liquid against the glass wall of the cartridge. Following reconstitution, gently invert the cartridge up and down 10 times until the contents are completely dissolved. DO NOT SHAKE. The resulting solution should be clear, without particulate matter. If the solution is cloudy or contains particulate matter, the contents MUST NOT be injected. If the solution is clear, the cartridge is ready to be attached to the HumatroPen. For complete instructions on the reconstitution of HUMATROPE cartridges, please refer to the reconstitution instruction leaflet provided with all HUMATROPE cartridges.

The diluent syringe is for single use only. Discard it after use.

If sensitivity to the accompanying diluent occurs, Sterile Water for Injection, USP, may be used for reconstitution. The Sterile Water for Injection, USP, should be administered using a sterile, disposable syringe and needle. The syringe should be of small enough volume that 3.15 mL can be measured with reasonable accuracy. Before and after injections, the septum of the cartridge should be wiped with rubbing alcohol or another alcoholic antiseptic solution. Inject 3.15 mL of Sterile Water for Injection, USP, into the cartridge through the rubber septum, aiming the stream of liquid against the glass wall of the cartridge. Following reconstitution, the cartridge should be gently inverted up and down 10 times until the contents are completely dissolved. DO NOT SHAKE. The resulting solution should be clear, without particulate matter. If the solution is cloudy or contains particulate matter, the contents MUST NOT be injected.

HUMATROPE reconstituted in this manner should be used immediately. Although not recommended, the solution can be stored refrigerated (2º to 8ºC) but must be used within 24 hours. Discard any unused portion. However, to minimize waste, vials of HUMATROPE rather than cartridges are recommended.

HUMATROPE cartridges are designed for use only with the HumatroPen family of pens. A sterile needle should be used for each administration of somatropin.

For complete instructions on the use of the HumatroPen, see the relevant HumatroPen Instruction Manual.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

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 Dose and Dosage Adjustments, Table 7.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

The following actions have been demonstrated for HUMATROPE (somatropin for injection) and/or human growth hormone of pituitary origin.

1. Tissue Growth:

a. *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.
b. *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 to normal pediatric populations. Treatment with human growth hormone of pituitary origin results in an increase in both the number and the size of muscle cells.

2. 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.

3. Carbohydrate Metabolism:

Pediatric patients with hypopituitarism sometimes experience fasting hypoglycemia, which is improved by treatment with HUMATROPE. Large doses of somatropin may impair glucose tolerance. Untreated patients with Turner syndrome have an increased incidence of glucose intolerance. Administration of somatropin to healthy 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.

4. Lipid Metabolism:

In growth hormone-deficient patients, long-term administration of human growth hormone of pituitary origin has resulted in lipid mobilization, reduction in body fat stores, and an increase in plasma fatty acids.

5. 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.

HUMATROPE stimulates linear growth in pediatric patients lacking adequate normal endogenous growth hormone. 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 in therapy with human growth hormone of pituitary origin.

As a result of replacement therapy in growth hormone deficient adults, body composition improved, HDL cholesterol values normalized, and health related quality of life measures concerning physical mobility and social isolation improved in placebo-controlled clinical trials. Exercise capacity improved as compared to placebo.

Pharmacokinetics

In vitro, preclinical, and clinical testing have demonstrated that HUMATROPE is therapeutically equivalent to human growth hormone of pituitary origin with equivalent pharmacokinetics in normal adults.

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 somatropin 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.

STORAGE AND STABILITY

Before Reconstitution: Vials of HUMATROPE (somatropin for injection), HUMATROPE cartridges for use with the HumatroPen and the supplied diluent for HUMATROPE are stable when stored at (2º to 8ºC). Avoid freezing the diluent for HUMATROPE. Expiration dates are stated on the labels.

After Reconstitution: When reconstituted with the supplied diluent and stored at 2º to 8ºC:

- HUMATROPE vials are stable for up to 21 days and
- HUMATROPE cartridges for use with the HumatroPen are stable for up to 28 days
- Avoid freezing the reconstituted vials and cartridges of HUMATROPE.

If HUMATROPE vials or cartridges are reconstituted with Sterile Water for Injection, USP, they should be used immediately after reconstitution. Although not recommended, the solution can be stored refrigerated (2º to 8ºC) but must be used within 24 hours. Discard any unused portion. To minimize waste, vials of HUMATROPE rather than the cartridges are recommended.

Light: Protect from light.

DOSAGE FORMS, COMPOSITION AND PACKAGING

HUMATROPE (somatropin for injection) is a sterile, white, lyophylized powder of highly purified rhGH, which is intended for subcutaneous or intramuscular use after reconstitution with the supplied diluent. HUMATROPE is available as a vial and cartridges (Table 8).

HUMATROPE Vials

Each vial of HUMATROPE contains 5 mg of somatropin for injection, in addition to mannitol, glycine, and dibasic sodium phosphate. Phosphoric acid and/or sodium hydroxide may have been used for pH adjustment.
Each vial of HUMATROPE is supplied in a combination pack with an accompanying vial of diluting solution. The diluent for HUMATROPE contains water for injection with 1.7% glycerin and 0.3% metacresol as a preservative. At a concentration of 2 mg HUMATROPE per mL diluent, the 1.7% glycerin makes the reconstituted product nearly isotonic. Reconstituted solutions have a pH of approximately 7.5.

HUMATROPE Cartridges

Each cartridge of HUMATROPE (for use with the HumatroPen) contains 6.0 mg, 12.0 mg, or 24.0 mg of somatropin for injection. The cartridge also contains mannitol, glycine, and dibasic sodium phosphate. Phosphoric acid and/or sodium hydroxide may have been added at the time of manufacture to adjust the pH.

Each cartridge is supplied in a combination package with an accompanying syringe containing 3.15 mL of diluting solution. The diluent for 6.0 mg cartridges contains water for injection, 0.3% metacresol as a preservative; and 1.7% glycerin. The diluent for 12.0 and 24.0 mg cartridges contains water for injection, 0.3% metacresol, and 0.29% glycerin. Glycerin is added to the diluent to modify tonicity of the reconstituted solutions. Reconstituted solutions have a pH

of approximately 7.5.

Table 8
HUMATROPE Dosage Forms and Packaging

Dosage Form	Combination Packages			
	HUMATROPE	Vial #	Diluent	Vial #
Vial	5 mg	7335	5 mL	7336
Cartridges (for use with HumatroPen*)	6.0 mg	7554	3.15 mL	7616
	12.0 mg 24.0 mg	7555 7556	3.15 mL	7617

* The HumatroPen family of pens are available separately with a HumatroPen Instruction Manual

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Somatropin [recombinant human growth hormone (rhGH)] is a polypeptide hormone of recombinant DNA origin. Somatropin has 191 amino acid residues and a molecular weight of about 22,125 daltons. The amino acid sequence is identical to that of human growth hormone of pituitary origin. Somatropin is synthesized in a strain of *E. coli*, which has been modified by the addition of the gene for human growth hormone production.

Proper name:	somatropin
Common Name:	recombinant human growth hormone (rhGH)
Molecular formula:	191 amino acid residues
Molecular mass:	~ 22,125 daltons
Structural formula:	Biosynthetic Human Growth Hormone (figure 1)

Product Characteristics

HUMATROPE (somatropin for injection) is a sterile, white, lyophilized powder of highly purified rhGH which is intended for subcutaneous or intramuscular administration after reconstitution with the supplied diluent.

CLINICAL TRIALS

Effect of HUMATROPE Treatment in Children with Growth Hormone Deficiency

Studies conducted for pediatric growth hormone deficiency were open-label multi-national trials with a combined population of 239 patients assessed in three groups; naïve patients in US and Canada (n= 158), multinational naïve patients (n=29), and previously treated patients (n= 52). Each patient served as their own control comparing growth velocity before and after treatment. Patients were administered 0.18 mg/kg/week of HUMATROPE either by subcutaneous or intramuscular injections at a frequency of 3 to 7 times/week.

Growth rates at 1, 3 and 6 month time points were significantly greater ($p<0.001$) than pretreatment growth rates for all three groups. Table 9 shows the increase in growth velocity from pretreatment compared to the patient's last visit.

Table 9
Mean Growth Rates (cm/year) from Pretreatment to Last Visit

	Age at study entry (years)	Mean Growth Velocity (cm/year)	
		Pretreatment	Last visit
Naïve patients in US and Canada (n= 158)	8.3	3.51	10.27
Multinational naïve patients (n= 29)	8.8	3.79	9.05
Previously treated patients (n= 52)	12.3	3.34	8.74

Effect 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 percent body fat (-3.60 vs 0.19%, $p<0.001$). 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 10). Patients with childhood-onset disease failed to demonstrate improvements in Nottingham Health Profile outcomes.

Table 10
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.

Effect of HUMATROPE Treatment in Patients with Turner Syndrome
One long-term, randomized, open-label multicenter concurrently controlled study, and one long-term, randomized, dose-response study were conducted to evaluate the efficacy of HUMATROPE for the treatment of patients with short stature due to Turner syndrome.

In the randomized study, GDCT, comparing HUMATROPE -treated patients to a concurrent control group who received no somatropin, the HUMATROPE -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 HUMATROPE therapy was a mean height increase of 5.4 cm (p=0.001).

In a randomized, blinded dose-response study, GDCI, patients were treated from a mean age of

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

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

The HUMATROPE efficacy data of these studies in patients with Turner syndrome is summarized in Table 11.

Table 11
Summary Table of Efficacy Results

Study/ Group	Study Design[a]	N at Adult Height	GH Age (yr)	Estrogen Age (yr)	GH Duration (y)	Adult Height Gain (cm)[b]
GDCT	RCT	27	11.7	13	4.7	5.4
GDCI	RDT	31	11.1	8-13.5	5.3	~5[c]

[a] RCT: randomized controlled trial; RDT: randomized dose-response trial.
[b] Analysis of covariance vs. controls.
[c] Compared with historical data.

Effect of HUMATROPE Treatment in Pediatric Patients with Idiopathic Short Stature
Two randomized, multicenter trials, 1 placebo-controlled and 1 open-label, dose-response**,** were conducted in pediatric patients with idiopathic 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.
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"). Final height measurements were available for 33 subjects (22 HUMATROPE, 11 placebo).

After a mean treatment duration of 4.4 years the GH-treated group had achieved a mean final height 0.51 SDS greater than the placebo-treated group (ANCOVA: GH -1.8 SDS vs. placebo -2.3 SDS, p=0.017); this difference translates to approximately 3.7 cm (range 2.8-5.0 cm) (see Table 12). 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 12 and 13). 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 12
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)	NA	0.77
BPH SDS	-2.1 (0.7)	-2.3 (0.8)	NA	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)	0.43

[a] For final height population.
[b] Between-group comparison was performed using analysis of covariance with baseline predicted height SDS as the covariate. Treatment effect is expressed as least squares mean (95% CI). One placebo-treated patient was not included in this analysis because baseline bone age X-ray was not available.
Abbreviations: FH = final height. SDS = standard deviation score. BPH = baseline predicted height. CI = confidence interval. NA= not applicable.

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 13). 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 13
Final Height Minus Baseline Predicted Height: Idiopathic Short Stature Trials

	Placebo-controlled Trial 3x per week dosing		Dose Response Trial 6x per week dosing		
	Placebo (N=10)	**HUMATROPE 0.22 mg/kg (n=22)**	**HUMATROPE 0.24 mg/kg (n=13)**	**HUMATROPE 0.24/0.37 mg/kg (n=13)**	**HUMATROPE 0.37 mg/kg (n=13)**
FH - Baseline PH Mean cm (95% CI)	-0.7 (3.6, 2.3)	+2.2 (0.4, 3.9)	+5.4 (2.8, 7.9)	+6.7 (4.1, 9.2)	+7.2 (4.6, 9.8)

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

Effect of HUMATROPE Treatment in Patients with SHOX Deficiency
SHOX deficiency may result either from a deletion of one copy of the short stature homeobox-containing gene (*SHOX*) or from a mutation within or outside one copy of the SHOX gene that impairs the production or function of SHOX protein. The SHOX gene is located on the pseudoautosomal region of the X chromosome and haploinsufficiency of the SHOX gene causes short stature analogous to Turner Syndrome.

A randomized, controlled, two-year, three-arm, open-label study was conducted to evaluate the efficacy of HUMATROPE treatment of short stature in pediatric patients with SHOX deficiency who were not GH deficient. 52 patients (24 male, 28 female) with SHOX deficiency, 3.0 to 12.3 years of age, were randomized to either a HUMATROPE-treated arm (27 patients; mean age 7.3 ± 2.1 years) or an untreated control arm (25 patients; mean age 7.5 ± 2.7 years). To determine the comparability of treatment effect between patients with SHOX deficiency and patients with Turner syndrome, the third study arm enrolled 26 patients with Turner syndrome, 4.5 to 11.8 years of age (mean age 7.5 ± 1.9 years), to HUMATROPE treatment. All patients were prepubertal at study entry. Patients in the HUMATROPE-treated group(s) received daily subcutaneous injections of 0.05 mg/kg of HUMATROPE. Patients in the untreated group received no injections.

Patients with SHOX deficiency who received HUMATROPE had significantly greater first-year height velocity than untreated patients (8.7 cm/year vs. 5.2 cm/year, $p<0.001$, primary efficacy analysis) and similar first-year height velocity to HUMATROPE-treated patients with Turner syndrome (8.7 cm/year vs. 8.9 cm/year, CI: (-1.3, 0.7). In addition, patients who received HUMATROPE had significantly greater second year height velocity, and first and second year height gain than untreated patients (Table 14).

At the end of the second year study period, 41% of HUMATROPE-treated subjects with SHOX deficiency and 31% of subjects with Turner syndrome had achieved height within the normal range for age and gender (>-2.0SDS).

Table 14
Summary of Efficacy Results in Patients with SHOX deficiency and Turner Syndrome

	SHOX Deficiency			Turner Syndrome
	Untreated (n=24)	HUMATROPE (n=27)	Treatment Difference[a] Mean (95%CI)	HUMATROPE (n=26)
Height Velocity (cm/yr)				
1st Year				
Mean (SD)	5.2 (1.1)	8.7 (1.6)[b]	+3.5 (2.8, 4.2)	8.9 (2.0)
2nd Year				
Mean (SD)	5.4 (1.2)	7.3 (1.1)[b]	+2.0 (1.3, 2.6)	7.0 (1.1)
Height change (cm)				
Baseline to 1st Year				
Mean (SD)	+5.4 (1.2)	+9.1 (1.5)[b]	+3.7 (2.9, 4.5)	+8.9 (1.9)
Baseline to 2nd Year				
Mean (SD)	+10.5 (1.9)	+16.4 (2.0)[b]	+5.8 (4.6, 7.1)	+15.7 (2.7)
Height SDS change				
Baseline to 1st Year				
Mean (SD)	+0.1 (0.5)	+0.7 (0.5)[b]	+0.5 (0.3, 0.8)	+0.8 (0.5)
Baseline to 2nd Year				
Mean (SD)	+0.2 (0.5)	+1.2 (0.7)[b]	+1.0 (0.7, 1.3)	+1.2 (0.7)
Patients with height SDS> -2.0 at 2 years	1 (4%)	11 (41%)[c]		8 (31%)

[a] *Positive values favor HUMATROPE*
[b] Statistically significantly different from untreated with p<0.001.
[c] Statistically significantly different from untreated with p<0.05.

Effect of Humatrope on Pediatric Patients Born Small for Gestational Age
Data from 2 clinical trials and one observational trial demonstrate the efficacy of Humatrope treatment of growth failure in children born SGA.

The primary objective of Study GDGB was to demonstrate that the increase from baseline in height SDS after 1 year of treatment would be similar when HUMATROPE is administered according to an individually adjusted dose (IAD) regimen or a fixed high dose (FHD) regimen. This 2-year, open-label, multicenter, European study enrolled 193 prepubertal, non-GH deficient children with mean chronological age 6.8 ± 2.4 years (range: 3.0 to 12.3). Additional study entry criteria included birth weight <10th percentile and/or birth length SDS <-2 for gestational age, and height SDS for chronological age ≤-3. Exclusion criteria included syndromal conditions (e.g., Turner syndrome), chronic disease (e.g., diabetes mellitus), and tumour activity.

Study 0908 was an open-label, multicenter, single-arm study conducted in France, during which 35 prepubertal, nonGH-deficient children were treated for 2 years with Humatrope 0.067 mg/kg/day (0.47 mg/kg/week). Mean chronological age at baseline was 9.3 ± 0.9 years (range: 6.7 to 10.8). Additional study entry criteria included birth length SDS <-2 or <3rd percentile for gestational age, and height SDS for chronological age <-2. Exclusion criteria included syndromal conditions (e.g., Turner syndrome), chronic disease (e.g., diabetes mellitus), and any active disease.

Additional safety information was obtained from 379 short children born SGA followed in an observational study (Study GDFC) who received an average Humatrope dosage of 0.041 mg/kg/day (maximum dose: 0.084 mg/kg/day) for an average of 3.0 years.

Table 15
Summary of Patient Demographics for Clinical Trials in Pediatric Patients Born Small for Gestational Age

Study #	Trial design	Dosage, frequency, route of administration and duration	Study subjects (N=number)	Mean age (Range)	Gender
B9R-EW-GDGB	Phase 3b, multi-center, randomized, open-label, 2-arm non-inferiority study of individually-adjusted (IAD) versus fixed high dose (FHD) regimen	FHD: 0.067 mg/kg/d for 2 years; IAD: 0.035 mg/kg/d for 3 months, increased to 0.067 mg/kg/d if predicted or actual 1-year height gain was <0.75 SDS; Daily, subcutaneous	200 patients entered, 193 received at least 1 dose of drug 175 completed 2 years	6.8 years (3.0 – 12.3)	M:102 F: 91
B9R-FP-0908	Phase 3b, randomized, open label multi-centre	0.47 mg/kg/wk; Daily; subcutaneous Initial treatment period was 2 yrs, followed by 2 years of untreated observation	35 patients entered, 18 completed	9.3 years (6.7-10.8)	M: 24 F: 11
B9R-EW-GDFC*	Phase 4, open label, observational, multi-center, post-marketing	Dosage regimen and duration of treatment are at the discretion of investigator (mean dose 0.29 mg/kg/wk); Typically daily, subcutaneous Duration: Median duration of treatment: 2.3 yrs (range 0.1 to 15.4)	429 patients entered 379 patients naive to treatment and had at least one post-baseline visit	8.4 years (0.1- 16.0)	M: 240 F: 189

Abbreviations: FHD=fixed high dosage (0.067 mg/kg/day); IAD=individually-adjusted dosage (0.035 to 0.067 mg/kg/day).
*Ongoing study, data as of 2009

Study 0908 showed that after 2 years of Humatrope treatment, mean height SDS increased from a baseline value of -2.7 ± 0.5 to -1.5 ± 0.6.

The primary objective of Study GDGB was to demonstrate that Humatrope given according to an individually adjusted dosage (IAD) regimen would result in a 1-year height SDS increase not inferior to that achieved with a fixed high dosage (FHD) regimen. The non-inferiority margin was 0.5 SDS; that is, the height increase for the IAD group would be considered non-inferior if the lower bound of the 95% confidence interval (CI) for the mean difference between the groups (IAD – FHD) was greater than -0.5 height SDS. In this open-label study 193 children with mean age 6.8 ± 2.4 years (range: 3 to 12) were randomized to either a fixed dosage group (0.067 mg/kg/day [67 µg/kg/day], equivalent to 0.47 mg/kg/week) or an individually-adjusted dosage group and received at least 1 dose of study drug. The initial Humatrope dosage for the IAD

group was 0.035 mg/kg/day (35 µg/kg/day), equivalent to 0.25 mg/kg/week. The dosage was increased to 0.067 mg/kg/day for those patients whose predicted 1-year height gain assessed at 3 months was < 0.75 SDS (n=40) or whose actual height gain measured at Year 1 was <0.75 SDS (n=11). Patients whose dose was increased at 3 months were approximately 2 years older at baseline than those who remained on the lower dose; a greater proportion of girls had their dosage increased than boys (58% vs. 43%, respectively). One-year efficacy data, available for 179 patients (FHD, n=93; IAD, n=86) demonstrated that the individually-adjusted regimen was statistically non-inferior to the fixed dosage regimen. Although the mean 1-year height increase in the IAD group was statistically significantly lower than that observed in the FHD group, the study achieved its primary objective by demonstrating that the increase from baseline in height SDS in the IAD group was clinically similar (noninferior) to that in the FHD group (mean between-group difference = -0.3 SDS [95% CI: -0.4, -0.2 SDS]). The mean changes from baseline in height SDS at the end of the 2-year study were 1.4 and 1.6 SDS in the IAD and FHD groups, respectively.

Efficacy results of this study are summarized in Table 16.

Table 16
Results from Study GDGB for Height SDS and Change from Baseline in Height SDS at Year 1 and Year 2 After Humatrope Treatment of Short Children Born SGA Who Fail to Demonstrate Catch-up Growth

	IAD Group Initial dose 0.035 mg/kg/day Mean (SD)	FHD Group 0.067 mg/kg/day Mean (SD)	Between-Group Difference IAD-FHD[a]
Baseline	(n=86) -3.9 (0.6)	(n=93) -3.9 (0.7)	-0.0 ± 0.1 (-0.2, 0.2) p-value = 0.95
Year 1 Height SDS Change from Baseline	(n=86)[b,c] -3.0 (0.7) 0.9 (0.4)	(n=93)[b] -2.7 (0.7) 1.1 (0.4)	-0.3 ± 0.1 (-0.4, -0.2) p-value <0.001
Year 2 Height SDS Change from Baseline	(n=82)[b,d] -2.5 (0.8) 1.4 (0.5)	(n=88)[b] -2.2 (0.7) 1.6 (0.5)	-0.3 ± 0.1 (-0.4, -0.1) p-value = 0.003

Abbreviations: IAD=individually adjusted dose; FHD=fixed high dose; SD=standard deviation; SDS=standard deviation score
[a] Least squares mean difference ± standard error and 95% confidence interval based on ANCOVA model with treatment and gender as fixed effects, and baseline height SDS, baseline chronological age, baseline bone age, and mid-parental target height SDS as covariates.
[b] Only children with actual height measurements were included in the Year 1 and Year 2 analyses.
[c] Initial dose 0.035 mg/kg/day, increased at 3 months to 0.067 mg/kg/day for 40 patients
[d] 11 additional patients increased dosage at 12 months

DETAILED PHARMACOLOGY

Somatropin (recombinant DNA-derived biosynthetic human growth hormone) has been shown to promote growth of skeletal and soft tissue and to influence the metabolism of carbohydrate, fat, and protein. Somatropin influences intestinal calcium transport by affecting the metabolism of vitamin D and has an anabolic effect on bone metabolism. Somatropin has a positive influence on the wound healing process of surgically-induced, full-thickness dermal wounds and heat-induced, full-thickness dermal burns in rodents. Studies conducted with somatropin have established that the biologic activities of recombinant DNA-derived hGH are identical to those produced by pituitary-sourced hGH.

When a growing rat is hypophysectomized, it stops gaining weight and growing in length. The bioactivity and biopotency of all somatropin preparations have been determined in a ten-day assay using hypophysectomized rats to measure increased proximal tibial cartilage width and body weight gain. Somatropin (6.25 mg/rat/day for seven days) administered subcutaneously induced elevations in general protein and collagen synthesis within the skin. While collagen synthesis was significantly increased, collagen content was reduced, and the percentage of total collagen that was determined to be Type III Collagen was significantly reduced in somatropin-treated rats.

Somatropin treatment induced a significant increase in general protein content, protein/DNA, and RNA/DNA in the skin of hypophysectomized rats. Elevations in these parameters are indicators of increased protein synthesis and cell size.

The composite of these studies indicates that somatropin, either alone or acting through other mediators (somatomedins), significantly contributed to the synthesis and turnover of skin proteins. The changes induced in collagen metabolism are similar to the changes that occur during skin maturation. In the absence of somatomedins, as in the case of incubation medium (without serum present), somatropin had no direct effect on general protein or collagen synthesis *in vitro*. Therefore, somatropin exerts its pharmacologic effects *in vivo* through the production of somatomedins.

The Effect of Somatropin on Bone Metabolism in Rats

Growth hormone, acting through the insulin-like growth factors is a major stimulus to new bone formation and has been demonstrated to cause epiphyseal cartilage proliferation (1). The anabolic effects of somatropin on bone metabolism were tested in adult male rats (4). Somatropin (400 mg/kg), administered by subcutaneous injection twice daily for 28 days, caused significant increases in bone mineral content (BMC) and bone density (BMC/BW) without causing increased bone width (BW) as measured by single [^{125}-I] photon absorptiometry. Confirmation of increased BMC was determined by bone ashing techniques. Somatropin treatment also induced significant body weight gain and bone hydroxyproline content. The data reported are consistent with the hypothesis that growth hormone has anabolic effects on bone metabolism.

The Effect of Somatropin on Intestinal Calcium Transport

Growth hormone influences intestinal calcium transport by influencing the metabolism of

vitamin D. Cholecalciferol (vitamin D_3) was administered with and without somatropin treatment (5). The inactive form of vitamin D_3 (cholecalciferol) and somatropin administered separately had no significant effect on calcium transport. Simultaneous administration of both substances, however, caused significant elevation in intestinal calcium transport.

TOXICOLOGY

The toxicity/safety of somatropin has been studied in five animal species after single or repeated parenteral injection by the subcutaneous, intramuscular, and intravenous routes. The tests involved young, healthy animals. In vitro tests were performed to investigate possible genetic toxicity of somatropin and to determine the compatibility of somatropin and diluent vehicles for injection with whole blood.

Acute Toxicity Studies

Single doses of somatropin have been studied in mice, rats, dogs, and rhesus monkeys using subcutaneous and intravenous administration.

Mice and rats received a single subcutaneous or intravenous dose of 12.5 mg/kg of body weight. This dose is approximately 200 fold the expected human clinical daily dose for the treatment of dwarfism. These animals appeared normal by two hours after dosing.

Table 17
Acute Toxicity Studies

Species	Animals M	Animals F	Duration of Study (Days)	Administration	Dose (mg/kg)	Signs of Toxicity
Rat	50	50	14	SC	12.5	None
Rat	40	40	14	IV	12.5	None
Mouse	40	40	14	SC	12.5	None
Mouse	40	40	14	IV	12.5	Leg Weakness
Dog	6	6	14	IV (rapid infusion)	0.125, 1.25, 3.125	No effects on BP, heart and resp. rates
Monkey	4	4	14	SC	6.25	None

Subacute Toxicity

Somatropin was administered daily for 30 days by intravenous and subcutaneous routes at doses of 0.125, 0.625, and 3.125 mg/kg. There were no deaths and there were no toxicologically significant treatment-related changes in clinical signs, hematology, clinical chemistry, urinalysis, or organ weight parameters.

Rhesus Monkey received somatropin administered intramuscularly daily for 5 weeks at doses of 0.125, 0.375, and 1.25 mg/kg (up to 20 fold the anticipated daily human clinical dose). All of the monkeys survived and there were no treatment-related abnormalities observed in clinical signs,

body weight, food consumption, hematology, or urinalysis parameters. Antibodies were not produced against somatropin or possible *E. coli* polypeptide components that could have been produced as a result of production by recombinant technology. In contrast, when monkeys were treated with methionyl growth hormone under similar study conditions, antibodies to the hormone were observed.

Reproduction Studies

Standard reproduction and teratology studies in laboratory animals have not been conducted with somatropin. The value of such studies is questionable considering the compound is identical to human growth hormone.

Genetic Toxicity

Somatropin did not produce any mutagenic effects and is unlikely to pose a genotoxic hazard in human chemotherapy.

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PART III: CONSUMER INFORMATION

HUMATROPE®
(somatropin for injection)
pronounced **HYOO-mah-trope**

This leaflet is for patients and caregivers. It is Part III of a three-part "Product Monograph" published when HUMATROPE was approved for sale in Canada. This leaflet is a summary and will not tell you everything about HUMATROPE. Contact your doctor or pharmacist if you have any questions about the drug.

Please read this information carefully before you start to take your medicine, even if you have just refilled your prescription. Some of the information may have changed. Keep this pamphlet since you may need to refer to it after starting treatment with HUMATROPE.

ABOUT THIS MEDICATION

What the medication is used for:
HUMATROPE is used to treat children and teenagers who do not develop to their normal height because of poor bone growth. Growth hormone deficiency, Turner syndrome, idiopathic short stature, SHOX (short stature homeobox-containing gene) deficiency, and born small for gestational age are medical conditions, which result in slow bone growth.

HUMATROPE is also used in some adults who had growth hormone deficiency when they were children or who do not have enough growth hormone as adults for some other reason.

What it does:
HUMATROPE is used to increase growth hormone levels. It stimulates bone growth in children unless the ends of the bones have hardened (closed epiphyses). In both adults and children with growth hormone deficiency, it also increases the growth of muscle and reduces body fat.

When it should not be used:
Treatment should not be started:

- To promote growth when the ends of the long bones have hardened (closed epiphyses).
- In patients with any evidence of an active cancer (either newly diagnosed or recurrent).
- While patients have a serious illness following surgery, or who have just had a serious accident, or those with acute respiratory failure (low level of oxygen in the blood or high level of the carbon dioxide in the blood)
- In patients with Prader-Willi syndrome, who are very overweight or have severe breathing problems.

Treatment should not be started:

- In patients known to be allergic to somatropin, to any of the ingredients in the powder for solution for injection or the diluent.
- In patients who have undergone renal transplant, until one year post-transplant.

What the medicinal ingredient is:
Somatropin (recombinant human growth hormone)

What the important nonmedicinal ingredients are:
The HUMATROPE powder contains dibasic sodium phosphate, glycine, and mannitol.
The diluent (solution for dissolving somatropin) contains metacresol and glycerin.
Phosphoric acid and/or sodium hydroxide may have been added at the time of manufacture to adjust the acidity of the liquid.

What dosage forms it comes in:
HUMATROPE is supplied as follows:
Vial: 5 mg vial plus 5 mL diluent
Cartridges: 6 mg, 12 mg, or 24 mg cartridges, each with 3.15 mL of diluent.

HUMATROPE cartridges require the use of a HumatroPen to inject the drug. HumatroPens are supplied separately.

WARNINGS AND PRECAUTIONS

A doctor trained in hormone disorders must examine the patient to decide if it is safe to use HUMATROPE.

Treatment with growth hormone (GH) can change blood sugar levels.

Following an overdose of HUMATROPE, the patient may feel sick, shaky or light-headed due to low blood sugar. These feelings quickly disappear, but the patient's blood sugar may then rise above normal 2-4 hours after injection. Therefore, the patient's blood sugar should be tested regularly after an overdose.

When medicine is injected into the same place over a long time, it can cause damage. It is therefore important to keep changing the injection site, and the doctor or nurse can tell you how.

Before you use HUMATROPE, the patient or caregiver should tell the doctor:

- if the patient has an active brain tumour or any other tumour (cancer). However, your doctor may prescribe HUMATROPE if the patient has had a brain tumour and needs no more anti-tumour treatment for it. The patient should be re-examined frequently to make sure

that the tumour has not come back or started to grow.
- if the patient is a survivor of childhood cancer.
- if the patient is very ill after a serious operation, or after being treated for multiple injuries from an accident, or if the patient has sudden serious breathing problems.
- if the patient has diabetes (because more or less insulin may be needed when taking HUMATROPE).
- if a member of the patient's family has diabetes.
- if the patient is taking a steroid (glucocorticoid) hormone such as cortisone or prednisone. This is because the combination may reduce the success of the HUMATROPE or because more of the steroid medication may be needed when the patient is also taking HUMATROPE.
- if the patient is taking a medication known to be metabolized by certain liver enzymes (e.g., cyclosporine, some anticonvulsants, and sex steroids such as estrogen and birth control pills). This is because the treatment with HUMATROPE may reduce the effectiveness of the drugs.
- if the patient, especially a child, develops abdominal pain.
- if the patient is or becomes pregnant or is breast-feeding.
- if the patient has hypothyroidism (low levels of thyroid hormone), because HUMATROPE may reduce the levels of thyroid hormone.
- if the patient suffers from a bad headache or frequent headaches, or from problems with eyesight, vomiting or feeling sick. Very rarely, swelling of the brain may develop, and the doctor may want to examine the patient to look for signs of brain swelling. If this occurs it may be necessary to stop the growth hormone treatment.
- if the patient develops a limp, or has hip or knee pain while being treated with HUMATROPE.

Do not use the diluent (the liquid used to mix with the HUMATROPE powder) if the patient is sensitive or allergic to metacresol or glycerol, which are components of the diluent.

If the patient has Turner syndrome and develops an ear infection or headaches tell your doctor about these problems.

Leukemia has been reported in a small number of pediatric patients who have been treated with growth hormone, including growth hormone of pituitary origin, and man-made growth hormone products such as somatrem and somatropin. The relationship, if any, between leukemia and growth hormone is uncertain.

INTERACTIONS WITH THIS MEDICATION

Tell the doctor if the patient is taking the following drugs:
- Steroid medications such as glucocorticoids (e.g. cortisone or prednisolone)
- Medications known to be metabolized by certain liver enzymes (e.g., cyclosporine, some anticonvulsants, and sex steroids such as estrogen and birth control pills)
- Insulin and anti-hyperglycemic agents

PROPER USE OF THIS MEDICATION

Be sure to change the injection site frequently to help prevent lipoatrophy (a loss of tissue under the skin).
In general, HUMATROPE should be injected in the evening or before bedtime.

Usual dose:
Your doctor will instruct you on what is the best dosage of HUMATROPE for you based on your individual needs. Use HUMATROPE exactly as your doctor tells you to.

Reconstitution Instructions:
HUMATROPE Vials: Please refer to the instruction leaflet provided in the vial package.

HUMATROPE Cartridges: Please refer to the instruction leaflet provided in the cartridge package.

Overdose:
Long-term overdosage may result in continued growth of the extremities (fingers, toes, nose, ears, jaw) and joint pain. If you think this is happening to you, tell your doctor.

Overdose may change blood sugar levels, and patients may experience symptoms of hypoglycaemia (low blood sugar), such as feeling shaky, dizzy and unwell or hyperglycemia (high blood sugar), such as increased urination or thirst.

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
Contact your physician or pharmacist if you have missed a dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Some people may be allergic to the diluent (liquid used to mix with the HUMATROPE powder). If there is any pain or redness at the injection site, or if there is any swelling, tell your doctor.

It is also important to have your blood glucose checked if you have diabetes or a family history of diabetes.

Children treated with HUMATROPE may have an increased risk of developing pancreatitis. If your child develops abdominal pain, please contact your doctor.

HUMATROPE may affect the way your body handles sugars from your food and drink. Your doctor may check the amount of sugar in your urine or blood.

HUMATROPE can affect the amount of thyroid hormone in the blood, so patients must have thyroid function tests from time to time. If the thyroid is not working properly, HUMATROPE may not work as well as it should.

Any child who begins to limp must be examined by a doctor.

HUMATROPE may cause intracranial hypertension (increased pressure within the skull). Call the doctor if the patient has: a headache that doesn't go away or is severe, or has headaches that become more frequent; problems with vision; nausea (feeling sick in the stomach) or vomiting.

Other possible side effects include headaches, muscle or joint pains, swelling, tingling sensations, feeling weak, high blood pressure, shortness of breath, and sleep apnea (pauses in breathing during sleep). Rarely the headaches may be bad or frequent, and with sickness or vision problems. Tell your doctor immediately if this happens.

For patients with Turner syndrome, growth hormone therapy may increase the already high frequency of ear infections. Your child should see her doctor if you think she has an ear infection.

This is not a complete list of side effects. For any unexpected effects while taking HUMATROPE, contact your doctor or pharmacist.

HOW TO STORE IT

Before reconstituted:
Store the vials or cartridges and diluent in the refrigerator at 2–8 °C.

After reconstituted:
When the vial or the cartridge is prepared with the supplied diluent, it may be stored in the refrigerator at 2 – 8 °C. Do NOT freeze.

- If prepared from the vial with the supplied diluent, it MUST be used within 21 DAYS
- If prepared from the cartridge with the supplied diluent, it MUST be used within 28 DAYS

When the vial or the cartridge is prepared with Sterile Water for Injection, USP, it should be used immediately. Although not recommended, it may be stored in the refrigerator at 2 – 8 °C, but must be used within 24 HOURS. Do NOT freeze.

Keep out of reach of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701D
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

For more information, please contact your healthcare professionals or pharmacist first, or Eli Lilly Canada Inc. at: 1-888-545-5972, or visit the website at: www.lilly.ca

The information in this document is current as of the last revision date shown below. For the most current information please visit our website or contact us directly.

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