Genotropin®
somatropin [rDNA origin] for injection

In a Two-Chamber Cartridge

DESCRIPTION

GENOTROPIN Lyophilized Powder contains somatropin [rDNA origin], which is a polypeptide hormone of recombinant DNA origin. It has 191 amino acid residues and a molecular weight of 22,124 daltons. The amino acid sequence of the product is identical to that of human growth hormone of pituitary origin (somatropin). GENOTROPIN is synthesized in a strain of *Escherichia coli* that has been modified by the addition of the gene for human growth hormone. GENOTROPIN is a sterile white lyophilized powder intended for subcutaneous injection.

GENOTROPIN 1.5 mg is dispensed in a two-chamber cartridge. The front chamber contains recombinant somatropin 1.5 mg (approximately 4.5 IU), glycine 27.6 mg, sodium dihydrogen phosphate anhydrous 0.3 mg, and disodium phosphate anhydrous 0.3 mg; the rear chamber contains 1.13 mL water for injection.

GENOTROPIN 5.8 mg is dispensed in a two-chamber cartridge. The front chamber contains recombinant somatropin 5.8 mg (approximately 17.4 IU), glycine 2.2 mg, mannitol 1.8 mg, sodium dihydrogen phosphate anhydrous 0.32 mg, and disodium phosphate anhydrous 0.31 mg; the rear chamber contains 0.3% m-Cresol (as a preservative) and mannitol 45 mg in 1.14 mL water for injection.

GENOTROPIN 13.8 mg is dispensed in a two-chamber cartridge. The front chamber contains recombinant somatropin 13.8 mg (approximately 41.4 IU), glycine 2.3 mg, mannitol 14.0 mg, sodium dihydrogen phosphate anhydrous 0.47 mg, and disodium phosphate anhydrous 0.46 mg; the rear chamber contains 0.3% m-Cresol (as a preservative) and mannitol 32 mg in 1.13 mL water for injection.

GENOTROPIN MINIQUICK® is dispensed as a single-use syringe device containing a two-chamber cartridge. GENOTROPIN MINIQUICK is available as individual doses of 0.2 mg to 2.0 mg in 0.2-mg increments. The front chamber contains recombinant somatropin 0.22 to 2.2 mg (approximately 0.66 to 6.6 IU), glycine 0.23 mg, mannitol 1.14 mg, sodium dihydrogen phosphate 0.05 mg, and disodium phosphate anhydrous 0.027 mg; the rear chamber contains mannitol 12.6 mg in water for injection 0.275 mL.

GENOTROPIN is a highly purified preparation. The reconstituted recombinant somatropin solution has an osmolality of approximately 300 mOsm/kg, and a pH of approximately 6.7. The concentration of the reconstituted solution varies by strength and presentation (see HOW SUPPLIED).

CLINICAL PHARMACOLOGY

In vitro, preclinical, and clinical tests have demonstrated that GENOTROPIN Lyophilized Powder is therapeutically equivalent to human growth hormone of pituitary origin and achieves similar pharmacokinetic profiles in normal adults. In pediatric patients who have growth hormone deficiency (GHD) or Prader-Willi syndrome (PWS), or who were born small for gestational age (SGA), treatment with GENOTROPIN stimulates linear growth. In patients with GHD or PWS, treatment with GENOTROPIN also normalizes concentrations of IGF-I (Insulin-like Growth Factor-I/Somatomedin C). In adults with GHD, treatment with GENOTROPIN results in reduced fat mass, increased lean body mass, metabolic alterations that include beneficial changes in lipid metabolism, and normalization of IGF-I concentrations.

In addition, the following actions have been demonstrated for GENOTROPIN and/or somatropin.

1. **Tissue Growth**

   A. ***Skeletal Growth:*** GENOTROPIN stimulates skeletal growth in pediatric patients with GHD, PWS, or SGA. The measurable increase in body length after administration of GENOTROPIN results from an effect on the epiphyseal plates of long bones. Concentrations of IGF-I, which may play a role in skeletal growth, are generally low in the serum of pediatric patients with GHD, PWS, or SGA, but tend to increase during treatment with GENOTROPIN. Elevations in mean serum alkaline phosphatase concentration 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 with the normal pediatric population. Treatment with somatropin results in an increase in both the number and 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 GENOTROPIN.

3. **Carbohydrate Metabolism**
   Pediatric patients with hypopituitarism sometimes experience fasting hypoglycemia that is improved by treatment with GENOTROPIN. Large doses of growth hormone may impair glucose tolerance.

4. **Lipid Metabolism**
   In GHD patients, administration of somatropin has resulted in lipid mobilization, reduction in body fat stores, and increased plasma fatty acids.

5. **Mineral Metabolism**
   Somatropin induces retention of sodium, potassium, and phosphorus. Serum concentrations of inorganic phosphate are increased in patients with GHD after therapy

with GENOTROPIN. Serum calcium is not significantly altered by GENOTROPIN. Growth hormone could increase calciuria.

6. Body Composition
Adult GHD patients treated with GENOTROPIN at the recommended adult dose (see DOSAGE AND ADMINISTRATION) demonstrate a decrease in fat mass and an increase in lean body mass. When these alterations are coupled with the increase in total body water, the overall effect of GENOTROPIN is to modify body composition, an effect that is maintained with continued treatment.

PHARMACOKINETICS

Absorption

Following a 0.03 mg/kg subcutaneous (SC) injection in the thigh of 1.3 mg/mL GENOTROPIN to adult GHD patients, approximately 80% of the dose was systemically available as compared with that available following intravenous dosing. Results were comparable in both male and female patients. Similar bioavailability has been observed in healthy adult male subjects.

In healthy adult males, following an SC injection in the thigh of 0.03 mg/kg, the extent of absorption (AUC) of a concentration of 5.3 mg/mL GENOTROPIN was 35% greater than that for 1.3 mg/mL GENOTROPIN. The mean (± standard deviation) peak (C_{max}) serum levels were 23.0 (± 9.4) ng/mL and 17.4 (± 9.2) ng/mL, respectively.

In a similar study involving pediatric GHD patients, 5.3 mg/mL GENOTROPIN yielded a mean AUC that was 17% greater than that for 1.3 mg/mL GENOTROPIN. The mean C_{max} levels were 21.0 ng/mL and 16.3 ng/mL, respectively.

Adult GHD patients received two single SC doses of 0.03 mg/kg of GENOTROPIN at a concentration of 1.3 mg/mL, with a one- to four-week washout period between injections. Mean C_{max} levels were 12.4 ng/mL (first injection) and 12.2 ng/mL (second injection), achieved at approximately six hours after dosing.

There are no data on the bioequivalence between the 12-mg/mL formulation and either the 1.3-mg/mL or the 5.3-mg/mL formulations.

Distribution

The mean volume of distribution of GENOTROPIN following administration to GHD adults was estimated to be 1.3 (± 0.8) L/kg.

Metabolism

The metabolic fate of GENOTROPIN involves classical protein catabolism in both the liver and kidneys. In renal cells, at least a portion of the breakdown products are returned to the systemic circulation. The mean terminal half-life of intravenous GENOTROPIN in normal adults is 0.4 hours, whereas subcutaneously administered GENOTROPIN has a half-life of 3.0 hours in GHD adults. The observed difference is due to slow absorption from the subcutaneous injection site.

Excretion
The mean clearance of subcutaneously administered GENOTROPIN in 16 GHD adult patients was 0.3 (± 0.11) L/hrs/kg.

Special Populations
Pediatric: The pharmacokinetics of GENOTROPIN are similar in GHD pediatric and adult patients.

Gender: No gender studies have been performed in pediatric patients; however, in GHD adults, the absolute bioavailability of GENOTROPIN was similar in males and females.

Race: No studies have been conducted with GENOTROPIN to assess pharmacokinetic differences among races.

Renal or hepatic insufficiency: No studies have been conducted with GENOTROPIN in these patient populations.

Table 1
Mean SC Pharmacokinetic Parameters in Adult GHD Patients

	Bioavailability (%) (N=15)	**T_{max} (hours) (N=16)**	**CL/F (L/hr x kg) (N=16)**	**Vss/F (L/kg) (N=16)**	**$T_{1/2}$ (hours) (N=16)**
Mean (± SD)	80.5 *	5.9 (± 1.65)	0.3 (± 0.11)	1.3 (± 0.80)	3.0 (± 1.44)
95% CI	70.5 – 92.1	5.0 – 6.7	0.2 – 0.4	0.9 – 1.8	2.2 – 3.7

T_{max} = time of maximum plasma concentration
CL/F = plasma clearance
Vss/F = volume of distribution
$T_{1/2}$ = terminal half-life
SD = standard deviation
CI = confidence interval

* The absolute bioavailability was estimated under the assumption that the log-transformed data follow a normal distribution. The mean and standard deviation of the log-transformed data were mean = 0.22 (± 0.241).

CLINICAL STUDIES
Adult Patients with Growth Hormone Deficiency (GHD)
GENOTROPIN Lyophilized Powder was compared with placebo in six randomized clinical trials involving a total of 172 adult GHD patients. These trials included a 6-month double-blind treatment period, during which 85 patients received GENOTROPIN and 87 patients received placebo, followed by an open-label treatment period in which participating patients received GENOTROPIN for up to a total of 24 months. GENOTROPIN was administered as a daily SC injection at a dose of 0.04 mg/kg/week for the first month of treatment and 0.08 mg/kg/week for subsequent months.

Beneficial changes in body composition were observed at the end of the 6-month treatment period for the patients receiving GENOTROPIN as compared with the placebo patients. Lean body mass, total body water, and lean/fat ratio increased while total body fat mass and waist

circumference decreased. These effects on body composition were maintained when treatment was continued beyond 6 months. Bone mineral density declined after 6 months of treatment but returned to baseline values after 12 months of treatment.

Pediatric Patients with Prader-Willi Syndrome (PWS)

The safety and efficacy of GENOTROPIN in the treatment of pediatric patients with Prader-Willi syndrome (PWS) were evaluated in two randomized, open-label, controlled clinical trials. Patients received either GENOTROPIN or no treatment for the first year of the studies, while all patients received GENOTROPIN during the second year. GENOTROPIN was administered as a daily SC injection, and the dose was calculated for each patient every 3 months. In Study 1, the treatment group received GENOTROPIN at a dose of 0.24 mg/kg/week during the entire study. During the second year, the control group received GENOTROPIN at a dose of 0.48 mg/kg/week. In Study 2, the treatment group received GENOTROPIN at a dose of 0.36 mg/kg/week during the entire study. During the second year, the control group received GENOTROPIN at a dose of 0.36 mg/kg/week.

Patients who received GENOTROPIN showed significant increases in linear growth during the first year of study, compared with patients who received no treatment (see Table 2). Linear growth continued to increase in the second year, when both groups received treatment with GENOTROPIN.

Table 2
Efficacy of GENOTROPIN in Pediatric Patients with Prader-Willi Syndrome (Mean ± SD)

	Study 1		Study 2	
	GENOTROPIN (0.24 mg/kg/week) n=15	Untreated Control n=12	GENOTROPIN (0.36 mg/kg/week) n=7	Untreated Control n=9
Linear growth (cm)				
Baseline height	112.7 ± 14.9	109.5 ± 12.0	120.3 ± 17.5	120.5 ± 11.2
Growth from months 0 to 12	11.6* ± 2.3	5.0 ± 1.2	10.7* ± 2.3	4.3 ± 1.5
Height Standard Deviation Score (SDS) for age				
Baseline SDS	-1.6 ± 1.3	-1.8 ± 1.5	-2.6 ± 1.7	-2.1 ± 1.4
SDS at 12 months	-0.5† ± 1.3	-1.9 ± 1.4	-1.4† ± 1.5	-2.2 ± 1.4

* $p \leq 0.001$
† $p \leq 0.002$ (when comparing SDS change at 12 months)

Changes in body composition were also observed in the patients receiving GENOTROPIN (see Table 3). These changes included a decrease in the amount of fat mass, and increases in the amount of lean body mass and the ratio of lean-to-fat tissue, while changes in body weight were similar to those seen in patients who received no treatment. Treatment with GENOTROPIN did not accelerate bone age, compared with patients who received no treatment.

Table 3
Effect of GENOTROPIN on Body Composition
in Pediatric Patients with Prader-Willi Syndrome (Mean ± SD)

	GENOTROPIN n=14	Untreated Control n=10
Fat mass (kg)		
Baseline	12.3 ± 6.8	9.4 ± 4.9
Change from months 0 to 12	-0.9* ± 2.2	2.3 ± 2.4
Lean body mass (kg)		
Baseline	15.6 ± 5.7	14.3 ± 4.0
Change from months 0 to 12	4.7* ± 1.9	0.7 ± 2.4
Lean body mass/Fat mass		
Baseline	1.4 ± 0.4	1.8 ± 0.8
Change from months 0 to 12	1.0* ± 1.4	-0.1 ± 0.6
Body weight (kg) †		
Baseline	27.2 ± 12.0	23.2 ± 7.0
Change from months 0 to 12	3.7‡ ± 2.0	3.5 ± 1.9

* $p < 0.005$
† n=15 for the group receiving GENOTROPIN; n=12 for the Control group
‡ n.s.

Pediatric Patients Born Small for Gestational Age (SGA) Who Fail to Manifest Catch-up Growth by Age 2

The safety and efficacy of GENOTROPIN in the treatment of children born small for gestational age (SGA) were evaluated in 4 randomized, open-label, controlled clinical trials. Patients (age range of 2 to 8 years) were observed for 12 months before being randomized to receive either GENOTROPIN (two doses per study, most often 0.24 and 0.48 mg/kg/week) as a daily SC injection or no treatment for the first 24 months of the studies. After 24 months in the studies, all patients received GENOTROPIN.

Patients who received any dose of GENOTROPIN showed significant increases in growth during the first 24 months of study, compared with patients who received no treatment (see Table 4). Children receiving 0.48 mg/kg/week demonstrated a significant improvement in height standard deviation score (SDS) compared with children treated with 0.24 mg/kg/week. Both of these doses resulted in a slower but constant increase in growth between months 24 to 72 (data not shown).

Table 4
Efficacy of GENOTROPIN in Children Born Small for Gestational Age (Mean ± SD)

	GENOTROPIN (0.24 mg/kg/week) n=76	GENOTROPIN (0.48 mg/kg/week) n=93	Untreated Control n=40
Height Standard Deviation Score (SDS)			
Baseline SDS	-3.2 ± 0.8	-3.4 ± 1.0	-3.1 ± 0.9
SDS at 24 months	-2.0 ± 0.8	-1.7 ± 1.0	-2.9 ± 0.9
Change in SDS from baseline to month 24	1.2* ± 0.5	1.7*† ± 0.6	0.1 ± 0.3

* p = 0.0001 vs Untreated Control group
† p = 0.0001 vs group treated with GENOTROPIN 0.24 mg/kg/week

Pediatric Patients with Turner Syndrome (TS)

Two randomized, open-label, clinical trials were conducted that evaluated the efficacy and safety of GENOTROPIN in Turner Syndrome patients with short stature. Turner Syndrome patients were treated with GENOTROPIN alone or GENOTROPIN plus adjunctive hormonal therapy (ethinylestradiol or oxandrolone). A total of 38 patients were treated with GENOTROPIN alone in the two studies. In Study 055, 22 patients were treated for 12 months, and in Study 092, 16 patients were treated for 12 months. Patients received GENOTROPIN at a dose between 0.13 to 0.33 mg/kg/week.

SDS for height velocity and height are expressed using either the Tanner (Study 055) or Sempé (Study 092) standards for age-matched normal children as well as the Ranke standard (both studies) for age-matched, untreated Turner Syndrome patients. As seen in Table 5, height velocity SDS and height SDS values were smaller at baseline and after treatment with Genotropin when the normative standards were utilized as opposed to the Turner Syndrome standard.

Both studies demonstrated statistically significant increases from baseline in all of the linear growth variables (i.e., mean height velocity, height velocity SDS, and height SDS) after treatment with Genotropin (see Table 5). The linear growth response was greater in Study 055 wherein patients were treated with a larger dose of Genotropin.

Table 5
Growth Parameters (mean ± SD) after 12 Months of Treatment with GENOTROPIN in Pediatric Patients with Turner Syndrome in Two Open Label Studies

	GENOTROPIN 0.33 mg/kg/week Study 055^ n=22	GENOTROPIN 0.13-0.23 mg/kg/week Study 092# n=16
Height Velocity (cm/yr)		
Baseline	4.1 ± 1.5	3.9 ± 1.0
Month 12	7.8 ± 1.6	6.1 ± 0.9
Change from baseline (95% CI)	3.7 (3.0, 4.3)	2.2 (1.5, 2.9)
Height Velocity SDS (Tanner^/Sempé# Standards)	(n=20)	
Baseline	-2.3 ± 1.4	-1.6 ± 0.6
Month 12	2.2 ± 2.3	0.7 ± 1.3
Change from baseline (95% CI)	4.6 (3.5, 5.6)	2.2 (1.4, 3.0)
Height Velocity SDS (Ranke Standard)		
Baseline	-0.1 ± 1.2	-0.4 ± 0.6
Month 12	4.2 ± 1.2	2.3 ± 1.2
Change from baseline (95% CI)	4.3 (3.5, 5.0)	2.7 (1.8, 3.5)
Height SDS (Tanner^/Sempé# Standards)		
Baseline	-3.1 ± 1.0	-3.2 ± 1.0
Month 12	-2.7 ± 1.1	-2.9 ± 1.0
Change from baseline (95% CI)	0.4 (0.3, 0.6)	0.3 (0.1, 0.4)
Height SDS (Ranke Standard)		
Baseline	-0.2 ± 0.8	-0.3 ± 0.8
Month 12	0.6 ± 0.9	0.1 ± 0.8
Change from baseline (95% CI)	0.8 (0.7, 0.9)	0.5 (0.4, 0.5)

SDS = Standard Deviation Score
Ranke standard based on age-matched, untreated Turner Syndrome patients
Tanner^/Sempé# standards based on age-matched normal children
$p<0.05$, for all changes from baseline

INDICATIONS AND USAGE

GENOTROPIN Lyophilized Powder is indicated for:
Pediatric Patients:

- Long-term treatment of pediatric patients who have growth failure due to an inadequate secretion of endogenous growth hormone.

- Long-term treatment of pediatric patients who have growth failure due to Prader-Willi syndrome (PWS). The diagnosis of PWS should be confirmed by appropriate genetic testing (see CONTRAINDICATIONS).

- Long-term treatment of growth failure in children born small for gestational age (SGA) who fail to manifest catch-up growth by age 2.

- Long-term treatment of growth failure associated with Turner Syndrome in patients who have open epiphyses.

Other causes of short stature in pediatric patients should be excluded.

Adult Patients:
GENOTROPIN (somatropin [rDNA origin] for injection) is indicated for replacement of endogenous growth hormone in adults with growth hormone deficiency who meet either of the following two criteria:

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

Childhood Onset: Patients who were growth hormone deficient during childhood as a result of congenital, genetic, acquired, or idiopathic causes.

In general, confirmation of the diagnosis of adult growth hormone deficiency in both groups usually requires an appropriate growth hormone stimulation test. 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 used for growth promotion in pediatric patients with closed epiphyses.

Somatropin is contraindicated in patients with active proliferative or severe non-proliferative diabetic retinopathy.

In general, somatropin is contraindicated in the presence of active malignancy. Any pre-existing malignancy should be inactive and its treatment complete prior to instituting therapy with somatropin. Somatropin should be discontinued if there is evidence of recurrent activity. Since growth hormone deficiency may be an early sign of the presence of a pituitary tumor (or, rarely, other brain tumors), the presence of such tumors should be ruled out prior to initiation of treatment. Somatropin should not be used in patients with any evidence of progression or recurrence of an underlying intracranial tumor.

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

Somatropin is contraindicated in patients with Prader-Willi syndrome who are severely obese or have severe respiratory impairment (see WARNINGS).

WARNINGS

The 5.8-mg and 13.8-mg presentations of GENOTROPIN Lyophilized Powder contain m-Cresol as a preservative. These products should not be used by patients with a known

sensitivity to this preservative. The GENOTROPIN 1.5-mg and GENOTROPIN MINIQUICK presentations are preservative-free (see HOW SUPPLIED).

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

There have been reports of 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 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).

PRECAUTIONS

General

Treatment with GENOTROPIN Lyophilized Powder, as with other growth hormone preparations, should be directed by physicians who are experienced in the diagnosis and management of patients with GHD, Prader-Willi syndrome (PWS), Turner Syndrome (TS) or those who were born small for gestational age (SGA).

Treatment with somatropin may decrease insulin sensitivity, particularly at higher doses in susceptible patients. As a result, previously undiagnosed impaired glucose tolerance and overt diabetes mellitus may be unmasked during somatropin treatment. Therefore, glucose levels should be monitored periodically in all patients treated with somatropin, especially in those with risk factors for diabetes mellitus, such as obesity (including obese patients with Prader-Willi syndrome), Turner syndrome, or a family history of diabetes mellitus. Patients with preexisting type 1 or type 2 diabetes mellitus or impaired glucose tolerance should be monitored closely during somatropin therapy. The doses of antihyperglycemic drugs (i.e., insulin or oral agents) may require adjustment when somatropin therapy is instituted in these patients.

Patients with preexisting tumors or growth hormone deficiency secondary to an intracranial lesion should be examined routinely for progression or recurrence of the underlying disease process. In pediatric patients, clinical literature has revealed no relationship between somatropin replacement therapy and central nervous system (CNS) tumor recurrence or new extracranial tumors. However, in childhood cancer survivors, an increased risk of a second

neoplasm has been reported in patients treated with somatropin after their first neoplasm. Intracranial tumors, in particular meningiomas, in patients treated with radiation to the head for their first neoplasm, were the most common of these second neoplasms. In adults, it is unknown whether there is any relationship between somatropin replacement therapy and CNS tumor recurrence.

Intracranial hypertension (IH) with papilledema, visual changes, headache, nausea and/or vomiting has been reported in a small number of patients treated with somatropin products. Symptoms usually occurred within the first eight (8) weeks after the initiation of somatropin therapy. In all reported cases, IH-associated signs and symptoms rapidly resolved after cessation of therapy or a reduction of the somatropin dose. Funduscopic examination should be performed routinely before initiating treatment with somatropin to exclude preexisting papilledema, and periodically during the course of somatropin therapy. If papilledema is observed by funduscopy during somatropin treatment, treatment should be stopped. If somatropin-induced IH is diagnosed, treatment with somatropin can be restarted at a lower dose after IH-associated signs and symptoms have resolved. Patients with Turner syndrome, Prader-Willi syndrome, and chronic renal insufficiency may be at increased risk for the development of IH.

In patients with hypopituitarism (multiple hormonal deficiencies), standard hormonal replacement therapy should be monitored closely when somatropin therapy is administered.

Undiagnosed/untreated hypothyroidism may prevent an optimal response to somatropin, in particular, the growth response in children. Patients with Turner syndrome have an inherently increased risk of developing autoimmune thyroid disease and primary hypothyroidism. In patients with growth hormone deficiency, central (secondary) hypothyroidism may first become evident or worsen during somatropin treatment. Therefore, patients treated with somatropin should have periodic thyroid function tests and thyroid hormone replacement therapy should be initiated or appropriately adjusted when indicated.

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

When somatropin is administered subcutaneously at the same site over a long period of time, tissue atrophy may result. This can be avoided by rotating the injection site.

As with any protein, local or systemic allergic reactions may occur. Parents/Patients should be informed that such reactions are possible and that prompt medical attention should be sought if allergic reactions occur.

Pediatric Patients (see PRECAUTIONS, General)
Slipped capital femoral epiphyses may occur more frequently in patients with endocrine disorders (including GHD and Turner syndrome) or in patients undergoing rapid growth. Any pediatric patient with the onset of a limp or complaints of hip or knee pain during somatropin therapy should be carefully evaluated.

Progression of scoliosis can occur in patients who experience rapid growth. Because somatropin increases growth rate, patients with a history of scoliosis who are treated with

somatropin should be monitored for progression of scoliosis. However, somatropin has not been shown to increase the occurrence of scoliosis. Skeletal abnormalities including scoliosis are commonly seen in untreated Turner syndrome patients. Scoliosis is also commonly seen in untreated patients with Prader-Willi syndrome. Physicians should be alert to these abnormalities, which may manifest during somatropin therapy.

Patients with Turner syndrome should be evaluated carefully for otitis media and other ear disorders since these patients have an increased risk of ear and hearing disorders. Somatropin treatment may increase the occurrence of otitis media in patients with Turner syndrome. In addition, patients with Turner syndrome should be monitored closely for cardiovascular disorders (e.g., stroke, aortic aneurysm/dissection, hypertension) as these patients are also at risk for these conditions.

Adult Patients (see PRECAUTIONS, General)

Patients with epiphyseal closure who were treated with somatropin replacement therapy in childhood should be reevaluated according to the criteria in the INDICATIONS AND USAGE section before continuing on somatropin therapy at the reduced dose level recommended for GHD adults. Fluid retention during somatropin replacement therapy in adults may occur. Clinical manifestations of fluid retention are usually transient and dose dependent (see ADVERSE REACTIONS).

Experience with prolonged somatropin treatment in adults is limited.

Information for Patients

Patients being treated with GENOTROPIN (and/or their parents) should be informed about the potential benefits and risks associated with GENOTROPIN treatment. This information is intended to better educate patients (and caregivers); it is not a disclosure of all possible adverse or intended effects.

Patients and caregivers who will administer GENOTROPIN should receive appropriate training and instruction on the proper use of GENOTROPIN from the physician or other suitably qualified health care professional. A puncture-resistant container for the disposal of used syringes and needles should be strongly recommended. Patients and/or parents should be thoroughly instructed in the importance of proper disposal, and cautioned against any reuse of needles and syringes. This information is intended to aid in the safe and effective administration of the medication.

Laboratory Tests

Serum levels of inorganic phosphorus, alkaline phosphatase, parathyroid hormone (PTH) and IGF-I may increase during somatropin therapy.

Drug Interactions

Somatropin inhibits 11β-hydroxysteroid dehydrogenase type 1 (11βHSD-1) in adipose/hepatic tissue and may significantly impact the metabolism of cortisol and cortisone. As a consequence, in patients treated with somatropin, previously undiagnosed central (secondary)

hypoadrenalism may be unmasked requiring glucocorticoid replacement therapy. In addition, patients treated with glucocorticoid replacement therapy for previously diagnosed hypoadrenalism may require an increase in their maintenance or stress doses; this may be especially true for patients treated with cortisone acetate and prednisone since conversion of these drugs to their biologically active metabolites is dependent on the activity of the 11βHSD-1 enzyme.

Excessive glucocorticoid therapy may attenuate the growth promoting effects of somatropin in children. Therefore, glucocorticoid replacement therapy should be carefully adjusted in children with concomitant GH and glucocorticoid deficiency to avoid both hypoadrenalism and an inhibitory effect on growth.

Limited published data indicate that somatropin treatment increases cytochrome P450 (CP450) mediated antipyrine clearance in man. These data suggest that somatropin administration may alter the clearance of compounds known to be metabolized by CP450 liver enzymes (e.g., corticosteroids, sex steroids, anticonvulsants, cyclosporine). Careful monitoring is advisable when somatropin is administered in combination with other drugs known to be metabolized by CP450 liver enzymes. However, formal drug interaction studies have not been conducted.

In adult women on oral estrogen replacement, a larger dose of somatropin may be required to achieve the defined treatment goal (see DOSAGE AND ADMINISTRATION).

In patients with diabetes mellitus requiring drug therapy, the dose of insulin and/or oral agent may require adjustment when somatropin therapy is initiated (see PRECAUTIONS, General).

Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenicity studies have not been conducted with GENOTROPIN. No potential mutagenicity of GENOTROPIN was revealed in a battery of tests including induction of gene mutations in bacteria (the Ames test), gene mutations in mammalian cells grown in vitro (mouse L5178Y cells), and chromosomal damage in intact animals (bone marrow cells in rats). See PREGNANCY section for effect on fertility.

Pregnancy
Pregnancy Category B. Reproduction studies carried out with GENOTROPIN at doses of 0.3, 1, and 3.3 mg/kg/day administered SC in the rat and 0.08, 0.3, and 1.3 mg/kg/day administered intramuscularly in the rabbit (highest doses approximately 24 times and 19 times the recommended human therapeutic levels, respectively, based on body surface area) resulted in decreased maternal body weight gains but were not teratogenic. In rats receiving SC doses during gametogenesis and up to 7 days of pregnancy, 3.3 mg/kg/day (approximately 24 times human dose) produced anestrus or extended estrus cycles in females and fewer and less motile sperm in males. When given to pregnant female rats (days 1 to 7 of gestation) at 3.3 mg/kg/day a very slight increase in fetal deaths was observed. At 1 mg/kg/day (approximately seven times human dose) rats showed slightly extended estrus cycles, whereas at 0.3 mg/kg/day no effects were noted.

In perinatal and postnatal studies in rats, GENOTROPIN doses of 0.3, 1, and 3.3 mg/kg/day produced growth-promoting effects in the dams but not in the fetuses. Young rats at the highest dose showed increased weight gain during suckling but the effect was not apparent by 10 weeks of age. No adverse effects were observed on gestation, morphogenesis, parturition, lactation, postnatal development, or reproductive capacity of the offsprings due to GENOTROPIN. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers
There have been no studies conducted with GENOTROPIN 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 GENOTROPIN is administered to a nursing woman.

Geriatric Use
The safety and effectiveness of GENOTROPIN in patients aged 65 and over have not been evaluated in clinical studies. Elderly patients may be more sensitive to the action of GENOTROPIN, and therefore may be more prone to develop adverse reactions. A lower starting dose and smaller dose increments should be considered for older patients (see DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS
As with all protein drugs, a small number of patients may develop antibodies to the protein. Growth hormone antibody with binding lower than 2 mg/L has not been associated with growth attenuation. In some cases when binding capacity is > 2 mg/L, interference with growth response has been observed.

In 419 pediatric patients evaluated in clinical studies with GENOTROPIN Lyophilized Powder, 244 had been treated previously with GENOTROPIN or other growth hormone preparations and 175 had received no previous growth hormone therapy. Antibodies to growth hormone (anti-hGH antibodies) were present in six previously treated patients at baseline. Three of the six became negative for anti-hGH antibodies during 6 to 12 months of treatment with GENOTROPIN. Of the remaining 413 patients, eight (1.9%) developed detectable anti-hGH antibodies during treatment with GENOTROPIN; none had an antibody binding capacity > 2 mg/L. There was no evidence that the growth response to GENOTROPIN was affected in these antibody-positive patients.

Preparations of GENOTROPIN contain a small amount of periplasmic *Escherichia coli* peptides (PECP). Anti-PECP antibodies are found in a small number of patients treated with GENOTROPIN, but these appear to be of no clinical significance.

In clinical studies with GENOTROPIN in pediatric GHD patients, the following events were reported infrequently: injection site reactions, including pain or burning associated with the injection, fibrosis, nodules, rash, inflammation, pigmentation, or bleeding; lipoatrophy; headache; hematuria; hypothyroidism; and mild hyperglycemia.

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 somatropin. The relationship, if any, between leukemia and growth hormone therapy is uncertain.

In two clinical studies with GENOTROPIN in pediatric patients with Prader-Willi syndrome, the following drug-related events were reported: edema, aggressiveness, arthralgia, benign intracranial hypertension, hair loss, headache, and myalgia.

In clinical studies of 273 pediatric patients born small for gestational age treated with GENOTROPIN, the following clinically significant events were reported: mild transient hyperglycemia, one patient with benign intracranial hypertension, two patients with central precocious puberty, two patients with jaw prominence, and several patients with aggravation of pre-existing scoliosis, injection site reactions, and self-limited progression of pigmented nevi. Anti-hGH antibodies were not detected in any of the patients treated with GENOTROPIN.

In two clinical studies with GENOTROPIN in pediatric patients with Turner Syndrome the most frequently reported adverse events were respiratory illnesses (influenza, tonsillitis, otitis, sinusitis), joint pain, and urinary tract infection. The only treatment-related adverse event that occurred in more than 1 patient was joint pain.

In clinical trials with GENOTROPIN in 1,145 GHD adults, the majority of the adverse events consisted of mild to moderate symptoms of fluid retention, including peripheral swelling, arthralgia, pain and stiffness of the extremities, peripheral edema, myalgia, paresthesia, and hypoesthesia. These events were reported early during therapy, and tended to be transient and/or responsive to dosage reduction.

Table 6 displays the adverse events reported by 5% or more of adult GHD patients in clinical trials after various durations of treatment with GENOTROPIN. Also presented are the corresponding incidence rates of these adverse events in placebo patients during the 6-month double-blind portion of the clinical trials.

Table 6
Adverse Events Reported by ≥ 5% of 1,145 Adult GHD Patients During Clinical Trials of GENOTROPIN and Placebo, Grouped by Duration of Treatment

Adverse Event	Double Blind Phase		Open Label Phase GENOTROPIN		
	Placebo 0-6 mo. n = 572 % Patients	GENOTROPIN 0-6 mo. n = 573 % Patients	6-12 mo. n = 504 % Patients	12-18 mo. n = 63 % Patients	18-24 mo. n = 60 % Patients
Swelling, peripheral	5.1	17.5*	5.6	0	1.7
Arthralgia	4.2	17.3*	6.9	6.3	3.3
Upper respiratory infection	14.5	15.5	13.1	15.9	13.3
Pain, extremities	5.9	14.7*	6.7	1.6	3.3
Edema, peripheral	2.6	10.8*	3.0	0	0
Paresthesia	1.9	9.6*	2.2	3.2	0
Headache	7.7	9.9	6.2	0	0
Stiffness of extremities	1.6	7.9*	2.4	1.6	0
Fatigue	3.8	5.8	4.6	6.3	1.7
Myalgia	1.6	4.9*	2.0	4.8	6.7
Back pain	4.4	2.8	3.4	4.8	5.0

* Increased significantly when compared to placebo, $P \leq .025$: Fisher´s Exact Test (one-sided)
n = number of patients receiving treatment during the indicated period.
% = percentage of patients who reported the event during the indicated period.

In expanded post-trial extension studies, diabetes mellitus developed in 12 of 3,031 patients (0.4%) during treatment with GENOTROPIN. All 12 patients had predisposing factors, e.g., elevated glycated hemoglobin levels and/or marked obesity, prior to receiving GENOTROPIN. Of the 3,031 patients receiving GENOTROPIN, 61 (2%) developed symptoms of carpal tunnel syndrome, which lessened after dosage reduction or treatment interruption (52) or surgery (9). Other adverse events that have been reported include generalized edema and hypoesthesia.

OVERDOSAGE

There is little information on acute or chronic overdosage with GENOTROPIN Lyophilized Powder. Intravenously administered growth hormone has been shown to result in an acute decrease in plasma glucose. Subsequently, hyperglycemia was seen. It is thought that the same effect might occur on rare occasions with a high dosage of GENOTROPIN administered SC. Long-term overdosage may result in signs and symptoms of acromegaly consistent with overproduction of growth hormone.

DOSAGE AND ADMINISTRATION

The dosage of GENOTROPIN Lyophilized Powder must be adjusted for the individual patient. The weekly dose should be divided into 6 or 7 **subcutaneous** injections. GENOTROPIN may be given in the thigh, buttocks, or abdomen; the site of SC injections should be rotated daily to help prevent lipoatrophy.

Pediatric GHD Patients: Generally, a dose of 0.16 to 0.24 mg/kg body weight/week is recommended.

Pediatric PWS Patients: Generally, a dose of 0.24 mg/kg body weight/week is recommended.

Pediatric SGA Patients: Generally, a dose of 0.48 mg/kg body weight/week is recommended.

Pediatric TS Patients: Generally, a dose of 0.33 mg/kg body weight/week is recommended.

Adult Growth Hormone Deficiency (GHD)
Based on the weight-based dosing utilized in the original pivotal studies described herein, the recommended dosage at the start of therapy is not more than 0.04 mg/kg/week given as a daily subcutaneous injection. The dose may be increased at 4- to 8-week intervals according to individual patient requirements to a maximum of 0.08 mg/kg/week. Clinical response, side effects, and determination of age-and gender-adjusted serum IGF-I levels may be used as guidance in dose titration.

Alternatively, taking into account more recent literature, a starting dose of approximately 0.2 mg/day (range, 0.15-0.30 mg/day) may be used without consideration of body weight. This dose can be increased gradually every 1-2 months by increments of approximately 0.1-0.2 mg/day, according to individual patient requirements based on the clinical response and serum IGF-I concentrations. During therapy, the dose should be decreased if required by the occurrence of adverse events and/or serum IGF-I levels above the age- and gender-specific normal range. Maintenance dosages vary considerably from person to person.

A lower starting dose and smaller dose increments should be considered for older patients, who are more prone to the adverse effects of somatropin than younger individuals. In addition, obese individuals are more likely to manifest adverse effects when treated with a weight-based regimen. In order to reach the defined treatment goal, estrogen-replete women may need higher doses than men. Oral estrogen administration may increase the dose requirements in women.

GENOTROPIN must not be injected intravenously.

GENOTROPIN is supplied in a two-chamber cartridge, with the lyophilized powder in the front chamber and a diluent in the rear chamber. A reconstitution device is used to mix the diluent and powder.

Follow the directions for reconstitution provided with each device. **Do not shake**; shaking may cause denaturation of the active ingredient.

All parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If the solution is cloudy, the contents **MUST NOT** be injected.

Patients and caregivers who will administer GENOTROPIN in medically unsupervised situations should receive appropriate training and instruction on the proper use of GENOTROPIN from the physician or other suitably qualified health professional.

STABILITY AND STORAGE

Except as noted below, store GENOTROPIN Lyophilized Powder under refrigeration at 2° to 8°C (36° to 46°F). Do not freeze. Protect from light.

The 1.5-mg cartridge of GENOTROPIN contains a diluent with no preservative. After reconstitution, the cartridge may be stored under refrigeration for up to 24 hours. Use only once and discard any remaining solution.

The 5.8-mg and 13.8-mg cartridges of GENOTROPIN contain a diluent with a preservative. Thus, after reconstitution, they may be stored under refrigeration for up to 21 days.

The GENOTROPIN MINIQUICK Growth Hormone Delivery Device should be refrigerated prior to dispensing, but may be stored at or below 25°C (77°F) for up to three months after dispensing. The diluent has no preservative. After reconstitution, the GENOTROPIN MINIQUICK may be stored under refrigeration for up to 24 hours before use. The GENOTROPIN MINIQUICK should be used only once and then discarded.

HOW SUPPLIED

GENOTROPIN Lyophilized Powder is available in the following packages:

1.5-mg two-chamber cartridge (without preservative)
concentration of 1.3 mg/mL (approximately 4 IU/mL)

Pre-assembled in a GENOTROPIN INTRA-MIX® Growth Hormone Reconstitution Device and packaged with a pressure release needle

Package of 5 NDC 0013-2606-94

5.8-mg two-chamber cartridge (with preservative)
concentration of 5 mg/mL (approximately 15 IU/mL)

For use with the GENOTROPIN PEN® 5 Growth Hormone Delivery Device and/or the GENOTROPIN MIXER™ Growth Hormone Reconstitution Device

Package of 5 NDC 0013-2626-94 Package of 1 NDC 0013-2626-81

Pre-assembled in a GENOTROPIN INTRA-MIX Growth Hormone Reconstitution Device and packaged with a pressure release needle

Package of 5 NDC 0013-2616-94 Package of 1 NDC 0013-2616-81

13.8-mg two-chamber cartridge (with preservative)
concentration of 12 mg/mL (approximately 36 IU/mL)

For use with the GENOTROPIN PEN 12 Growth Hormone Delivery Device and/or the GENOTROPIN MIXER Growth Hormone Reconstitution Device

Package of 5	NDC 0013-2646-94	Package of 1	NDC 0013-2646-81

Manufactured by: Pharmacia AB
Stockholm, Sweden
or
Vetter Pharma-Fertigung GmbH & Co. KG
Langenargen, Germany

GENOTROPIN MINIQUICK Growth Hormone Delivery Device containing a two-chamber cartridge of GENOTROPIN (without preservative)

After reconstitution, each GENOTROPIN MINIQUICK delivers a fixed volume of 0.25 mL, regardless of strength. Available in the following strengths, each in a package of 7:

0.2 mg	NDC 0013-2649-02	1.2 mg	NDC 0013-2654-02
0.4 mg	NDC 0013-2650-02	1.4 mg	NDC 0013-2655-02
0.6 mg	NDC 0013-2651-02	1.6 mg	NDC 0013-2656-02
0.8 mg	NDC 0013-2652-02	1.8 mg	NDC 0013-2657-02
1.0 mg	NDC 0013-2653-02	2.0 mg	NDC 0013-2658-02

Please see accompanying directions for use of the reconstitution and/or delivery device.

Rx only

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