GENOTROPIN

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1. NAME OF THE MEDICINAL PRODUCT

GENOTROPIN

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Somatropin (INN) recombinant DNA-derived human growth hormone (GH) produced in *E. coli*.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

In the two-chamber cartridge, there is a white powder in the front compartment and a clear solution in the rear compartment. After reconstitution, one cartridge contains 5.3 mg (16 IU) somatropin in 1 mL. The two-chamber cartridge is supplied for use sealed in a disposable multidose pre-filled pen (GoQuick).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Children
Growth disturbance due to insufficient secretion of growth hormone and growth disturbance associated with Turner syndrome.

Improvement of growth and body composition in children with Prader-Willi syndrome (PWS). The diagnosis of PWS should be confirmed by appropriate genetic testing.

Adults
Replacement therapy in adults with pronounced growth hormone deficiency.

4.2 Posology and method of administration

The dosage and administration schedule should be individualized. Somatropin should be given subcutaneously and the injection site varied to prevent lipoatrophy.

Children
Growth disturbance due to insufficient secretion of growth hormone in children: Generally, a dose of 0.07 - 0.10 IU/kg (0.025 - 0.035 mg/kg) body weight per day or 2.1 - 3.0 IU/m^2 (0.7 - 1.0 mg/m^2) body surface area per day is recommended. Even higher doses have been used.

Growth disturbance due to Turner syndrome: A dose of 0.14 IU/kg (0.045 - 0.050 mg/kg) body weight per day or 4.3 IU/m^2 (1.4 mg/m^2) body surface area per day is recommended.

Prader-Willi syndrome in children: A dose of 0.10 IU/kg (0.035 mg/kg) body weight per day or 3.0 IU/m^2 (1.0 mg/m^2) body surface area per day is recommended.

Adults

Growth hormone deficient adult patients: The recommended starting dose is 0.45 - 0.90 IU (0.15 - 0.30 mg) per day. The final dose should be individually titrated as needed with respect to age and gender. The daily maintenance dose seldom exceeds 4 IU (1.33 mg) per day. Women may require higher doses than men. This means that there is a risk that women, especially those on oral estrogen replacement may be under-treated. As normal physiological growth hormone production decreases with age, dose requirements may be reduced. Clinical response, side effects, and determination of insulin-like growth factor-I (IGF-I) in serum may be used as guidance for dose titration.

4.3 Contraindications

Somatropin is contraindicated in patients who have evidence of neoplastic activity and in patients with uncontrolled growth of benign intracranial tumors. Anti-tumor therapy must be completed prior to starting somatropin.

Somatropin is contraindicated in patients with acute critical illness due to complications following open heart or abdominal surgery, multiple accidental trauma, or acute respiratory failure. Two placebo-controlled clinical trials (N=522), conducted in adult patients to evaluate the effects of somatropin 5.3 or 8 mg (16 or 24 IU) on length of stay in intensive care units, showed significantly higher mortality (41.9% vs. 19.3%) in patients treated with somatropin compared with those who received placebo (see section **4.4 Special warnings and precautions for use** in patients who are receiving somatropin for growth hormone replacement).

Hypersensitivity to the active substance or to any of the excipients.

Prader-Willi Syndrome in Children

Somatropin is contraindicated in patients with Prader-Willi syndrome who are severely obese, have a history of upper airway obstruction or sleep apnea, or have severe respiratory impairment. There have been reports of sudden death when somatropin was used in such patients (see section **4.4 Special warnings and precautions for use)**.

4.4 Special warnings and precautions for use

There have been reports of fatalities associated with the use of growth hormone in pediatric patients with Prader-Willi syndrome who had one or more of the following risk factors: severe obesity, history of respiratory impairment or sleep apnea, or unidentified respiratory infection. Another possible risk factor may be male gender. Patients with Prader-Willi syndrome should be evaluated for upper airway obstruction before initiation of treatment with somatropin. If during treatment with somatropin patients show signs of upper airway obstruction (including onset of or increased snoring), treatment should be interrupted. All patients with Prader-Willi syndrome should be evaluated for sleep apnea and monitored if sleep apnea is suspected. These patients should also have effective weight control and be monitored for signs of respiratory infections, which should be diagnosed as early as possible and treated aggressively. In adults, perform tests periodically so that the serum IGF-I value does not exceed the upper limit of the reference range (see section **4.2 Posology and method of administration**).

Diagnosis and therapy with somatropin should be initiated and monitored by physicians who are appropriately qualified and experienced in the diagnosis and management of patients with the therapeutic indication of use.

Myositis is a very rare adverse event that may be related to the preservative m-cresol. If myalgia or disproportionate pain at injection site develops, myositis should be considered and, if confirmed, a presentation of somatropin without m-cresol should be used.

Somatropin may induce a state of insulin resistance and, in some patients, hyperglycemia. Therefore, patients should be observed for evidence of glucose intolerance. In rare cases, therapy with somatropin may produce sufficient glucose intolerance to meet the diagnostic criteria for Type 2 diabetes mellitus. The risk of developing diabetes during treatment with somatropin is greatest in those patients with other risk factors for Type 2 diabetes mellitus, such as obesity, family history of diabetes, treatment with steroids, or prior impaired glucose tolerance. In patients with pre-existing diabetes mellitus, the dose of anti-diabetic therapy might require adjustment when somatropin is instituted.

In general, peripheral thyroid hormone levels remain within the normal reference range during treatment with somatropin. However, there is an enhanced conversion of T4 to T3 that may result in a reduction in serum T4 and an increase in serum T3 concentrations. This effect may be of clinical relevance for patients with central subclinical hypothyroidism in whom hypothyroidism may theoretically develop. Conversely, mild hyperthyroidism may occur in patients receiving replacement therapy with thyroxin. It is therefore advisable to test thyroid function shortly after the start of treatment with somatropin, and after dose adjustments.

Introduction of somatropin treatment may result in inhibition of 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD-1) and reduced serum cortisol concentrations. In patients treated with somatropin, previously undiagnosed central (secondary) hypoadrenalism may be unmasked and glucocorticoid replacement may be required. In addition, patients treated with glucocorticoid replacement therapy for previously diagnosed hypoadrenalism may require an increase in their maintenance or stress doses, following initiation of somatropin treatment (see section **4.5 Interaction with other medicinal products and other forms of interaction**).

When somatropin is co-administered with hormones other than somatropin in adults, serum IGF-I concentration should be carefully monitored because the hormone to be used concomitantly may affect the serum IGF-I concentration. If a woman taking somatropin begins oral estrogen therapy, the dose of somatropin may need to be increased to maintain the serum IGF-I levels within the normal age-appropriate range. Conversely, if a woman on somatropin discontinues oral estrogen therapy, the dose of somatropin may need to be reduced to avoid excess of growth hormone and/or side effects (see section **4.5 Interaction with other medicinal products and other forms of interaction**).

In patients with growth hormone deficiency secondary to treatment of malignant disease, it is recommended to monitor for signs of relapse of the malignancy.

In patients with endocrine disorders, including growth hormone deficiency, slipped epiphyses of the hip may occur more frequently than in the general population. Children who develop a limp during treatment with somatropin should be evaluated (see section **4.8 Undesirable effects**).

In case of severe or recurrent headache, visual problems, nausea, or vomiting, a funduscopy for papilledema is recommended. If papilledema is confirmed, a diagnosis of benign intracranial hypertension should be considered and, if appropriate, growth hormone treatment should be discontinued. At present, there is insufficient evidence to guide the decision of whether or not to reintroduce growth hormone therapy in patients with resolved intracranial hypertension. If growth hormone treatment is restarted, careful monitoring for symptoms of intracranial hypertension is necessary.

Progression of scoliosis can occur in patients who experience rapid growth. Because growth hormone increases growth rate, physicians should be alert to this abnormality, which may manifest during growth hormone therapy. Scoliosis is commonly seen in pediatric patients with Prader-Willi syndrome. Scoliosis may progress in any child during rapid growth. Signs of scoliosis should be monitored during treatment.

Experience in patients above 60 years is limited.

In patients with chronic renal insufficiency, renal function should be below 50% of normal before institution of therapy with somatropin. To verify growth disturbance, growth should be followed for a year preceding institution of therapy. Conservative treatment for renal insufficiency should have been established and should be maintained during therapy with growth hormone. Somatropin should be discontinued at renal transplantation.

If patients who are receiving growth hormone replacement therapy become acutely critically ill, the potential benefit of continued treatment with somatropin should be weighed against the potential risk (see section **4.3 Contraindications**).

Somatropin is ineffective for growth promotion in children with closed epiphyses.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant treatment with glucocorticoids inhibits the growth-promoting effects of somatropin containing products. Patients with adrenocorticotropic hormone (ACTH) deficiency should have their glucocorticoid replacement therapy carefully adjusted to avoid any inhibitory effect on growth. Therefore, patients treated with glucocorticoids should have their growth monitored carefully to assess the potential impact of glucocorticoid treatment on growth.

Growth hormone decreases the conversion of cortisone to cortisol and may unmask previously undiscovered central hypoadrenalism or render low glucocorticoid replacement doses ineffective (see section **4.4 Special warnings and precautions for use**).

Administration of somatropin may increase the clearance of compounds metabolized by cytochrome P450 3A4 (e.g., sex steroids, corticosteroids, anticonvulsants, and cyclosporin). The clinical significance of this potential interaction is unknown.

In women on oral estrogen replacement, a higher dose of growth hormone may be required to achieve the treatment goal (see section **4.4 Special warnings and precautions for use**).

4.6 Fertility, pregnancy and lactation

Animal reproduction studies have not shown evidence of harmful effects on the fetus. There are, however, no studies in pregnant women. Treatment with Genotropin should be interrupted if pregnancy occurs.

During normal pregnancy, the levels of pituitary growth hormone markedly fall after Week 20 of gestation, being replaced almost entirely by placental growth hormone by Week 30. Therefore, it is unlikely that continued replacement therapy with somatropin would be necessary in growth hormone deficient women during the third trimester of pregnancy.

It is not known if somatropin is excreted into breast milk, but absorption of intact protein from the gastrointestinal tract of the infant is extremely unlikely.

4.7 Effects on ability to drive and use machines

No effects on the ability to drive and use machines have been observed.

4.8 Undesirable effects

Patients with growth hormone deficiency are characterized by extracellular volume deficit. When treatment with somatropin is started, this deficit is rapidly corrected. In general, in adult patients, adverse effects related to fluid retention, such as edema peripheral, face edema, musculoskeletal stiffness, arthralgia, myalgia and paresthesia are mild to moderate, arise within the first months of treatment, and subside spontaneously or with dose-reduction.

The incidence of these adverse effects is related to the administered dose, the age of the patients, and possibly inversely related to the age of the patients at the onset of growth hormone deficiency.

Tabulated list of adverse reactions

Tables 1-4 show the adverse reactions ranked under headings of System Organ Class and frequency using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data) for each of the indicated conditions.

Table 1: Clinical Trials in Children with GHD

Long-Term Treatment of Children with Growth Disturbance due to Insufficient Secretion of Growth Hormone						
System Organ Class	**Very Common ≥1/10**	**Common ≥1/100 to <1/10**	**Uncommon ≥1/1,000 to <1/100**	**Rare ≥1/10,000 to <1/1,000**	**Very Rare <1/10,000**	**Not Known (cannot be estimated from available data)**
Neoplasms Benign, Malignant, and Unspecified (including cysts and polyps)			Leukemia†			

Long-Term Treatment of Children with Growth Disturbance due to Insufficient Secretion of Growth Hormone						
System Organ Class	**Very Common ≥1/10**	**Common ≥1/100 to <1/10**	**Uncommon ≥1/1,000 to <1/100**	**Rare ≥1/10,000 to <1/1,000**	**Very Rare <1/10,000**	**Not Known (cannot be estimated from available data)**
Metabolism and Nutrition Disorders						Type 2 diabetes
Nervous System Disorders						Paresthesia* Benign intracranial hypertension
Skin and Subcutaneous Tissue Disorders			Rash** Pruritus** Urticaria**			
Musculoskeletal, Connective Tissue, and Bone Disorders			Arthralgia*			Myalgia* Musculoskeletal stiffness*
General Disorders and Administration Site Conditions	Injection site reaction$					Edema peripheral* Face edema*
Investigations						Blood cortisol decreased‡
* In general, these adverse effects are mild to moderate, arise within the first months of treatment, and subside spontaneously or with dose-reduction. The incidence of these adverse effects is related to the administered dose, the age of the patients, and possibly inversely related to the age of the patients at the onset of growth hormone deficiency. ** ADR identified post-marketing. $ Transient injection site reactions in children are common have been reported. ‡ Clinical significance is unknown. † Reported in growth hormone deficient children treated with somatropin, but the incidence appears to be similar to that in children without growth hormone deficiency.						

Table 2: Clinical Trials in Children with Turner Syndrome

Long-Term Treatment of Children with Growth Disturbance due to Turner Syndrome						
System Organ Class	**Very Common ≥1/10**	**Common ≥1/100 to <1/10**	**Uncommon ≥1/1,000 to <1/100**	**Rare ≥1/10,000 to <1/1,000**	**Very Rare <1/10,000**	**Not Known (cannot be estimated from available data)**
Neoplasms Benign, Malignant, and Unspecified (including cysts and polyps)						Leukemia†
Metabolism and Nutrition Disorders						Type 2 diabetes

Long-Term Treatment of Children with Growth Disturbance due to Turner Syndrome						
System Organ Class	**Very Common ≥1/10**	**Common ≥1/100 to <1/10**	**Uncommon ≥1/1,000 to <1/100**	**Rare ≥1/10,000 to <1/1,000**	**Very Rare <1/10,000**	**Not Known (cannot be estimated from available data)**
Nervous System Disorders						Paresthesia* Benign intracranial hypertension
Skin and Subcutaneous Tissue Disorders						Rash** Pruritus** Urticaria**
Musculoskeletal, Connective Tissue, and Bone Disorders	Arthralgia*					Myalgia* Musculoskeletal stiffness*
General Disorders and Administration Site Conditions						Edema peripheral* Face edema* Injection site reaction$
Investigations						Blood cortisol decreased‡

* In general, these adverse effects are mild to moderate, arise within the first months of treatment, and subside spontaneously or with dose-reduction. The incidence of these adverse effects is related to the administered dose, the age of the patients, and possibly inversely related to the age of the patients at the onset of growth hormone deficiency.
** ADR identified post-marketing.
$ Transient injection site reactions in children have been reported.
‡ Clinical significance is unknown.
† Reported in growth hormone deficient children treated with somatropin, but the incidence appears to be similar to that in children without growth hormone deficiency.

Table 3: Clinical Trials in Children with Prader-Willi Syndrome

Long-Term Treatment and Improvement of Body Composition of Children with Growth Disturbance due to Prader-Willi Syndrome						
System Organ Class	**Very Common ≥1/10**	**Common ≥1/100 to <1/10**	**Uncommon ≥1/1,000 to <1/100**	**Rare ≥1/10,000 to <1/1,000**	**Very Rare <1/10,000**	**Not Known (cannot be estimated from available data)**
Neoplasms Benign, Malignant, and Unspecified (including cysts and polyps)						Leukemia†
Metabolism and Nutrition Disorders						Type 2 diabetes

Long-Term Treatment and Improvement of Body Composition of Children with Growth Disturbance due to Prader-Willi Syndrome						
System Organ Class	**Very Common ≥1/10**	**Common ≥1/100 to <1/10**	**Uncommon ≥1/1,000 to <1/100**	**Rare ≥1/10,000 to <1/1,000**	**Very Rare <1/10,000**	**Not Known (cannot be estimated from available data)**
Nervous System Disorders		Paresthesia* Benign intracranial hypertension				
Skin and Subcutaneous Tissue Disorders		Rash**				Pruritus** Urticaria**
Musculoskeletal, Connective Tissue, and Bone Disorders		Arthralgia* Myalgia*				Musculoskeletal stiffness*
General Disorders and Administration Site Conditions		Edema peripheral*				Face edema* Injection site reaction$
Investigations						Blood cortisol decreased‡

* In general, these adverse effects are mild to moderate, arise within the first months of treatment, and subside spontaneously or with dose-reduction. The incidence of these adverse effects is related to the administered dose, the age of the patients, and possibly inversely related to the age of the patients at the onset of growth hormone deficiency.
** ADR identified post-marketing.
$ Transient injection site reactions in children have been reported.
‡ Clinical significance is unknown.
† Reported in growth hormone deficient children treated with somatropin, but the incidence appears to be similar to that in children without growth hormone deficiency.

Table 4: Clinical Trials in Adults with GHD

Replacement Therapy in Adults with Growth Hormone Deficiency						
System Organ Class	**Very Common ≥1/10**	**Common ≥1/100 to <1/10**	**Uncommon ≥1/1,000 to <1/100**	**Rare ≥1/10,000 to <1/1,000**	**Very Rare <1/10,000**	**Not Known (cannot be estimated from available data)**
Metabolism and Nutrition Disorders						Type 2 diabetes
Nervous System Disorders		Paresthesia* Carpel Tunnel Syndrome				Benign intracranial hypertension
Skin and Subcutaneous Tissue Disorders						Rash** Pruritus** Urticaria**

Replacement Therapy in Adults with Growth Hormone Deficiency						
System Organ Class	**Very Common ≥1/10**	**Common ≥1/100 to <1/10**	**Uncommon ≥1/1,000 to <1/100**	**Rare ≥1/10,000 to <1/1,000**	**Very Rare <1/10,000**	**Not Known (cannot be estimated from available data)**
Musculoskeletal, Connective Tissue, and Bone Disorders	Arthralgia*	Myalgia* Musculoskeletal stiffness*				
General Disorders and Administration Site Conditions	Edema peripheral*					Face edema* Injection site reaction[$]
Investigations						Blood cortisol decreased[‡]
* In general, these adverse effects are mild to moderate, arise within the first months of treatment, and subside spontaneously or with dose-reduction. The incidence of these adverse effects is related to the administered dose, the age of the patients, and possibly inversely related to the age of the patients at the onset of growth hormone deficiency. ** ADR identified post-marketing. $ Transient injection site reactions in children have been reported. ‡ Clinical significance is unknown.						

Transient injection site reactions in children have been reported.

Somatropin has been reported to reduce serum cortisol levels, possibly by affecting carrier proteins or by increased hepatic clearance. The clinical relevance of these findings may be limited. Nevertheless, corticosteroid replacement therapy should be optimized before initiation of Genotropin therapy.

Rare cases of leukemia have been reported in growth hormone deficient children treated with somatropin, but the incidence appears to be similar to that in children without growth hormone deficiency.

In the post-marketing experience, rare cases of sudden death have been reported in patients affected by Prader-Willi syndrome treated with somatropin, although no causal relationship has been demonstrated.

Slipped capital femoral epiphysis and Legg-Calve-Perthes disease have been reported in children treated with growth hormone. But, it is unknown if these 2 pathologies are more frequent or not while treated with somatropin.

4.9 Overdose

Acute overdosage could lead initially to hypoglycemia and subsequently to hyperglycemia. Long-term overdosage could result in signs and symptoms consistent with the effects of human growth hormone excess.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Somatropin is a potent metabolic hormone of importance for the metabolism of lipids, carbohydrates and proteins. In children with inadequate endogenous growth hormone, somatropin stimulates linear growth and increases growth rate. In adults, as well as in children, somatropin maintains a normal body composition by increasing nitrogen retention and stimulation of skeletal muscle growth, and by mobilization of body fat. Visceral adipose tissue is particularly responsive to somatropin. In addition to enhanced lipolysis, somatropin decreases the uptake of triglycerides into body fat stores. Serum concentrations of IGF-I (Insulin-like Growth Factor-I) and IGFBP3 (Insulin-like Growth Factor Binding Protein 3) are increased by somatropin. In addition, the following actions have been demonstrated:

- Lipid metabolism: Somatropin induces hepatic LDL cholesterol receptors, and affects the profile of serum lipids and lipoproteins. In general, administration of somatropin to growth hormone deficient patients results in reductions in serum LDL and apolipoprotein B. A reduction in serum total cholesterol may also be observed.

- Carbohydrate metabolism: Somatropin increases insulin but fasting blood glucose is commonly unchanged. Children with hypopituitarism may experience fasting hypoglycemia. This condition is reversed by somatropin.

- Water and mineral metabolism: Growth hormone deficiency is associated with decreased plasma and extracellular volumes. Both are rapidly increased after treatment with somatropin. Somatropin induces the retention of sodium, potassium and phosphorus.

- Bone metabolism: Somatropin stimulates the turnover of skeletal bone. Long-term administration of somatropin to growth hormone deficient patients with osteopenia results in an increase in bone mineral content and density at weight-bearing sites.

- Physical capacity: Muscle strength and physical exercise capacity are improved after long-term treatment with somatropin. Somatropin also increases cardiac output, but the mechanism has yet to be clarified. A decrease in peripheral vascular resistance may contribute to this effect.

Clinical trials

<u>Prader-Willi syndrome</u>

The safety and efficacy of somatropin in the treatment of pediatric patients with Prader-Willi syndrome (PWS) were evaluated in two randomized, open-label, controlled clinical trials. Patients received either somatropin or no treatment for the first year of the studies, while all patients received somatropin during the second year. Somatropin was administered as a daily subcutaneous (SC) injection, and the dose was calculated for each patient every 3 months. In Study 91-019, the treatment group received somatropin at a dose of 0.24 mg/kg/week during the entire study. During the second year, the control group received somatropin at a dose of 0.48 mg/kg/week. In Study 94-8129-007, the treatment group received somatropin at a dose of 0.36 mg/kg/week during the entire study. During the second year, the control group received somatropin at a dose of 0.36 mg/kg/week.

Patients who received somatropin showed significant increases in linear growth during the first year of study, compared with patients who received no treatment (see Table 5). Linear growth continued to increase in the second year, when both groups received treatment with somatropin.

Table 5: Efficacy of Somatropin in Pediatric Patients with Prader-Willi Syndrome (Mean ± SD)

	Study 91-019		**Study 94-8129-007**	
	Somatropin (0.24 mg/kg/week) n=15	**Untreated Control** n=12	**Somatropin** (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≤0.001. † p≤0.002 (when comparing SDS change at 12 months).				

Changes in body composition were also observed in the patients receiving somatropin (see Table 6). 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 somatropin did not accelerate bone age, compared with patients who received no treatment.

Table 6: Effect of Somatropin on Body Composition in Pediatric Patients with Prader-Willi Syndrome (Mean ± SD)

	Somatropin 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 somatropin; n=12 for the Control group. ‡ n.s..		

5.2 Pharmacokinetic properties

Absorption

The bioavailability of subcutaneously administered somatropin is approximately 80% in both healthy subjects and growth hormone deficient patients. Results were comparable in both male and female patients. A subcutaneous dose of 0.035 mg/kg of somatropin results in plasma C_{max} and t_{max} values in the range of 13 - 35 ng/mL and 3 - 6 hours, respectively.

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 somatropin was 35% greater than that for 1.3 mg/mL somatropin. 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 somatropin yielded a mean AUC that was 17% greater than that for 1.3 mg/mL somatropin. 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 somatropin 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 somatropin following administration to GHD adults was estimated to be 1.3 (± 0.8) L/kg.

Metabolism

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 are returned to the systemic circulation. The mean terminal half-life of intravenous somatropin in normal adults is 0.4 hours, whereas subcutaneously administered somatropin 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 somatropin in 16 GHD adult patients was 0.3 (± 0.11) L/h/kg.

Special Populations

Pediatric: The pharmacokinetics of somatropin 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 somatropin was similar in males and females.

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

Renal, hepatic, or cardiac insufficiency: Information about the pharmacokinetics of somatropin in patients with renal, hepatic, or cardiac insufficiency is either lacking or incomplete.

5.3 Preclinical safety data

In studies regarding general toxicity, local tolerance and reproduction toxicity, no clinically relevant effects have been observed.

In vitro and *in vivo* genotoxicity studies on gene mutations and induction of chromosome aberrations have been negative.

An increased chromosome fragility has been observed in one *in vitro* study on lymphocytes taken from patients after long-term treatment with somatropin and following the addition of the radiomimetic drug bleomycin. The clinical significance of this finding is unclear.

In another study, no increase in chromosomal abnormalities was found in the lymphocytes of patients who had received long-term somatropin therapy.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder: Front compartment	**Solvent: Rear compartment**
Glycine, Sodium dihydrogen phosphate anhydrous, Disodium phosphate anhydrous, Mannitol	Water for injections, m-Cresol, Mannitol

6.2 Incompatibilities

This medical product must not be mixed with other medical products and should only be reconstituted in the supplied solvent.

6.3 Shelf-life

Refer to expiry date on outer carton.

After reconstitution, chemical and physical in-use stability at 2°C - 8°C has been demonstrated for 28 days.

From a microbiological point of view, once reconstituted, the product may be stored at 2°C - 8°C for 28 days.

Other in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Before reconstitution: Store in a refrigerator (2°C - 8°C), with up to 1 month at or below 25°C allowed. Keep the two-chamber cartridge/pre-filled pen in the outer carton in order to protect from light.

After reconstitution: Store in a refrigerator (2°C - 8°C). Do not freeze. Keep the two-chamber cartridge/pre-filled pen in the outer carton in order to protect from light.

6.5 Nature and contents of container

Powder and 1.15 mL solvent in a two-chamber glass cartridge (Type 1 glass) separated by a rubber plunger (bromobutyl). The cartridge is sealed at one end with a rubber disc (bromobutyl) and an aluminum cap and at the other end by a rubber stopper (bromobutyl). The two-chamber cartridge is supplied for use sealed in a disposable multidose pre-filled pen, GoQuick.

The 5.3 mg pre-filled pen (GoQuick) is color-coded blue.

Pack size*:
1's x 5.3 mg pre-filled pen, 5's x 5.3 mg pre-filled pens

*Not all pack size is marketed.

6.6 Special precautions for disposal and other handling

Two-chamber cartridge: The solution is prepared by screwing the GoQuick pre-filled pen sections together so that the solvent will be mixed with the powder in the two-chamber cartridge. Gently dissolve the powder by gently tilting the pen from side to side. Do not shake vigorously; this might cause denaturation of the active ingredient. The reconstituted solution is almost colorless or slightly opalescent. The reconstituted solution for injection is to be inspected prior to use and only clear solutions without particles should be used.

Empty GoQuick pre-filled pens should never be refilled and must be properly discarded.

7. PRODUCT OWNER

Pfizer Inc
New York,
United States

GENOTROPIN GOQUICK

INSTRUCTIONS FOR USE

Please read these instructions completely before using your GoQuick Pen. If you have any questions about your dose or your treatment with Genotropin, call your doctor or nurse.

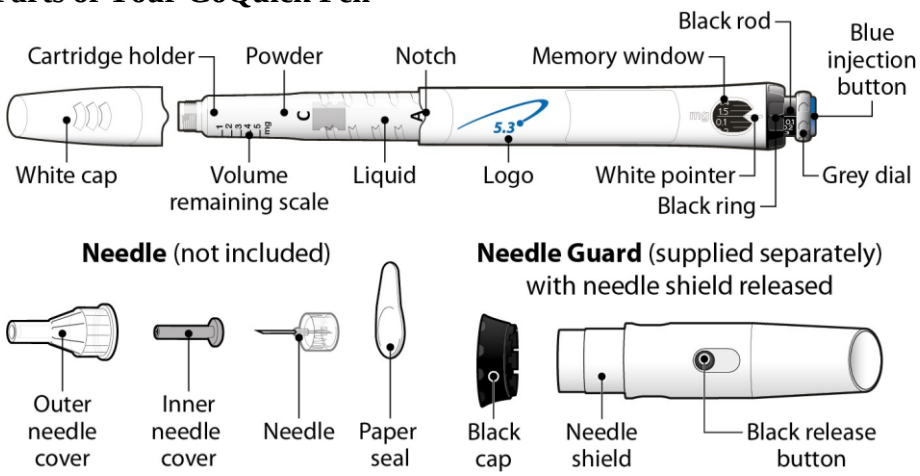
About GoQuick
GoQuick is a pre-filled, multidose, disposable injection pen that holds 5.3 mg of somatropin. Your pen can deliver doses from 0.1 mg to 1.5 mg of Genotropin. Each click of the black ring changes the dose by 0.05 mg. The Genotropin in your pen is mixed only once, when you start a new pen. You never have to change cartridges. When your pen is empty, you just start a new pen.

Your pen has dose memory. The dose is set once on a new pen. Your pen then allows you to draw up the same set dose for each injection. This will prevent you from drawing more than your set dose.

Important Information
- **Do not** mix the powder and liquid of your pen unless a needle is on your pen.
- **Do not** store your pen with the needle attached. The Genotropin may leak from your pen and air bubbles may form in the cartridge. Always remove the needle and attach your pen cap or needle guard cap before storing.
- Take care not to drop your pen. If you drop your pen and any part of it appears broken or damaged, **do not** use it. Contact your doctor or nurse for another pen. If you drop your pen and it is not damaged or broken, you must perform another prime as described in Step 6 (Setting up and using a new GoQuick Pen).
- Clean your pen with a damp cloth. **Do not** put your pen in water.
- Always use a new needle for each injection. **Do not** share your pen needles.
- The volume remaining scale along the side of the cartridge holder is a guide to show the volume of Genotropin left in your pen.

Storage and Disposal
- Store your pen in the refrigerator (2°C to 8°C) in the outer carton to protect from light. **Do not** freeze or expose it to frost.
- **Do not** use your pen after its expiry date.
- 28 days after mixing, throw away (dispose of) your pen even if there is some medicine left.
- Follow your local health and safety laws to throw away (dispose of) your pen. Ask your doctor or nurse if you are not sure what to do.

Parts of Your GoQuick Pen

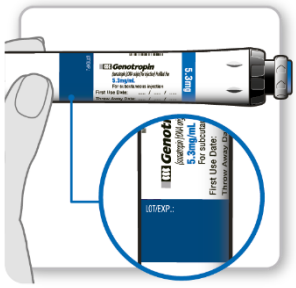


Pen needles are **not included** with your GoQuick Pen. You will need to get pen needles up to a length of 8 mm from your pharmacy.

- Needles to use with your GoQuick Pen:
  - 31G or 32G (Becton, Dickinson and Company)
  - 31G or 32G (Novo Nordisk®)
  - 32.5G or 34G (Terumo)

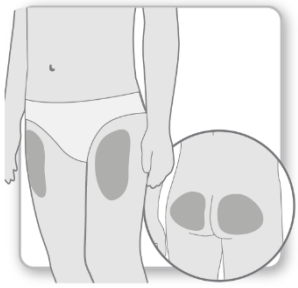
Setting Up and Using a New GoQuick Pen

Step 1. Preparation



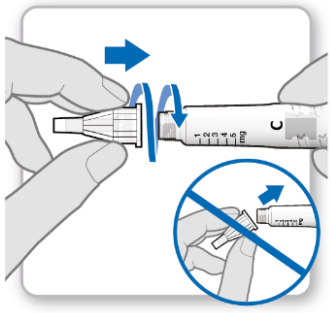
- **Wash and dry** your hands.
- **Gather** the following supplies on a clean flat surface:
  - A new GoQuick Pen
  - A new needle (not included)
  - Suitable sharps container (not included).
- **Check** the expiry date on your pen label. **Do not** use your pen if the pen has passed its expiry date.

Step 2. Choose Injection Site



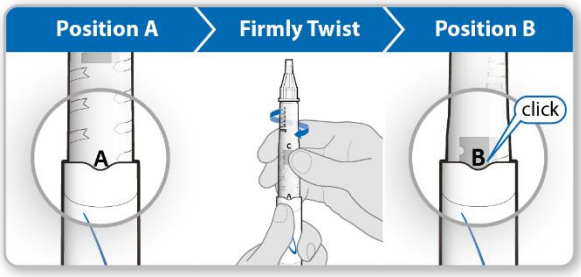
- **Choose and clean** an injection site as recommended by your doctor or nurse. Choose a different site each time you give yourself an injection. Each new injection should be given at least 2 cm from the site you used before.
- Avoid areas that are bony, bruised, red, sore or hard, and areas of the skin that have scars or skin conditions.

Step 3. Attach New Needle



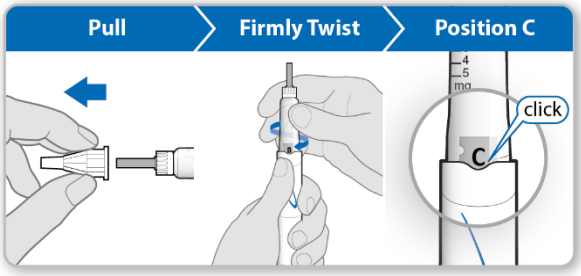
- **Pull** the white cap straight off the pen.
- Take a new needle and peel off the paper seal.
- **Gently push and then screw** the needle onto your pen. **Do not** overtighten.
  Note: Be careful not to attach the needle at an angle. This may cause your pen to leak.
- Leave both needle covers on the needle.

Step 4. Mix the Genotropin



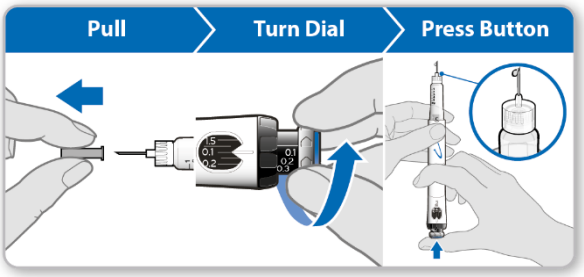
- **Hold** your pen with the needle-end pointing up and the **"A"** facing you.
- **Firmly** twist the cartridge holder into your pen until **"B"** clicks into the notch.
- **Gently tilt** your pen from side to side to help dissolve the powder completely. **Do not** shake. Shaking can damage the growth hormone.
- **Check** that the liquid in the cartridge is clear and all the powder is dissolved.
  - If the liquid is cloudy or you see any powder, gently tilt your pen from side to side a few more times.
  - If the liquid is still cloudy or you see any powder, **do not** use the pen and try again with a new pen.

Step 5. Remove the Air from Your Pen



- **Pull** the outer needle cover off. Keep it to remove the needle after your injection.
- Leave the inner needle cover on.
  Note: You should see an inner needle cover after you have removed the outer cover. If you do not see this, try to attach the needle again.
- **Hold** your pen with the needle-end pointing up.
- **Gently tap** the cartridge holder to help any trapped air move to the top.
- **Firmly twist** the cartridge holder into your pen until **"C"** clicks into the notch.
  - Some liquid may appear around the inner needle cover. This is normal.

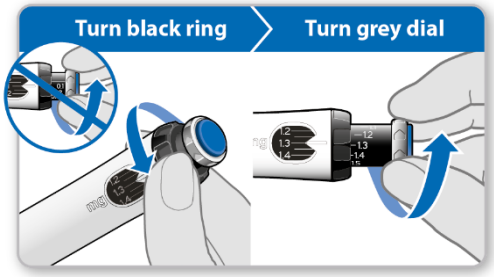
Step 6. Prime Your Pen



Priming removes any remaining air by pushing a small amount of liquid out of your pen. The priming dose is 0.1 mg and is different from the dose your doctor or nurse has prescribed. **Only prime your pen the first time you use it.**

- **Pull** the inner needle cover off and throw it away.
  Caution: Do not touch the needle to avoid a needle stick.
- **Check** that 0.1 mg is set in the memory window.
- **Turn** the **grey dial** in the direction of the arrows until it stops clicking.
- **Hold** your pen with the needle pointing **straight** up.
- **Push** the blue injection button all the way in.
- **Check** for liquid at the needle tip. If liquid appears, your pen is primed.
  - If liquid does not appear, repeat the priming steps up to two additional times.
  - If liquid still does not appear, do not use your pen. Contact your doctor or nurse for advice.

Step 7. Set and Draw Up Your Dose



The first time you use your pen you will set the dose that your doctor or nurse has prescribed. You do not need to set the dose again until you start a new pen or your doctor or nurse tells you.

- **Turn** the **black ring counterclockwise** until your dose is lined up with the white pointer in the memory window. **Be careful not to turn the grey dial**.
  - If you turn your dose past the white pointer, turn the black ring back to set your correct dose.

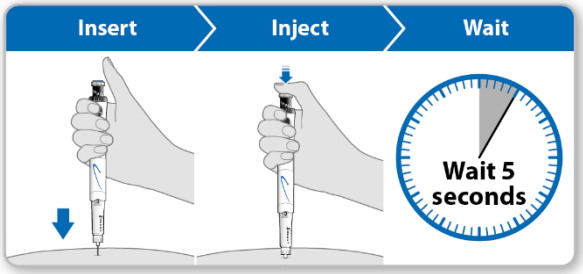
  Note: If you cannot turn the black ring, press the blue injection button until it stops clicking. Then try and set your dose again. Note that liquid will come out of the needle.
- **Turn** the **grey dial** in the direction of the arrows until it stops clicking.

Step 8. Check Your Dose

Your dose on the black rod should **line up** with the white pointer.

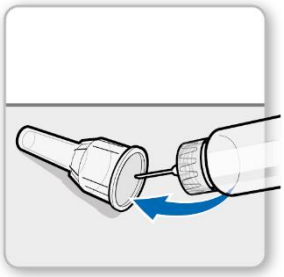
- **Check** that the dose you drew up on the black rod is the same as the dose you set in the memory window.
  - If the doses match, your pen is ready to give your injection.
  - If the doses do not match, make sure you have turned the grey dial in the direction of the arrows until it does not click anymore.

Step 9. Give Your Injection of Genotropin



- **Hold** your pen over the injection site.
- **Insert** the needle straight into the skin.
- **Push** the blue injection button down until it stops clicking.
- **Wait** for a full 5 seconds to ensure that your complete dose is injected. Keep lightly pressing on the blue injection button while you count.
- After 5 seconds, pull the needle straight out of your skin.
  Note: If you see a drop of liquid at the injection site or needle tip, then with your next injection try pressing the blue injection button for longer before pulling the needle out of your skin.

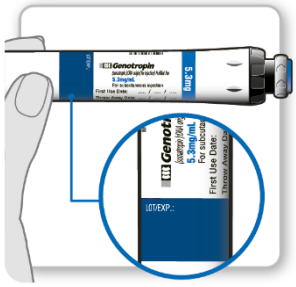
Step 10. Remove Needle



- **Carefully cover** the needle with the outer needle cover.
  Caution: Do not touch the needle to avoid a needle stick.
- Use the needle cover to unscrew the needle.
- **Throw away** (dispose of) the needle in a suitable sharps container.
- **Push** the white cap onto your pen.
- Store your pen in the refrigerator until your next injection.

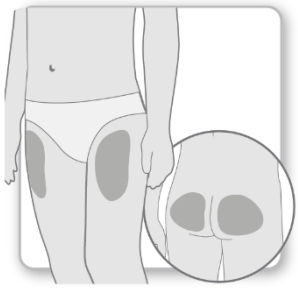
Routine (Daily) Use of GoQuick Pen

Step 1 Preparation



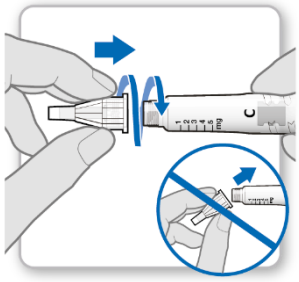
- **Wash and dry** your hands.
- **Gather** the following supplies on a clean flat surface:
  - An already mixed GoQuick Pen
  - A new needle (not included)
  - Suitable sharps container (not included).
- **Check** the expiry date on your pen label. **Do not** use your pen if the pen has passed its expiry date.
  Do not use your pen 28 days after first use.

Step 2 Choose Injection Site



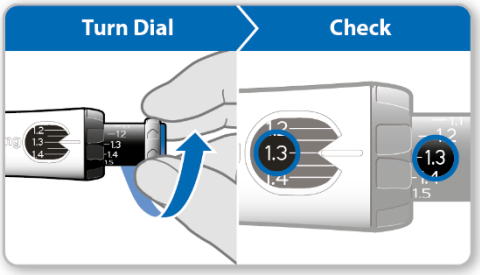
- **Choose and clean** an injection site as recommended by your doctor or nurse. Choose a different site each time you give yourself an injection. Each new injection should be given at least 2 cm from the site you used before.
- Avoid areas that are bony, bruised, red, sore or hard, and areas of the skin that have scars or skin conditions.

Step 3 Attach New Needle



- **Pull** the white cap straight off your pen.
- Take a new needle and peel off the paper seal.
- **Gently push and then screw** the needle onto your pen. **Do not** overtighten.
  Note: Be careful not to attach the needle at an angle. This may cause your pen to leak.
- **Remove** both needle covers.
  - Keep the outer needle cover to remove the needle after your injection.

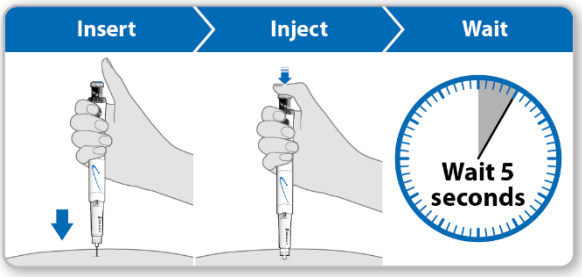
Step 4 Draw Up Your Dose



- **Turn** the **grey dial** in the direction of the arrows until it stops clicking.
- Your dose on the black rod should **line up** with the white pointer.
- **Check** that the dose you drew up on the black rod is the same as the dose you set in the memory window.
  - If the doses match, your pen is ready to give your injection.

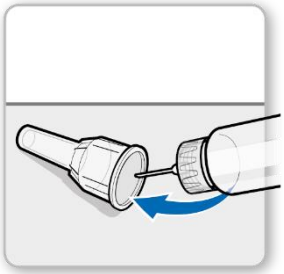
Note: If the dose you drew up is smaller, your pen does not have a full dose of Genotropin. Follow what your doctor or nurse told you to do when your pen does not have a full dose. Or contact your doctor or nurse for advice.

Step 5 Give Your Injection of Genotropin



- **Hold** your pen over the injection site.
- **Insert** the needle straight into the skin.
- **Push** the blue injection button down until it stops clicking.
- **Wait** for a full 5 seconds to ensure that your complete dose is injected. Keep lightly pressing on the blue injection button while you count.
- After 5 seconds, pull the needle straight out of your skin.
  Note: If you see a drop of liquid at the injection site or needle tip, then with your next injection try pressing the blue injection button for longer before pulling the needle out of your skin.

Step 6 Remove Needle



- **Carefully cover** the needle with the outer needle cover.
  Caution: Do not touch the needle to avoid a needle stick.
- Use the needle cover to unscrew the needle.
- **Throw away** (dispose of) the needle in a suitable sharps container.
- **Push** the white cap onto your pen.
- Store your pen in the refrigerator until your next injection.

Using the Needle Guard (Optional)
The needle guard is an optional feature supplied separately to hide the needle during injection.

Attach the needle guard:
Attach the needle guard after Step 5 (Setting up and using a new GoQuick Pen) to avoid a needle stick.

- Pull the black cap off the needle guard.
  - If the needle shield slides out, push it back into the needle guard until it clicks into place.
- Line up the black logo on the needle guard with the blue logo on your pen. Carefully push the needle guard onto your pen until it snaps into place.
- After Step 6 (Setting up and using a new GoQuick Pen), press the black button to release the shield from the needle guard.
- Follow the instructions as described from Step 7 (Setting up and using a new GoQuick Pen).

To remove the needle with needle guard in place:

- Place the outer needle cover into the end of the needle shield.
- Use the outer needle cover to push in the needle shield until it locks into place.
- Use the needle cover to unscrew the needle and throw away (dispose of) in a suitable sharps container.
- Leave the needle guard on your pen.
- Place the black cap on the needle guard. Store your pen in the refrigerator.

To remove the needle guard:

- Remove the needle first, then gently pull the needle guard off the pen.
- **Do not** throw away the needle guard. It can be used with your next pen.

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