PRODUCT MONOGRAPH

PrGENOTROPIN®GoQuick™

Somatropin [rDNA origin] for injection
Lyophilized Powder for reconstitution
5 mg, 5.3 mg, 12 mg pre-filled pen, GoQuick

and

PrGENOTROPIN®MiniQuick™

Somatropin [rDNA origin] for injection
Lyophilized Powder for reconstitution
0.2 mg, 0.4 mg, 0.6 mg, 0.8 mg, 1.0 mg, 1.2 mg, 1.4 mg, 1.6 mg, 1.8 mg, and 2.0 mg prefilled syringe, MiniQuick

Human Growth Hormone

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PrGENOTROPIN®GoQuick™
and
PrGENOTROPIN®MiniQuick™

Somatropin [rDNA origin] for injection

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Non-medicinal Ingredients
Subcutaneous injection	Available as 0.2 mg, 0.4 mg, 0.6 mg, 0.8 mg, 1.0 mg, 1.2 mg, 1.4 mg, 1.6 mg, 1.8 mg, and 2.0 mg Single Dose Syringe, With Sterile Powder and liquid	None *For a complete listing see Dosage Forms, Composition and Packaging section.*
	Available as 5 mg, 5.3 mg, 12 mg Multidose disposable pre-filled pen, With Sterile Powder and liquid	metacresol *For a complete listing see Dosage Forms, Composition and Packaging section.*

DESCRIPTION

GENOTROPIN (somatropin for injection) is a polypeptide hormone of recombinant DNA origin. It has 191 amino acid residues, a molecular weight of 22,124 daltons, and an isoelectric point (pH) of 5.0. 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.

INDICATIONS AND CLINICAL USE

GENOTROPIN (somatropin for injection) is indicated for:

Children

The long-term treatment of children who have growth failure due to an inadequate secretion of endogenous growth hormone (growth hormone deficiency (GHD)). Other causes of short stature should be excluded.

SGA Indication

GENOTROPIN is indicated for the treatment of growth failure (current height standard deviation score [SDS] < - 2) in short children born SGA (birth weight and/or length below -2 SD) and who fail to achieve catch-up growth (height velocity SDS < 0 during the last year) by 2 to 4 years or later.

TS Indication

The treatment of short stature associated with Turner syndrome in patients whose epiphyses are not closed.

ISS Indication

The long-term treatment of idiopathic short stature (ISS), also called non-growth hormone-deficient short stature, defined by height standard deviation score (SDS) <-2.25, and associated with growth rates unlikely to permit attainment of adult height in the normal range, in pediatric patients for whom diagnostic evaluation excludes other causes associated with short stature that should be observed or treated by other means. Genotropin treatment for ISS should be prescribed only for those patients whose epiphyses are not closed.

PWS Indication

GENOTROPIN is indicated for the 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. GENOTROPIN is also indicated for improvement of body composition in children with Prader-Willi syndrome.

Adults

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 (AO): 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 (CO): Patients who were growth hormone deficient during childhood as a result of congenital, genetic, acquired, or idiopathic causes.

Patients who were treated with somatropin for growth hormone deficiency in childhood and whose epiphyses are closed should be reevaluated before continuation of somatropin therapy at the reduced dose level recommended for growth hormone deficient adults. According to current standards, confirmation of the diagnosis of adult growth hormone deficiency in both groups involves an appropriate growth hormone provocative test with two exceptions: (1) patients with multiple other pituitary hormone deficiencies due to organic disease; and (2) patients with congenital/genetic growth hormone deficiency.

Geriatrics

The safety and effectiveness of GENOTROPIN in patients aged 65 and over have not been evaluated in clinical studies. (see **WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics**).

CONTRAINDICATIONS

GENOTROPIN (somatropin for injection) should not be used when there is any evidence of neoplastic activity. Intracranial lesions must be inactive and antitumour therapy complete prior to the institution of therapy. GENOTROPIN should be discontinued if there is evidence of tumour growth.

Growth hormone should not be used for growth promotion in children with fused epiphyses.

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

GENOTROPIN is contraindicated in patients with acute critical illness due to complications following open heart or abdominal surgery, multiple accidental trauma, or acute respiratory failure. (see **WARNINGS AND PRECAUTIONS**).

GENOTROPIN is contraindicated in patients with a history of hypersensitivity to any of its components.

GENOTROPIN is contraindicated in patients with Prader-Willi syndrome who have uncontrolled diabetes, or active psychosis, or have active cancer.

GENOTROPIN is contraindicated in patients with Prader-Willi syndrome who are severely obese or 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 **SERIOUS WARNINGS AND PRECAUTIONS**).

Certain formulations of growth hormones contain metacresol as a preservative. These formulations should not be used by patients with a known sensitivity to these preservatives (see **WARNINGS AND PRECAUTIONS**, **General**).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- **There have been reports of fatalities associated with the use of somatropin in pediatric patients with Prader-Willi syndrome who have one or more of the following risk factors: severe obesity, history of respiratory impairment or sleep apnea or unidentified (i.e. previously undiagnosed/mildly symptomatic) respiratory infections (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS, Congenital Disorders).**
- **Therapy with GENOTROPIN should be excluded for pediatric patients with Prader-Willi syndrome who have one or more of the following risk factors: uncontrolled diabetes, active cancer, active psychosis.**
- **Therapy with GENOTROPIN should be supervised by a physician who is experienced in the diagnosis and management of patients with growth hormone deficiency and that any change in brand of somatropin products should be made cautiously and only under medical supervision.**
- **Reconstituted GENOTROPIN must only be used if the solution is water-clear and contains no particles (see DOSAGE AND ADMINISTRATION, Reconstitution and Specific Precautions).**

General

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

The 5 mg, 5.3 mg and 12 mg presentations of GENOTROPIN GoQuick 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 MiniQuick presentations are preservative-free.

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.

The site of SC injections of GENOTROPIN should be rotated daily between the thigh, buttocks and abdomen in order to avoid lipoatrophy.

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

To avoid transmission of disease, GENOTROPIN cartridges must not be used by more than one person.

Acute Critical Illness

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 has

been reported after treatment with pharmacologic amounts of somatropin (see **CONTRAINDICATIONS**). 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.

The effects of GENOTROPIN on recovery were studied in two placebo controlled trials involving 522 critically ill adult patients suffering complications following open heart surgery, abdominal surgery, multiple accidental trauma or acute respiratory failure. Mortality was higher in patients treated with daily doses of 5.3 or 8 mg GENOTROPIN compared to patients receiving placebo, 42% vs. 19%. Based on this information, these types of patients should not be treated with GENOTROPIN.

Carcinogenesis and Mutagenesis

Carcinogenesis studies have not been conducted with rhGH. rhGH is not expected to be carcinogenic in human as the rhGH molecule is identical to the native hormone and the treatment is substitution therapy. No potential mutagenicity of rhGH was revealed in a battery of tests including the Ames test, a test designed to demonstrate chromosome damaging potential, induction of gene mutations in mammalian cells (L5178Y) in vitro and in intact bone marrow cells (rats).

Leukemia has been reported in a small number of growth hormone-deficient patients, treated with growth hormone, including growth hormone of pituitary origin as well as of recombinant DNA origin (somatrem and somatropin). Based on the current evidence, experts cannot conclude that growth hormone therapy is responsible for these occurrences.

Patients treated with growth hormone may have an increased risk of developing neoplasm.

Neoplasms

Patients with pre-existing tumours or with GHD secondary to an intracranial lesion should be examined frequently 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) tumour recurrence or new extracranial tumours. 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 tumours, in particular meningiomas were the most common of these second neoplasms especially in patients treated with radiation to the head. In adults, it is unknown whether there is any relationship between somatropin replacement therapy and CNS tumour recurrence. Patients should be monitored carefully for any malignant transformation of skin lesions.

Closed Epiphyses

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

Treatment of pediatric growth disorders with growth hormones should be discontinued when the patient has reached satisfactory adult height, or when the epiphyses are closed.

Congenital Disorders

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. (see **CONTRAINDICATIONS**).

Prader Willi Syndrome:
Patients with Prader Willi syndrome should be evaluated for signs of upper airway obstruction and sleep apnea before initiation of treatment with somatropin.

If a somatropin treated patient shows signs of upper airway obstruction (including onset of or increased snoring) and /or new onset of sleep apnea, somatropin treatment should be interrupted and the patient should be treated for upper airway obstruction and/or sleep apnea.

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**).

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 patients with Prader-Willi syndrome.

Turner's syndrome:
Patients with Turner syndrome may be at increased risk for development of intracranial hypertension. Therefore, these patients should be evaluated for signs and symptoms of intracranial hypertension and, if present, this condition should be treated before initiation of treatment with somatropin.

Patients with Turner syndrome should be evaluated carefully for otitis media and other ear disorders before and during treatment with somatropin because these patients have an increased risk of ear and hearing disorders (see **ADVERSE REACTIONS**).

Patients with Turner syndrome are at risk for cardiovascular disorders (e.g. hypertension, stroke, and aortic dilatation, aneurysm and dissection) and these patients should be monitored closely for development or worsening of these conditions before and during treatment with somatropin.

Patients with Turner syndrome have an inherently increased risk of developing autoimmune thyroid disease. Therefore, these patients should have periodic thyroid function tests performed and be treated appropriately (see Endocrine and Metabolism).

Note: Skeletal abnormalities including scoliosis are commonly seen in untreated patients with Turner syndrome.

Dependence/Liability
GENOTROPIN is not considered to be a drug that has potential to produce drug dependency. GENOTROPIN does not have stimulant, depressant or hallucinogenic effects on the central nervous system that could be expected to lead to psychological or physical dependency.

Potential for Misuse: Inappropriate use of somatropin by individuals who do not have indications for which somatropin is approved, may result in clinically significant negative health consequences.

Endocrine and Metabolism

Patients with diabetes mellitus or glucose intolerance should be monitored closely during therapy with somatropin, as an adjustment of their antidiabetic therapy may be required.

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

In patients with hypopituitarism standard hormonal replacement therapy should be monitored closely when somatropin therapy is administered.

Somatropin can increase the extrathyroidal conversion of thyroxine (T4) to triiodothyronine (T3) and may unmask incipient hypothyroidism. Because inadequate treatment of hypothyroidism may prevent optimal response to somatropin, thyroid function should be evaluated before starting somatropin therapy and should be monitored regularly during treatment, not less frequently than annually.

Notes Regarding Potential Effects of Somatropin on Glucocorticoid Metabolism: The microsomal enzyme 11β-hydroxysteroid dehydrogenase type 1 (11βHSD-1) is required for conversion of cortisone to its active metabolite, cortisol in hepatic and adipose tissue. Endogenous growth hormone and exogenous somatropin inhibit the activity of 11βHSD-1. Therefore growth hormone deficiency is associated with a relative increase in 11βHSD-1 activity, which in turn results in a relative increase in serum cortisol. Somatropin treatment may inhibit 11βHSD-1, resulting in relative reduction of serum cortisol concentrations.

In addition, somatropin may enhance the activity of CYP3A4, a cytochrome P450 enzyme involved in glucocorticoid catabolism. Therefore, by increasing the activity of CYP3A4, somatropin could potentially decrease serum cortisol concentration. Because somatropin may both inhibit 11βHSD-1 (an enzyme required for production of cortisol) and induce activity of CYP3A4 (an enzyme involved in cortisol breakdown), careful monitoring of serum cortisol concentrations is required for all patients receiving concomitant glucocorticoid and somatropin therapy.

As a consequence of its actions on enzymes involved in cortisol metabolism, somatropin treatment may unmask previously undiagnosed central (secondary) hypoadrenalism, and glucocorticoid replacement may be required. In addition, patients treated with glucocorticoids for previously diagnosed hypoadrenalism (primary or secondary) may require adjustments of their maintenance or stress doses following initiation of somatropin treatment; this may be especially true for patients treated with cortisone acetate and prednisone, because conversion of these drugs to their biologically active metabolites is dependent on the activity of 11βHSD-1 (see **Monitoring and Laboratory Tests**).

Fluid Retention

Fluid retention during somatropin replacement therapy in adults may occur. Clinical manifestations of fluid retention are usually transient and dose dependent.

Immune

Local allergic reactions:

Patients receiving somatropin treatment may experience redness, swelling, pain, inflammation, or itching at the site of injection (see **ADVERSE REACTIONS**).

Most of these minor reactions usually resolve in a few days to a few weeks. Such reactions may occur if the injection is given incorrectly (irritants in the skin cleansing agent or poor injection technique), or if the patient is allergic to somatropin or any non-medicinal ingredient (see **CONTRAINDICATIONS**).

Rarely, subcutaneous administration of somatropin can result in lipoatrophy or lipohypertrophy. Regular rotation of the injection site may help reduce or prevent these reactions.

Patients should be advised to consult their doctor if they notice any of the conditions described above.

On rare occasions, injection site reactions may require discontinuation of somatropin therapy.

Systemic allergic reactions:

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.

These reactions may be characterized by a generalized rash (with pruritus), shortness of breath, wheezing, angioneurotic edema and drop in blood pressure (see **ADVERSE REACTIONS**).

Severe cases of generalized allergy including anaphylactic reaction may be life threatening (see **CONTRAINDICATIONS**).

If any serious hypersensitivity or allergic reaction occurs, somatropin therapy should be discontinued immediately and appropriate therapy initiated.

Serious systemic hypersensitivity reactions including anaphylactic reactions and angioedema have been reported with post-marketing use of somatropin products. Patients and caregivers should be informed that such reactions are possible and that prompt medical attention should be sought if an allergic reaction occurs (see **CONTRAINDICATIONS**).

Antibody production:

A small percentage of patients treated with somatropin may develop antibodies during treatment that could potentially reduce treatment response (see **ADVERSE REACTIONS**).

Patients who have demonstrated an allergic reaction to other somatropin products may demonstrate an allergic reaction to GENOTROPIN.

Intracranial Hypertension

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

Musculoskeletal

Musculoskeletal discomfort (pain, swelling and/or stiffness) may occur during treatment with somatropin (see **ADVERSE REACTIONS**). These symptoms may resolve spontaneously, with analgesic therapy, or after reducing the dosage (see **DOSAGE AND ADMINISTRATION**).

Swelling of the hands and feet may occur during treatment with somatropin and may lead to carpal tunnel syndrome, which may be improved by decreasing the dosage of somatropin.

Somatropin has not been shown to increase the occurrence of scoliosis. However, progression of pre existing scoliosis can occur in pediatric patients who experience rapid growth. Therefore, because somatropin increases growth rate, patients with a history of scoliosis who are treated with somatropin should be monitored for progression of scoliosis.

Slipped capital femoral epiphysis may occur more frequently in patients with endocrine disorders (including pediatric growth hormone deficiency, Turner syndrome and hypothyroidism) 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 (see **Monitoring and Laboratory Tests**).

Pancreatitis

Cases of pancreatitis have been reported rarely in children and adults receiving somatropin treatment, with some evidence supporting a greater risk in children compared with adults. Pancreatitis should be considered in any somatropin treated patients, especially a child, who develops persistent severe abdominal pain

Renal/Hepatic/Biliary/Pancreatic Impairments

Somatropin doses may need to be adjusted in patients with renal and/or hepatic and/or biliary and/or pancreatic impairments.

Reproduction Studies

No adequate and well-controlled clinical studies with GENOTROPIN on reproductive function have been performed (see **Special Populations, Pregnant Women**)

Animal reproductive studies in rats and rabbits treated during the period of organogenesis have not given evidence of any harmful effects on the fetus. There are however, no adequate and well-

controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Information for Patients

Patients and/or their caregivers should be informed about potential advantages and disadvantages of GENOTROPIN therapy including the possible side effects. It should be noted that although serious adverse events may be rare, their occurrence needs to be outweighed by the benefits.

If home use is determined to be desirable by the physician, patients should also be offered instruction for use of injection devices, storage, travelling and other pertinent information. (see **CONSUMER INFORMATION**, INSTRUCTION **FOR USE**).

Special Populations

Pregnant Women:
There are no adequate and well controlled studies of GENOTROPIN treatment in pregnant women. Therefore, the safety of GENOTROPIN has not been established in this subpopulation. It is not known whether GENOTROPIN can cause fetal harm when administered to a pregnant woman. GENOTROPIN should be given to a pregnant woman only if the benefits clearly outweigh the risks and only under medical supervision.

Female patients should be advised to inform their doctor if they are, or become pregnant, or are contemplating pregnancy.

Nursing Women:
There is no experimental data available that suggests whether peptide hormones, such as growth hormone, pass over into the breast milk but absorption in the gastrointestinal tract of the infant of intact protein is extremely unlikely.

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

Pediatric Patients: (see **INDICATIONS AND CLINICAL USE**)

Children who have endocrine disorders, including growth hormone deficiency, may develop slipped capital femoral epiphyses more frequently than children in the general population. Any pediatric patient with onset of a limp during somatropin therapy should be evaluated.

Note: Some of the height gain obtained with somatropin treatment may be lost if treatment is stopped before final height is reached.

Turner Syndrome: see **Congenital Disorders**.

Idiopathic Short Stature: Other medical reasons or treatments that could explain growth disturbance should be ruled out before starting GENOTROPIN treatment for children with idiopathic short stature.

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

Small for Gestational Age: In short children born small for gestational age (SGA) other medical reasons or treatments that could explain growth disturbance should be ruled out before starting treatment with somatropin (GENOTROPIN). Experience with SGA patients with Silver-Russell syndrome is limited, as is experience in initiating treatment in SGA patients near onset of puberty.

In short children born SGA, it is recommended that IGF-I concentration should be measured before initiation of treatment and monitored every 6 months thereafter. If on repeated measurements IGF-I concentrations exceed +2 SD compared to references for age and pubertal status, the IGF-I/IGFBP-3 ratio could be taken into account to consider dose adjustment.

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

Experience with prolonged treatment in adults is limited. Adverse events such as peripheral edema, myalgia, arthralgia, and paresthesiae have been reported during post-marketing studies (see **ADVERSE REACTIONS**).

Growth hormone deficiency in the adult is a lifelong condition and should be treated accordingly. Experience with patients over sixty years of age is limited.

Note: Based on assessment of clinical trial data, post-marketing data, and spontaneous reports carpal tunnel syndrome appears to occur more frequently in patients over 40 years of age than in younger patients. In almost half of the reported cases the recommended maximum somatropin dose had been exceeded. In the majority of cases, the condition resolved spontaneously or with a decrease in dosage, interruption of treatment, or discontinuation of treatment. The maximum recommended dosage should not be exceeded.

Geriatrics:
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.

Monitoring and Laboratory Tests

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

Adults: Adult patients, during GH treatment, should be monitored at 1- to 2-month intervals during dose titration and every 6 months thereafter with clinical assessment, evaluation for adverse effects,

IGF-I levels, and other parameters of GH response. Other laboratory testing should include a lipid profile and a fasting glucose. These should be assessed annually.

Patients with an intra- or extra-cranial neoplasm in remission who are receiving treatment with somatropin should be examined carefully and at regular intervals by the physician. In case of persistent edema or severe paraesthesia the dosage should be decreased in order to avoid the development of carpal tunnel syndrome (see **ADVERSE REACTIONS**).

Children:
Children, during GH treatment, should be monitored every 3 to 6 months with measurement of IGF-1/IGFBP-3 levels and clinical assessment expressed as increase in height (SD per year) and change in height velocity.

Bone age should be monitored periodically during somatropin administration.

Patients with an intra- or extra-cranial neoplasm in remission who are receiving treatment with somatropin should be examined carefully and at regular intervals by the physician.

In short children born SGA, it is recommended that IGF I concentration be measured before initiation of treatment and monitored every 6 months thereafter. If on repeated measurements IGF-I concentrations exceed +2 SD compared to references for age and pubertal status, the IGF-I/IGFBP-3 ratio could be taken into account to consider dose adjustment.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Patients with growth hormone deficiency are characterized by extracellular volume deficit. When treatment with somatropin is started this deficit is rapidly corrected. In adult patients adverse effects related to fluid retention, such as peripheral edema, face edema, stiffness in the extremities, arthralgia, myalgia and paraesthesia are common. In general these adverse effects are mild to moderate, arise within the first months of treatment and subside spontaneously or with dose-reduction. Severe hypersensitivity has been reported in post-marketing use of somatropin products.

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

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 optimised before initiation of GENOTROPIN (somatropin for injection) therapy (see **WARNINGS AND PRECAUTIONS, Endocrine and Metabolism**).

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates

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

Children

Anti-hGH Antibodies

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to GENOTROPIN with the incidence of antibodies to other products may be misleading. In the case of growth hormone, antibodies with binding capacities lower than 2 mg/mL have not been associated with growth attenuation. In a very small number of patients treated with somatropin, when binding capacity was greater than 2 mg/mL, interference with the growth response was 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.

Clinical Trials in children with GHD

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

Clinical Trials in children with SGA

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 preexisting scoliosis, injection site reactions, and self-limited progression of pigmented nevi. IGF-I levels ranged from <20ng/ml to 593 ng/ml.

Anti-GH antibodies were assessed at baseline, 12 and 24 months in Genotropin-treated SGA children enrolled in study 89-041. At 12 months, the study included 27 untreated SGA children, 59 SGA children treated with Genotropin at a dose of 33 µg/kg body weight/day and 51 short SGA children treated with Genotropin at a dose of 67µg/kg body weight/day. At 24 months, the study included 10 untreated SGA children, 62 short SGA children treated with Genotropin at a dose of 33 µg/kg body weight/day (including 9 children who received no treatment during the first 12 months of the study) and 56 SGA children treated with Genotropin at a dose of 67 µg/kg body weight/day (including 8 children who received no treatment during the first 12 months of the study). None of these patients

were determined to be positive for anti-GH antibodies at baseline or at any time during the course of the 24 months of the study.

TABLE 1: ADVERSE EVENTS REPORTED IN ≥ 1% OF CHILDREN (BASELINE TO MONTH 12) ALL CAUSALITY

Body system / Preferred Term	Untreated N=76	0.033 mg/kg/day N=105	0.067 mg/kg/day N=117	0.1 mg/kg/day N=19
	n(%)	n(%)	n(%)	n(%)
Skin & Appendage				
Naevus	0	0	1(0.9)	2(10.5)
Nail disorder	0	1(1.0)	0	0
Rash erythematous	0	1(1.0)	0	0
Skin disorder	0	1(1.0)	0	0
Urticaria acute	0	1(1.0)	0	0
Musculoskeletal				
Fracture	0	1(1.0)	1(0.9)	0
Skeletal malformation	0	0	0	1(5.3)
Tooth malformation	0	1(1.0)	0	0
Central & Peripheral Nervous System				
Convulsions	0	1(1.0)	0	0
Dysphonia	0	1(1.0)	0	0
Headache	0	1(1.0)	0	0
Vision				
Strabismus	1(1.3)	0	1(0.9)	0
Hearing & Vestibular system				
Ear disorder nos	0	1(1.0)	1(0.9)	0
Psychiatric				
Nervousness	0	1(1.0)	0	0
Personality disorder	1(1.3)	0	0	1(5.3)
Gastrointestinal				
Abdominal pain	0	0	1(0.9)	0
Anorexia	1(1.3)	2(1.9)	0	0
Anus disorder	1(1.3)	0	0	0
Enteritis	1(1.3)	0	0	0
Gastroenteritis	0	2(1.9)	2(1.7)	0
Hernia nos	1(1.3)	0	1(0.9)	0
Surgical intervention	0	1(1.0)	2(1.7)	0
Vomiting	2(2.6)	0	1(0.9)	0
Metabolism and Nutritional				
Hyperglycaemia	0	1(1.0)	0	0
Extra Cardiac				
Vein distended	0	1(1.0)	0	0
Respiratory Total				
Surgical intervention	1(1.3)	2(1.9)	4(3.4)	1(5.3)
Apnea	0	1(1.0)	0	0
Asthma	2(2.6)	0	3(2.6)	0
Bronchitis	0	5(4.8)	4(3.4)	0
Coughing	2(2.6)	0	4(3.4)	1(5.3)
Epistaxis	1(1.3)	0	0	0
Laryngitis	0	0	1(0.9)	1(5.3)
Pneumonia	0	2(1.9)	2(1.7)	1(5.3)
Rhinitis	1(1.3)	2(1.9)	6(5.1)	1(5.3)
Upper respiratory tract infection	1(1.3)	7(6.7)	7(6.0)	2(10.5)
Red Blood Cell				

Body system / Preferred Term	Untreated N=76	0.033 mg/kg/day N=105	0.067 mg/kg/day N=117	0.1 mg/kg/day N=19
	n(%)	n(%)	n(%)	n(%)
Anemia	1(1.3)	0	0	0
White Cell				
Lymphadenopathy	1(1.3)	0	0	0
Platelet/Bleed				
Purpura thrombocytopenic	0	1(1.0)	0	0
Thrombocytopenia	0	1(1.0)	0	0
Reproductive-Male				
Testis disorder	1(1.3)	1(1.0)	0	0
General Total				
Surgical intervention	0	1(1.0)	2(1.7)	0
Accident	0	0	0	1(5.3)
Allergic reaction	0	1(1.0)	0	0
Allergy	2(2.6)	0	1(0.9)	0
Fever	2(2.6)	0	1(0.9)	1(5.3)
Influenza-like symptoms	0	0	2(1.7)	0
Application Site				
Injection site reaction	0	1(1.0)	0	0
Tympanic membrane perforation	0	1(1.0)	0	0
Resistance Mechanism				
Herpes zoster	0	1(1.0)	1(0.9)	0
Infection	0	3(2.9)	3(2.6)	0
Infection bacterial	1(1.3)	3(2.9)	0	0
Infection fungal	0	1(1.0)	0	0
Infection viral	6(7.9)	7(6.7)	8(6.8)	0
Otitis media	1(1.3)	8(7.6)	8(6.8)	0
Pharyngitis	6(7.9)	5(4.8)	5(4.3)	0

Less Common Clinical Trial Adverse Drug Reactions (Baseline to Month 12)

Clinical trial adverse drug reactions with a frequency of less than 1% are presented in the following listing:

Skin & Appendage disorders: *eczema*
Musculoskeletal disorders: *bone development abnormal, spine malformation*
Central and Peripheral nervous system disorders: a*taxia*
Psychiatric disorders: *aggressive reaction, concentration impaired*
Gastrointestinal disorders: *abdominal pain, malabsorption*
Endocrine disorders: *gynaecomastia, puberty precocious*
Respiratory disorders: *sinusitis*
Urinary disorders: *dysuria*
General disorders: *hepatomegaly*

TABLE 2: ADVERSE EVENTS REPORTED IN ≥ 1% OF CHILDREN (12 TO 24 MONTH) ALL CAUSALITY

Body system / Preferred Term	Untreated N=53	0.033 mg/kg/day N=106	0.067 mg/kg/day N=118	0.1 mg/kg/day N=19
	n(%)	n(%)	n(%)	n(%)
Skin & Appendage				
Eczema	0	1(0.9)	2(1.7)	0
Skin discolouration	0	0	2(1.7)	0
Musculoskeletal				
Osteomyelitis	0	0	0	1(5.3)
Central & Peripheral Nervous System				

Body system / Preferred Term	Untreated N=53	0.033 mg/kg/day N=106	0.067 mg/kg/day N=118	0.1 mg/kg/day N=19
	n(%)	n(%)	n(%)	n(%)
Convulsions	0	0	0	1(5.3)
Vision				
Myopia	0	0	1(0.8)	2(10.5)
Strabismus	0	0	0	1(5.3)
Vision abnormal	1(1.9)	0	0	0
Psychiatric				
Agitation	0	0	2(1.7)	0
Gastrointestinal				
Gastroenteritis	2(3.8)	1(0.9)	2(1.7)	0
Surgical intervention	1(1.9)	2(1.9)	4(3.4)	0
Respiratory				
Surgical intervention	0	4(3.8)	3(2.5)	1(5.3)
Asthma	0	2(1.9)	2(1.7)	0
Bronchitis	0	3(2.8)	3(2.5)	1(5.3)
Coughing	1(1.9)	4(3.8)	2(1.7)	0
Pneumonia	1(1.9)	1(0.9)	1(0.8)	1(5.3)
Rhinitis	1(1.9)	4(3.8)	4(3.4)	1(5.3)
Sinusitis	0	0	0	1(5.3)
Upper respiratory tract infection	2(3.8)	5(4.7)	2(1.7)	0
Urinary				
Urinary incontinence	1(1.9)	0	0	0
General				
Surgical intervention	2(3.8)	3(2.8)	5(4.2)	1(5.3)
Allergic reaction	1(1.9)	1(0.9)	0	0
Allergy	1(1.9)	1(0.9)	3(2.5)	0
Fever	0	1(0.9)	2(1.7)	0
Influenza-like symptoms	0	2(1.9)	4(3.4)	1(5.3)
Edema pharynx	1(1.9)	0	0	0
Pain	2(3.8)	0	1(0.8)	0
Resistance Mechanism				
Balanoposthitis	0	0	0	1(5.3)
Herpes simplex	0	1(0.9)	0	1(5.3)
Infection	0	1(0.9)	2(1.7)	0
Infection bacterial	2(3.8)	3(2.8)	0	0
Infection viral	3(5.7)	13(12.3)	5(4.2)	0
Otitis media	1(1.9)	7(6.6)	5(4.2)	4(21.1)
Pharyngitis	2(3.8)	8(7.5)	8(6.8)	0

Less Common Clinical Trial Adverse Drug Reactions (12 to 24 Month)

Clinical trial adverse drug reactions with a frequency of less than 1% are presented in the following listing:

Skin & Appendage disorders: *acne, nail disorder, pruritus, skin dry, sweating increased, urticaria*
Musculoskeletal disorders: *arthralgia, fracture, spine malformation*
Central and Peripheral nervous system disorders: *absences, headaches*
Vision: *conjunctivitis*
Hearing and Vestibular system disorders: *earache*
Gastrointestinal disorders: *abdominal pain, anorexia, enteritis*
Metabolism and nutritional system disorders: *hypoglycemia*
Endocrine disorders: *puberty precocious*
Extra cardiac: *vein distended*
Respiratory disorders: *thyroid adenoma*

Red blood cell: *anemia*
White blood cell: *lymphadenopathy*
Platelet/bleed disorder: *purpura, thrombocytopenia*
Urinary disorders: *cystitis, urinary tract infection, urogenital malformation*
Neoplasm disorder: *neoplasm nos*
General disorders: *accident*

TABLE 3: MOST FREQUENT ADVERSE EVENTS (REPORTED IN ≥1% OF CHILDREN TREATED WITH SOMATROPIN CONTINUOUSLY UP TO MONTH 72) –0-72 POPULATION

Body system / Preferred Term	0.033 mg/kg/day N=37	0.067 mg/kg/day N=25	Total N=62
	n(%)	n(%)	n(%)
Skin & Appendage			
Angioedema	1(2.7)	0	1(1.6)
Eczema	1(2.7)	0	1(1.6)
Fistula incomplete	0	1(4.0)	1(1.6)
Nail disorder	1(2.7)	0	1(1.6)
Pruritus	0	1(4.0)	1(1.6)
Rash erythematous	1(2.7)	0	1(1.6)
Skin disorder	3(8.1)	0	3(4.8)
Skin exfoliation	0	1(4.0)	1(1.6)
Sweating increased	1(2.7)	0	1(1.6)
Urticaria	1(2.7)	1(4.0)	2(3.2)
Verruca	0	1(4.0)	1(1.6)
Musculo-Skeletal			
Arthrosis	1(2.7)	0	1(1.6)
Fracture	3(8.1)	1(4.0)	4(6.5)
Joint malformation	1(2.7)	0	1(1.6)
Spine malformation	1(2.7)	0	1(1.6)
Tooth malformation	1(2.7)	0	1(1.6)
Central & Peripheral Nervous System			
Absences	1(2.7)	0	1(1.6)
Headache	2(5.4)	0	2(3.2)
Hyperkinesia	0	2(8.0)	2(3.2)
Muscle contractions involuntary	0	1(4.0)	1(1.6)
Neuritis	1(2.7)	0	1(1.6)
Paralysis	0	1(4.0)	1(1.6)
Vision			
Conjunctivitis	1(2.7)	1(4.0)	2(3.2)
Hearing & Vestibular System			
Ear disorder nos	1(2.7)	1(4.0)	2(3.2)
Earache	1(2.7)	0	1(1.6)
Psychiatric			
Concentration impaired	1(2.7)	0	1(1.6)
Thinking abnormal	0	1(4.0)	1(1.6)
Gastro-Intestinal			
Abdominal pain	3(8.1)	1(4.0)	4(6.5)
Anorexia	1(2.7)	0	1(1.6)
Diarrhoea	1(2.7)	0	1(1.6)
Enteritis	1(2.7)	0	1(1.6)
Gastroenteritis	4(10.8)	6(24.0)	10(16.1)
Hernia nos	1(2.7)	0	1(1.6)
Intestinal obstruction	1(2.7)	0	1(1.6)

Body system / Preferred Term	0.033 mg/kg/day N=37	0.067 mg/kg/day N=25	Total N=62
	n(%)	n(%)	n(%)
Stomatitis aphthous	1(2.7)	0	1(1.6)
Surgical intervention	1(2.7)	2(8.0)	3(4.8)
Tooth disorder	1(2.7)	0	1(1.6)
Vomiting	1(2.7)	0	1(1.6)
Metabolic & Nutritional			
Hypoglycaemia	0	1(4.0)	1(1.6)
Endocrine			
Osteomalacia	0	1(4.0)	1(1.6)
Puberty precocious	1(2.7)	1(4.0)	2(3.2)
Respiratory			
Surgical intervention	7(18.9)	4(16.0)	11(17.7)
Asthma	1(2.7)	1(4.0)	2(3.2)
Bronchitis	4(10.8)	5(20.0)	9(14.5)
Coughing	5(13.5)	2(8.0)	7(11.3)
Laryngitis	1(2.7)	1(4.0)	2(3.2)
Pneumonia	2(5.4)	1(4.0)	3(4.8)
Rhinitis	13(35.1)	6(24.0)	19(30.6)
Sinusitis	2(5.4)	0	2(3.2)
Upper respiratory tract infection	9(24.3)	9(36.0)	18(29.0)
Red blood cell			
Anaemia	0	1(4.0)	1(1.6)
White cell			
Lymphadenopathy	1(2.7)	1(4.0)	2(3.2)
Platelet/Bleed			
Haematoma	1(2.7)	0	1(1.6)
Urinary			
Cystitis	1(2.7)	0	1(1.6)
Urinary incontinence	1(2.7)	1(4.0)	2(3.2)
Urinary tract infection	0	1(4.0)	1(1.6)
Urogenital malformation	1(2.7)	0	1(1.6)
Reproductive-Male			
Penis disorder	0	1(4.0)	1(1.6)
Testis disorder	1(2.7)	0	1(1.6)
Neoplasms			
Neoplasm nos	1(2.7)	0	1(1.6)
General			
Surgical intervention	0	3(12.0)	3(4.8)
Allergic reaction	3(8.1)	0	3(4.8)
Allergy	2(5.4)	0	2(3.2)
Deviating laboratory value	0	1(4.0)	1(1.6)
Fatigue	1(2.7)	0	1(1.6)
Fever	1(2.7)	2(8.0)	3(4.8)
Hepatomegaly	0	1(4.0)	1(1.6)
Hypothermia	1(2.7)	0	1(1.6)
Inflammatory reaction nos	0	1(4.0)	1(1.6)
Influenza-like symptoms	2(5.4)	2(8.0)	4(6.5)
Pain	1(2.7)	0	1(1.6)
Application Site			
Injection site atrophy	0	1(4.0)	1(1.6)
Injection site fibrosis	0	1(4.0)	1(1.6)
Injection site reaction	0	1(4.0)	1(1.6)

Body system / Preferred Term	0.033 mg/kg/day N=37	0.067 mg/kg/day N=25	Total N=62
	n(%)	n(%)	n(%)
Otitis externa	0	1(4.0)	1(1.6)
Resistance Mechanism			
Abscess	0	1(4.0)	1(1.6)
Herpes ocular	0	1(4.0)	1(1.6)
Herpes simplex	2(5.4)	1(4.0)	3(4.8)
Infection	5(13.5)	6(24.0)	11(17.7)
Infection bacterial	6(16.2)	0	6(9.7)
Infection fungal	1(2.7)	0	1(1.6)
Infection viral	14(37.8)	3(12.0)	17(27.4)
Otitis media	9(24.3)	8(32.0)	17(27.4)
Pharyngitis	12(32.4)	7(28.0)	19(30.6)
Sepsis	0	1(4.0)	1(1.6)
Events			
Bite	2(5.4)	0	2(3.2)
Molluscum contagiosa	0	1(4.0)	1(1.6)

Adverse Events Leading to Termination of Treatment

Clinical trial adverse drug reactions that lead to treatment termination are listed below by dose group:
0.033 mg/kg/day: Thrombocytopenic purpura
0.067 mg/kg/day: Aggressive reaction, Ataxia, Retinal dystrophy (2 patients)
Discontinuous therapy: Diabetes mellitus, Surgical intervention, Muscle malformation.

Respiratory Adverse Events in children with SGA

In the open- label SGA studies, the percentage of respiratory adverse events for the 3 active treatment groups (16.2% in 0.033 mg/kg/day, 20.5% in 0.067 mg/kg/day and 26.3% in 0.1 mg/kg/day) were higher than in the untreated group (10.5%) between 0 - 12 months. Between 12 - 24 months, the incidence of respiratory events was also higher in the 3 active treatment groups (18.9% in 0.033 mg/kg/day; 13.6% in 0.067 mg/kg/day; 21.1% in 0.1 mg/kg/day) compared to 7.5% in the untreated control group. Respiratory adverse events included mostly upper respiratory tract infections. Adverse events classified as 'resistance mechanism' which included viral infection, otitis media, and pharyngitis occurred at a higher rate in 2 of the active treatment groups (21.9% in 0.033 mg/kg/day; 19.7% in 0.067 mg/kg/day; 0% in 0.1 mg/kg/day) compared to the untreated control group (15.8%) between 0 - 12 months. Between 12 - 24 months, the incidence of resistance mechanism adverse events was higher in all 3 active treatment groups (25.5% in 0.033 mg/kg/day; 16.1% in 0.067 mg/kg/day; 31.6% in 0.1 mg/kg/day) compared to 13.2% in the untreated control group. However, none of the differences among the four study groups were evaluated for statistical significance.

The adverse events most frequently reported for the study periods were: viral infections, otitis media, pharyngitis, upper respiratory tract infections, and rhinitis. Overall, these events were consistent with the pattern of normal childhood illnesses in this age group. No evidence of a dose-related pattern was apparent. There were a higher number of patients in 2 of the somatropin-treated groups (0.033 mg/kg/day, n=105; 0.067 mg/kg/day, n=117) than in the untreated group (n=76); however the highest dose group (0.1 mg/kg/day) had only 19 patients. While, the investigators did not consider these events to be treatment-related, this cannot be ruled out.

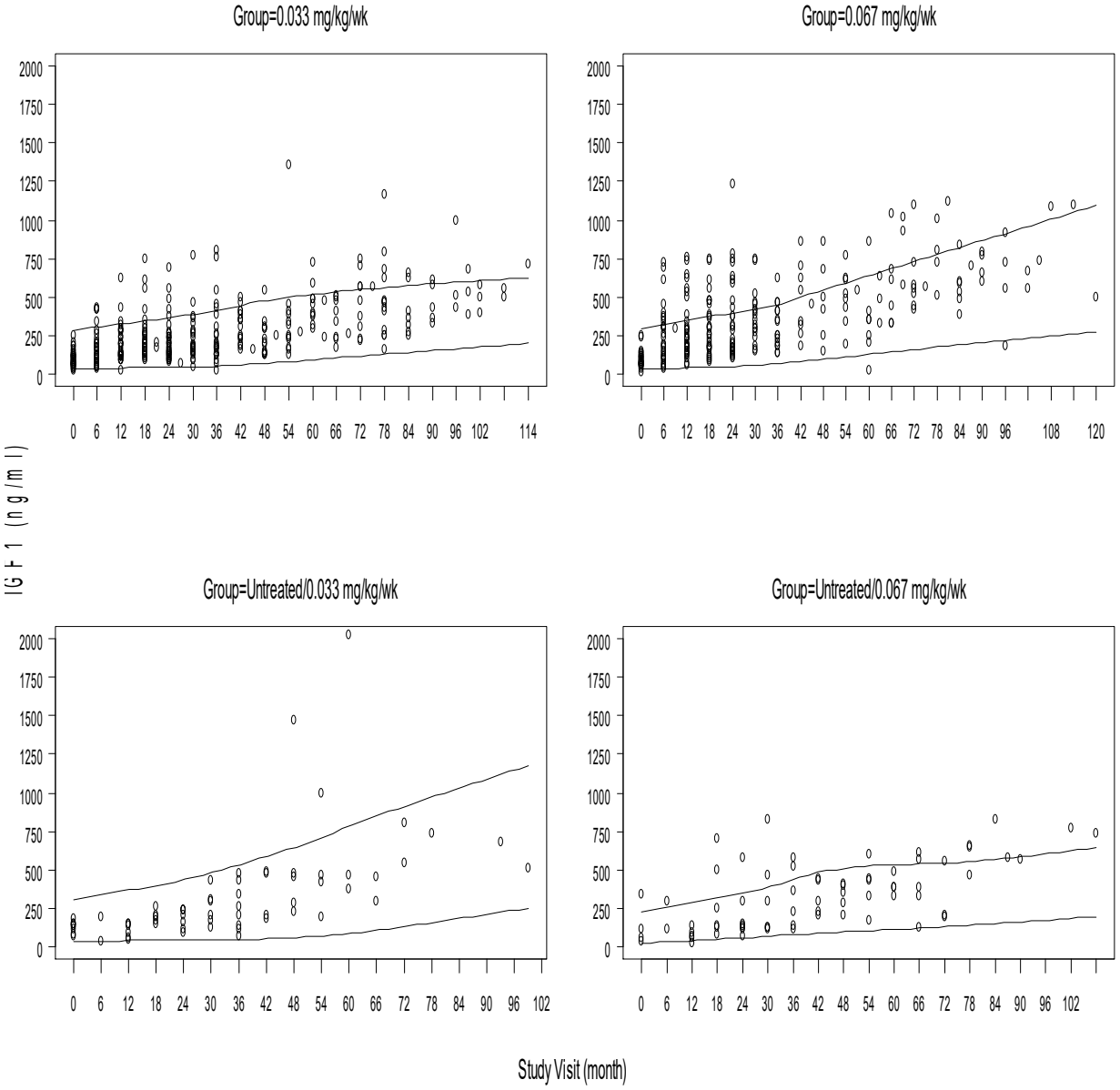
IGF-I levels:

Table 4 summarizes the frequencies of subjects with IGF-I levels below/above or within normal range, organized for all treatment groups side-by-side and across all visits from CTN 89-041 (France). Subject groups Untreated/0.033 mg/kg/wk and Untreated/0.067 mg/kg/wk include subjects who served as untreated controls for 12 months or longer, and were subsequently treated with Genotropin 0.033 mg/kg/wk or 0.067 mg/kg/wk, respectively. In figure 1, the solid reference lines were created by averaging individual upper and lower limits of normal ranges across all subjects with observed IGF-I levels at a given time-point. As such, the reference lines are for overall inference, as they represent an approximation of the exact normative values. As can be seen in the various graphs, IGF-1 levels generally ranged from <20ng/ml to 593 ng/ml.

TABLE 4: FREQUENCY OF SUBJECTS WITH IGF-I LEVELS BELOW/ABOVE OR WITHIN NORMAL RANGE FOR ALL TREATMENT GROUPS AND ACROSS ALL VISITS (STUDY 89-041)

Month	Treatment group																							
	0.033 mg/kg/wk						0.067 mg/kg/wk						Untreated/0.033 mg/kg/wk						Untreated/0.067 mg/kg/wk					
	IGF-I status						IGF-I status						IGF-I status						IGF-I status					
	Below		Normal		Above		Below		Normal		Above		Below		Normal		Above		Below		Normal		Above	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
0	1	2.5	38	95.0	1	2.5	1	3.2	30	96.8	-	-	-	-	7	87.5	1	12.5	-	-	4	100.0	-	-
6	-	-	24	85.7	4	14.3	3	11.1	20	74.1	4	14.8	-	-	2	100.0	-	-	-	-	2	100.0	-	-
12	2	5.4	31	83.8	4	10.8	2	5.7	22	62.9	11	31.4	2	33.3	4	66.7	-	-	2	40.0	3	60.0	-	-
18	1	3.4	23	79.3	5	17.2	3	10.7	17	60.7	8	28.6	-	-	4	80.0	1	20.0	-	-	5	83.3	1	16.7
24	4	10.8	27	73.0	6	16.2	3	11.1	14	51.9	10	37.0	1	14.3	6	85.7	-	-	-	-	6	85.7	1	14.3
30	1	4.3	18	78.3	4	17.4	-	-	12	70.6	5	29.4	-	-	6	100.0	-	-	-	-	5	83.3	1	16.7
36	3	11.5	17	65.4	6	23.1	-	-	10	66.7	5	33.3	1	12.5	6	75.0	1	12.5	-	-	6	100.0	-	-
42	-	-	8	53.3	7	46.7	-	-	3	37.5	5	62.5	-	-	4	100.0	-	-	-	-	3	60.0	2	40.0
48	1	7.1	11	78.6	2	14.3	-	-	4	66.7	2	33.3	-	-	3	60.0	2	40.0	-	-	4	80.0	1	20.0
54	1	8.3	8	66.7	3	25.0	-	-	5	62.5	3	37.5	-	-	2	40.0	3	60.0	-	-	4	80.0	1	20.0
60	-	-	6	60.0	4	40.0	1	14.3	5	71.4	1	14.3	-	-	2	66.7	1	33.3	-	-	2	50.0	2	50.0
66	-	-	6	75.0	2	25.0	-	-	5	83.3	1	16.7	-	-	2	66.7	1	33.3	-	-	3	60.0	2	40.0
72	-	-	6	66.7	3	33.3	-	-	5	62.5	3	37.5	-	-	2	100.0	-	-	-	-	2	66.7	1	33.3

FIGURE 1: SGA 89-041: IGF-I VALUES BY STUDY MONTH



Clinical Trials in children with Turner Syndrome

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 one study in children with TS, none of the 42 patients discontinued from the study early while in the second study, none of the patients discontinued before 18 months.

TABLE 5: SUMMARY OF ADVERSE EVENTS (AE) THAT OCCURRED IN AT LEAST 1 PATIENT IN STUDY 87-055 - ALL CAUSALITY

WHO Dictionary Term	**Genotropin** N= 22	**Genotropin plus ethinyloestradiol** N=20
Joint Pain	4 (18.2%)	3 (15.0%)
Epilepsy	1 (4.5%)	1 (5.0%)
Sinusitis	1 (4.5%)	1(5.0%)
Cellulitis	1 (4.5%)	0
Urinary Tract Infection	0	1 (5.0%)
Dysfunctional voiding	0	1 (5.0%)
Menarche	1 (4.5%)	0
Varicella	1 (4.5%)	0
Measles	1 (4.5%)	0
Herpes Zoster	1 (4.5%)	0
Total AEs	9(41.0%)	6 (30.0%)

TABLE 6: SUMMARY OF ADVERSE EVENTS THAT OCCURRED IN AT LEAST 1 PATIENT IN STUDY 86-092 – ALL CAUSALITY

WHO dictionary term	Genotropin N=17	Genotropin + oxandrolone N=17
Skin and appendage disorders		
Furonculosis	1 (5.9%)	0
Loss of hair	1 (5.9%)	0
Eczema	0	1 (5.9%)
Musculo-skeletal system disorders		
Joint Pain	1 (5.9%)	1 (5.9%)
Radius fracture	0	1 (5.9%)
Hearing and vestibular disorders		
Tympanic membrane	1 (5.9%)	0
Psychiatric disorders		
Nervousness	1 (5.9%)	0
Increased Appetite	0	2 (11.8 %)
Liver and biliary system		
Hepatitis A	1 (5.9%)	0
Hepatic injury	0	1 (5.9%)
Metabolic and nutritional disorders		
Insulin value increased	0	1 (5.9%)
Endocrine disorders		
Hypothyroidism	1 (5.9%)	0
Thyroiditis	1 (5.9%)	0
Vascular (extra cardiac) disorders		
Flushing	1 (5.9%)	0
Respiratory Infections		
Otitis	3 (17.6%)	1 (5.9%)
Tonsillitis	2 (11.8%)	3 (17.6%)
Rhinitis	1	0
Sinusitis	2 (11.8%)	1 (5.9%)
Influenza	1 (5.9%)	4 (23.5%)
Pneumonia	0	1 (5.9%)
Bronchitis	0	2 (11.8 %)
White cell and res disorders		
Neutropenia, chronic	1 (5.9%)	0
Platelet, bleeding and clotting disorders		
Epistaxis	2 (11.8%)	0
Hematoma	0	1 (5.9%)
Urinary system disorders		
Urinary Tract Infection	3 (17.6%)	0
Hematuria	1 (5.9%)	0
Enuresis	0	1 (5.9%)
Reproductive disorders		
Metrorrhagia	0	1 (5.9%)
Leukorrhea	0	1 (5.9%)
Spotting	0	1 (5.9%)
Hemorrhage	0	1 (5.9%)
Vaginitis	0	1 (5.9%)
Body as a whole – General disorders		
Car accident	0	1 (5.9%)
Fatigue	0	1 (5.9%)
Voice alteration	0	1 (5.9%)

Clinical Trials in children with Turner's syndrome

In one study with patients with TS, respiratory infections (otitis, tonsillitis, sinusitis, influenza, bronchitis) represented the majority of adverse events in children with TS with eight patients in the Genotropin group and 11 patients in the Genotropin and oxandrolone groups. The instances of the respiratory infections were assessed as unrelated to study drug. No patient discontinued treatment due to a treatment related adverse event. Younger patients, including patients with TS, treated or untreated, are known to have generally greater incidence of otitis media and ear problems.

In a second study, one patient experienced sinusitis, orbital cellulitis and grand mal seizure. These events were considered to be unlikely related to the study drug as per the investigator and they were also low in frequency.

Clinical Trials in children with Idiopathic Short Stature

In two open-label clinical studies with GENOTROPIN in pediatric patients with ISS, the most commonly encountered adverse events include upper respiratory tract infections, influenza, tonsillitis, nasopharyngitis, gastroenteritis, headaches, increased appetite, pyrexia, fracture, altered mood, and arthralgia. In one of the two studies, during GENOTROPIN treatment, the mean IGF-1 standard deviation (SD) scores were maintained in the normal range. IGF-1 SD scores above +2 SD were observed as follows: 1 subject (3%), 10 subjects (30%) and 16 subjects (38%) in the untreated control, 0. 23 and the 0.47 mg/kg/week groups, respectively, had at least one measurement; while 0 subjects (0%), 2 subjects (7%) and 6 subjects (14%) had two or more consecutive IGF-1 measurements above +2 SD.

TABLE 7: INCIDENCE OF TREATMENT-EMERGENT ADVERSE EVENTS THAT OCCURRED IN AT LEAST 1 PATIENT

	Prepubertal			Pubertal		Genotropin[a]	Untreated
	0.033 mg/kg/day N = 47	0.067 mg/kg/day N = 49	Untreated Controls N = 46	0.067 mg/kg/day N = 16	Untreated Controls N = 15	0.033 and 0.067 mg/kg/day N = 112	Controls[b] N = 61
Body system / Preferred Term	**n(%)**	**n(%)**	**n(%)**	**n(%)**	**n(%)**	**n(%)**	**n(%)**
Blood and lymphatic system disorders							
Anaemia	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Eosinophilia	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Iron deficiency anaemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.7)	0 (0.0)	1 (1.6)
Lymphadenopathy	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Mononucleosis syndrome	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Congenital, familial and genetic disorders							
Epidermal naevus	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Pigmented naevus	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Skeleton dysplasia	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Ear and labyrinth disorders							
Motion sickness	0 (0.0)	0 (0.0)	1 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)
Vertigo	0 (0.0)	0 (0.0)	1 (2.2)	1 (6.3)	0 (0.0)	1 (0.9)	1 (1.6)
Endocrine disorders							
Delayed puberty	0 (0.0)	0 (0.0)	4 (8.7)	0 (0.0)	0 (0.0)	0 (0.0)	4 (6.6)
Goitre	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Pituitary cyst	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Precocious puberty	0 (0.0)	0 (0.0)	1 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)
Thyroid disorder	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Eye disorders							
Astigmatism	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Conjunctivitis	1 (2.1)	1 (2.0)	1 (2.2)	1 (6.3)	0 (0.0)	3 (2.7)	1 (1.6)
Conjunctivitis allergic	1 (2.1)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.8)	0 (0.0)
Eye inflammation	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	1 (0.9)	0 (0.0)
Eye redness	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	1 (0.9)	0 (0.0)
Visual disturbance	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)

	Prepubertal			Pubertal		Genotropin[a] 0.033 and 0.067 mg/kg/day N = 112	Untreated Controls[b] N = 61
	0.033 mg/kg/day N = 47	0.067 mg/kg/day N = 49	Untreated Controls N = 46	0.067 mg/kg/day N = 16	Untreated Controls N = 15		
Body system / Preferred Term	**n(%)**	**n(%)**	**n(%)**	**n(%)**	**n(%)**	**n(%)**	**n(%)**
Gastrointestinal disorders							
Abdominal pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.7)	0 (0.0)	1 (1.6)
Abdominal pain upper	1 (2.1)	4 (8.2)	0 (0.0)	0 (0.0)	0 (0.0)	5 (4.5)	0 (0.0)
Constipation	2 (4.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.8)	0 (0.0)
Nausea	0 (0.0)	2 (4.1)	1 (2.2)	0 (0.0)	0 (0.0)	2 (1.8)	1 (1.6)
Tooth disorder	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Vomiting	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
General disorders and administration site conditions							
Chest discomfort	1 (2.1)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.8)	0 (0.0)
Chest pain	1 (2.1)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.8)	0 (0.0)
Disease recurrence	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Fatigue	1 (2.1)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.8)	0 (0.0)
Hunger	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	1 (0.9)	0 (0.0)
Edema peripheral	1 (2.1)	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	2 (1.8)	0 (0.0)
Pain	0 (0.0)	0 (0.0)	1 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)
Pyrexia	8 (17.0)	4 (8.2)	2 (4.3)	1 (6.3)	0 (0.0)	13 (11.6)	2 (3.3)
Thirst	0 (0.0)	2 (4.1)	0 (0.0)	1 (6.3)	0 (0.0)	3 (2.7)	0 (0.0)
Immune system disorders							
Hypersensitivity	1 (2.1)	3 (6.1)	2 (4.3)	0 (0.0)	0 (0.0)	4 (3.6)	2 (3.3)
Seasonal allergy	1 (2.1)	3 (6.1)	1 (2.2)	1 (6.3)	1 (6.7)	5 (4.5)	2 (3.3)
Infections and infestations							
Appendicitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.7)	0 (0.0)	1 (1.6)
Borrelia infection	0 (0.0)	1 (2.0)	1 (2.2)	0 (0.0)	0 (0.0)	1 (0.9)	1 (1.6)
Ear infection	1 (2.1)	3 (6.1)	0 (0.0)	0 (0.0)	0 (0.0)	4 (3.6)	0 (0.0)
Eye infection	1 (2.1)	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	2 (1.8)	0 (0.0)
Gastroenteritis	7 (14.9)	4 (8.2)	0 (0.0)	1 (6.3)	1 (6.7)	12 (10.7)	1 (1.6)
Impetigo	1 (2.1)	2 (4.1)	0 (0.0)	0 (0.0)	0 (0.0)	3 (2.7)	0 (0.0)
Infectious mononucleosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.7)	0 (0.0)	1 (1.6)
Influenza	8 (17.0)	7 (14.3)	2 (4.3)	3 (18.8)	1 (6.7)	18 (16.1)	3 (4.9)
Mycoplasma infection	2 (4.3)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (2.7)	0 (0.0)
Nasopharyngitis	7 (14.9)	5 (10.2)	1 (2.2)	0 (0.0)	0 (0.0)	12 (10.7)	1 (1.6)
Orchitis	0 (0.0)	0 (0.0)	1 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)
Otitis media acute	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Parotitis	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Pertussis	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Pharyngitis	3 (6.4)	0 (0.0)	1 (2.2)	1 (6.3)	0 (0.0)	4 (3.6)	1 (1.6)
Pneumonia	1 (2.1)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.8)	0 (0.0)
Pyelonephritis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.7)	0 (0.0)	1 (1.6)
Respiratory tract infection	0 (0.0)	2 (4.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.8)	0 (0.0)
Rhinitis	1 (2.1)	2 (4.1)	0 (0.0)	0 (0.0)	0 (0.0)	3 (2.7)	0 (0.0)
Scarlet fever	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Sinusitis	0 (0.0)	1 (2.0)	1 (2.2)	0 (0.0)	0 (0.0)	1 (0.9)	1 (1.6)
Streptococcal infection	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Tonsillitis	7 (14.9)	5 (10.2)	2 (4.3)	1 (6.3)	1 (6.7)	13 (11.6)	3 (4.9)
Upper respiratory tract infection	14 (29.8)	20 (40.8)	5 (10.9)	2 (12.5)	2 (13.3)	36 (32.1)	7 (11.5)
Urinary tract infection	0 (0.0)	0 (0.0)	1 (2.2)	1 (6.3)	0 (0.0)	1 (0.9)	1 (1.6)
Varicella	1 (2.1)	0 (0.0)	2 (4.3)	1 (6.3)	0 (0.0)	2 (1.8)	2 (3.3)
Viral infection	0 (0.0)	0 (0.0)	0 (0.0)	2 (12.5)	0 (0.0)	2 (1.8)	0 (0.0)
Injury, poisoning and procedural complications							
Ankle fracture	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Clavicle fracture	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Concussion	2 (4.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.8)	0 (0.0)
Contusion	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Eye injury	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Fall	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Femur fracture	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Hand fracture	1 (2.1)	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	2 (1.8)	0 (0.0)
Head injury	0 (0.0)	0 (0.0)	1 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)
Joint dislocation	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.7)	1 (0.9)	1 (1.6)
Joint injury	2 (4.3)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (2.7)	0 (0.0)
Limb injury	1 (2.1)	1 (2.0)	1 (2.2)	0 (0.0)	1 (6.7)	2 (1.8)	2 (3.3)

	Prepubertal			Pubertal		Genotropin[a] 0.033 and 0.067 mg/kg/day N = 112	Untreated Controls[b] N = 61
	0.033 mg/kg/day N = 47	0.067 mg/kg/day N = 49	Untreated Controls N = 46	0.067 mg/kg/day N = 16	Untreated Controls N = 15		
Body system / Preferred Term	**n(%)**	**n(%)**	**n(%)**	**n(%)**	**n(%)**	**n(%)**	**n(%)**
Lower limb fracture	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Mouth injury	0 (0.0)	0 (0.0)	1 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)
Overdose	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Radius fracture	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Road traffic accident	1 (2.1)	1 (2.0)	1 (2.2)	0 (0.0)	1 (6.7)	2 (1.8)	2 (3.3)
Skull fracture	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.7)	0 (0.0)	1 (1.6)
Tibia fracture	1 (2.1)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.8)	0 (0.0)
Wound	2 (4.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.8)	0 (0.0)
Investigations							
Blood immunoglobulin G decreased	0 (0.0)	0 (0.0)	1 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)
Blood testosterone decreased	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Blood thyroid stimulating hormone decreased	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	1 (6.7)	1 (0.9)	1 (1.6)
Cardiac murmur	0 (0.0)	0 (0.0)	1 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)
Haemoglobin decreased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.7)	0 (0.0)	1 (1.6)
Heart rate irregular	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.7)	0 (0.0)	1 (1.6)
Heart sounds abnormal	0 (0.0)	0 (0.0)	1 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)
Thyroxine decreased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.7)	0 (0.0)	1 (1.6)
Thyroxine free decreased	0 (0.0)	2 (4.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.8)	0 (0.0)
Metabolism and nutrition disorders							
Appetite disorder	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Decreased appetite	2 (4.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.8)	0 (0.0)
Increased appetite	6 (12.8)	5 (10.2)	0 (0.0)	3 (18.8)	0 (0.0)	14 (12.5)	0 (0.0)
Lactose intolerance	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	1 (0.9)	0 (0.0)
Markedly reduced dietary intake	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Musculoskeletal and connective tissue disorders							
Arthralgia	2 (4.3)	5 (10.2)	1 (2.2)	0 (0.0)	1 (6.7)	7 (6.3)	2 (3.3)
Back disorder	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Back pain	0 (0.0)	5 (10.2)	1 (2.2)	0 (0.0)	2 (13.3)	5 (4.5)	3 (4.9)
Jaw disorder	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Limb discomfort	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Lower limb deformity	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Muscle cramp	0 (0.0)	0 (0.0)	1 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)
Neck pain	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Osteochondrosis	0 (0.0)	0 (0.0)	1 (2.2)	1 (6.3)	0 (0.0)	1 (0.9)	1 (1.6)
Pain in extremity	1 (2.1)	3 (6.1)	0 (0.0)	0 (0.0)	0 (0.0)	4 (3.6)	0 (0.0)
Patellofemoral pain syndrome	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Periostitis	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Scoliosis	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	1 (0.9)	0 (0.0)
Tendonitis	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Torticollis	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	1 (0.9)	0 (0.0)
Nervous system disorders							
Disturbance in attention	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Epilepsy	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Facial paresis	0 (0.0)	0 (0.0)	1 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)
Headache	5 (10.6)	9 (18.4)	5 (10.9)	2 (12.5)	0 (0.0)	16 (14.3)	5 (8.2)
Migraine	1 (2.1)	1 (2.0)	1 (2.2)	1 (6.3)	1 (6.7)	3 (2.7)	2 (3.3)
Movement disorder	0 (0.0)	0 (0.0)	1 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)
Nervous system disorder	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Paraesthesia	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	1 (0.9)	0 (0.0)
Petit mal epilepsy	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Psychomotor hyperactivity	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Syncope	2 (4.3)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (2.7)	0 (0.0)
Psychiatric disorders							
Aggression	3 (6.4)	3 (6.1)	0 (0.0)	0 (0.0)	0 (0.0)	6 (5.4)	0 (0.0)
Apathy	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Attention deficit/hyperactivity disorder	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Depressed mood	1 (2.1)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.8)	0 (0.0)
Depression	0 (0.0)	0 (0.0)	1 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)
Dissociative identity disorder	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)

	Prepubertal			Pubertal		Genotropin[a] 0.033 and 0.067 mg/kg/day N = 112	Untreated Controls[b] N = 61
	0.033 mg/kg/day N = 47	0.067 mg/kg/day N = 49	Untreated Controls N = 46	0.067 mg/kg/day N = 16	Untreated Controls N = 15		
Body system / Preferred Term	**n(%)**	**n(%)**	**n(%)**	**n(%)**	**n(%)**	**n(%)**	**n(%)**
Eating disorder	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Elevated mood	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Euphoric mood	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Impulse-control disorder	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Irritability	2 (4.3)	2 (4.1)	0 (0.0)	0 (0.0)	0 (0.0)	4 (3.6)	0 (0.0)
Mental disorder	1 (2.1)	0 (0.0)	2 (4.3)	0 (0.0)	0 (0.0)	1 (0.9)	2 (3.3)
Mood altered	3 (6.4)	7 (14.3)	0 (0.0)	2 (12.5)	0 (0.0)	12 (10.7)	0 (0.0)
Mood swings	3 (6.4)	3 (6.1)	1 (2.2)	0 (0.0)	0 (0.0)	6 (5.4)	1 (1.6)
Personality change	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
School refusal	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Sleep disorder	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Social phobia	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Stress symptoms	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Renal and urinary disorders							
Calculus bladder	0 (0.0)	0 (0.0)	1 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)
Reproductive system and breast disorders							
Dysmenorrhoea	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.7)	0 (0.0)	1 (1.6)
Gynaecomastia	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Hydrocele	0 (0.0)	1 (2.0)	1 (2.2)	0 (0.0)	0 (0.0)	1 (0.9)	1 (1.6)
Menorrhagia	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Phimosis	1 (2.1)	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	2 (1.8)	0 (0.0)
Testicular torsion	0 (0.0)	1 (2.0)	0 (0.0)	1 (6.3)	0 (0.0)	2 (1.8)	0 (0.0)
Respiratory, thoracic and mediastinal disorders							
Asthma	1 (2.1)	3 (6.1)	2 (4.3)	1 (6.3)	0 (0.0)	5 (4.5)	2 (3.3)
Cough	2 (4.3)	2 (4.1)	1 (2.2)	1 (6.3)	0 (0.0)	5 (4.5)	1 (1.6)
Dyspnoea	1 (2.1)	0 (0.0)	1 (2.2)	0 (0.0)	0 (0.0)	1 (0.9)	1 (1.6)
Nasal congestion	1 (2.1)	2 (4.1)	0 (0.0)	0 (0.0)	0 (0.0)	3 (2.7)	0 (0.0)
Pharyngolaryngeal pain	1 (2.1)	5 (10.2)	2 (4.3)	0 (0.0)	0 (0.0)	6 (5.4)	2 (3.3)
Rhinitis allergic	1 (2.1)	3 (6.1)	0 (0.0)	0 (0.0)	0 (0.0)	4 (3.6)	0 (0.0)
Skin and subcutaneous tissue disorders							
Cafe au lait spots	0 (0.0)	0 (0.0)	1 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)
Dermal cyst	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Dermatitis allergic	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	1 (0.9)	0 (0.0)
Eczema	2 (4.3)	1 (2.0)	1 (2.2)	0 (0.0)	0 (0.0)	3 (2.7)	1 (1.6)
Hyperhidrosis	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Ingrowing nail	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Pigmentation disorder	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	1 (0.9)	0 (0.0)
Prurigo	1 (2.1)	0 (0.0)	1 (2.2)	0 (0.0)	0 (0.0)	1 (0.9)	1 (1.6)
Psoriasis	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Skin disorder	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Urticaria	1 (2.1)	0 (0.0)	2 (4.3)	0 (0.0)	0 (0.0)	1 (0.9)	2 (3.3)
Social circumstances							
Corrective lens user	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Death of parent	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Death of relative	1 (2.1)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.8)	0 (0.0)
Death of sibling	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Divorced parents	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.7)	0 (0.0)	1 (1.6)
Physical assault	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Smoker	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Social problem	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Surgical and medical procedures							
Appendicectomy	1 (2.1)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.8)	0 (0.0)
Brain tumour operation	0 (0.0)	0 (0.0)	1 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)
Ear tube insertion	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Hernia repair	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Meniscus operation	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Skin neoplasm excision	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Surgery	1 (2.1)	0 (0.0)	1 (2.2)	1 (6.3)	0 (0.0)	2 (1.8)	1 (1.6)
Tonsillectomy	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Tooth extraction	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Vascular disorders							

	Prepubertal			Pubertal		Genotropin[a] 0.033 and 0.067 mg/kg/day N = 112	Untreated Controls[b] N = 61
	0.033 mg/kg/day N = 47	0.067 mg/kg/day N = 49	Untreated Controls N = 46	0.067 mg/kg/day N = 16	Untreated Controls N = 15		
Body system / Preferred Term	**n(%)**	**n(%)**	**n(%)**	**n(%)**	**n(%)**	**n(%)**	**n(%)**
Hypertension	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Hypotension	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)

TABLE 8: STUDY TRN 88-080: TREATMENT-RELATED ADVERSE EVENTS BASED ON PROBABLE, POSSIBLE, NOT ASSESSABLE, AND UNKNOWN DEFINITION AND REPORTED IN ≥2% OF GENOTROPIN TREATED SUBJECTS

Adverse Event	Genotropin[a] 0.033 and 0.067 mg/kg/day N = 112		Untreated Controls[b] N = 61		Prepubertal						Pubertal			
					0.033 mg/kg/day N = 47		0.067 mg/kg/day N = 49		Untreated Controls N = 46		0.067 mg/kg/day N = 16		Untreated Controls N = 15	
	n	%	N	%	N	%	n	%	N	%	N	%	n	%
Upper respiratory infection	15	13.4	2	3.3	8	17.0	6	12.2	2	4.3	1	6.3	0	0.0
Increased appetite	14	12.5	0	0.0	6	12.8	5	10.2	0	0.0	3	18.8	0	0.0
Mood altered	11	9.8	0	0.0	3	6.4	6	12.2	0	0.0	2	12.5	0	0.0
Headache	10	8.9	1	1.6	5	10.6	4	8.2	1	2.2	1	6.3	0	0.0
Influenza	9	8.0	0	0.0	5	10.6	3	6.1	0	0.0	1	6.3	0	0.0
Gastroenteritis	6	5.4	0	0.0	3	6.4	3	6.1	0	0.0	0	0.0	0	0.0
Nasopharyngitis	6	5.4	1	1.6	4	8.5	2	4.1	1	2.2	0	0.0	0	0.0
Aggression	5	4.5	0	0.0	3	6.4	2	4.1	0	0.0	0	0.0	0	0.0
Fracture[c]	4	3.6	0	0.0	2	4.2	2	4.1	0	0.0	0	0.0	0	0.0
Pharyngolaryngeal pain	4	3.6	1	1.6	1	2.1	3	6.1	1	2.2	0	0.0	0	0.0
Rhinitis allergic	4	3.6	0	0.0	1	2.1	3	6.1	0	0.0	0	0.0	0	0.0
Mood swings	4	3.6	1	1.6	3	6.4	1	2.0	1	2.2	0	0.0	0	0.0
Ear infection	3	2.7	0	0.0	1	2.1	2	4.1	0	0.0	0	0.0	0	0.0
Tonsillitis	3	2.7	2	3.3	0	0.0	2	4.1	2	4.3	1	6.3	0	0.0
Cough	3	2.7	1	1.6	1	2.1	2	4.1	1	2.2	0	0.0	0	0.0

[a]Includes all Genotropin Treated Subjects in the Safety Analysis Population.
[b]Includes all Untreated Controls in the Safety Analysis Population.
[c]Consists of: ankle fracture (n = 1 Genotropin), clavicle fracture (n = 1 Genotropin), radius fracture (n = 1 Genotropin), tibia fracture (n = 2 Genotropin).

Study 88-080: Adverse Events Leading to Termination of Treatment

Clinical trial adverse drug reactions that lead to treatment termination are listed below:
Dissociative identity disorder, pituitary cyst, mood swings and irritability.

TABLE 9: STUDY CTN 89-050: INCIDENCE (%) OF TREATMENT-EMERGENT ADVERSE EVENTS REPORTED IN ≥ 1% OF PATIENTS

Body system / Preferred Term	Genotropin 0.047 mg/kg/day N = 18		Control group N = 19	
	n	%	N	%
ENDOCRINE DISORDERS				
Hypothyroidism	2	11.1	0	0.0
Infection	3	16.7	1	5.3
EYE DISORDERS				

TABLE 9: STUDY CTN 89-050: INCIDENCE (%) OF TREATMENT-EMERGENT ADVERSE EVENTS REPORTED IN ≥ 1% OF PATIENTS				
Hypermetropia	1	5.6	0	0.0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS				
Influenza like illness	2	11.1	0	0.0
Injection site rash	1	5.6	0	0.0
Pyrexia	1	5.6	0	0.0
INVESTIGATIONS				
Increased alanine aminotransferase	1	5.6	0	0.0
Increased aspartate aminotransferase	1	5.6	0	0.0
Increased blood insulin	1	5.6	0	0.0
Decreased blood thyroid stimulating hormone	1	5.6	0	0.0
Increased blood thyroid stimulating hormone	1	5.6	0	0.0
Increased tri-iodothyronine	1	5.6	0	0.0
Increased blood triglycerides	1	5.6	0	0.0
Eosinophil percentage increased	2	11.1	0	0.0
Decreased oestradiol	1	5.6	0	0.0
METABOLISM AND NUTRITION DISORDERS				
Impaired glucose tolerance	1	5.6	0	0.0
Trace element deficiency	1	5.6	0	0.0
EAR AND LABYRINTH DISORDERS				
Middle ear effusion	1	5.6	0	0.0
GASTROINTESTINAL DISORDERS				
Diarrhoea	1	5.6	1	5.3
Nausea	1	5.6	0	0.0
Umbilical hernia	1	5.6	0	0.0
Vomiting	2	11.1	1	5.3
INFECTIONS AND INFESTATIONS				
Acute tonsillitis	4	22.2	0	0.0
Bronchitis	3	16.7	3	15.8
Ear infection	1	5.6	0	0.0
Febrile infection	2	11.1	1	5.3
Gastroenteritis	2	11.1	1	5.3
Measles	0	0.0	1	5.3
Nasopharyngitis	2	11.1	0	0.0
Otitis media	1	5.6	1	5.3
Otitis media acute	0	0.0	1	5.3
Rhinitis	2	11.1	0	0.0
Rubella	1	5.6	0	0.0
Scarlet fever	1	5.6	1	5.3
Sinusitis	1	5.6	0	0.0
Skin infection	1	5.6	0	0.0
Tonsillitis	3	16.7	0	0.0
INFECTIONS AND INFESTATIONS				
Upper respiratory tract infection	2	11.1	1	5.3
Varicella	0	0.0	1	5.3
Viral infection	2	11.1	0	0.0
Viral upper respiratory tract infection	0	0.0	1	5.3
INJURY, POISONING AND PROCEDURAL COMPLICATIONS				

TABLE 9: STUDY CTN 89-050: INCIDENCE (%) OF TREATMENT-EMERGENT ADVERSE EVENTS REPORTED IN ≥ 1% OF PATIENTS				
Arthropod bite	1	5.6	0	0.0
Concussion	1	5.6	0	0.0
Fall	1	5.6	0	0.0
Foot fracture	1	5.6	0	0.0
Skin injury	1	5.6	0	0.0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS				
Arthralgia	1	5.6	0	0.0
NERVOUS SYSTEM DISORDERS				
Disturbance in attention	1	5.6	0	0.0
Dizziness	1	5.6	0	0.0
Headache	4	22.2	0	0.0
Mental impairment	1	5.6	0	0.0
Petit mal epilepsy	1	5.6	0	0.0
RENAL AND URINARY DISORDERS				
Leukocyturia	1	5.6	0	0.0
REPRODUCTIVE SYSTEM AND BREAST DISORDERS				
Balanitis	0	0.0	1	5.3
Breast induration	1	5.6	0	0.0
Breast swelling	1	5.6	0	0.0
Gynaecomastia	1	5.6	0	0.0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS				
Asthma	0	0.0	1	5.3
Cough	1	5.6	0	0.0
Pharyngolaryngeal pain	1	5.6	0	0.0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS				
Dermatitis allergic	1	5.6	0	0.0
Dermatitis atopic	1	5.6	0	0.0
Eczema	1	5.6	0	0.0
Hyperhidrosis	1	5.6	0	0.0
Neurodermatitis	1	5.6	1	5.3
Pruritus	1	5.6	0	0.0
Psoriasis	1	5.6	0	0.0
SURGICAL AND MEDICAL PROCEDURES				
Adenoidectomy	0	0.0	1	5.3
Adenotonsillectomy	0	0.0	1	5.3
Myringotomy	0	0.0	1	5.3
Nasal polypectomy	0	0.0	1	5.3
Umbilical hernia repair	1	5.6	0	0.0

Clinical Trials in children with Idiopathic Short Stature

In ISS studies, the most frequently encountered respiratory adverse events, seen in ≥5% of subjects, included infections and infestations (upper respiratory tract infections, influenza, tonsillitis, nasopharyngitis).

In the pivotal study, eight of the 15 subjects with upper respiratory infection were in the lower dose Genotropin treatment group (0.033 mg/kg/day; prepubertal) and seven received 0.067 mg/kg/day (six prepubertal and one pubertal).

Influenza occurred in four subjects that received 0.067 mg/kg/day (three prepubertal and one pubertal) and in five subjects that received 0.033 mg/kg/day. Nasopharyngitis was also reported only in prepubertal Genotropin treated subjects (four at 0.033 mg/kg/day and two at 0.067 mg/kg/day).

Adults

Clinical Trials in adults with GHD

Recurrence of pituitary adenoma and of craniopharyngioma were reported in one case each. In these patient categories tumour recurrence is not uncommon, but it is as yet not possible to compare rates between patients on GH treatment and those without such substitution.

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 10 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 10: ADVERSE EVENTS REPORTED BY ≥ 5% OF 1,145 ADULT GHD PATIENTS DURING CLINICAL TRIALS OF GENOTROPIN AND PLACEBO, GROUPED BY DURATION OF TREATMENT

	Double Blind Phase		Open Label Phase GENOTROPIN		
Adverse Event	**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.

Post-Trial Extension Studies in Adults

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 glycosylated 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.

Clinical Trials in children with Prader-Willi Syndrome

In the two clinical studies with GENOTROPIN in pediatric patients with Prader-Willi Syndrome, the most frequently reported adverse events were as reported in table 11.

TABLE 11: ADVERSE DRUG REACTIONS REPORTED BY ≥ 1% OF PATIENTS DURING CLINICAL TRIALS OF GENOTROPIN IN PWS

Body system / Preferred Term	**Incidence** N (%)
Nervous System Disorders	
Paraesthesia*	1 (2.2)
Benign Intracranial hypertension	1 (2.2)
Headache	2 (4.4)
Musculoskeletal, Connective Tissue Disorders and Bone Disorders	
Arthralgia*	1 (2.2)
Myalgia*	1 (2.2)
Back pain	2 (4.4)
General Disorders and Administration Site Conditions	
Oedema peripheral*	2 (4.4)
Hair loss	1 (2.2)
Aggressiveness	1 (2.2)

**In general, these adverse effects are mild to moderate, arise within the first months of treatment, and subside spontaneously or with dose-reduction.*

Post-Market Adverse Drug Reactions

Because these adverse events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. The adverse events reported during post-marketing surveillance do not differ from those listed/discussed above (see Clinical Trials Adverse Reactions) in children and adults.

Leukemia has been reported in a small number of GHD children treated with somatropin, somatrem (methionylated rhGH) and GH of pituitary origin. It is uncertain whether these cases of leukemia are related to GH therapy, the pathology of GHD itself, or other associated treatments such as radiation therapy. On the basis of current evidence, experts have not been able to conclude that GH therapy per se was responsible for these cases of leukemia. The risk for children with GHD, if any, remains to be established [see Contraindications and Warnings and Precautions)].

The following additional adverse reactions have been observed during the appropriate use of somatropin: headaches (children and adults), gynecomastia (children), pancreatitis (see Warnings and Precautions), rash (children and adults), pruritus (children and adults) and urticaria (children and adults).

Serious systemic hypersensitivity reactions including anaphylactic reactions and angioedema have been reported with post- marketing use of somatropin products (see **CONTRAINDICATIONS** and **WARNINGS and PRECAUTIONS** – Immune).

New-onset type 2 diabetes mellitus has been reported.

Slipped capital femoral epiphysis and Legg-Calve-Perthes disease have been reported in children treated with growth hormone. No causal relationship has been demonstrated with somatropin.

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

DRUG INTERACTIONS

Overview

No studies on the interactions with other drugs have been performed since recombinant somatropin has the same amino acid sequence as pituitary-derived growth hormone.

Cytochrome P450 (CYP450)-Metabolized Drugs

Limited published data indicate that growth hormone treatment increases cytochrome P450 (CP450) mediated antipyrine clearance in human. These data suggest that growth hormone 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 growth hormone is administered in combination with other drugs known to be metabolized by CP450 liver enzymes.

β-Hydroxysteroid Dehydrogenase Type 1

The microsomal enzyme 11β-hydroxysteroid dehydrogenase type 1 (11βHSD-1) is required for conversion of cortisone to its active metabolite, cortisol, in hepatic and adipose tissue. GH and somatropin inhibit 11βHSD-1. Consequently, individuals with untreated GH deficiency have relative increases in 11βHSD-1 and serum cortisol. Introduction of somatropin treatment may result in inhibition of 11βHSD-1 and reduced serum cortisol concentrations. As a consequence, previously undiagnosed central (secondary) hypoadrenalism may be unmasked and glucocorticoid replacement may be required in patients treated with somatropin. In addition, patients treated with glucocorticoid replacement for previously diagnosed hypoadrenalism may require an increase in their maintenance or stress doses following initiation of somatropin treatment; 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 11βHSD-1.

Concomitant Glucocorticoids

Concomitant glucocorticoid treatment may inhibit the growth promoting effect of human growth hormone. GHD children with coexisting ACTH deficiency should have their glucocorticoid replacement dose carefully adjusted to avoid an 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. (see **WARNINGS AND PRECAUTIONS – Endocrine and Metabolism** and **DRUG INTERACTIONS - β-Hydroxysteroid Dehydrogenase Type 1**)

Patients with ACTH deficiency should be carefully monitored to avoid adrenal insufficiency.

Oral Estrogen

In patients on oral estrogen replacement, a larger dose of somatropin may be required to achieve the defined treatment goal. If a woman taking somatropin begins oral estrogen therapy, the dose of somatropin may need to be increased to maintain the serum insulin-like growth factor-I (IGF-I) levels within the normal age-appropriate range. However, the maximum recommended weekly dose should not be exceeded.

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.

Insulin and/or Oral/Injectable Hypoglycemic Agents

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

DOSAGE AND ADMINISTRATION

Therapy with GENOTROPIN (somatropin for injection) should be supervised by a physician who is experienced in the diagnosis and management of pediatric patients with growth failure associated with growth hormone deficiency (GHD), Turner syndrome (TS), those who were born small for gestational age (SGA) or Idiopathic Short Stature (ISS), and adult patients with either childhood onset or adult onset GHD.

The GENOTROPIN dosage and administration schedule should be individualized based on the growth response of each patient.

Response to somatropin therapy in pediatric patients tends to decrease with time. However, in pediatric patients, the failure to increase growth rate, particularly during the first year of therapy, indicates the need for close assessment of compliance and evaluation for other causes of growth failure, such as hypothyroidism, undernutrition, advanced bone age and antibodies to recombinant human GH (rhGH).

Treatment with GENOTROPIN for short stature should be discontinued when the epiphyses are fused.

Recommended Dose and Dosage Adjustment

Table 12: The recommended dosage of GENOTROPIN

Indication	Recommended Dose (mg/kg body weight)	Route[4]	Comments
Pediatric Growth Hormone Deficiency[1]	0.16 - 0.24 mg/kg body weight/**week**	SC	Divided into 6-7 doses Diagnosis of GHD should be confirmed before GENOTROPIN is administered.
Adults Growth Hormone Deficiency	0.15 - 0.3 mg/day[2]	SC	Divided into 6-7 doses
Turner Syndrome[1]	0.33 mg/kg body weight per **week**	SC	Divided into 6-7 doses
Idiopathic Short Stature[1]	UP TO 0.47 mg/kg body weight per **week**[3]	SC	Divided into 6-7 doses
Small for Gestational Age[1]	UP TO 0.48 mg/kg body weight per **week**	SC	Divided into 6-7 doses
Pediatric Prader-Willi Syndrome	0.24 mg/kg body weight per **week**	SC	Divided into 6-7 doses

[1]GENOTROPIN dosage must be adjusted for the individual patient.
[2]Final dose should be individually increased as required with respect to age and gender to a maximum daily maintenance dose of 1.33 mg. 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.
[3] Treatment should stop when near adult height is achieved (height velocity <2cm/yr and/or bone age >16 yr in boys and >14 yr in girls) or when height is in the normal adult range (above -2 SDS).
[4]GENOTROPIN may be administered in the thigh, buttocks or abdomen; the site of SC injections should be rotated daily to help prevent lipoatrophy.

Adults Growth Hormone Deficiency

Clinical response, side effects and determination of IGF-1 in serum may be used as guidance for dose titration. The level of IGF-1 should not exceed the upper limit of normal IGF-1 levels matched to age and sex.

It is recommended that IGF-I concentrations be monitored regularly and GH dose be reduced in children with a plasma IGF-1 above + 2SD.

Small for Gestational Age

Recent literature has recommended initial treatment with larger doses of somatropin (e.g., 0.48 mg/kg/week), especially in very short children (i.e., height SDS <–3), and/or older/ pubertal children, and that a reduction in dosage (e.g., gradually towards 0.24 mg/kg/week) should be considered if substantial catch-up growth is observed during the first few years of therapy. On the other hand, in younger SGA children (e.g., approximately <4 years) with less severe short stature (i.e., baseline height SDS values between -2 and -3), consideration should be given to initiating treatment at a lower dose (e.g., 0.24 mg/kg/week), and titrating the dose as needed over time. In all children, clinicians should carefully monitor the growth response, and adjust the somatropin dose as necessary.

Dosing should continue until final height is reached (see **DETAILED PHARMACOLOGY**, **Human Pharmacology, Pharmacodynamics**). Treatment should be discontinued after the first year of treatment if the height velocity SDS is below + 1. Treatment should be discontinued if height velocity is < 2 cm/year and, if confirmation is required, bone age is > 14 years (girls) or > 16 years (boys)

corresponding to closure of the epiphyseal growth plates.

In short children born SGA, it is recommended that IGF I concentration be measured before initiation of treatment and monitored every 6 months thereafter. If on repeated measurements IGF-I concentrations exceed +2 SD compared to references for age and pubertal status, the IGF-I/IGFBP-3 ratio could be taken into account to consider dose adjustment.

Administration
See **CONSUMER INFORMATION** for detailed information.

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

OVERDOSAGE

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

Short-Term
There is little information on acute or chronic overdosage with GENOTROPIN (somatropin for injection). It is known that intravenously administered growth hormone has been shown to result in an acute decrease in plasma glucose and subsequently to hyperglycemia. It is thought that the same effect might occur on rare occasions with high dosages of GENOTROPIN administered subcutaneously or intramuscularly.

Long-Term
Long-term overdosage may result in signs and symptoms of acromegaly consistent with overproduction of human growth hormone.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action
GENOTROPIN (somatropin for injection) is a polypeptide hormone of recombinant DNA origin. The amino acid sequence of the product is identical to that of human growth hormone of pituitary origin. GENOTROPIN stimulates linear growth in children with growth hormone deficiency. In vitro, preclinical and clinical tests have demonstrated that GENOTROPIN is therapeutically equivalent to pituitary growth hormone and achieves similar pharmacokinetic profiles in normal adults.

Treatment of growth hormone deficient (GHD) children with GENOTROPIN produces increased growth rate and IGF – I (Insulin like Growth Factor- I) concentrations that are similar to those seen after therapy with pituitary growth hormone.

Treatment of GH deficient adults with GENOTROPIN increases serum IGF-I to normal levels, improves body composition and Quality of Life.

In addition, the following actions have been demonstrated for GENOTROPIN and/or pituitary growth

hormone:

Tissue Growth
Skeletal Growth: GENOTROPIN stimulates skeletal growth in children with GHD. The measurable increase in body length after administration of either GENOTROPIN or pituitary growth hormone 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 GHD children but tend to increase during treatment with GENOTROPIN. Elevations in mean serum alkaline phosphatase concentration are also seen.

Cell Growth: It has been shown that there are fewer skeletal muscle cells in short statured children who lack endogenous growth hormone as compared with normal children. Treatment with Somatropin for Injection results in an increase in both the number and size of muscle cells.

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 pituitary growth hormone. Treatment with GENOTROPIN results in a similar decrease in serum urea nitrogen. In adults with GHD, treatment with GENOTROPIN increases protein synthesis and increases overall lean body mass.

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

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

Mineral and Bone Marker Metabolism
Somatropin induces retention of sodium, potassium, and phosphorus. Retention of sodium, potassium, and phosphorus is induced by pituitary growth hormone in children. In treated adults, osteocalcin and procollagen levels are significantly increased. Serum concentrations of inorganic phosphate are increased in patients with GHD after therapy with GENOTROPIN or pituitary growth hormone. Serum calcium is not significantly altered by either GENOTROPIN or pituitary growth hormone. Growth hormone could increase calciuria.

Quality of Life
Quality of Life as measured by the Nottingham Health Profile showed significant improvements in "energy" and "sleep" in the GH-treated group in comparison with the placebo group. The total well-being score, produced by the Psychological General Well-Being Scale, was significantly better for the GH-group than for the placebo group. For "anxiety", "depression" and "positive well-being" a trend towards improvement was found in the GH treated group but the effect was not statistically significant.

Pharmacokinetics
There is no apparent difference in the positive growth response to GENOTROPIN administered by either the IM or SC route when the frequency of dosing is the same.

When the relative bioavailability was compared with the reference (Kabi-Vial 4 IU) at a common dose of 0.1 IU/kg, both MiniQuick formulations (0.4 mg and 2.0 mg) met the standards for bioequivalence as stated in the Canadian guidance document, Comparative Bioavailability Standards: Formulations Used for Systemic Effects.

Absorption
The pharmacokinetic profile after an intramuscular injection (IM) is similar to SC injection. No significant differences have been noted in $T_{max,}$ C_{max} or area under the curve between these two routes of administration.

Approximately 80% of GENOTROPIN is absorbed following subcutaneous (SC) injection. Maximum serum concentrations are achieved 3 - 4 hours following SC injection.

STORAGE AND STABILITY

GENOTROPIN GoQuick:
Before reconstitution:
Keep refrigerated. Store at 2°C – 8°C until expiry. Do not freeze. Do not shake. Keep the GoQuick pen in the outer carton in order to protect from light.

The GoQuick pen can be stored for a maximum of 4 weeks unrefrigerated (at or below 25°C). During and/or at the end of the 4 weeks period, the product should not be put back in the refrigerator. After this 4 week period, the GoQuick pen must be discarded.

After reconstitution:
Keep refrigerated. Store at 2°C – 8°C for a maximum of 4 weeks. Do not freeze. Do not shake. Keep the reconstituted GoQuick pen in the outer carton in order to protect from light.

Once removed from the refrigerator, the reconstituted solution can remain at room temperature for up to 2 hours prior to each injection. Once the injection is administered, the reconstituted solution must be returned to the refrigerator. The cycle can be repeated over the allowable 4 week period.

GENOTROPIN MiniQuick:
Before reconstitution:
Keep refrigerated. Store at 2ºC – 8ºC until expiry. Do not freeze. Do not shake. Keep the MiniQuick syringe in the outer carton in order to protect from light.

The MiniQuick syringe can be stored for a maximum of 6 months unrefrigerated (at or below 25°C). During and/or at the end of this 6 months period, the product should not be put back in the refrigerator. After this, the MiniQuick syringe must be discarded.

After reconstitution:
Use immediately or store in a refrigerator at 2ºC – 8ºC and use within 24 hours. Do not freeze. Do not shake. Keep the MiniQuick syringe in the outer carton in order to protect from light.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Availability of Dosage Forms

GENOTROPIN GoQuick:
Growth Hormone Delivery Device containing a two-chamber cartridge of GENOTROPIN (with preservative)
The 5 mg pre-filled pen GoQuick is colour coded green.
The 5.3 mg pre-filled pen GoQuick is colour coded blue.
The 12 mg pre-filled pen GoQuick is colour coded purple.

5.0, 5.3 and 12 mg: Packages of 1s and Packages of 5s

Not all pack sizes and strengths may be marketed in Canada.

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

1.2, 1.6, 1.8 and 2.0 mg: Packages of 4s
0.2, 0.4, 0.6, 0.8, 1.0, 1.2, 1.4, 1.6, 1.8, and 2.0 mg: Packages of 7s and Packages of 28 (4 x 7 Packages)

Not all package sizes and strengths may be marketed in Canada.

Please see directions for use accompanying each delivery device.

Composition

GENOTROPIN (somatropin for injection) is a sterile white lyophilized powder containing (or of) highly purified rhGH, intended for subcutaneous injection.

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.

GENOTROPIN GoQuick:
Powder and 1.14 ml liquid in a two-chamber glass cartridge (type I glass) separated by a rubber plunger (bromobutyl). The cartridge is sealed at one end with a rubber disc (bromobutyl) and an aluminium cap and at the other end by a rubber stopper (bromobutyl). The two-chamber cartridge is supplied for use in a disposable multidose pre-filled pen. The 5 mg, 5.3mg and 12 mg presentations of **GENOTROPIN** GoQuick lyophilized powder contain m-cresol as a preservative. These products should not be used by patients with a known sensitivity to this preservative.

GENOTROPIN MiniQuick:
Powder and 0.275 - 0.282 ml liquid in a two chamber glass cartridge (type I glass) separated by a rubber plunger (bromobutyl), supplied as a single dose syringe. The cartridge is sealed at both ends with rubber stoppers (bromobutyl) and is enclosed in a plastic sleeve with a plunger rod and a finger grip. The GENOTROPIN MiniQuick presentations are preservative-free.

Composition of the Genotropin MiniQuick After Reconstitution

Dosage Form	Quantity per Syringe
GENOTROPIN MiniQuick 0.2 mg, 0.4 mg, 0.6 mg, 0.8 mg, 1.0 mg, 1.2 mg, 1.4 mg, 1.6 mg, 1.8 mg, and 2.0 mg/syringe	0.22 mg - 2.26 mg Somatropin for Injection 0.23 - 0.24 mg glycine 13.8 - 14.1 mg mannitol 0.050 - 0.051 mg sodium dihydrogen phosphate anhydrous 0.027 - 0.028 mg disodium phosphate anhydrous to 0.28 mL Water for injection

Composition of the Genotropin GoQuick After Reconstitution

Dosage Form	Quantity per mL
GENOTROPIN GoQuick 5 mg/pen 5.3 mg/pen	5.0 -5.3 mg Somatropin for Injection 2 mg glycine 41 mg mannitol 0.29 mg sodium dihydrogen phosphate anhydrous 0.28 mg disodium phosphate anhydrous 3 mg metacresol to 1 mL Water for injection
GENOTROPIN GoQuick 12 mg/pen	12.0 mg Somatropin for Injection 2 mg glycine 40 mg mannitol 0.41 mg sodium dihydrogen phosphate anhydrous 0.40 mg disodium phosphate anhydrous 3 mg metacresol to 1 mL Water for injection

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Somatropin (USAN, BAN)
Recombinant somatropin = somatropin (rbe)

Common Names: rhGH, authentic human somatropin
Authentic human growth hormone
Genuine human somatropin

Chemical Name: Recombinant human somatropin
Recombinant human growth hormone

Molecular Formula: $C_{900}H_{1528}N_{262}O_{300}S_7$

Molecular Weight: 22,124 daltons

Structural Formula: Single polypeptide chain of 191 L-isomer amino acid residues; 2 disulphide bonds (Cys53-Cys165; Cys182-Cys189)

CLINICAL TRIALS

Efficacy and Safety Studies

Children

Patient response to GENOTROPIN 5.3 mg/mL and 1.3 mg/mL has been monitored through the Kabi International Growth Study (KIGS). 46 patients received the 5.3 mg/mL formulation and 342 received the 1.3 mg/mL formulation at a dose of (0.17 - 0.23 IU/kg/wk) for at least one year for growth hormone insufficiency. After 12 months the group treated with GENOTROPIN 1.3 mg/mL showed an increase in mean height from 123.5±19.2 cm to 131.9±18.8 cm, and the group treated with GENOTROPIN 5.3 mg/mL showed an increase in mean height from 125.0 ±20.2 cm to 139.1±17.1 cm. Therefore, although the two formulations have not been shown to be equally bioavailable, they are both efficacious when used in a clinical setting.

SGA

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 pivotal, randomized, open-label, controlled multicenter, multinational clinical trials that each evaluated 3 parallel groups (2 somatropin-treated groups and one untreated control group). Studies were conducted at study sites in France, the northern European countries of Sweden, Finland, Denmark, and Norway, Germany, and Belgium. All studies used height velocity SDS (HV SDS) as the primary endpoint. Since it is a measure of change in height over a set

time period (usually a year), HV SDS is the most appropriate measure for comparisons among treatment groups during periods of rapid growth, such as catch-up growth. HV SDS was measured over two 12-month periods, from baseline to month 12 and from month 12 to month 24. The measurement of height with a Harpenden stadiometer, or comparable wall-mounted device, was used in the studies and is widely employed as an objective measure to assess growth response. Further, to minimize bias, the effects of the drug were assessed relative to an untreated control group, using appropriate statistical methods that incorporated correction for multiple comparisons.

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 GH treatment accelerated the growth of SGA children in a dose dependent manner. At entry to the study, the mean growth rate SD score (SDS) was -1.1±1.1 for untreated controls (n = 72), -1.2±1.4 for the 0.033 mg/kg/day group (n = 104), and -1.2±1.1 for the 0.067 mg/kg/day group (n = 117). After the start of the study, the growth rate SDS in the respective groups were: -0.8±1.2 (n = 76), 2.5±1.8 (n = 105), and 4.4±2.1 (n = 117) during the first year; and -0.7±1.0 (n = 59), 0.9±1.8 (n = 105), and 2.1±2.0 (n = 117) during the second year (see table 13).

Children receiving 0.48 mg/kg/week demonstrated a significant improvement in height SDS (secondary endpoint) compared with children treated with 0.24 mg/kg/week. Height SDS at entry was -3.1±0.9 for the untreated control (n = 40), -3.2±0.8 for the 0.033 mg/kg/day group (n = 76), and -3.4±1.0 for the 0.067 mg/kg/day group (n = 93). The corresponding values after 24 months of treatment were -2.9±0.9 (n = 40), -2.0±0.8 (n = 76), and -1.7±1.0 (n = 93). Thus, treatment with somatropin improved the height of short-stature children born SGA by 1.2 SDS at 0.033 mg/kg/day and by 1.7 SDS at 0.067 mg/kg/day (Table 14). Both of these doses resulted in a slower but constant increase in growth between months 24 to 72

TABLE 13: EFFICACY OF GENOTROPIN IN CHILDREN BORN SMALL FOR GESTATIONAL AGE

(Mean ± SD)

	GENOTROPIN (0.24 mg/kg/week)	**GENOTROPIN (0.48 mg/kg/week)**	**Untreated Control**
Mean growth rate SD Score (SDS) Baseline SDS	-1.2±1.4 (n = 104)	-1.2±1.1 (n = 117)	-1.1±1.1 (n = 72)
Growth rate SDS at 12 months	2.5*±1.8 (n = 105)	4.4*±2.1 (n = 117)	-0.8±1.2 (n = 76)
Growth rate SDS at 24 months	0.9*±1.8 (n = 105)	2.1*±2.0 (n = 117)	-0.7±1.0 (n = 59)

*p = 0.0001 vs Untreated Control group

TABLE 14: 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

A supplementary analysis of the change in height SDS from baseline to month 24 was performed that included height SDS at baseline, age at baseline, and sex as covariates. The analysis indicates that the effect of somatropin on the change in height SDS is greater at a younger age but that the effect is prominent up to 8 years of age at the start of treatment.

Patients enrolled in the four randomized, multicenter studies of the safety and efficacy of Genotropin therapy in patients with short stature born small for gestational age (SGA) were followed as controls or treated patients for 2 and 6 years, respectively. Forty nine of the total cohort of 188 patients were followed for 2 years as untreated controls, 62 received continuous Genotropin treatment for 6 years and 77 received discontinuous Genotropin treatment for 6 years. Of the 62 patients who received continuous therapy, 35 received a daily Genotropin dose of 33 µg/kg body weigh/day and 27 received a daily Genotropin dose of 67 µg/kg body weigh/day. The 77 patients who were treated with discontinuous therapy received Genotropin treatment for 2 to 3 years followed by a withdrawal phase of 1 to 2 yr, and then by either no or 1 or more episodes of further Genotropin treatment at a dose of 33 µg/kg body weigh/day, averaged over 6 years.

At the start of the studies, the average age of the 188 patients was 5.2 yr (range, 2–8 yr) and the mean height SDS was - 3.4. After 2 yr, the untreated control group experienced an increase in height, of 0.1 ± 0.1 SD over baseline (not shown in table 15). Continuous Genotropin treatment at a dose of 33 µg/kg/day and 67 µg/kg/day for 2 years resulted in an increase in height over baseline of 1.2 SD and 1.7 SD respectively, and an increase in height over baseline of 2.1 SD and 2.6 SD, in the 0.033 mg/kg/day and 0.067 mg/kg/day groups at 6 years, respectively. After 2 years there were no untreated control patients available for comparison. The height SDS at 72 months in all groups is greater than - 2, in the normal range.

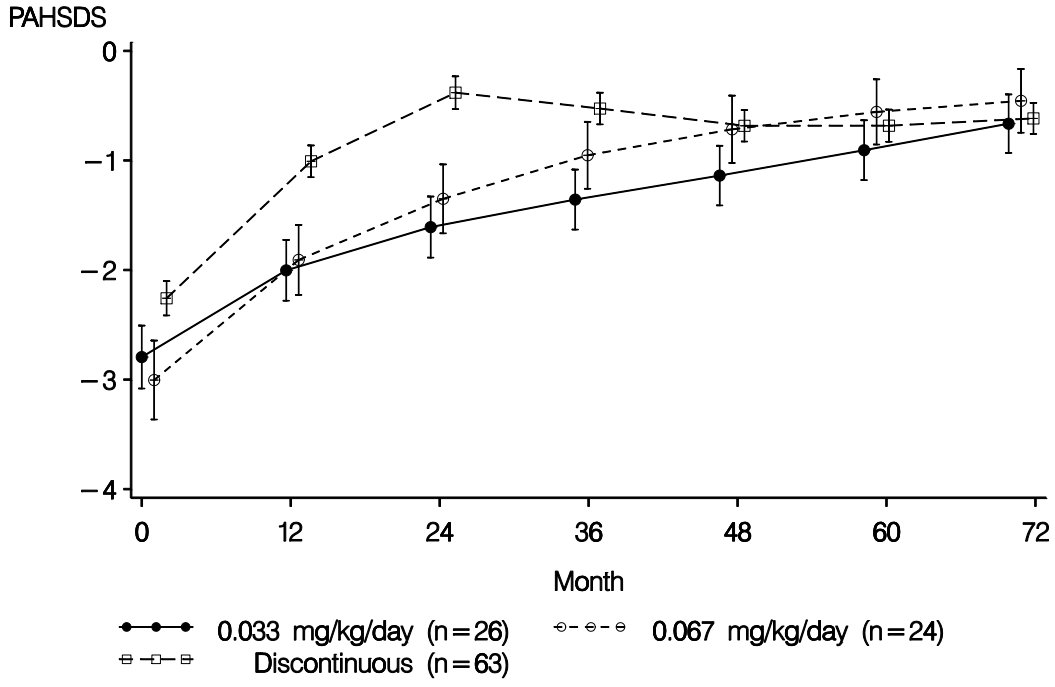
TABLE 15: Effect of No Treatment, Some Treatment, or Continuous Treatment on Height SDS During Month 24 to Month 72 - PP 0-72 Population

Mean Height SDS	Treatment Group			
	Disc/Not Re-trt N=15	Disc/Some Re-trt N=50	Continuous 0.033 mg/kg/day N=27	Continuous 0.067 mg/kg/day N=25
Change from baseline to month 24	2.4	1.7	1.2	1.7
Change from baseline to month 72	1.6	1.6	2.1	2.6
Change from month 24 to month 72	-0.8	-0.1	0.9	0.9
Height SDS at month 72	-1.7	-1.6	-1.4	-1.3

Abbreviations: Disc/Not Re-trt= patients in the discontinuous group who were not treated during month 24 to month 72; Disc/some trt=patients in the discontinuous group who received some treatment during month 24 to month 72

Mean PAH SDS during the baseline to month 72 period is displayed graphically in Figure 2. As expected, the mean PAH SDS curves over the 72-month treatment period show a pattern similar to the non-adjusted mean height SDS curves. The PAH SDS curves for all treatment groups approached 0 SD, thus indicating a normalization of childhood stature when adjusted for genetic potential.

FIGURE 2. EFFECT OF SOMATROPIN TREATMENT ON MEAN (±SEM) PAH SDS PP 0-72 POPULATION



Note: 13 patients excluded (1 in the 0.033 mg/kg/day group, 1 in the 0.067 mg/kg/day group and 11 in the discontinuous group) due to missing observations.

Turner Syndrome

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.

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 16). The linear growth response was greater in Study 055 wherein patients were treated with a larger dose of GENOTROPIN.

TABLE 16: 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

Idiopathic Short Stature

The long-term efficacy and safety of GENOTROPIN in patients with idiopathic short stature (ISS) were evaluated in one randomized, open-label, clinical trial that enrolled 105 prepubertal children with ISS and in one small supportive open-label trial that included 37 randomized prepubertal children with ISS. In the pivotal trial, patients were enrolled on the basis of short stature, stimulated GH secretion > 10 ng/mL. A total of 177 patients were intitially enrolled, but criteria for idiopathic short stature were retrospectively applied and therefore patients with SGA and those that were pubertal were removed from the ISS pre-pubertal analysis. All patients were observed for height progression for 12 months and were subsequently randomized to GENOTROPIN or observation only and followed to final height. Two GENOTROPIN doses were evaluated in this trial: 0.23 mg/kg/week (0.033 mg/kg/day) and 0.47 mg/kg/week (0.067 mg/kg/day). Baseline patient characteristics for the ISS patients who remained prepubertal at randomization (n= 105) were: mean (± SD): chronological age 11.4 (1.3) years, height SDS -2.4 (0.4), height velocity SDS -1.1 (0.8), and height velocity 4.4 (0.9) cm/yr, IGF-1 SDS -0.8 (1.4). Patients were treated for a median duration of 5.7 years. Results for final height SDS are displayed by treatment arm in Table 17. GENOTROPIN therapy improved final height in ISS children relative to untreated controls. The observed mean gain in final height was 9.8 cm for females and 5.0 cm for males for both doses combined compared to untreated control subjects. A height gain of 1 SDS was observed in 10 % of untreated subjects, 50% of subjects receiving 0.23 mg/kg/week and 69% of subjects receiving 0.47 mg/kg/week.

TABLE 17: FINAL HEIGHT SDS RESULTS FOR PRE-PUBERTAL PATIENTS WITH ISS*

	Untreated (n=30)	GEN 0.033 mg/kg/day (0.23 mg/kg/week) (n=33)	GEN 0.067 mg/kg/day (0.47 mg/kg/week) (n=42)	GEN 0.033 mg/kg/day (0.23 mg/kg/week) vs. Untreated (95% CI) **	GEN 0.067 mg/kg/day (0.47 mg/kg/week) vs. Untreated (95% CI)**	GEN 0.033 mg/kg/day (0.23 mg/kg/week) vs. GEN 0.067 mg/kg/day (0.47 mg/kg/week)**
Final height SDS minus baseline SDS	0.41 (0.58)	0.95 (0.75)	1.36 (0.64)	+0.53 (0.20, 0.87) p=0.0022	+0.94 (0.63, 1.26) p<0.0001	-0.41(-0.72,-0.10) p=0.0105
Final height SDS minus baseline predicted final height SDS	0.23 (0.66)	0.73 (0.63)	1.05 (0.83)	+0.60 (0.09, 1,11) p=0.0217	+0.90 (0.42, 1.39) p=0.0004	-0.30(-0.69,0.09) p= 0.1272

*Mean (SD) are observed values.

**Least square means based on ANCOVA (final height SDS and final height SDS minus baseline predicted height SDS were adjusted for baseline height SDS)

Supportive Study CTN 89-050 was a randomized, open-label, multicenter study that evaluated the efficacy and safety of GENOTROPIN treatment in prepubertal children diagnosed with ISS. Thirty seven children who fulfilled the study entry criteria were randomly assigned to receive GENOTROPIN at a dosage of 0.047 mg/kg body weight per day (n=18) or to serve as untreated controls (n=19). The primary efficacy variable, the change in height SDS for bone age (HSDS-BA) after 36 months, was evaluated in the ITT population, which included 18 subjects in each group who were randomized and had at least one post-baseline efficacy measurement. All subjects were prepubertal at study start and remain so throughout the study. After 36 months, the mean HSDS-BA increased by 0.34 ± 1.60 from baseline in the treated group (n = 18) and decreased -0.46 ± 1.58 SD in the untreated control group (n = 17), but the difference in the mean change (0.8 SD) did not reach statistical significance (p = 0.192).

Height SDS, however, increased significantly compared to untreated controls at both Months 12 and 36 ($p<0.001$), as did growth velocity SDS for bone age and growth velocity SDS (each $p<0.001$) at both time points. Mean changes from baseline in height (cm) and growth velocity (cm/year) were both significantly greater in the GENOTROPIN group compared to the untreated control group (each $p<0.001$). The number of subjects who achieved an increase of at least 1.0 SDS in height SDS was significantly greater in the GENOTROPIN group at Month 36 than in the untreated control group ($p<0.001$). Improvements in growth variables involving chronologic age were better predictors of response to therapy than variables that were adjusted for bone age.

Prader-Willi Syndrome

The safety and efficacy of Genotropin in pediatric patients with Prader Willi syndrome was first investigated over twenty years ago in two studies (trial 91-019 and trial 94-8129-007). Both trials were performed in prepubertal PWS children, aged 3 to 12 years at study start. There were 27 patients in trial 91-019 and 16 patients in trial 94-8129-007. Taken together, 22 patients (12 boys and 10 girls) were treated with GH for two years and 21 patients (12 boys and 9 girls) for one year, as the latter patient group served as controls during the first study year.

Study 91-019 evaluated the efficacy of Genotropin on linear growth, particularly height and height SDS, changes in body composition and changes in lipid metabolism. Safety evaluation included assessment of adverse events (AEs), serious AEs (SAEs) and deaths. There were no deaths and none of the SAEs and AEs were considered related to Genotropin treatment. Height and height SDS increased and there were clinically meaningful improvements in body composition in treated subjects compared to controls (fat mass decreased, and lean body mass increased).

Similarly, study 94-8129-007 evaluated the safety and efficacy of Genotropin on linear growth, fat metabolism and body composition. Three SAEs were considered related to the Genotropin treatment; one patient developed a pseudotumor cerebri shortly after initiation of the treatment, which resolved without remarkable residuals after treatment was stopped. A restart on half the dose was well tolerated. In two patients, scoliosis, already present before the start of the therapy, worsened during the study period. Most of the non-serious AEs were rated mild to moderate. Height increased with an average gain of 1.0 SD, the waist/hip ratio and skinfold thickness improved and all PWS patients had low IGF-1 and IGFBP-3 compared to normal healthy children.

Longer-term information derived from the Kabi International Growth Study (KIGS) database also supported the beneficial effects of hGH on linear growth and body mass index (BMI) stabilization. In addition, three supportive publications (Carrel et al 1999, Haqq et al 2003, Whitman et al 2004) provided additional evidence that hGH therapy in infants and children with PWS (aged 4 months to 15 years) was safe and beneficial when given at doses between 0.21 and 0.31 mg/kg per week. The benefit of hGH therapy in infants and children with PWS was also supported by more recent publications (Festen et al. 2008, Meinhardt et al. 2013, Bakker 2015, Corripio et al. 2019, Yang et al. 2019).

Adults

Adult 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.

DETAILED PHARMACOLOGY

Animal Pharmacology

Pharmacodynamics
The efficacy of recombinant human growth hormone has been measured by different methods, mostly in the rat. Growth hormone is an anabolic hormone, and exerts a wide spectrum of actions *in vivo* and *in vitro*. Some of these important effects are as follows: stimulation of postnatal somatic growth; insulin-like effects; lipolytic effects; diabetogenic effects; lactogenic effects; "feminizing" activity; and refractoriness.

The growth effects of GENOTROPIN (somatropin for injection) have been compared with those of pituitary growth hormone in hypophysectomized rats. Measurements comprised total body weight gain, longitudinal bone growth, relative weight / wet weight of different visceral organs, uptake of radioactive sulfite into cartilage and serum IGF levels. The results showed that GENOTROPIN induced a dose-dependent and significant stimulation of growth parameters. Furthermore, the bioactivity of GENOTROPIN was equal to that of pituitary growth hormone and no difference between the products could be demonstrated.

Other pharmacodynamic properties of GENOTROPIN and pituitary growth hormone have been studied and the two compounds have been found to be identical and equipotent with respect to the following: insulin-like effects (*in vivo* assay for transient hypoglycemia and membrane transport or uptake of amino acids, and *in vitro* assay of oxidation of ^{14}C glucose); lipolytic effects (*in vivo* assay in the obese mouse for fasting hyperglycemia and glucose intolerance, and *in vitro* assay for lipolysis in fat tissue from hypophysectomized and intact rats); refractoriness (*in vitro* assay of oxidation of ^{14}C glucose after pre-treatment with pituitary growth hormone or GENOTROPIN); hepatic feminizing activity (*in vivo* assay for increase in hepatic lactogenic receptors in rats); and *in vitro* binding assays (rat adipocytes, pregnant rat liver membrane).

Pharmacokinetics

The pharmacokinetics of GENOTROPIN have been investigated in rats. T_{max} has been found to be 1 hour whether administered SC or IM. The maximum concentrations were dose dependent. The absorption from the subcutaneous or intramuscular depot was rate-limiting with half lives of 0.85 hours (2 IU/kg) and 1.07 hours (21 IU/kg) after subcutaneous administration, and 1.15 hours (2 IU/kg) and 1.22 hours (12 IU/kg) after intramuscular administration. The elimination half-lives, determined on the rising part of the curves, were found to be 20 minutes and 33 minutes after subcutaneous administration and 19 and 27 minutes after intramuscular administration at the two different doses. The bioavailability was calculated from these studies to average 75% for the intramuscular administration and 43% for the subcutaneous administration.

Human Pharmacology

Pharmacodynamics

The pharmacologic aspects of growth hormone replacement therapy have been extensively reported.

Pituitary secretion of growth hormone is regulated by growth hormone releasing factor (GRF) and growth hormone inhibiting factor (somatostatin), both of which are secreted from the hypothalamus. Secreted growth hormone stimulates the production of IGF-I in tissues such as cartilage and liver. IGF-I is known to enhance the uptake of SO_4^{2-} into cartilage tissues and thereby promote cartilage growth.
Pharmacologic studies in humans showed a dose-dependent increase in IGF-I values following GH administration. Pharmacodynamic data after single subcutaneous doses of 0.06, 0.12 and 0.24 IU/kg to 24 Japanese and 24 Caucasian healthy adult male volunteers showed a clear dose-response relationship for AUC_{0-t} for serum IGF-I concentrations. Following an increase in dose of somatropin from 0.06 to 0.12 IU/kg, the AUC for IGF-I in serum increased 1.1 fold in Japanese and 1.2 fold in Caucasians. With a 4-fold increase in dose from 0.06 to 0.24 IU/kg, there were 1.3 fold and 1.8 fold increases in AUC in the respective ethnic groups. These data suggest that somatropin caused a relatively constant pharmacological response at doses in this range (0.06-0.24 IU/kg).

The pharmacokinetic profile of somatropin was evaluated after single subcutaneous or intramuscular administration of 8 IU to 8 healthy adult males in a cross-over fashion. An interval of 2-week wash-out was included between the two treatment phases. IGF-I levels were determined before and 24 hours after subcutaneous or intramuscular injection. Blood levels of free fatty acid were also determined before and 4 hours after administration. Levels of IGF-I and blood free fatty acid were significantly increased from the pretreatment levels but not significantly different between the two routes of administration.

Pituitary growth hormone is known to have the following effects:

Lipolytic effects GENOTROPIN gives rise to a post-injection increase in fatty acids.

Somatomedins GENOTROPIN has been shown to increase IGF-I in healthy volunteers and increase alkaline phosphatase in growth hormone deficient children.

Osteoblastic activity Signs of growth hormone stimulation of this activity are high levels of alkaline phosphatase which can be seen in most patients during GENOTROPIN treatment.

Nitrogen Balance Two short-term studies have demonstrated a positive effect of recombinant somatropin on nitrogen balance in both GH-deficient and non-GH-deficient children. In the earlier of

the two studies, ^{15}N-labelled ammonium chloride was administered before and after two days of recombinant somatropin administration (3 IU/m^2/day SC). In nine GH-deficient patients, basal ^{15}N balance was +79 ± 15 mg/m^2, while after two days of recombinant somatropin treatment, it was found to be 166 ± 16 mg/m^2, an increase to over 200 percent of the basal level. In the second study, a mixed preparation of ^{15}N-labelled amino acids was administered to three GH-deficient children, as well as 34 non-GH-deficient children of short stature, before and after four days of recombinant somatropin administration (16 µg/kg, SC, q12h). Before growth hormone challenge, mean whole body protein turnover, synthesis and catabolism for all subjects were 4.38 ± 0.56, 3.52 ± 0.60, and 3.38 ± 0.5 g/kg/d, respectively. Growth hormone challenge increased body protein turnover by enhancing both protein synthesis and catabolism with synthesis increased to a greater degree than catabolism, resulting in a net body protein accretion increase over pre-treatment of more than 200% from 0.14 ± 0.03 to 0.35 ± 0.02 g/kg/d ($p < 0.001$).

Body fat balance and energy expenditure. Six weeks' administration of recombinant somatropin to nine GH-deficient and six short-statured children at a mean (± SE) dose of 15.1 ± 0.8 IU/m^2/week in divided daily doses, resulted in mean increases in weight of 0.96 kg and fat-free mass of 1.37 kg, accompanied by a mean decrease of 0.41 kg in fat mass. In addition, significant increases both in resting energy expenditure and free daily living energy expenditure were observed.

Immune response. The immune response of recombinant somatropin is complex and requires further study, however in separate studies it has been found to produce a decrease in the percentage of B cells and T cells, accompanied by modest transient alterations in mitogenic responses and Interleukin-2 receptor levels and to enhance NK activity but not to affect LAK function.

Renal effects. Recombinant somatropin has been found to exert an effect on the kidney that causes phosphorus conservation. Increased renal calcitriol levels during phosphorus deprivation in growth hormone-deficient children were significantly correlated with IGF-I levels suggesting the possibility of an IGF-I-mediated effect of growth hormone.

Recombinant somatropin has been found to have a dose-dependent effect on basal osteoblastic activity and nocturnal pattern of osteocalcin. While administration of 2 IU daily to growth hormone-deficient children was inadequate to elevate serum osteocalcin levels to those observed in a parallel group of normal volunteers, the nocturnal patterns of serum osteocalcin in patients receiving 4 or 6 IU per day were statistically no different from the normal volunteers.

In clinical trials in short children born SGA doses of 0.24 mg/kg/wk (0.033 and 0.067 mg/kg/day) have been used for treatment until final height. A dose of 0.10 mg/kg/day has also been used for treatment but was associated with serious adverse events within a 24 month study period.

Pharmacokinetics
In study CTN:93-8122-003, the comparison of pharmacokinetic (pK) profiles in short children born small for gestational age (SGA) were assessed before (at baseline) and after 6 months of continuous Genotropin treatment. Eighteen short (median height = - 3.5 SDS) SGA children (7 females) with a median age of 7.6 years (range: 3.9 - 11.5 years) at study start were included in this portion of the study. All patients were prepubertal at the time of both tests, which were performed at baseline and after 180 days (range 144 to 259 days) of Genotropin treatment at a dose of treatment at a dose of 67 µg/kg body weight/day.

For the pK studies, a Genotropin dose of 67µg/kg was administered at baseline (before Genotropin therapy was started) and 24 hours after the last Genotropin dose. Blood samples were collected hourly for the first 6 hours, every two hours up to 16 hours and at 20 and 24 hours. Descriptive statistics were calculated for the pharmacokinetic parameters AUC, Cmax, and tmax at baseline and after 6 months of treatment. One child was excluded from the pharmacokinetic evaluation due to incorrect dosing.
The GH serum concentration vs. time profiles varied between the patients. The disposition of the serum GH was characterized by a slow absorption phase, with maximum concentration reached after about 3 hours (range 1.9 - 6.0 for both profiles). At baseline, the given dose resulted in a median C_{max} at baseline of 33.9 µg/L (range: 23.1 - 60.4). After 6 months of Genotropin therapy the median C_{max} was comparable at 32.6 µg/L (range: 17.7 - 66.9). There were no significant differences between median values for the other pharmacokinetic profiles at baseline and after 6 months of Genotropin therapy. However, despite the similarity between the two overall pK profiles, there was considerable intra-individual variation in the serum concentrations of GH with respect to the variables AUC, Cmax and tmax.

The results indicated that there was no accumulation of GH in SGA children following 6 months of daily Genotropin treatment and that there was no tendency towards an increase or decrease with respect to the parameters studied.

GENOTROPIN MiniQuick Range
The relative bioavailability of GENOTROPIN MiniQuick and GENOTROPIN 1.3 mg powder for injection with diluent was investigated in two separate single dose studies each comparing a single strength of the GENOTROPIN MiniQuick to GENOTROPIN 1.3 mg without preservative in a two way crossover design. The second lowest strength, 0.4 mg, and the highest strength, 2.0 mg, of MiniQuick were selected to encompass the whole range. The dose of 0.03 mg/kg body weight was considered to result in too large an injection volume for the lowest MiniQuick strength, 0.2 mg, to be used. These studies were conducted with adult growth hormone deficient patients to remove possible variability and analytical error due to endogenous growth hormone. Patients were required to be abstinent from somatropin injections for at least one week before the start of the study.

Both strengths of GENOTROPIN MiniQuick met the standard criterion for bioequivalence with GENOTROPIN in that the 90% confidence interval (CI) for ratio between test and reference formulations was between 80.00% and 125.00% and the point estimate for the analogous Cmax ratio was between 80.00% and 125.00%. The corrected AUC ratio for 0.4 mg MiniQuick/GENOTROPIN was 89.14 (90% CI, 81.14 – 97.93) and for 2.0 mg MiniQuick/GENOTROPIN was 94.72 (90% CI, 85.44 – 105.01). The corresponding C_{max} ratios for the 0.4 mg and 2.0 mg formulations were 87.54 and 101.06 respectively.

TOXICOLOGY

Animal Toxicity

Acute Toxicity
A single subcutaneous dose of 300 mg/kg of GENOTROPIN (somatropin for injection) (more than 8000 times the intended human dose) was given to Sprague Dawley rats with no lethality during the 48 hour observation period.

Short Term Toxicity
The general toxicity of GENOTROPIN in Sprague Dawley rats has been studied after repeated intramuscular administration of 0.34 (0.125 mg), 1.7 (0.625 mg) and 8.14 (3.125 mg) IU/kg/day. A positive control group received pituitary human growth hormone (pit hGH) at 3.125 mg/ day, and a negative control group received glycine phosphate solution.

No deaths occurred and no drug related clinical signs were observed. A dose related increase in body weight gain, as compared to the controls, was recorded in females receiving 0.625 or 3.125 mg/kg/day recombinant somatropin. Females given pit hGH (3.125 mg/kg/day) also showed increased weight gain. The body weight gain of male rats was similar in all groups, including control. The food consumption of drug treated animals was comparable to that of the controls, except for an increase in food intake in females given 3.125 mg/kg/day of either recombinant somatropin or pit hGH.

Organ weight analysis showed statistically significant increased absolute and relative group mean weights of the adrenals in males, but not in females, receiving 0.625 or 3.125 mg/kg/day of GENOTROPIN, as well as in males given pit hGH. A marginal increase in the absolute group mean weights of the ovaries was recorded in females receiving 3.125 mg/kg/day of recombinant somatropin or pit hGH.

In total, intramuscular treatment with GENOTROPIN for one month was well tolerated in all treatment groups. A growth promoting effect (increase in body weight gain) was demonstrated in female rats at the two highest dose levels, but in none of the male groups, with an associated increase in food consumption. A small uterine nodule, compatible with a decidual cell reaction, was observed in one rat from the high dose GENOTROPIN group. A hormonal influence was also evidenced by a dose related mammary gland hyperplasia in females at the two highest dose levels of GENOTROPIN as well as in females from the pit hGH group.

Chronic Toxicity
The general toxicity of GENOTROPIN has been evaluated in cynomolgus monkeys following daily subcutaneous injections of 0.13, 0.65 or 3.23 mg/kg for 52 weeks. Administration at dose levels up to 3.23 mg/kg did not produce any clinical toxic effects. Drug-related changes associated with a dose level of 3.23 mg/kg were a decrease of serum progesterone levels at the estimated luteal phase and a tendancy to reduce serum prolactin levels for males and females. In addition, there was an indication of increased immunoreactivite insulin levels in serum from male animals. Prolonged menstual cycles, and/or absence of cyclicity was seen in some high dose females.

Microscopic examination showed a dose-related adipocyte hypertrophy in the abdominal fat in treated males and females alveolar dilatation/hyperplasia of the mammary gland. The alveolar dilitation was found in three females from each of the treatment groups. Mammary gland hyperplasia was seen only in high dose animals (one male and one female). The microscopic findings showed regression during the recovery period.

Reproductive Studies
Studies for effects on embro-fetal development carried out with GENOTROPIN at doses of 1, 3 and 10 IU/kg/day administered SC in the rat and 0.25, 1 and 4 IU/kg/day administered IM in the rabbit, resulted in effects on maternal body weight gains (increased in rats and decreased in rabbits) but were not teratogenic. In rats receiving SC doses during gametogenesis and up to seven days of pregnancy, 10 IU/kg/day produced anestrus or extended estrus cycles and fewer and less motile sperm in males. When given to pregnant female rats (days one to seven of gestation) at 10 IU/kg/day a very slight increase in fetal deaths were observed. At 3 IU/kg/day rats showed slightly extended estrus cycles, whereas at 1 IU/kg/day no effects were noted.

In perinatal and postnatal studies in rats, GENOTROPIN doses of 1, 3 and 10 IU/kg/day produced growth-promoting effects in the dams but not in the fetuses. Young rats at the highest doses 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 offspring due to GENOTROPIN.

Mutagenicity Studies
No potential mutagenicity of GENOTROPIN was revealed in a battery of mutagenicity tests including bacterial tests to demonstrate induction of gene mutations (Ames test in Salmonella and E. coli), a test to demonstrate the chromosome damaging potential in human cells cultured in vitro (human lymphocytes), a test to demonstrate the induction of gene mutations in mammalian cells grown in vitro (mouse lymphoma L5178Y cells) and a test to demonstrate the induction of chromosomal damage in vivo (bone marrow cells in rats).

Immunotoxicity
In the three month monkey study the immunological investigation comprised assays for antibodies both to growth hormone and to periplasmic E. coli peptides in selected animals at completion of the treatment period. No antibodies could be detected either to growth hormone or to periplasmic E. coli peptides. Furthermore, no changes suggestive of an immunological response or changes in the immune system were seen.

Human Toxicity

Juvenile
The percentage of patients in the clinical studies who experienced adverse events possibly attributable to GENOTROPIN were low.

Injection site reactions were reported by 10.7% of the patients treated. Most common were pain and/or burning sensation; however atrophy, fibrosis, nodules, rash, inflammatory pigmentation and bleeding were also reported. Mild hypothyroidism reversed by supplemental thyroid preparations was reported by 3.8% of the subjects; none were withdrawn from treatment. Occasional hematuria was reported by

0.5% of respondents.

Adult
62% of patients reported adverse events in the first 6 months of treatment. The rate of adverse events reported was the same (35%) in the placebo group as it was in patients treated with pituitary growth hormone from 6-12 months. The most common events associated with treatment were edema (37.4% of patients), arthralgia (19.1%), musculo-skeletal (MS) pain (15.7%), paraesthesia (7.8%) and MS stiffness (6.1%). Myalgia, carpal tunnel syndrome, hypoesthesia, back pain and headache were also infrequently reported. Only 1 serious adverse event, the development of diabetes mellitus, was probably related to treatment.

Anti Somatropin Antibodies
419 patients were evaluated for anti somatropin (anti hGH) antibodies, in the clinical studies. Of these, six were positive for anti hGH antibodies at baseline. Three of these six became negative during the study. Of the remaining 413, 9 developed detectable anti hGH antibodies.

Anti periplasmic *E. coli* peptides
GENOTROPIN preparation contains a very small amount of periplasmic E. coli peptides. In the clinical studies few patients developed any evidence of a positive antibody titer during the trials and most of these positive findings had reverted to undetectable by 12 months. As normal subjects may show low levels of antibodies due to E. coli gastroenteritis there would appear to be little risk from these results.

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PART III: CONSUMER INFORMATION

[Pr]Genotropin GoQuick

Somatropin [rDNA origin] for injection

This leaflet is part III of a three-part "Product Monograph" published when Genotropin was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Genotropin. Contact your doctor if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

In children, Genotropin is used to treat the following growth problems:

- If you are not growing properly and you do not have enough of your own growth hormone.
- If you have Turner syndrome. Turner syndrome is a chromosomal error in girls that can affect growth - your doctor will have told you if you have this.
- If you have Prader-Willi syndrome, a genetic disorder that can reduce your growth, increase the amount of fat and decrease the amount of muscle in your body - your doctor will have told you if you have this.
- If you were small or too light at birth. Growth hormone **may** help you grow taller if you have not been able to catch up or maintain normal growth by two years of age or later.
- If you have idiopathic (unknown cause) short stature.

In adults, Genotropin is used to treat persons with pronounced growth hormone deficiency. This can start during adult life, or it can continue from childhood.

If you have been treated with Genotropin for growth hormone deficiency during childhood, your growth hormone status will be retested after completion of growth. If severe growth hormone deficiency is confirmed, your doctor will propose continuation of Genotropin treatment.

What it does:

Genotropin is a recombinant human growth hormone (also called somatropin). It has the same structure as natural human growth hormone which is needed for bones and muscles to grow. It also helps your fat and muscle tissues to develop in the right amounts. Recombinant means it is made using bacteria instead of being taken out of human or animal tissue.

When it should not be used:

- You are allergic (hypersensitive) to somatropin or any of the other ingredients of Genotropin.
- You have an active tumour. Tumours must be inactive and you must have finished your anti-tumour treatment before you start using Genotropin.
- You are seriously ill (for example, complications following open heart surgery, abdominal surgery, acute respiratory failure, accidental trauma or similar conditions). If you are about to have, or have had, a major operation, or go into hospital for any reason, tell your doctor and remind the other doctors you are seeing that you use growth hormone.
- Genotropin has been prescribed to stimulate growth but you have already stopped growing (the growth plates on your long bones are closed).
- In patients with Prader-Willi syndrome who are very obese or have severe breathing problems. There have been reports of sudden deaths in children with Prader-Willi syndrome who were treated with growth hormone and had one or more of the following risk factors: severe obesity, breathing problems, colds or lung infections.
- In patients with diabetic retinopathy, a complication of diabetes that results from damage to the blood vessels of the light-sensitive tissue at the back of the eye (retina).
- You have uncontrolled diabetes or active psychosis.

What the medicinal ingredient is:

Genotropin is a recombinant human growth hormone (also called somatropin).

What the important nonmedicinal ingredients are:

Each cartridge in the pre-filled pen contains 5mg, 5.3 mg or 12 mg of somatropin. The Genotropin powder contains glycine, sodium dihydrogen phosphate anhydrous, disodium phosphate anhydrous and mannitol.
The diluent (solution for dissolving somatropin) contains water for injection, mannitol and metacresol.

What dosage forms it comes in:

Genotropin is presented in a cartridge with two sections that is contained in a multi-dose, disposable pre-filled pen called GoQuick. One section contains the powder for solution for injection and the other contains the liquid for solution for injection. The powder is white and the liquid is clear.

When mixed together, the powder and the liquid make 1 ml of solution for injection.

Genotropin is available in pack sizes of 1 GoQuick pre-filled pen and 5 GoQuick pre-filled pens. Not all strengths and pack sizes are marketed in Canada.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Before taking GENOTROPIN, talk to your doctor or pharmacist if:

- **The child has Prader-Willi Syndrome and breathing**

problems, sleep apnea (not breathing while sleeping), snoring, severe obesity, uncontrolled diabetes, active psychosis or a respiratory infection.

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

After the GENOTROPIN powder has been dissolved it must be water-clear and free of particles.

BEFORE using Genotropin, the patient or caregiver should tell the doctor:

- If the patient is at risk of developing diabetes, the doctor will need to monitor their blood sugar level during treatment with Genotropin.
- If the patient has diabetes, they should closely monitor their blood sugar level during treatment with Genotropin and discuss the results with their doctor to determine whether they need to change the dose of their medicines to treat diabetes.
- If the patient is receiving treatment with thyroid hormones it may be necessary to adjust their thyroid hormone dose.
- If the patient is taking growth hormone to stimulate growth and walk with a limp or if they start to limp during their growth hormone treatment due to pain in their hip, they should inform their doctor.
- If the patient develops a strong headache, visual disturbances or vomiting they should inform their doctor about it.
- If their doctor confirms that the patient has developed inflammation of the muscles near the injection site because of the preservative metacresol, they should use a Genotropin product without metacresol.
- If the patient is receiving Genotropin for growth hormone deficiency following a previous tumour, they should be examined regularly for recurrence of the tumour.
- If the patient is a survivor of childhood cancer.
- If the patient, especially a child, develops severe abdominal pain (inflammation of the pancreas).
- If the patient is, or plans to become pregnant or is breast-feeding.
- If the patient develop a limp while being treated with GENOTROPIN.
- If the patient has Turner syndrome and develops an ear infection or headaches her doctor should be told about these problems.
- If the patient has hypopituitarism and is receiving standard hormone replacement therapy, the doctor should monitor the hormone replacement therapy closely during GENOTROPIN treatment.

After starting Genotropin treatment some patients may need to start thyroid hormone replacement.

Progression of pre-existing scoliosis (curvature of the spine) can occur in children who have rapid growth.

The patient should not use Genotropin if they are pregnant or are trying to become pregnant.

INTERACTIONS WITH THIS MEDICATION

Please tell your doctor or pharmacist if you are using or have recently used any other medicines, including medicines obtained without a prescription.

You should tell your doctor if you are using:

- medicines to treat diabetes,
- thyroid hormones,
- synthetic adrenal hormones (corticosteroids),
- sex hormones (for example oral estrogens),
- cyclosporine (a medicine that weakens the immune system after transplantation),
- medicines to control epilepsy (anticonvulsants).

Your doctor may need to adjust the dose of these medicines or the dose of Genotropin.

PROPER USE OF THIS MEDICATION

Recommended dosage

The dose depends on your size, the condition for which you are being treated and how well growth hormone works for you. Everyone is different. Your doctor will advise you about your individualized dose of Genotropin in milligrams (mg) from either your body weight in kilograms (kg), as well as your treatment schedule. Do not change the dosage and treatment schedule without consulting your doctor.

Children with growth hormone deficiency:
0.16-0.24 mg/kg body weight per week. Higher doses can be used. When growth hormone deficiency continues into adolescence, Genotropin should be continued until completion of physical development.

Children with Turner syndrome:
0.33 mg/kg body weight per week.

Children with idiopathic short stature:
UP TO 0.47 mg/kg body weight per week

Children born smaller or lighter than expected and with growth disturbance:
UP TO 0.48 mg/kg body weight per week. Your doctor will determine the most appropriate dose and length of treatment. Treatment should be discontinued if: i) after the first year if you are not responding or ii) if you have reached your final height and stopped growing.

Adults with growth hormone deficiency:
You should start with 0.15-0.3 mg per day.
This dosage should be gradually increased or decreased according to blood test results as well as clinical response and side effects.

Children with Prader-Willi syndrome:
0.035 mg/kg body weight per day or 1.0 mg/m^2 body surface area per day. The weekly dosage should not exceed 0.24 mg/kg. Treatment should not be used in children who have almost stopped growing after puberty.

If you are a woman on oral estrogen replacement, a higher dose of growth hormone may be required to achieve the treatment goal. Conversely, if you are a woman on somatropin and you discontinue oral estrogen therapy, the dose of somatropin may need to be reduced to avoid excess of growth hormone and/or side effects.

Follow the instructions given to you by your doctor.

Injecting Genotropin
Genotropin is intended for subcutaneous use. This means that it is injected through a short injection needle into the fatty tissue just under your skin. Your doctor should have already shown you how to use Genotropin. Always inject Genotropin exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Read carefully the GoQuick Instructions for Use included in this package leaflet. You must use the pen as described in the Instructions for Use.

The needle must be screwed on to the GoQuick pen before mixing. Use a new needle before each injection. Needles must not be re-used.

- Preparing the injection:

You can take your Genotropin out of the refrigerator up to 2 hours before your injection. This lets it warm up slightly and can make your injections more comfortable. Once the injection is administered, the reconstituted solution must be returned to the refrigerator. The cycle can be repeated over the allowable 4 week period.

The two-chamber cartridge that contains both the growth hormone and the dissolving liquid is contained in the GoQuick pen. The growth hormone and the dissolving liquid are mixed together by twisting the cartridge holder (see the detailed steps in Instructions for Use). Dissolve the powder by gently tipping the GoQuick pen back and forth 5-10 times until the powder is dissolved.

When you are mixing your Genotropin, **DO NOT SHAKE** the pen. Mix it gently. Shaking the solution could make your growth hormone foam and damage the active substance. Check the solution and do not inject if the solution is cloudy or has particles in it.

- Injecting Genotropin:

Remember to wash your hands and clean your skin first.

Inject your growth hormone at about the same time every day. Bedtime is a good time because it is easy to remember. It is also natural to have a higher level of growth hormone at night.

Most people do their injections into their thigh or their bottom. Do your injection in the place you have been shown by your doctor. Fatty tissue of the skin can shrink at the site of injection. To avoid this, use a slightly different place for your injection each time. This gives your skin and the area under your skin time to recover from one injection before it gets another one in the same place.

Remember to put your Genotropin back in the refrigerator straight after your injection.

If you use more Genotropin than you should
If you inject much more than you should, contact your doctor or pharmacist as soon as possible. Your blood sugar level could fall too low and later rise too high. You might feel shaky, sweaty, sleepy or "not yourself", and you might faint.

If you forget to use Genotropin
Do not use a double dose to make up for a forgotten dose.
It is best to use your growth hormone regularly. If you forget to use a dose, have your next injection at the usual time the next day. Keep a note of any missed injections and tell your doctor at your next check-up.

If you stop using Genotropin
Ask for advice from your doctor before you stop using Genotropin.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

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

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, Genotropin can cause side effects, although not everybody gets them.

Common side effects (likely to occur in fewer than 1 in 10 patients) include:
Formation of antibodies to the injected growth hormone but these do not seem to stop the growth hormone from working.

In children:

- Temporary reddening, itchiness or pain at the injection site.
- Rash
- Raised itchy bumps on the skin

In adults:

- Numbness / tingling,
- Stiffness in the arms and legs, joint pain, muscle pain,
- Water retention (which shows as puffy fingers or swollen ankles). These symptoms may be seen for a short time at the start of treatment, but they

disappear spontaneously or when the dosage is lowered.

These common side effects in adults may start within the first months of treatment and may either stop spontaneously or if your dose is reduced.

Uncommon side effects (likely to occur in fewer than 1 in 100 patients) include:
In children:

- Numbness / tingling,
- Stiffness in the arms and legs, joint pain, muscle pain,
- Water retention (which shows as puffy fingers or swollen ankles, for a short time at the start of treatment).
- Itching

In adults:

- Pain or burning sensation in the hands or underarms (known as Carpal Tunnel Syndrome).

Rare side effects (likely to occur in fewer than 1 in 1,000 patients) include:

- Type 2 diabetes mellitus,
- Intracranial hypertension (increased pressure within the skull due to swelling of the brain) which causes symptoms such as a strong headache that doesn't go away, vision problems, nausea or vomiting. Call your doctor if the patient has any of these symptoms.
- Rash
- Itching
- Raised itchy bumps on the skin

Very rare side effects (likely to occur in fewer than 1 in 10,000 patients) include:

- Leukemia
- hair loss
- aggressiveness
- headache
- back pain

The skin around the injection area can get uneven or lumpy, but this should not happen if you inject in a different place each time.

A very rare side effect that can occur because of the preservative metacresol is inflammation of the muscles near the injection site. If your doctor confirms that you have developed this, you should use a Genotropin product without metacresol.

Slipped capital femoral epiphysis and Legg-Calve-Perthes disease may be considered by your doctor if discomfort or pain in the hip or knee is experienced whilst being treated with Genotropin.

Since Genotropin has been on the market, serious strong reactions have occurred in patients including very bad allergic reactions that can cause difficulty breathing and swelling of the face and lips. Patients and caregivers should get medical attention immediately if an allergic reaction occurs.

There have been rare cases of sudden death in patients with Prader-Willi syndrome. However, no link has been made between these cases and treatment with Genotropin.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

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

HOW TO STORE IT

Keep out of the reach and sight of children.

Do not use Genotropin after the expiry date which is stated on the pack. The expiry date refers to the last day of that month.

Before mixing the powder with the liquid, your growth hormone should be stored in a refrigerator (2° to 8°C) until no later than the expiry date. It can be stored for a maximum of 4 weeks unrefrigerated (at or below 25°C). During and/or at the end of the 4 weeks period, the product should not be put back in the refrigerator. After this it must be discarded.

Genotopin is sensitive to light. You should keep the GoQuick pen in the outer carton in order to protect your Genotropin from light.

After mixing the powder with the liquid, Genotropin must be stored in a refrigerator (2° to 8°C), for up to 4 weeks. The reconstituted solution can remain at room temperature for up to 2 hours prior to each injection. Once the injection is administered, the reconstituted solution must be returned to the refrigerator. The cycle can be repeated over the allowable 4 week period. If you use the needle guard, store your pen with the needle guard and black cap in place. If you do not use the needle guard, store your pen with the white pen cap in place. See the Instructions for Use. These measures will help to protect your Genotropin from light.

Do not freeze or expose Genotropin to frost. If it freezes, do not use it.

Never throw away needles with your ordinary garbage. When you have finished with a needle, you must discard it carefully so that no-one will be able to use it or prick themselves on it. You can get a special "sharps" bin from your hospital or growth clinic.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

REPORTING SUSPECTED SIDE EFFECTS

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

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to:**

    Canada Vigilance Program
    Health Canada
    Postal Locator 0701E
    Ottawa, Ontario
    K1A 0K9

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

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

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at www.pfizer.ca or can be obtained by contacting the sponsor, Pfizer Canada ULC, at: 1-800-463-6001 (Medical Information)

This leaflet was prepared by Pfizer Canada ULC
Last revised: L3 28 July 2020

PART III: CONSUMER INFORMATION

[Pr]Genotropin MiniQuick

Somatropin [rDNA origin] for injection

This leaflet is part III of a three-part "Product Monograph" published when Genotropin was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Genotropin. Contact your doctor if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

In children, Genotropin MiniQuick is used to treat growth problems:

- If you are not growing properly and you do not have enough of your own growth hormone.
- If you have Turner syndrome. Turner syndrome is a chromosomal error in girls that can affect growth - your doctor will have told you if you have this.
- If you have Prader-Willi syndrome, a genetic disorder that can reduce your growth, increase the amount of fat and decrease the amount of muscle in your body - your doctor will have told you if you have this.
- If you were small or too light at birth. Growth hormone **may** help you grow taller if you have not been able to catch up or maintain normal growth by two years of age or later.
- If you have idiopathic (unknown cause) short stature.

In adults, Genotropin MiniQuick is used to treat persons with pronounced growth hormone deficiency. This can start during adult life, or it can continue from childhood.

If you have been treated with Genotropin MiniQuick for growth hormone deficiency during childhood, your growth hormone status will be retested after completion of growth. If severe growth hormone deficiency is confirmed, your doctor will propose continuation of Genotropin MiniQuick treatment.

What it does:

Genotropin MiniQuick is a recombinant human growth hormone (also called somatropin). It has the same structure as natural human growth hormone which is needed for bones and muscles to grow. It also helps your fat and muscle tissues to develop in the right amounts. Recombinant means it is made using bacteria instead of being taken out of human or animal tissue.

When it should not be used:

- You are allergic (hypersensitive) to somatropin or any of the other ingredients of Genotropin MiniQuick.
- You have an active tumour. Tumours must be inactive and you must have finished your anti-tumour treatment before you start using Genotropin MiniQuick.
- You are seriously ill (for example, complications following open heart surgery, abdominal surgery, acute respiratory failure, accidental trauma or similar conditions). If you are about to have, or have had, a major operation, or go into hospital for any reason, tell your doctor and remind the other doctors you are seeing that you use growth hormone.
- Genotropin MiniQuick has been prescribed to stimulate growth but you have already stopped growing (the growth plates on your long bones are closed).
- In patients with Prader-Willi syndrome who are very obese or have severe breathing problems. There have been reports of sudden deaths in children with Prader-Willi syndrome who were treated with growth hormone and had one or more of the following risk factors: severe obesity, breathing problems, colds or lung infections.
- In patients with diabetic retinopathy, a complication of diabetes that results from damage to the blood vessels of the light-sensitive tissue at the back of the eye (retina).
- You have uncontrolled diabetes or active psychosis.

What the medicinal ingredient is:

The active substance is recombinant somatropin.

What the important nonmedicinal ingredients are:

Each syringe contains 0.2 mg, 0.4 mg, 0.6 mg, 0.8 mg, 1.0 mg, 1.2 mg, 1.4 mg, 1.6 mg, 1.8 mg, or 2.0 mg of somatropin. The other ingredients in the powder are: glycine, mannitol, sodium dihydrogen phosphate anhydrous, and disodium phosphate anhydrous. The ingredients in the liquid are: water for injection and mannitol.
Genotropin MiniQuick does not contain preservatives.

What dosage forms it comes in:

Genotropin MiniQuick is presented in a cartridge with two sections, in a single dose syringe. One section contains the powder for solution for injection and the other contains the liquid for solution for injection. The powder is white and the liquid is clear.

When mixed together, the powder and the liquid make 0.25 ml of solution for injection.

Genotropin MiniQuick is available in pack sizes of 4 syringes, 7 syringes and 28 syringes. Not all strengths and pack sizes are marketed in Canada.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Before taking GENOTROPIN, talk to your doctor or pharmacist if:

- **The child has Prader-Willi Syndrome and breathing problems, sleep apnea (not breathing while sleeping), snoring, severe obesity, uncontrolled diabetes, active psychosis or a respiratory infection.**

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

After the GENOTROPIN powder has been dissolved it must be water-clear and free of particles.

BEFORE using Genotropin, the patient or caregiver should tell the doctor:

- If the patient is at risk of developing diabetes, the doctor will need to monitor their blood sugar level during treatment with Genotropin.
- If the patient has diabetes, they should closely monitor their blood sugar level during treatment with Genotropin and discuss the results with their doctor to determine whether they need to change the dose of their medicines to treat diabetes.
- If the patient is receiving treatment with thyroid hormones it may be necessary to adjust their thyroid hormone dose.
- If the patient is taking growth hormone to stimulate growth and walk with a limp or if they start to limp during their growth hormone treatment due to pain in their hip, they should inform their doctor.
- If the patient develops a strong headache, visual disturbances or vomiting they should inform their doctor about it.
- If their doctor confirms that the patient has developed inflammation of the muscles near the injection site because of the preservative metacresol, they should use a Genotropin product without metacresol.
- If the patient is receiving Genotropin for growth hormone deficiency following a previous tumour, they should be examined regularly for recurrence of the tumour.
- If the patient is a survivor of childhood cancer.
- If the patient, especially a child, develops severe abdominal pain (inflammation of the pancreas).
- If the patient is, or plans to become pregnant or is breast-feeding.
- If the patient develop a limp while being treated with GENOTROPIN.
- If the patient has Turner syndrome and develops an ear infection or headaches her doctor should be told about these problems.
- If the patient has hypopituitarism and is receiving standard hormone replacement therapy, the doctor should monitor the hormone replacement therapy closely during GENOTROPIN treatment.

After starting Genotropin treatment some patients may need to start thyroid hormone replacement.

Progression of pre-existing scoliosis (curvature of the spine) can occur in children who have rapid growth.

The patient should not use Genotropin if they are pregnant or are trying to become pregnant.

INTERACTIONS WITH THIS MEDICATION

Please tell your doctor or pharmacist if you are using or have recently used any other medicines, including medicines obtained without a prescription.

You should tell your doctor if you are using:

- medicines to treat diabetes,
- thyroid hormones,
- synthetic adrenal hormones (corticosteroids),
- sex hormones (for example oral estrogens),
- cyclosporine (a medicine that weakens the immune system after transplantation),
- medicines to control epilepsy (anticonvulsants).

Your doctor may need to adjust the dose of these medicines or the dose of Genotropin MiniQuick.

PROPER USE OF THIS MEDICATION

Recommended dosage

The dose depends on your size, the condition for which you are being treated and how well growth hormone works for you. Everyone is different. Your doctor will advise you about your individualized dose of Genotropin in milligrams (mg) from either your body weight in kilograms (kg), as well as your treatment schedule. Do not change the dosage and treatment schedule without consulting your doctor.

Children with growth hormone deficiency:
0.16-0.24 mg/kg body weight per week. Higher doses can be used. When growth hormone deficiency continues into adolescence, Genotropin should be continued until completion of physical development.

Children with Turner syndrome:
0.33 mg/kg body weight per week.

Children with idiopathic short stature:
UP TO 0.47 mg/kg body weight per week

Children born smaller or lighter than expected and with growth disturbance:
UP TO 0.48 mg/kg body weight per week. Your doctor will determine the most appropriate dose and length of treatment. Treatment should be discontinued if: i) after the first year if you are not responding or ii) if you have reached your final height and stopped growing.

Adults with growth hormone deficiency:
Adults with growth hormone deficiency:
You should start with 0.15-0.3 mg per day.
This dosage should be gradually increased or decreased according to blood test results as well as clinical response and side effects.

Children with Prader-Willi syndrome:
0.035 mg/kg body weight per day or 1.0 mg/m^2 body surface area per day. Treatment should not be used in children who have almost stopped growing after puberty.

If you are a woman on oral estrogen replacement, a higher dose of growth hormone may be required to achieve the treatment goal. Conversely, if you are a woman on somatropin and you discontinue oral estrogen therapy, the dose of somatropin may need to be reduced to avoid excess of growth hormone and/or side effects.

Follow the instructions given to you by your doctor.

Injecting Genotropin MiniQuick
Genotropin MiniQuick is intended for subcutaneous use. This means that it is injected through a short injection needle into the fatty tissue just under your skin. Your doctor should have already shown you how to use Genotropin MiniQuick. Always inject Genotropin MiniQuick exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

If you cannot remember what to do, do not try to do your injection. Ask your doctor to show you again.

You can take your growth hormone out of the refrigerator half an hour before your injection. This lets it warm up slightly and can make your injections more comfortable.

Remember to wash your hands and clean your skin first.

Inject your growth hormone at about the same time every day. Bedtime is a good time because it is easy to remember. It is also natural to have a higher level of growth hormone at night.

Most people do their injections into their thigh or their bottom. Do your injection in the place you have been shown by your doctor. Fatty tissue of the skin can shrink at the site of injection. To avoid it, use a slightly different place for your injection each time. This gives your skin and the area under your skin time to recover from one injection before it gets another one in the same place.

If you use more Genotropin MiniQuick than you should
If you inject much more than you should, contact your doctor or pharmacist as soon as possible. Your blood sugar level could fall too low and later rise too high. You might feel shaky, sweaty, sleepy or "not yourself", and you might faint.

If you forget to use Genotropin MiniQuick
Do not take a double dose to make up for a forgotten dose. It is best to take your growth hormone regularly. If you forget to take a dose, have your next injection at the usual time the next day. Keep a note of any missed injections and tell your doctor at your next check-up.

If you stop using Genotropin MiniQuick
Ask for advice from your doctor before you stop using Genotropin MiniQuick.

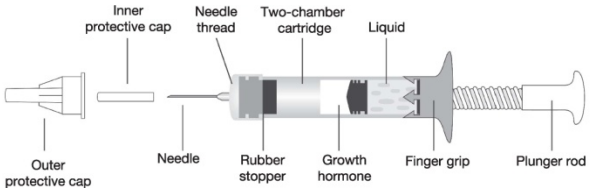
If you have any further questions on the use of this product, ask your doctor or pharmacist.

Detailed Instructions for use
Genotropin MiniQuick is a syringe used to mix and administer a single dose of Genotropin (growth hormone).

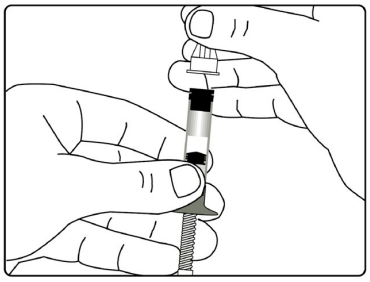
Each Genotropin MiniQuick comes preloaded with a cartridge with two sections and a needle. If you need additional needles, ask for the same Becton Dickinson Micro-Fine needles provided with the MiniQuick. The injection volume is always 0.25 ml.

The Genotropin MiniQuick is disposable; after you have administered a dose, dispose of it as described by your pharmacist.

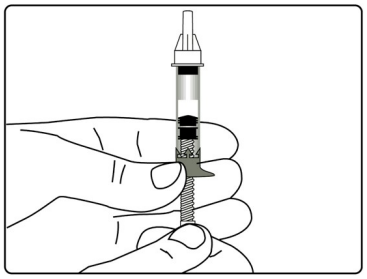
The diagram below identifies the different components.



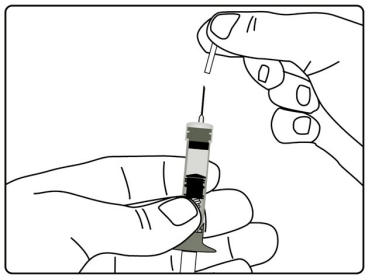
The cartridge of Genotropin MiniQuick contains the growth hormone powder in one section and a liquid in the other. When you turn the plunger rod clockwise, the growth hormone powder and the liquid mix and the powder dissolves.



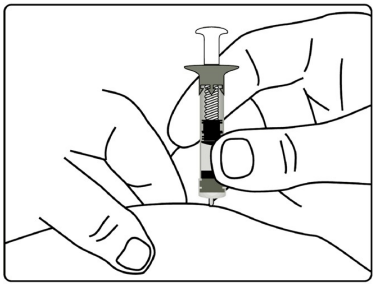
1. Peel the paper covering from the injection needle. Attach the needle onto the Genotropin MiniQuick by pushing it down and turning it until it no longer can turn. Make sure the needle is positioned squarely onto the end of the rubber stopper before screwing it to the Genotropin MiniQuick.



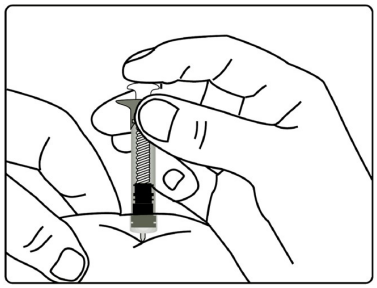
2. Hold the Genotropin MiniQuick with the needle pointing upwards. Turn the plunger rod clockwise until it will go no further.
DO NOT shake the solution. Mix it gently. Shaking the solution could make your growth hormone foam and damage the active substance. Check the solution for clarity, and only use clear solutions that are particle free.



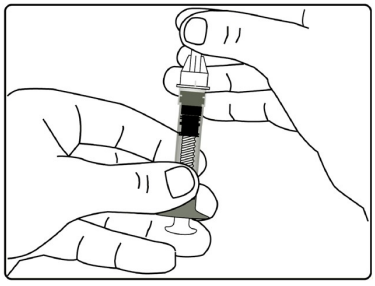
3. Remove the inner and outer protective caps of the needle.



4. Pinch a fold of skin at the injection site firmly and push the needle into the skinfold.



5. Push the plunger rod as far as possible to inject the entire content of the Genotropin MiniQuick. Wait a few seconds before withdrawing the needle to ensure that all the growth hormone is injected.



6. After injection replace the outer protective cap on the needle. Follow your standard guidelines for disposal of syringe and needle.

Additional Information

Is it a problem if I see air bubbles in the syringe?
No. There is no need to remove the air from Genotropin MiniQuick. The small amount of air in the syringe has no consequence on the injection.

What should I do if there is resistance when I turn the plunger rod (step 2) or when I make the injection (step 5)?
The resistance could be because the needle has been inserted at an angle into the rubber stopper.
Carefully replace the outer protective cap (the opaque white one) over the needle and unscrew counter clockwise to remove the needle. Hold the MiniQuick syringe with the needle-end pointing up and reposition the needle squarely on top of the syringe. Screw the needle into the syringe.

What should I do if the needle is damaged or bent?
Discard the needle and use a new needle with the MiniQuick.

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

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, Genotropin MiniQuick can cause side effects, although not everybody gets them.

Common side effects (likely to occur in fewer than 1 in 10 patients) include:
Formation of antibodies to the injected growth hormone but these do not seem to stop the growth hormone from working.

In children:
- Temporary reddening, itchiness or pain at the injection site.
- Rash
- Raised itchy bumps on the skin

In adults:
- Numbness / tingling,
- Stiffness in the arms and legs, joint pain, muscle pain,
- Water retention (which shows as puffy fingers or swollen ankles). These symptoms may be seen for a short time at the start of treatment, but they disappear spontaneously or when the dosage is lowered.

These common side effects in adults may start within the first months of treatment and may either stop spontaneously or if your dose is reduced.

Uncommon side effects (likely to occur in fewer than 1 in 100 patients) include:
In children:
- Numbness / tingling,
- Stiffness in the arms and legs, joint pain, muscle pain,
- Water retention (which shows as puffy fingers or swollen ankles, for a short time at the start of treatment).
- Itching

In adults:
- Pain or burning sensation in the hands or underarms(known as Carpal Tunnel Syndrome).

Rare side effects (likely to occur in fewer than 1 in 1,000 patients) include:
- Type 2 diabetes mellitus,
- Intracranial hypertension (increased pressure within the skull due to swelling of the brain) which causes symptoms such as a strong headache that doesn't go away, vision problems, nausea or vomiting. Call your doctor if the patient has any of these symptoms.
- Rash
- Itching
- Raised itchy bumps on the skin

Very rare side effects (likely to occur in fewer than 1 in 10,000 patients) include:

- Leukemia
- hair loss
- aggressiveness
- headache
- back pain

The skin around the injection area can get uneven or lumpy, but this should not happen if you inject in a different place each time.

Slipped capital femoral epiphysis and Legg-Calve-Perthes disease may be considered by your doctor if discomfort or pain in the hip or knee is experienced whilst being treated with Genotropin.

Since Genotropin has been on the market, serious strong reactions have occurred in patients including very bad allergic reactions that can cause difficulty breathing and swelling of the face and lips. Patients and caregivers should get medical attention immediately if an allergic reaction occurs.

There have been rare cases of sudden death in patients with Prader-Willi syndrome. However, no link has been made between these cases and treatment with Genotropin.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

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

HOW TO STORE IT

Keep out of the reach and sight of children.

Do not use Genotropin MiniQuick after the expiry date which is stated on the pack. The expiry date refers to the last day of that month.

Before mixing the powder with the liquid, your growth hormone should be stored in a refrigerator (2°C to 8°C) until the expiry date. It can be stored for up to 6 months unrefrigerated (at or below 25ºC). During and/or at the end of this 6 months period, the product should not be put back in the refrigerator. After this it must be discarded.

Genotopin MiniQuick is sensitive to light. You should keep the container in the outer carton in order to protect your Genotropin MiniQuick from light.

After mixing the powder with the liquid, you should use your growth hormone immediately. If necessary you can store it in the refrigerator (2°C to 8°C) for up to 24 hours in the outer carton in order to protect your Genotropin MiniQuick from light. If you do not use it within 24 hours, do not use it.

Do not freeze or expose Genotropin MiniQuick to frost. If it freezes, do not use it.

Do not use Genotropin MiniQuick if you notice particles, if the solution is not clear or if it has frozen.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required.

Never throw away needles or empty syringes with your ordinary garbage. When you have finished with a needle, you must discard it carefully so that no-one will be able to use it or prick themselves on it. You can get a special 'sharps' bin from your hospital or growth clinic.

These measures will help to protect the environment.

REPORTING SUSPECTED SIDE EFFECTS

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

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

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

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

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at www.pfizer.ca or can be obtained by contacting the sponsor, Pfizer Canada ULC, at: 1-800-463-6001 (Medical Information)

This leaflet was prepared by Pfizer Canada ULC
Last revised L3 28 July 2020

GENOTROPIN®GOQUICK™ 5

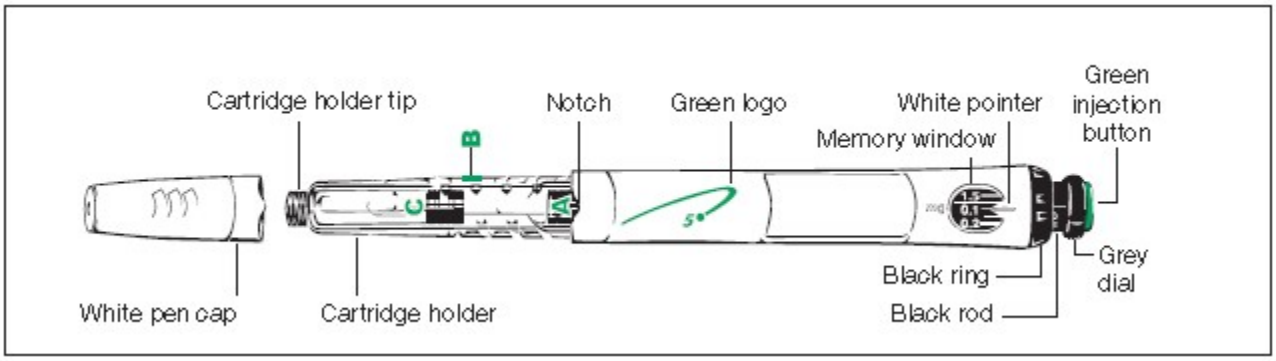
INSTRUCTIONS FOR USE

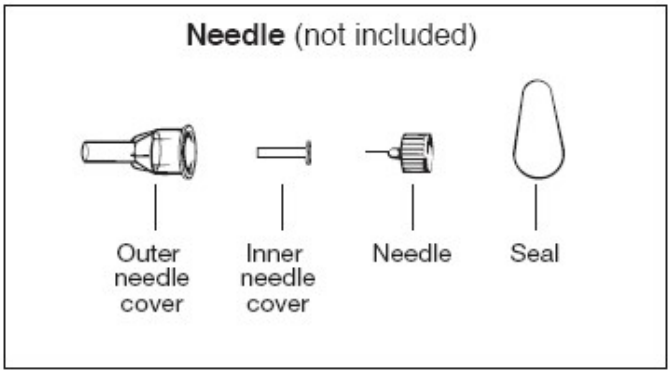
Important Information
Please read these instructions completely before using GoQuick.
If you have any questions about your dose or your treatment with Genotropin, call your doctor or nurse.

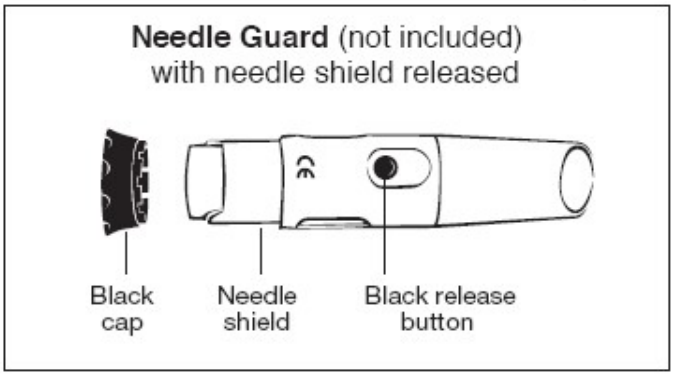
About GoQuick
GoQuick is a prefilled, multidose, disposable injection pen that holds 5.0 mg of somatropin. After reconstitution the concentration of somatropin is 5.0 mg per mL. The Genotropin in the pen is mixed only once, when you start a new pen. A single pen can be used up to 28 days after mixing. You never have to change cartridges. When the pen is empty, you just start a new pen.

The pen has dose memory. The dose is set once on a new pen. The pen then gives the same dose for each injection. You can use the pen with or without the optional needle guard.

Before You Use GoQuick
- Get training from your doctor or nurse.
- Know your dose. Know the pen parts.
- Make sure you have the pen with the green injection button.
- Wash your hands.



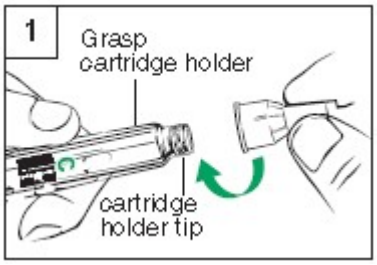




Setting Up and Using a New GoQuick

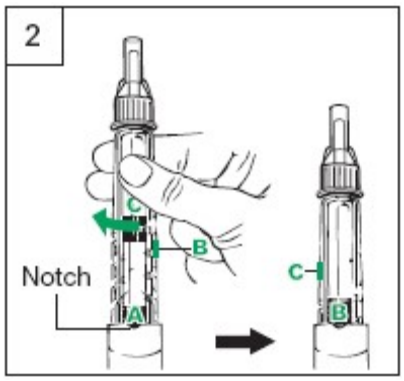
Step 1. Attach the Needle

a. Pull the white pen cap straight off the pen.
b. Peel the seal from a new needle.
c. Firmly grasp the cartridge holder. (Figure 1)
d. Push the needle onto the cartridge holder tip.
e. Gently screw the needle onto the pen. Do not overtighten.
f. Leave both needle covers on the needle.



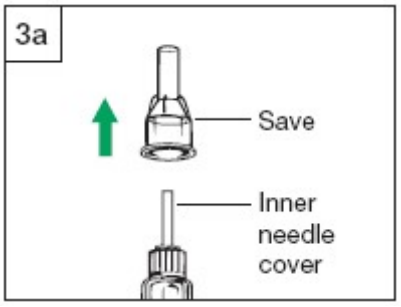
Step 2. Mix the Genotropin

a. Hold the pen with the needle-end pointing up and the **A** facing you. (Figure 2)
b. **Firmly** twist the cartridge holder into the pen until B clicks into the notch.
   - Gently tilt the pen from side to side. Do not shake the pen. Shaking may damage the growth hormone.
c. Check that the liquid in the cartridge is clear. All the powder should be dissolved.
   - If not, gently tilt the pen from side to side a few more times.
d. Check the liquid again. Make sure it is clear.
   - If the liquid is clear, go to Step 3.
   - If the liquid is still cloudy or you see any powder, use a new pen.

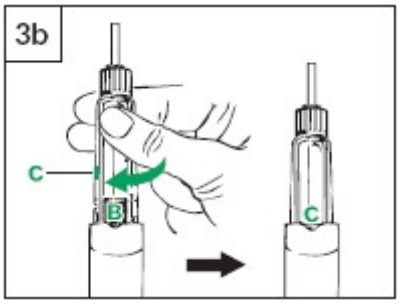


Step 3. Remove the Air

a. Pull the outer needle cover off. Save it to re-cap the needle. (Figure 3a)
b. Leave the inner needle cover on.

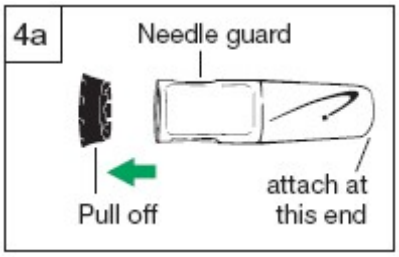


c. Hold the pen with the needle-end pointing up. (Figure 3b)
d. Tap the cartridge holder gently to help any trapped air move to the top.
e. **Firmly,** twist the cartridge holder into the pen until **C** clicks into the notch.
   - Some liquid may appear around the inner needle cover.

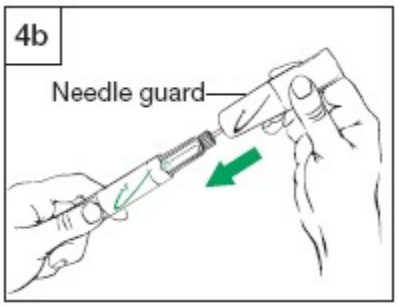


Step 4. Attach the Needle Guard (Optional)

a. Pull the black cap off the needle guard. (Figure 4a)
   - If the needle shield slides out, push it back into the needle guard until it clicks into place.

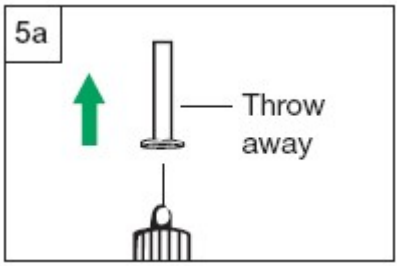


- Hold the pen in one hand below the green logo. With the other hand, hold the needle guard below the needle shield. (Figure 4b)
- Line up the black logo on the needle guard with the green logo on the pen. Carefully push the needle guard onto the pen until it snaps into place.

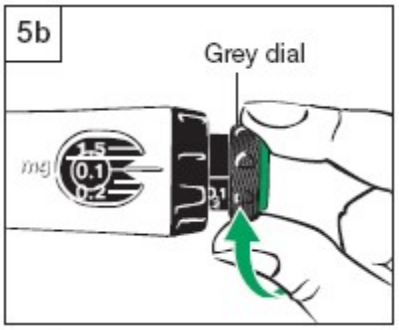


Step 5. Prime the Pen

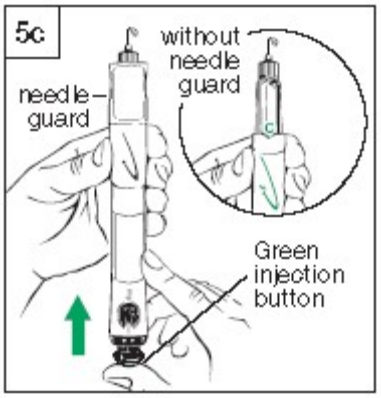
a. Pull the inner needle cover off. Throw it away. (Figure 5a)



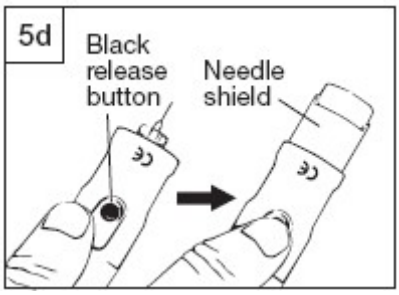
b. Check that 0.1 mg is set in the memory window.
c. Turn the grey dial in the direction of the arrows until it stops clicking. (Figure 5b)



d. Hold the pen with the needle pointing up. (Figure 5c with and without needle guard)
e. Push the green injection button until liquid appears.
f. If liquid does not appear at Step "e", repeat Steps b-e in this section up to two more times.
g. If liquid still does not appear, do not use the pen.
   - See the Questions and Answers section below for more information.



h. If you use the needle guard, press the black button to release the needle shield. (Figure 5d)



Step 6. Set the Dose

- Use the black ring to set the dose. Be careful not to turn the grey dial while setting the dose.

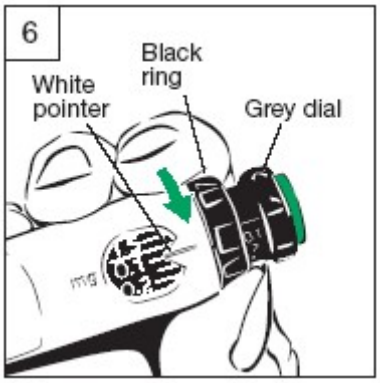
a. Hold the black ring as shown in Figure 6.

b. Turn the black ring until your dose lines up with the white pointer. Your doctor or nurse has told you your dose.

c. If you turn your dose past the white pointer, just turn the black ring back to set the correct dose.

d. Once you have set your dose, do not change it unless your doctor or nurse tells you.

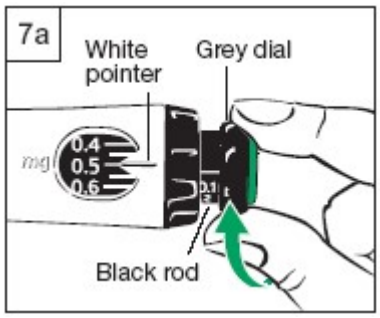
Note: If you cannot turn the black ring, press in the green injection button until it stops clicking. Then continue to set your dose using the black ring (for more information, see also the Questions and Answers section below).



Step 7. Draw Up a Dose

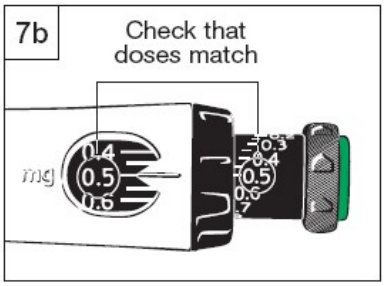
a. Turn the grey dial in the direction of the arrow until the clicking stops. (Figure 7a)

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



c. Check that the dose you drew up on the black rod is the same as the dose you set in the memory window. Figure 7b shows an example.

d. If the doses do not match, make sure you have turned the grey dial in the direction of the arrow until it does not click anymore.



Step 8. Give the Injection

a. Prepare an injection site as your doctor or nurse has told you.

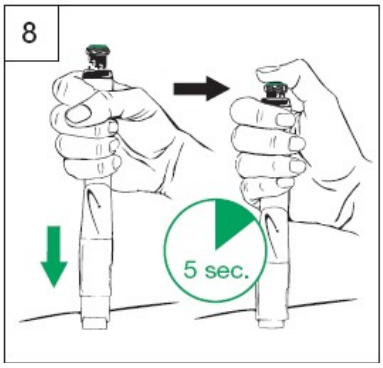
b. Hold the pen over the injection site.

c. Push the pen down to insert the needle into the skin.

d. Using your thumb, push the green injection button down until it stops clicking. (Figure 8)

- Count for 5 seconds before you pull the needle out of the skin. Keep light pressure on the button with your thumb while you count.

e. Pull the pen straight out from the skin.



Step 9. Remove the Needle; Cap and Store Your Pen

Step 9a: With needle guard

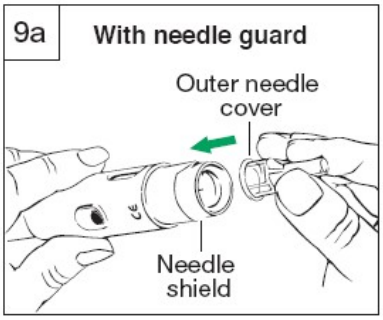
a. Place the outer needle cover into the end of the needle shield. (Figure 9a)

b. Use the needle cover to push in the needle shield until it locks into place.

c. Use the needle cover to unscrew the needle and put it in a proper container for used needles.

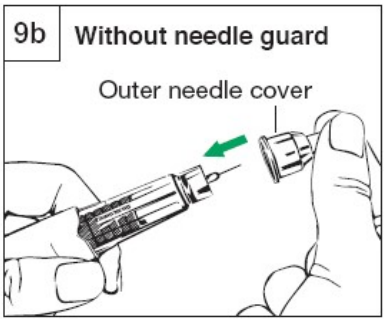
d. Leave the needle guard on the pen.

e. Place the black cap on the needle guard. Store your pen in the refrigerator.



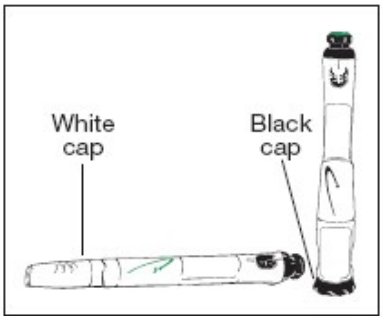
Step 9b: Without needle guard

a. Do not touch the needle.
b. Carefully cap the needle with the outer needle cover. (Figure 9b)
c. Use the needle cover to unscrew the needle and put it in a proper container for used needles.
d. Place the white cap on the pen. Store your pen in the refrigerator.

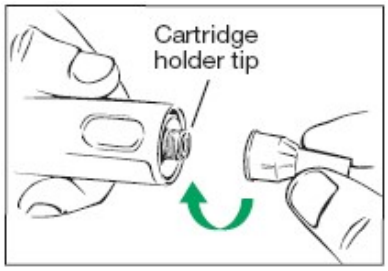


Routine Use of GoQuick

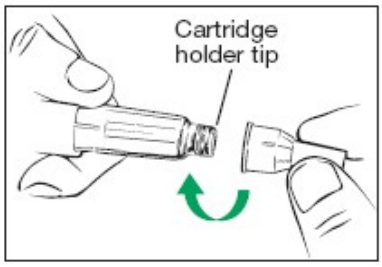
1. Pull the black cap from the needle guard or the white cap from the pen.



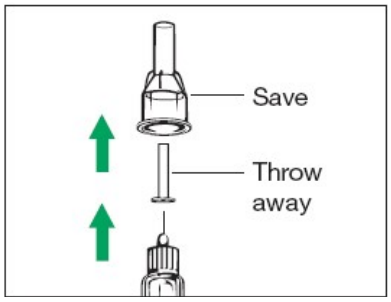
2. Attach a new needle.
   - With the needle guard:
     - If the needle shield releases, push it back into place.
     - Attach a new needle to the cartridge holder tip.



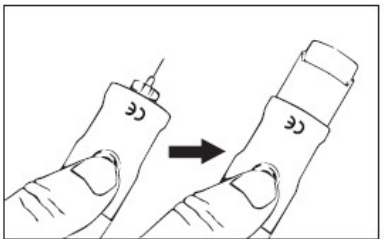
   - Without the needle guard:
     - Attach a new needle to the cartridge holder tip.



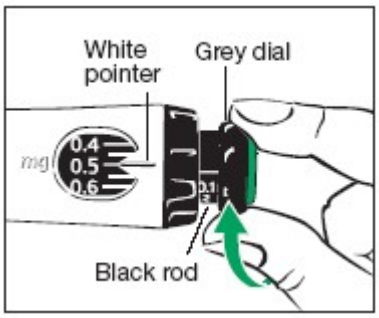
3. Remove both needle covers. Save the outer needle cover.



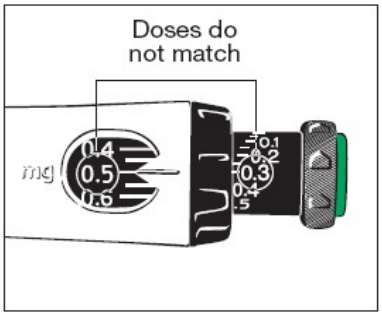
4. If you use the needle guard, press the black release button to extend the needle shield.



5. To draw up the dose, turn the grey dial until it stops clicking.

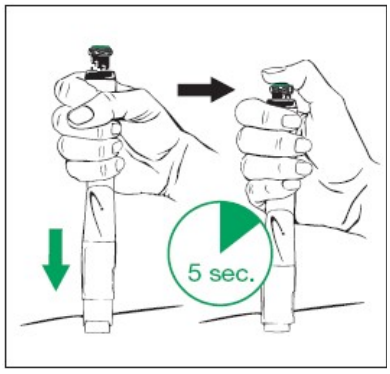


6. Check that the dose you drew up is the same as the dose you set in the memory window.
    - If the dose you drew up is smaller, the pen does not have a full dose of Genotropin.
    - Follow what your doctor or nurse told you to do when the pen does not have a full dose left.

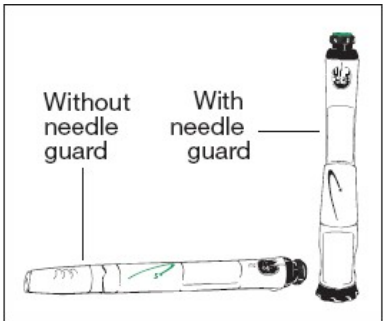


7. Prepare an injection site as your doctor or nurse has told you.

8. Give the injection.
    - Push the pen down to insert the needle into the skin.
    - Push the green injection button down until it stops clicking.
    - Count for 5 seconds before you pull the needle out of the skin. Keep light pressure on the button with your thumb while you count.
    - Pull the pen straight out from the skin.



9. Remove the needle.
    - With the needle guard:
        - Use the outer needle cover to push in the needle shield until it locks into place.
    - Without the needle guard:
        - Carefully cap the needle with the outer needle cover.
    - Use the outer needle cover to unscrew the needle. Throw the needle away in a proper container for used needles.



10. Cap your needle guard or pen and store it in the refrigerator.

ADDITIONAL INFORMATION

Storage

- See the other side of this leaflet for how to store your GoQuick.
- After 4 weeks, dispose of the pen (or discard) even if there is some medicine left.
- Do not freeze or expose GoQuick to frost.
- Do not use your GoQuick after its expiry date.
- Follow your local health and safety laws to dispose of (or discard) your pen. Ask your doctor or nurse, if you are not sure what to do.

Handling

- Do not mix the powder and liquid of GoQuick unless a needle is on the pen.
- Do not store your GoQuick with the needle attached. The Genotropin may leak from the pen and air bubbles may form in the cartridge. Always remove the needle and attach the pen cap or needle guard cap before storing.
- Take care not to drop your GoQuick.
- If you do drop the pen you must perform another prime as described in Step 5 (Setting Up and Using a New GoQuick). But if any part of your GoQuick appears broken or damaged, do not use the pen. Contact your doctor or nurse for another pen.
- Clean the pen and needle guard with a damp cloth. Do not put the pen in water.

Needles

- Always use a new needle for each injection.
- Put all used needles in an appropriate “sharps” container. Follow your local health and safety laws to dispose of your needles. Ask your doctor or nurse, if you are not sure what to do.
- Do not share your pen or needles.

General

- The numbers and lines on the cartridge holder can help you estimate how much Genotropin is left in the pen.
- If in routine use Step 6 the pen does not have a full dose of Genotropin, the scale on the black rod indicates the amount of drug remaining in the pen.
- Patients who are blind or who do not see well should only use GoQuick with the help of someone trained to use the pen.
- Follow your doctor or nurse’s instructions for cleaning your hands and skin when you prepare and give the injection.
- Do not discard your needle guard, to remove it from the pen just twist it off. Save it to use with each new pen.
- If you have questions about how to use GoQuick, ask your doctor or nurse.

QUESTIONS AND ANSWERS

Question	**Answer**
What should I do if I see more than a small drop of liquid on the needle after giving my injection?	For your next injection wait the full time of 5 seconds before taking the needle from the skin. If you still see some liquid after you take out the needle, hold in for a little longer next time.
Is it a problem if I see air bubbles in the cartridge?	No, small amounts of air may be present in the cartridge during normal use.
What should I do if I see Genotropin leaking from the pen?	Make sure that the needle has been attached correctly.
What should I do if the pen that I am using was not put in the refrigerator overnight?	Discard the pen and use a new GoQuick.
What should I do if I can't turn the black ring?	You have probably accidentally turned the grey dial. If you have turned the grey dial the pen will prevent you from turning the black ring so that your dose does not change during your injection. To release the black ring, press in the green injection button until it stops. Note that liquid will come out of the needle. Then continue to set your dose using the black ring.
What if my doctor changes my dose when I've already started a pen?	Set the new dose by turning the black ring.
What if I inject the wrong dose?	Call your doctor or nurse immediately and follow his/her instructions.
What if my pen will not prime (i.e. if liquid did not appear in step 5g)?	Call your doctor or nurse and follow his/her instructions.
What doses can my pen deliver?	The pen can deliver doses from 0.10mg to 1.5mg of Genotropin. Each click of the black ring changes the dose by 0.05mg.

GENOTROPIN®GOQUICK™ 5.3

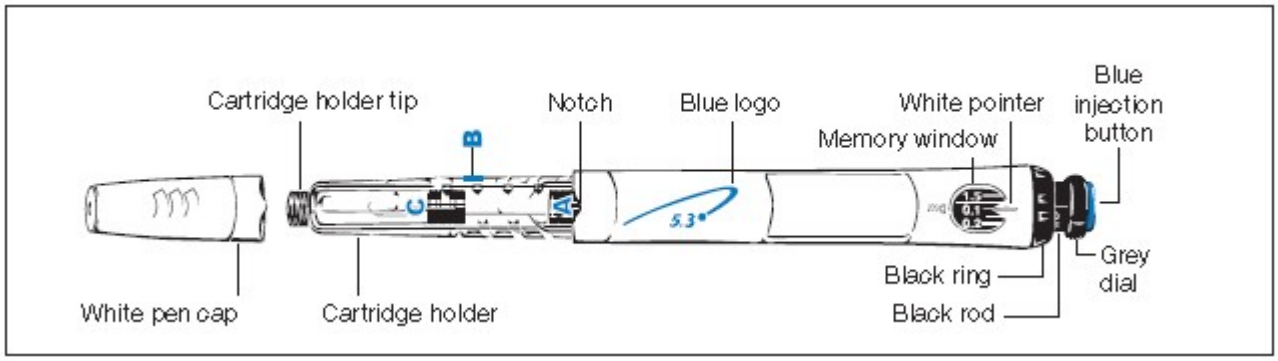
INSTRUCTIONS FOR USE

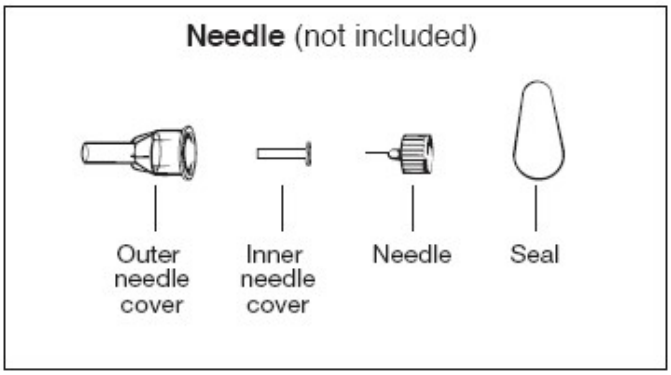
Important Information
Please read these instructions completely before using GoQuick.
If you have any questions about your dose or your treatment with Genotropin, call your doctor or nurse.

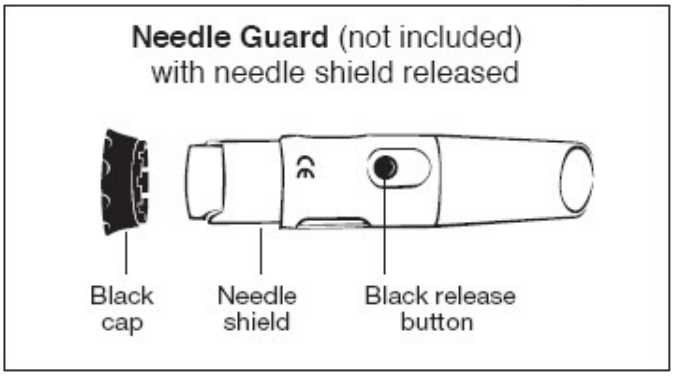
About GoQuick
GoQuick is a prefilled, multidose, disposable injection pen that holds 5.3 mg of somatropin. After reconstitution the concentrati somatropin is 5.3 mg per mL The Genotropin in the pen is mixed only once, when you start a new pen. A single pen can be used 28 days after mixing. You never have to change cartridges. When the pen is empty, you just start a new pen.

The pen has dose memory. The dose is set once on a new pen. The pen then gives the same dose for each injection. You can use the pen with or without the optional needle guard.

Before You Use GoQuick
- Get training from your doctor or nurse.
- Know your dose. Know the pen parts.
- Make sure you have the pen with the blue injection button.
- Wash your hands.

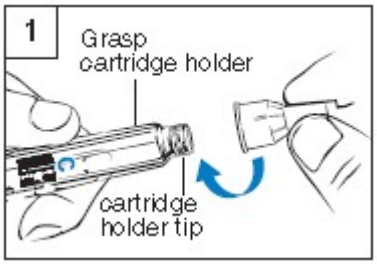






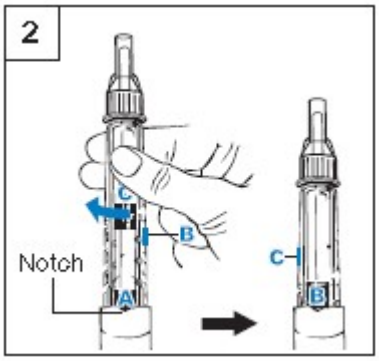
Setting Up and Using a New GoQuick

Step 1. Attach the Needle
a. Pull the white pen cap straight off the pen.
b. Peel the seal from a new needle.
c. Firmly grasp the cartridge holder. (Figure 1)
d. Push the needle onto the cartridge holder tip.
e. Gently screw the needle onto the pen. Do not overtighten.
f. Leave both needle covers on the needle.



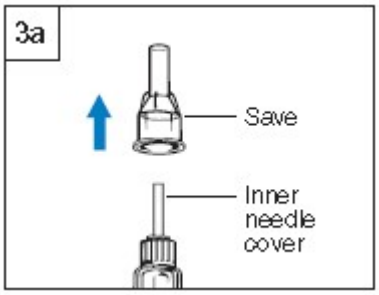
Step 2. Mix the Genotropin

a. Hold the pen with the needle-end pointing up and the **A** facing you. (Figure 2)
b. **Firmly** twist the cartridge holder into the pen until **B** clicks into the notch.
   - Gently tilt the pen from side to side. Do not shake the pen. Shaking may damage the growth hormone.
c. Check that the liquid in the cartridge is clear. All the powder should be dissolved.
   - If not, gently tilt the pen from side to side a few more times.
d. Check the liquid again. Make sure it is clear.
   - If the liquid is clear, go to Step 3.
   - If the liquid is still cloudy or you see any powder, use a new pen.

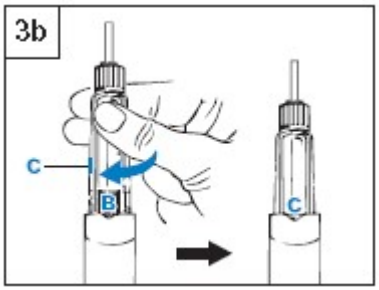


Step 3. Remove the Air

a. Pull the outer needle cover off. Save it to re-cap the needle. (Figure 3a)
b. Leave the inner needle cover on.

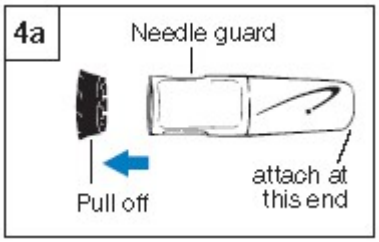


c. Hold the pen with the needle-end pointing up. (Figure 3b)
d. Tap the cartridge holder gently to help any trapped air move to the top.
e. **Firmly,** twist the cartridge holder into the pen until **C** clicks into the notch.
   - Some liquid may appear around the inner needle cover.

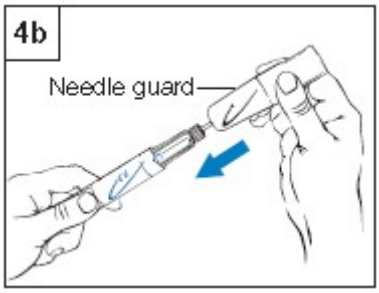


Step 4. Attach the Needle Guard (Optional)

a. Pull the black cap off the needle guard. (Figure 4a)
   - If the needle shield slides out, push it back into the needle guard until it clicks into place.

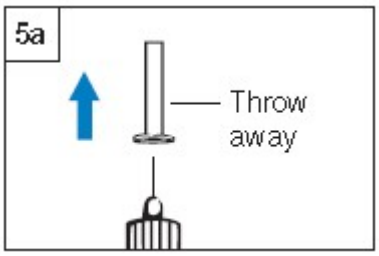


b. Hold the pen in one hand below the blue logo. With the other hand, hold the needle guard below the needle shield. (Figure 4b)
c. Line up the black logo on the needle guard with the blue logo on the pen. Carefully push the needle guard onto the pen until it snaps into place.



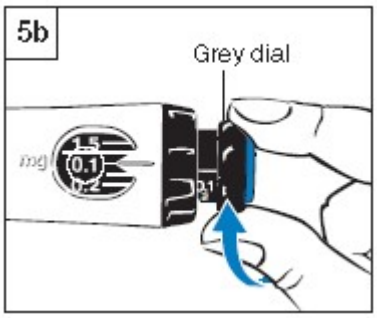
Step 5. Prime the Pen

a. Pull the inner needle cover off. Throw it away. (Figure 5a)



b. Check that 0.1 mg is set in the memory window.

c. Turn the grey dial in the direction of the arrows until it stops clicking. (Figure 5b)



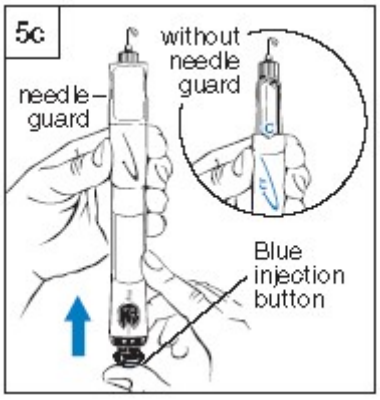
d. Hold the pen with the needle pointing up. (Figure 5c with and without needle guard)

e. Push the blue injection button until liquid appears.

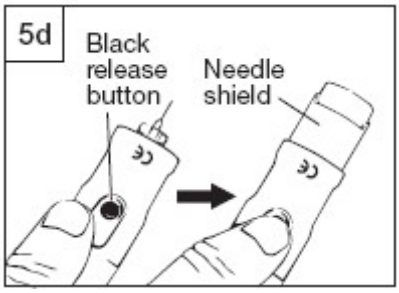
f. If liquid does not appear at Step "e", repeat Steps b-e in this section up to two more times.

g. If liquid still does not appear, do not use the pen.

- See the Questions and Answers section below for more information.



h. If you use the needle guard, press the black button to release the needle shield. (Figure 5d)



Step 6. Set the Dose

- Use the black ring to set the dose. Be careful not to turn the grey dial while setting the dose.

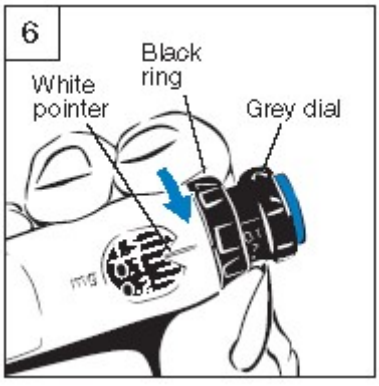
a. Hold the black ring as shown in Figure 6.

b. Turn the black ring until your dose lines up with the white pointer. Your doctor or nurse has told you your dose.

c. If you turn your dose past the white pointer, just turn the black ring back to set the correct dose.

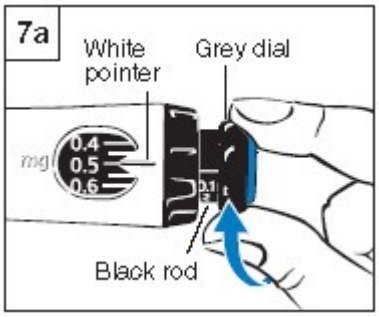
d. Once you have set your dose, do not change it unless your doctor or nurse tells you.

Note: If you cannot turn the black ring, press in the blue injection button until it stops clicking. Then continue to set your dose using the black ring (for more information, see also the Questions and Answers section below).

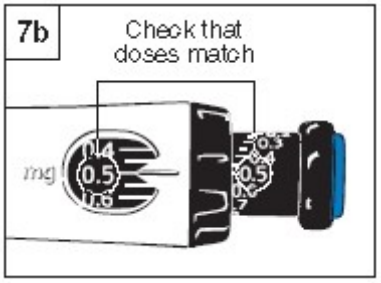


Step 7. Draw Up a Dose

a. Turn the grey dial in the direction of the arrow until the clicking stops. (Figure 7a)
b. Your dose on the black rod should line up with the white pointer.

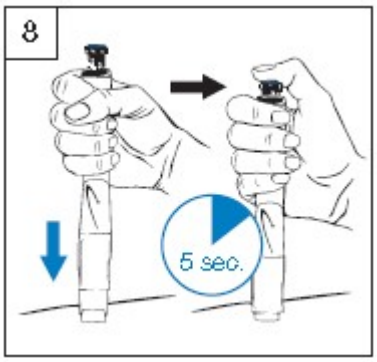


c. Check that the dose you drew up on the black rod is the same as the dose you set in the memory window. Figure 7b shows an example.
d. If the doses do not match, make sure you have turned the grey dial in the direction of the arrow until it does not click anymore.



Step 8. Give the Injection

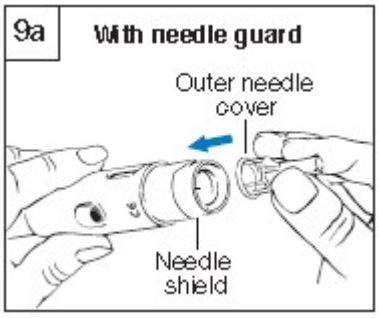
a. Prepare an injection site as your doctor or nurse has told you.
b. Hold the pen over the injection site.
c. Push the pen down to insert the needle into the skin.
d. Using your thumb, push the blue injection button down until it stops clicking. (Figure 8)
   - Count for 5 seconds before you pull the needle out of the skin. Keep light pressure on the button with your thumb while you count.
e. Pull the pen straight out from the skin.



Step 9. Remove the Needle; Cap and Store Your Pen

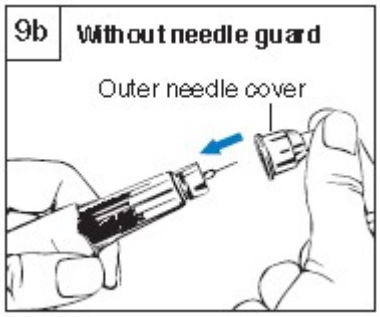
Step 9a: With needle guard

a. Place the outer needle cover into the end of the needle shield. (Figure 9a)
b. Use the needle cover to push in the needle shield until it locks into place.
c. Use the needle cover to unscrew the needle and put it in a proper container for used needles.
d. Leave the needle guard on the pen.
e. Place the black cap on the needle guard. Store your pen in the refrigerator.



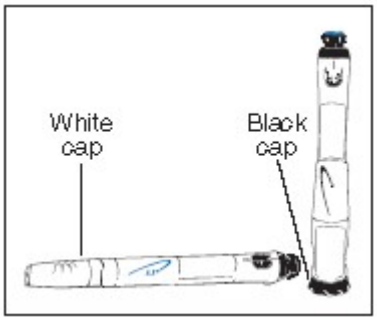
Step 9b: Without needle guard

a. Do not touch the needle.
b. Carefully cap the needle with the outer needle cover. (Figure 9b)
c. Use the needle cover to unscrew the needle and put it in a proper container for used needles.
d. Place the white cap on the pen. Store your pen in the refrigerator.

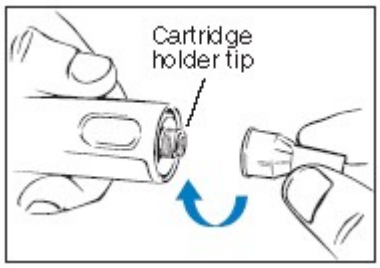


Routine Use of GoQuick

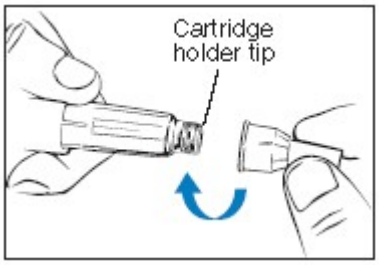
1. Pull the black cap from the needle guard or the white cap from the pen.



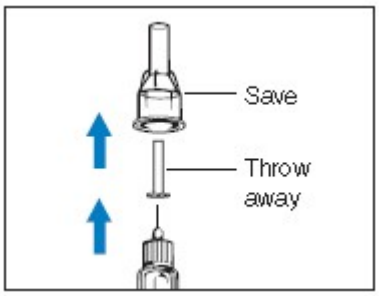
2. Attach a new needle.
   - With the needle guard:
     - If the needle shield releases, push it back into place.
     - Attach a new needle to the cartridge holder tip.



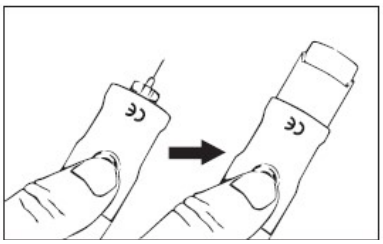
   - Without the needle guard:
     - Attach a new needle to the cartridge holder tip.



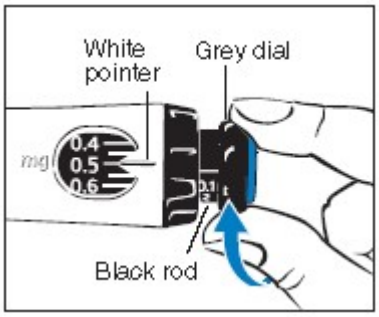
3. Remove both needle covers. Save the outer needle cover.



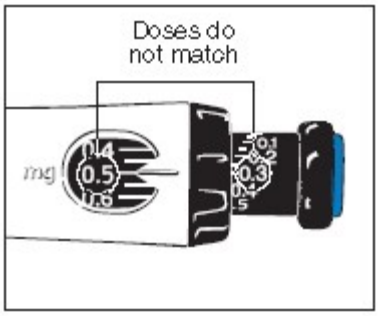
4. If you use the needle guard, press the black release button to extend the needle shield.



5. To draw up the dose, turn the grey dial until it stops clicking.

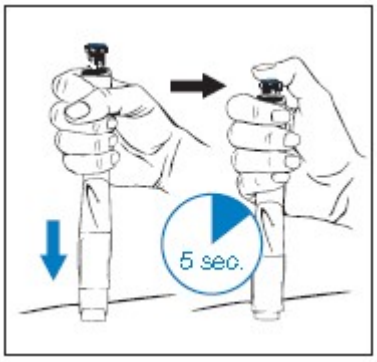


6. Check that the dose you drew up is the same as the dose you set in the memory window.
   - If the dose you drew up is smaller, the pen does not have a full dose of Genotropin.
   - Follow what your doctor or nurse told you to do when the pen does not have a full dose left.

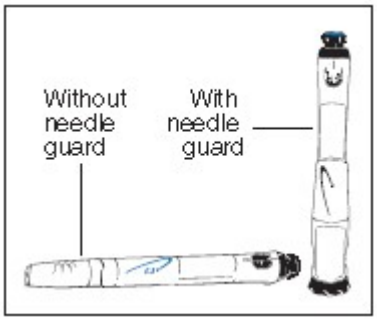


7. Prepare an injection site as your doctor or nurse has told you.

8. Give the injection.
   - Push the pen down to insert the needle into the skin.
   - Push the blue injection button down until it stops clicking.
   - Count for 5 seconds before you pull the needle out of the skin. Keep light pressure on the button with your thumb while you count.
   - Pull the pen straight out from the skin.



9. Remove the needle.
   - With the needle guard:
     - Use the outer needle cover to push in the needle shield until it locks into place.
   - Without the needle guard:
     - Carefully cap the needle with the outer needle cover.
   - Use the outer needle cover to unscrew the needle. Throw the needle away in a proper container for used needles.



10. Cap your needle guard or pen and store it in the refrigerator.

ADDITIONAL INFORMATION

Storage

- See the other side of this leaflet for how to store your GoQuick.
- After 4 weeks, dispose of the pen (or discard) even if there is some medicine left.
- Do not freeze or expose GoQuick to frost.
- Do not use your GoQuick after its expiry date.
- Follow your local health and safety laws to dispose of (or discard) your pen. Ask your doctor or nurse, if you are not sure what to do.

Handling

- Do not mix the powder and liquid of GoQuick unless a needle is on the pen.
- Do not store your GoQuick with the needle attached. The Genotropin may leak from the pen and air bubbles may form in the cartridge. Always remove the needle and attach the pen cap or needle guard cap before storing.
- Take care not to drop your GoQuick.
- If you do drop the pen you must perform another prime as described in Step 5 (Setting Up and Using a New GoQuick). But if any part of your GoQuick appears broken or damaged, do not use the pen. Contact your doctor or nurse for another pen.
- Clean the pen and needle guard with a damp cloth. Do not put the pen in water.

Needles

- Always use a new needle for each injection.
- Put all used needles in an appropriate "sharps" container. Follow your local health and safety laws to dispose of your needles. Ask your doctor or nurse, if you are not sure what to do.
- Do not share your pen or needles.

General

- The numbers and lines on the cartridge holder can help you estimate how much Genotropin is left in the pen.
- If in routine use Step 6 the pen does not have a full dose of Genotropin, the scale on the black rod indicates the amount of drug remaining in the pen.
- Patients who are blind or who do not see well should only use GoQuick with the help of someone trained to use the pen.
- Follow your doctor or nurse's instructions for cleaning your hands and skin when you prepare and give the injection.
- Do not discard your needle guard, to remove it from the pen just twist it off. Save it to use with each new pen.
- If you have questions about how to use GoQuick, ask your doctor or nurse.

QUESTIONS AND ANSWERS

Question	**Answer**
What should I do if I see more than a small drop of liquid on the needle after giving my injection?	For your next injection wait the full time of 5 seconds before taking the needle from the skin. If you still see some liquid after you take out the needle, hold in for a little longer next time.
Is it a problem if I see air bubbles in the cartridge?	No, small amounts of air may be present in the cartridge during normal use.
What should I do if I see Genotropin leaking from the pen?	Make sure that the needle has been attached correctly.
What should I do if the pen that I am using was not put in the refrigerator overnight?	Discard the pen and use a new GoQuick.
What should I do if I can't turn the black ring?	You have probably accidentally turned the grey dial. If you have turned the grey dial the pen will prevent you from turning the black ring so that your dose does not change during your injection. To release the black ring, press in the blue injection button until it stops. Note that liquid will come out of the needle. Then continue to set your dose using the black ring.
What if my doctor changes my dose when I've already started a pen?	Set the new dose by turning the black ring.
What if I inject the wrong dose?	Call your doctor or nurse immediately and follow his/her instructions.

What if my pen will not prime (i.e. if liquid did not appear in step 5g)?	Call your doctor or nurse and follow his/her instructions.
What doses can my pen deliver?	The pen can deliver doses from 0.10mg to 1.5mg of Genotropin. Each click of the black ring changes the dose by 0.05mg.

GENOTROPIN®GOQUICK™ 12

INSTRUCTIONS FOR USE

Important Information

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

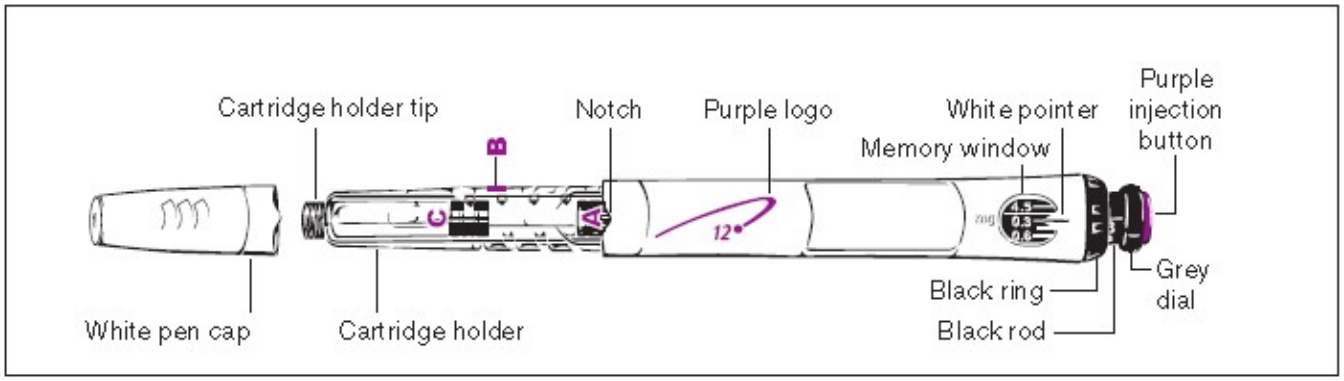
About GoQuick

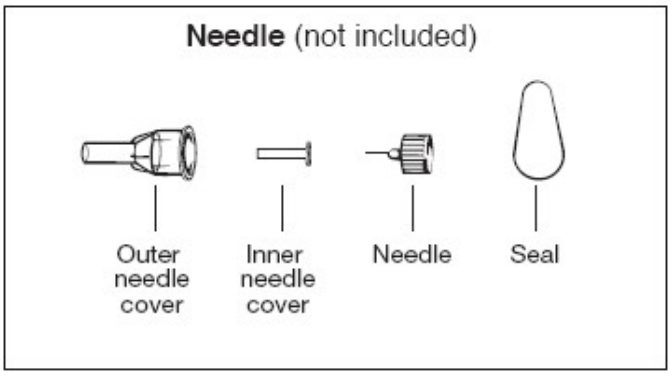
GoQuick is a prefilled, multidose, disposable injection pen that holds 12 mg of somatropin. After reconstitution the concentrati somatropin is 12 mg per mL The Genotropin in the pen is mixed only once, when you start a new pen. A single pen can be used 28 days after mixing. You never have to change cartridges. When the pen is empty, you just start a new pen.

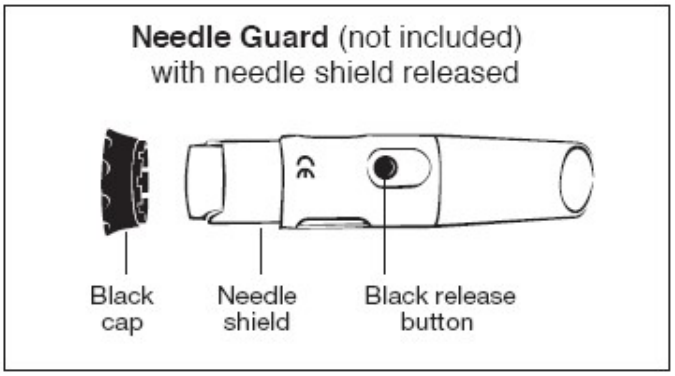
The pen has dose memory. The dose is set once on a new pen. The pen then gives the same dose for each injection. You can use the pen with or without the optional needle guard.

Before You Use GoQuick

- Get training from your doctor or nurse.
- Know your dose. Know the pen parts.
- Make sure you have the pen with the purple injection button.
- Wash your hands.



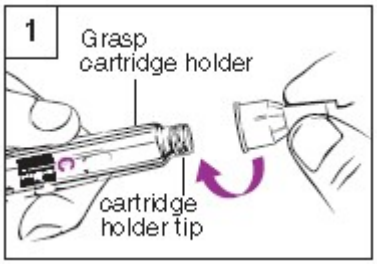




Setting Up and Using a New GoQuick

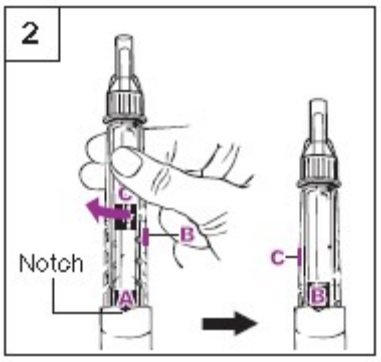
Step 1. Attach the Needle

a. Pull the white pen cap straight off the pen.
b. Peel the seal from a new needle.
c. Firmly grasp the cartridge holder. (Figure 1)
d. Push the needle onto the cartridge holder tip.
e. Gently screw the needle onto the pen. Do not overtighten.
f. Leave both needle covers on the needle.



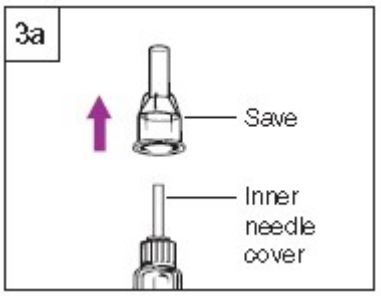
Step 2. Mix the Genotropin

a. Hold the pen with the needle-end pointing up and the **A** facing you. (Figure 2)
b. **Firmly** twist the cartridge holder into the pen until **B** clicks into the notch.
   - Gently tilt the pen from side to side. Do not shake the pen. Shaking may damage the growth hormone.
c. Check that the liquid in the cartridge is clear. All the powder should be dissolved.
   - If not, gently tilt the pen from side to side a few more times.
d. Check the liquid again. Make sure it is clear.
   - If the liquid is clear, go to Step 3.
   - If the liquid is still cloudy or you see any powder, use a new pen.

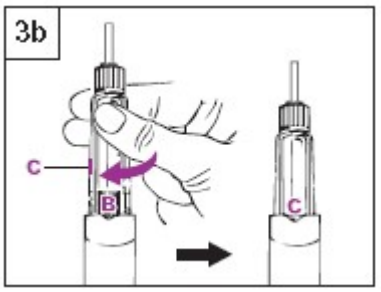


Step 3. Remove the Air

a. Pull the outer needle cover off. Save it to re-cap the needle. (Figure 3a)
b. Leave the inner needle cover on.

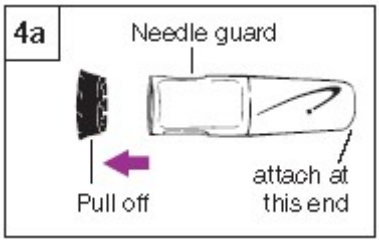


c. Hold the pen with the needle-end pointing up. (Figure 3b)
d. Tap the cartridge holder gently to help any trapped air move to the top.
e. **Firmly,** twist the cartridge holder into the pen until **C** clicks into the notch.
   - Some liquid may appear around the inner needle cover.

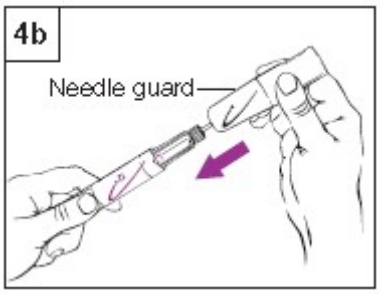


Step 4. Attach the Needle Guard (Optional)

a. Pull the black cap off the needle guard. (Figure 4a)
   - If the needle shield slides out, push it back into the needle guard until it clicks into place.

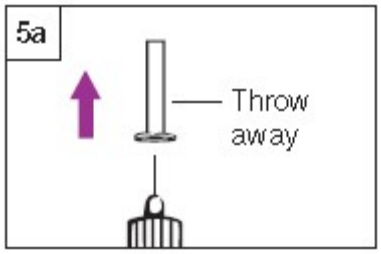


b. Hold the pen in one hand below the purple logo. With the other hand, hold the needle guard below the needle shield. (Figure 4b)
c. Line up the black logo on the needle guard with the purple logo on the pen. Carefully push the needle guard onto the pen until it snaps into place.

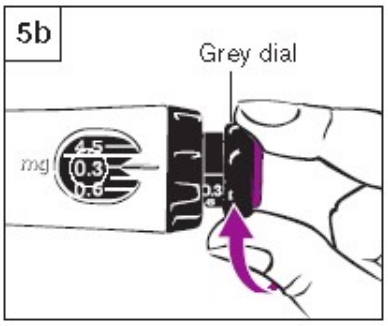


Step 5. Prime the Pen

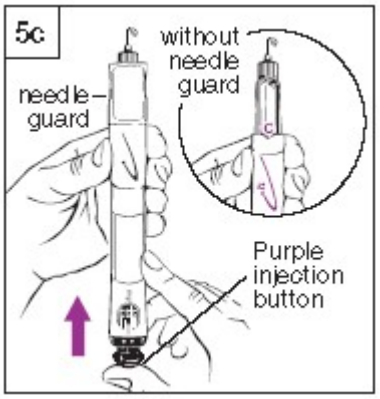
a. Pull the inner needle cover off. Throw it away. (Figure 5a)



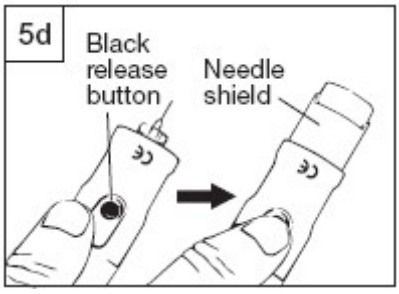
b. Check that 0.3 mg is set in the memory window.
c. Turn the grey dial in the direction of the arrows until it stops clicking. (Figure 5b)



d. Hold the pen with the needle pointing up. (Figure 5c with and without needle guard)
e. Push the purple injection button until liquid appears.
f. If liquid does not appear at Step "e", repeat Steps b-e in this section up to two more times.
g. If liquid still does not appear, do not use the pen.
   - See the Questions and Answers section below for more information.

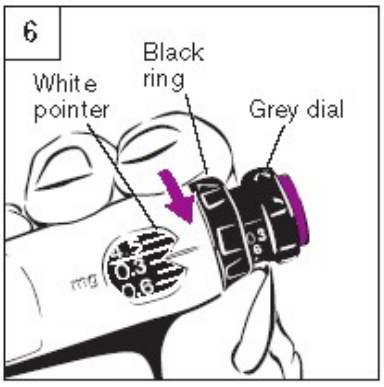


h. If you use the needle guard, press the black button to release the needle shield. (Figure 5d)



Step 6. Set the Dose

- Use the black ring to set the dose. Be careful not to turn the grey dial while setting the dose.

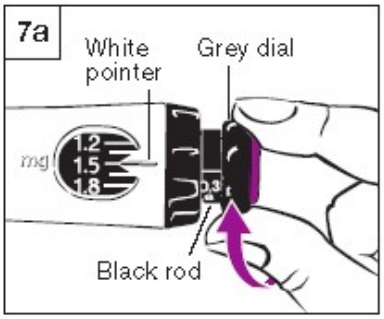


a. Hold the black ring as shown in Figure 6.
b. Turn the black ring until your dose lines up with the white pointer. Your doctor or nurse has told you your dose.
c. If you turn your dose past the white pointer, just turn the black ring back to set the correct dose.
d. Once you have set your dose, do not change it unless your doctor or nurse tells you.

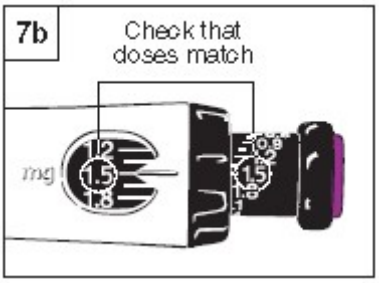
Note: If you cannot turn the black ring, press in the purple injection button until it stops clicking. Then continue to set your dose using the black ring (for more information, see also the Questions and Answers section below).

Step 7. Draw Up a Dose

a. Turn the grey dial in the direction of the arrow until the clicking stops. (Figure 7a)
b. Your dose on the black rod should line up with the white pointer.

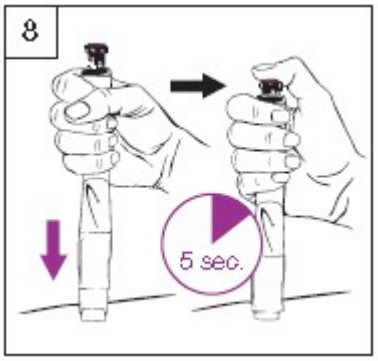


c. Check that the dose you drew up on the black rod is the same as the dose you set in the memory window. Figure 7b shows an example.
d. If the doses do not match, make sure you have turned the grey dial in the direction of the arrow until it does not click anymore.

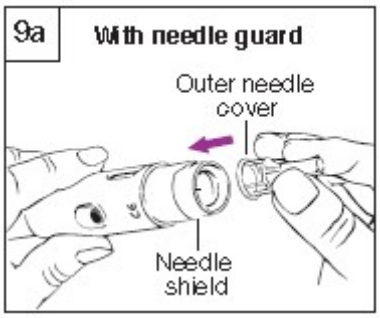


Step 8. Give the Injection

a. Prepare an injection site as your doctor or nurse has told you.
b. Hold the pen over the injection site.
c. Push the pen down to insert the needle into the skin.
d. Using your thumb, push the purple injection button down until it stops clicking. (Figure 8)
   - Count for 5 seconds before you pull the needle out of the skin. Keep light pressure on the button with your thumb while you count.
e. Pull the pen straight out from the skin.

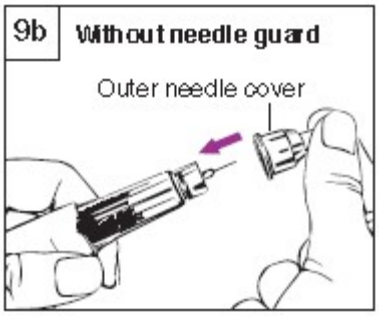


Step 9. Remove the Needle; Cap and Store Your Pen



Step 9a: With needle guard

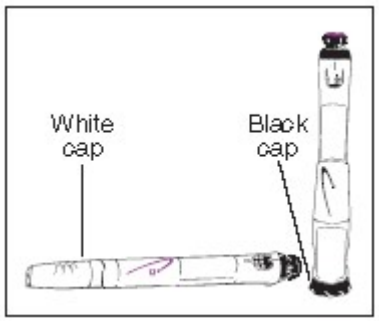
a. Place the outer needle cover into the end of the needle shield. (Figure 9a)
b. Use the needle cover to push in the needle shield until it locks into place.
c. Use the needle cover to unscrew the needle and put it in a proper container for used needles.
d. Leave the needle guard on the pen.
e. Place the black cap on the needle guard. Store your pen in the refrigerator.



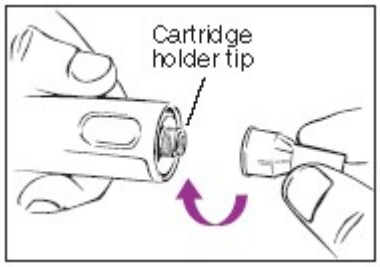
Step 9b: Without needle guard

a. Do not touch the needle.
b. Carefully cap the needle with the outer needle cover. (Figure 9b)
c. Use the needle cover to unscrew the needle and put it in a proper container for used needles.
d. Place the white cap on the pen. Store your pen in the refrigerator.

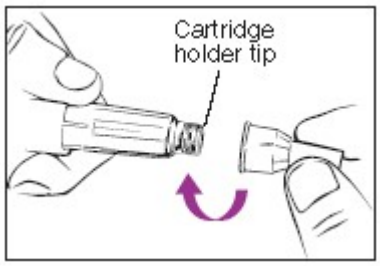
Routine Use of GoQuick



1. Pull the black cap from the needle guard or the white cap from the pen.

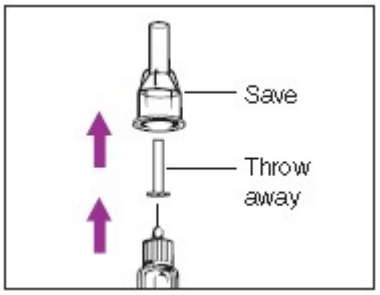


2. Attach a new needle.
   - With the needle guard:
     - If the needle shield releases, push it back into place.
     - Attach a new needle to the cartridge holder tip.

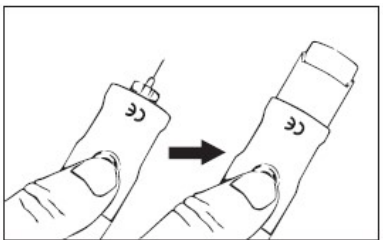


   - Without the needle guard:
     - Attach a new needle to the cartridge holder tip.

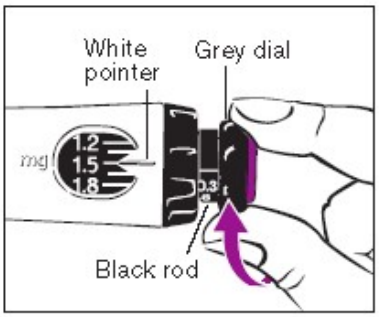
3. Remove both needle covers. Save the outer needle cover.



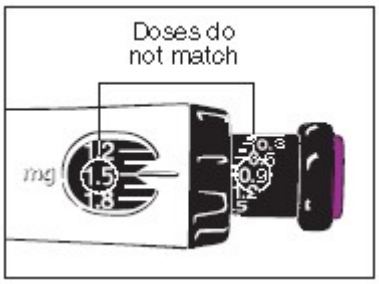
4. If you use the needle guard, press the black release button to extend the needle shield.



5. To draw up the dose, turn the grey dial until it stops clicking.

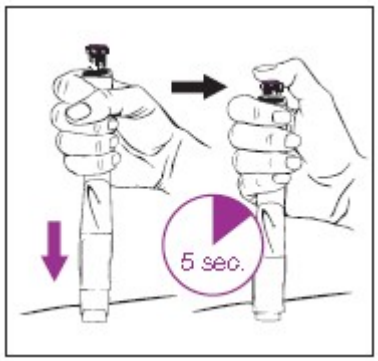


6. Check that the dose you drew up is the same as the dose you set in the memory window.
   - If the dose you drew up is smaller, the pen does not have a full dose of Genotropin.
   - Follow what your doctor or nurse told you to do when the pen does not have a full dose left.



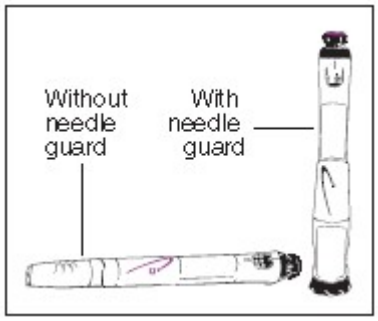
7. Prepare an injection site as your doctor or nurse has told you.

8. Give the injection.
   - Push the pen down to insert the needle into the skin.
   - Push the purple injection button down until it stops clicking.
   - Count for 5 seconds before you pull the needle out of the skin. Keep light pressure on the button with your thumb while you count.
   - Pull the pen straight out from the skin.



9. Remove the needle.
    - With the needle guard:
        - Use the outer needle cover to push in the needle shield until it locks into place.
    - Without the needle guard:
        - Carefully cap the needle with the outer needle cover.

    - Use the outer needle cover to unscrew the needle. Throw the needle away in a proper container for used needles.



10. Cap your needle guard or pen and store it in the refrigerator.

ADDITIONAL INFORMATION

Storage

- See the other side of this leaflet for how to store your GoQuick.
- After 4 weeks, dispose of the pen (or discard) even if there is some medicine left.
- Do not freeze or expose GoQuick to frost.
- Do not use your GoQuick after its expiry date.
- Follow your local health and safety laws to dispose of (or discard) your pen. Ask your doctor or nurse, if you are not sure what to do.

Handling

- Do not mix the powder and liquid of GoQuick unless a needle is on the pen.
- Do not store your GoQuick with the needle attached. The Genotropin may leak from the pen and air bubbles may form in the cartridge. Always remove the needle and attach the pen cap or needle guard cap before storing.
- Take care not to drop your GoQuick.
- If you do drop the pen you must perform another prime as described in Step 5 (Setting Up and Using a New GoQuick). But if any part of your GoQuick appears broken or damaged, do not use the pen. Contact your doctor or nurse for another pen.
- Clean the pen and needle guard with a damp cloth. Do not put the pen in water.

Needles

- Always use a new needle for each injection.
- Put all used needles in an appropriate "sharps" container. Follow your local health and safety laws to dispose of your needles. Ask your doctor or nurse, if you are not sure what to do.
- Do not share your pen or needles.

General

- The numbers and lines on the cartridge holder can help you estimate how much Genotropin is left in the pen.
- If in routine use Step 6 the pen does not have a full dose of Genotropin, the scale on the black rod indicates the amount of drug remaining in the pen.
- Patients who are blind or who do not see well should only use GoQuick with the help of someone trained to use the pen.
- Follow your doctor or nurse's instructions for cleaning your hands and skin when you prepare and give the injection.
- Do not discard your needle guard, to remove it from the pen just twist it off. Save it to use with each new pen.
- If you have questions about how to use GoQuick, ask your doctor or nurse.

QUESTIONS AND ANSWERS

Question	**Answer**
What should I do if I see more than a small drop of liquid on the needle after giving my injection?	For your next injection wait the full time of 5 seconds before taking the needle from the skin. If you still see some liquid after you take out the needle, hold in for a little longer next time.
Is it a problem if I see air bubbles in the cartridge?	No, small amounts of air may be present in the cartridge during normal use.
What should I do if I see Genotropin leaking from the pen?	Make sure that the needle has been attached correctly.
What should I do if the pen that I am using was not put in the refrigerator overnight?	Discard the pen and use a new GoQuick.
What should I do if I can't turn the black ring?	You have probably accidentally turned the grey dial. If you have turned the grey dial the pen will prevent you from turning the black ring so that your dose does not change during your injection. To release the black ring, press in the purple injection button until it stops. Note that liquid will come out of the needle. Then continue to set your dose using the black ring.
What if my doctor changes my dose when I've already started a pen?	Set the new dose by turning the black ring.
What if I inject the wrong dose?	Call your doctor or nurse immediately and follow his/her instructions.
What if my pen will not prime (i.e. if liquid did not appear in step 5g)?	Call your doctor or nurse and follow his/her instructions.
What doses can my pen deliver?	The pen can deliver doses from 0.30 mg to 4.5 mg of Genotropin. Each click of the black ring changes the dose by 0.15 mg.