Recombinant Somatropin for Injection I.P.

Genotropin® GoQuick®

1. GENERIC NAME

Recombinant Somatropin for Injection I.P.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Recombinant Somatotropin I.P. (Sterile, Lyophilized Powder); 12 mg (36IU) with sterile diluents (Metacresol-Mannitol-Water) for injection.

List of Excipients

Glycine, Mannitol, Sodium dihydrogen phosphate anhydrous (added as Monohydrate), Disodium phosphate anhydrous (added as dodecahydrate), Metacresol and Water for Injection.

All strengths/presentations mentioned in this document might not be available in the market.

3. DOSAGE FORM AND STRENGTH

Powder and solvent for solution for injection with or without preservative, for subcutaneous (S.C.) administration.

Recombinant Somatropin for Injection I.P. 12 mg (36 IU).

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Genotropin GoQuick is indicated for the long-term treatment of children with growth disturbance due to the following conditions:

- Short stature due to inadequate or failed secretion of pituitary growth hormone.
- Turner syndrome.
- Chronic renal insufficiency.
- Born small for gestational age.
- For improvement of body composition in children with Prader-Willi syndrome.
- For replacement therapy in adults with growth hormone deficiency.
- For the treatment of idiopathic short stature.

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4.2 Posology and Method of Administration

The dosage and administration schedule should be individualized.

The injection should be given subcutaneously and the site varied to prevent lipoatrophy.

Growth disturbance due to insufficient secretion of growth hormone in children: Generally, a dose of 0.025 - 0.035 mg/kg body weight per day or 0.7 - 1.0 mg/m² body surface area per day is recommended. Even higher doses have been used.

Where childhood onset growth hormone deficiency (GHD) persists into adolescence, treatment should be continued to achieve full somatic development (e.g., body composition, bone mass). For monitoring, the attainment of a normal peak bone mass defined as a T score > - 1 (i.e., standardized to average adult peak bone mass measured by dual energy X-ray absorptiometry taking into account sex and ethnicity) is one of the therapeutic objectives during the transition period. For guidance on dosing see adult section below.

Prader-Willi syndrome (PWS), for improvement of growth and body composition in children: Generally, a dose of 0.035 mg/kg body weight per day or 1.0 mg/m^2 body surface area per day is recommended. Daily doses of 2.7 mg should not be exceeded. Treatment should not be used in children with a growth velocity of less than 1 cm per year and near closure of epiphyses.

Growth disturbance due to Turner syndrome: A dose of 0.045 - 0.050 mg/kg body weight per day or 1.4 mg/m² body surface area per day is recommended.

Growth disturbance in chronic renal insufficiency: A dose of 0.045 - 0.050 mg/kg body weight per day (1.4 mg/m² body surface area per day) is recommended. Higher doses can be needed if growth velocity is too low. A dose correction can be needed after six months of treatment.

Growth disturbance in short children born small for gestational age (SGA): A dose of 0.035 mg/kg body weight per day (1 mg/m² body surface area per day) is usually recommended until final height is reached (see section **5.2 Pharmacodynamic Properties**). 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.

Table 1. Dosage recommendations in pediatric patients

Indication	Daily Dose			
	mg/kg body weight dose per day	IU/kg body weight	mg/m² body surface area dose per day	IU/m² body surface area
Growth hormone deficiency in children	0.025 - 0.035	0.07 - 0.10	0.7 - 1.0	2.1 - 3.0
Turner syndrome	0.045 - 0.050	0.14	1.4	4.3
Chronic renal insufficiency	0.045 - 0.050	0.14	1.4	4.3
Prader-Willi syndrome in children	0.035	0.10	1.0	3.0

Children born small for gestational age	0.035	0.10 – 0.20	1.0	3.0 - 6.0
Idiopathic short stature	Up to 0.067	Up to 0.20	Up to 2.0	Up to 6.0

Growth hormone deficient adult patients: In patients who continue growth hormone therapy after childhood GHD, the recommended dose to restart is 0.2 – 0.5 mg per day. The dose should be gradually increased or decreased according to individual patient requirements as determined by the IGF-I concentration.

In patients with adult-onset GHD, therapy should start with a low dose, 0.15 – 0.3 mg per day. The dose should be gradually increased according to individual patient requirements as determined by the IGF-I concentration.

In both cases treatment goal should be IGF-I concentrations within 2 SDS from the age corrected mean. Patients with normal IGF-I concentrations at the start of the treatment should be administered growth hormone up to an IGF-I level into upper range of normal, not exceeding the 2 SDS. Clinical response and side effects may also be used as guidance for dose titration. It is recognised that there are patients with GHD who do not normalize IGF-I levels despite a good clinical response, and thus do not require dose escalation. The maintenance dose seldom exceeds 1.0 mg per day. Women may require higher doses than men, with men showing an increasing IGF-I sensitivity over time. This means that there is a risk that women, especially those on oral oestrogen replacement are under-treated while men are over-treated. The accuracy of the growth hormone dose should therefore be controlled every 6 months. As normal physiological growth hormone production decreases with age, dose requirements are reduced. In patients above 60 years, therapy should start with a dose of 0.1 - 0.2 mg per day and should be slowly increased according to individual patient requirements. The minimum effective dose should be used. The maintenance dose in these patients seldom exceeds 0.5 mg per day.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section **2 QUALITATIVE AND QUANTITATIVE COMPOSITION**.

Somatropin must not be used when there is any evidence of activity of a tumour. Intracranial tumours must be inactive and antitumour therapy must be completed prior to starting growth hormone therapy. Treatment should be discontinued if there is evidence of tumour growth.

Genotropin GoQuick should not be used for growth promotion in children with closed epiphyses.

Patients with acute critical illness suffering complications following open heart surgery, abdominal surgery, multiple accidental trauma, acute respiratory failure or similar conditions should not be treated with Genotropin GoQuick (regarding patients undergoing substitution therapy, see section **4.4 Special Warnings and Precautions for Use**).

4.4 Special Warnings and Precautions for Use

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

Myositis is a very rare adverse event that may be related to the preservative metacresol. In the case of myalgia or disproportionate pain at injection site, myositis should be considered and if confirmed, a Genotropin GoQuick presentation without metacresol should be used.

The maximum recommended daily dose should not be exceeded (see section **4.2 Posology and Method of Administration**).

Insulin sensitivity
Somatropin may reduce insulin sensitivity. For patients with diabetes mellitus, the insulin dose may require adjustment after somatropin therapy is instituted. Patients with diabetes, glucose intolerance, or additional risk factors for diabetes should be monitored closely during somatropin therapy.

Thyroid function
Growth hormone increases the extrathyroidal conversion of T4 to T3 which may result in a reduction in serum T4 and an increase in serum T3 concentrations. Whereas the peripheral thyroid hormone levels have remained within the reference ranges in the majority of healthy subjects hypothyroidism theoretically may develop in subjects with subclinical hypothyroidism. Consequently, monitoring of thyroid function should therefore be conducted in all patients. In patients with hypopituitarism on standard replacement therapy, the potential effect of growth hormone treatment on thyroid function must be closely monitored.

Hypoadrenalism
Introduction of somatropin treatment may result in inhibition of 11βHSD-1 and reduced serum cortisol concentrations. In patients treated with somatropin, previously undiagnosed central (secondary) hypoadrenalism may be unmasked and glucocorticoid replacement may be required. In addition, patients treated with glucocorticoid replacement therapy for previously diagnosed hypoadrenalism may require an increase in their maintenance or stress doses, following initiation of somatropin treatment (see section **4.5 Drug Interactions**).

Use with oral oestrogen therapy
If a woman taking somatropin begins oral oestrogen therapy, the dose of somatropin may need to be increased to maintain the serum IGF-1 levels within the normal age-appropriate range. Conversely, if a woman on somatropin discontinues oral oestrogen therapy, the dose of somatropin may need to be reduced to avoid excess of growth hormone and/or side effects (see section **4.5 Drug Interactions**).

In growth hormone deficiency secondary to treatment of malignant disease, it is recommended to pay attention to signs of relapse of the malignancy. 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, in patients treated with radiation to the head for their first neoplasm, were the most common of these second neoplasms.

In patients with endocrine disorders, including growth hormone deficiency, slipped epiphyses of the hip may occur more frequently than in the general population. Children limping during treatment with somatropin, should be examined clinically.

Benign intracranial hypertension
In case of severe or recurrent headache, visual problems, nausea and/or vomiting, a fundoscopy for papilloedema is recommended. If papilloedema is confirmed, a diagnosis of benign intracranial hypertension should be considered and, if appropriate, the growth hormone treatment should be discontinued. At present there is insufficient evidence to give specific advice on the continuation of growth hormone treatment in patients with resolved intracranial hypertension. If growth hormone treatment is restarted, careful monitoring for symptoms of intracranial hypertension is necessary.

Leukaemia
Leukaemia has been reported in a small number of growth hormone deficiency patients, some of whom have been treated with somatropin. However, there is no evidence that leukaemia incidence is increased in growth hormone recipients without predisposition factors.

Antibodies
As with all somatropin containing products, a small percentage of patients may develop antibodies to Genotropin GoQuick. Genotropin GoQuick has given rise to the formation of antibodies in approximately 1% of patients. The binding capacity of these antibodies is low and there is no effect on growth rate. Testing for antibodies to somatropin should be carried out in any patient with otherwise unexplained lack of response.

Elderly patients
Experience in patients above 80 years is limited. Elderly patients may be more sensitive to the action of Genotropin GoQuick, and therefore may be more prone to develop adverse reactions.

Acute critical illness
The effects of Genotropin GoQuick 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 5.3 or 8 mg Genotropin GoQuick daily compared to patients receiving placebo, 42% vs. 19%. Based on this information, these types of patients should not be treated with Genotropin GoQuick. As there is no information available on the safety of growth hormone substitution therapy in acutely critically ill patients, the benefits of continued treatment in this situation should be weighed against the potential risks involved.

In all patients developing other or similar acute critical illness, the possible benefit of treatment with Genotropin GoQuick must be weighed against the potential risk involved.

Pancreatitis
Although rare, pancreatitis should be considered in somatropin-treated patients, especially children who develop abdominal pain.

Prader-Willi syndrome
In patients with Prader-Willi syndrome, treatment should always be in combination with a calorie-restricted diet.

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 (those patients exceeding a weight/height of 200 %), history of respiratory impairment or sleep apnoea, or unidentified respiratory infection. Patients with one or more of these factors may be at increased risk.

Before initiation of treatment with somatropin in patients with Prader-Willi syndrome, signs for upper airway obstruction, sleep apnoea, or respiratory infections should be assessed.

If during the evaluation of upper airway obstruction, pathological findings are observed, the child should be referred to an Ear, nose and throat (ENT) specialist for treatment and resolution of the respiratory disorder prior to initiating growth hormone treatment.

Sleep apnoea should be assessed before onset of growth hormone treatment by recognised methods such as polysomnography or overnight oxymetry, and monitored if sleep apnoea is suspected.

If during treatment with somatropin patients show signs of upper airway obstruction (including onset of or increased snoring), treatment should be interrupted and a new ENT assessment performed.

All patients with Prader-Willi syndrome should be monitored if sleep apnoea is suspected.

Patients should be monitored for signs of respiratory infections, which should be diagnosed as early as possible and treated aggressively.

All patients with Prader-Willi syndrome should also have effective weight control before and during growth hormone treatment.

Scoliosis is common in patients with Prader-Willi syndrome. Scoliosis may progress in any child during rapid growth. Signs of scoliosis should be monitored during treatment.

Experience with prolonged treatment in adults and in patients with Prader-Willi syndrome is limited.

<u>Small for gestational age</u>
In short children born SGA other medical reasons or treatments that could explain growth disturbance should be ruled out before starting treatment.

In SGA children it is recommended to measure fasting insulin and blood glucose before start of treatment and annually thereafter. In patients with increased risk for diabetes mellitus (e.g., familial history of diabetes, obesity, severe insulin resistance, acanthosis nigricans) oral glucose tolerance testing (OGTT) should be performed. If overt diabetes occurs, growth hormone should not be administered.

In SGA children it is recommended to measure the IGF-I level before start of treatment and twice a year thereafter. If on repeated measurements IGF-I levels 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.

Experience in initiating treatment in SGA patients near onset of puberty is limited. It is therefore, not recommended to initiate treatment near onset of puberty. Experience in patients with Silver-Russell syndrome is limited.

Some of the height gain obtained with treating short children born SGA with growth hormone may be lost if treatment is stopped before final height is reached.

Chronic renal insufficiency
In patients with chronic renal insufficiency, renal function should be below 50% of normal before institution of therapy. To verify growth disturbance, growth should be followed for a year preceding institution of therapy. During this period, conservative treatment for renal insufficiency (which includes control of acidosis, hyperparathyroidism and nutritional status) should have been established and should be maintained during treatment. The treatment should be discontinued at renal transplantation.

To date, no data on final height in patients with chronic renal insufficiency treated with Genotropin GoQuick are available.

Sodium content
This medicinal product contains less than 1 mmol sodium (23 mg) per dose. Patients on low sodium diets can be informed that this medicinal product is essentially 'sodium free'.

4.5 Drug Interactions

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

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

Data from an interaction study performed in growth hormone deficient adults, suggests that somatropin administration may increase the clearance of compounds known to be metabolised by cytochrome P450 isoenzymes. The clearance of compounds metabolised by cytochrome P450 3A4 (e.g., sex steroids, corticosteroids, anticonvulsants, and ciclosporin) may be especially increased resulting in lower plasma levels of these compounds. The clinical significance of this is unknown.

Also see section **4.4 Special Warnings and Precautions for Use** for statements regarding diabetes mellitus and thyroid disorder.

In women on oral oestrogen replacement, a higher dose of growth hormone may be required to achieve the treatment goal (see section **4.4 Special Warnings and Precautions for Use**).

4.6 Use in Special Populations

Pregnancy

Animal studies are insufficient with regard to effects on pregnancy, embryofoetal development, parturition or postnatal development (see section **6.1 Animal Toxicology or Pharmacology**). No clinical studies on exposed pregnancies are available. Therefore, somatropin containing products are not recommended during pregnancy and in women of childbearing potential not using contraception.

Lactation

There have been no clinical studies conducted with somatropin containing products in breast-feeding women. It is not known whether somatropin is excreted in human milk, but absorption of intact protein from the gastrointestinal tract of the infant is extremely unlikely. Therefore, caution should be exercised when somatropin containing products are administered to breast-feeding women.

4.7 Effects on Ability to Drive and Use Machines

Genotropin GoQuick has no influence on the ability to drive and use machines.

4.8 Undesirable Effects

Patients with growth hormone deficiency are characterized by extracellular volume deficit. When treatment with somatropin is started, this deficit is rapidly corrected. In adult patients, adverse effects related to fluid retention, such as oedema peripheral, face oedema, musculoskeletal stiffness, 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.

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.

Genotropin GoQuick has given rise to the formation of antibodies in approximately 1% of the patients. The binding capacity of these antibodies has been low and no clinical changes have been associated with their formation, see section 4.4 **Special Warnings and Precautions for Use**.

Tabulated list of adverse reactions

Table 2 shows the adverse reactions ranked under headings of system organ class and frequency for children and adults, using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

Table 2: Tabulated list of adverse reactions

System organ class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)	Very rare (<1/10,000)	Not known (cannot be estimated from available data)
Neoplasms benign, malignant, and			(Children) Leukaemia†			

Table 2: Tabulated list of adverse reactions

System organ class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)	Very rare (<1/10,000)	Not known (cannot be estimated from available data)
unspecified (including cysts and polyps)						
Metabolism and nutrition disorders						(Adults and Children) Type 2 diabetes mellitus
Nervous system disorders		(Adults) Paraesthesia* (Adults) Carpal tunnel syndrome	(Children) Benign intracranial hypertension (Children) Paraesthesia*			(Adults) Benign intracranial hypertension
Skin and subcutaneous tissue disorders			(Children) Rash**, Pruritus**, Urticaria**			(Adults) Rash**, Pruritis**, Urticaria**
Musculoskeletal and connective tissue disorders	(Adults) Arthralgia*	(Adults) Myalgia* (Adults) Musculoskeletal stiffness* (Children) Arthralgia*	(Children) Myalgia*			(Children) Musculoskeletal stiffness*
Reproductive system and breast disorders			(Adults and Children) Gynaecomastia			
General disorders and administration site conditions	(Adults) Oedema peripheral*	(Children) Injection-site reaction$	(Children) Oedema peripheral*			(Adults and Children) Face oedema* (Adults) Injection-site reaction$
Investigations						(Adults and Children) Blood cortisol decreased‡

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

Reduced serum cortisol levels

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 GoQuick therapy.

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

Leukaemia
Cases of leukaemia have been reported in children with a GH deficiency, some of whom were treated with somatropin and included in the post-marketing experience. However, there is no evidence of an increased risk of leukaemia without predisposition factors, such as radiation to the brain or head.

Slipped capital femoral epiphysis and Legg-Calve-Perthes disease
Slipped capital femoral epiphysis and Legg-Calve-Perthes disease have been reported in children treated with growth hormone. Slipped capital femoral epiphysis occurs more frequently in case of endocrine disorders and Legg-Calve-Perthes is more frequent in case of short stature. But it is unknown if these two pathologies are more frequent or not while treated with somatropin. Their diagnosis should be considered in a child with a discomfort or pain in the hip or knee.

Other adverse drug reactions
Other adverse drug reactions may be considered somatropin class effects, such as possible hyperglycaemia caused by decreased insulin sensitivity, decreased free thyroxin level and benign intra-cranial hypertension.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions.

4.9 Overdose

Symptoms
Acute overdosage could lead initially to hypoglycaemia and subsequently to hyperglycaemia.

Long-term overdosage could result in signs and symptoms consistent with the known effects of human growth hormone excess.

5. PHARMACOLOGICAL PROPERTIES

5.1 Mechanism of Action

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

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

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

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

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

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

5.2 Pharmacodynamic Properties

Pharmacotherapeutic group: Anterior pituitary lobe hormones and analogues, ATC code: H01A C01

In clinical trials in short children born SGA doses of 0.033 and 0.067 mg/kg body weight per day have been used for treatment until final height. In 56 patients who were continuously treated and have reached (near) final height, the mean change from height at start of treatment was +1.90 SDS (0.033 mg/kg body weight per day) and +2.19 SDS (0.067 mg/kg body weight per day). Literature data from untreated SGA children without early spontaneous catch-up suggest a late growth of 0.5 SDS.

5.3 Pharmacokinetic Properties

Absorption

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

Elimination

The mean terminal half-life of somatropin after intravenous administration in growth hormone deficient adults is about 0.4 hours. However, after subcutaneous administration, half-lives of 2-3 hours are achieved. The observed difference is likely due to slow absorption from the injection site following subcutaneous administration.

Sub-populations
The absolute bioavailability of somatropin seems to be similar in males and females following S.C. administration.

Information about the pharmacokinetics of somatropin in geriatric and paediatric populations, in different races and in patients with renal, hepatic or cardiac insufficiency is either lacking or incomplete.

6. NONCLINICAL PROPERTIES

6.1 Animal Toxicology or Pharmacology

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

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

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

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

7. DESCRIPTION

Powder and solvent for solution for injection. In the two-chamber cartridge there is a white powder in the front compartment and a clear solution in the rear compartment.

8. PHARMACEUTICAL PARTICULARS

8.1 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

8.2 Shelf-life

The powder for injection 12 mg (36 IU) has a shelf life of 36 months.

8.3 Packaging Information

The two compartment cartridge is composed of:
- Glass cartridge of Glass type one.
- Plungers of Bromobutyl rubber.
- Cap of Aluminum with a disc of bromobutyl rubber.
- The front compartment (I) of the cartridge is sealed with a rubber disc and a cap, and the rear compartment (II) is sealed with a plunger.

Presentation	Container
12 mg	Powder and 1 ml solvent 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 re-usable injection device Genotropin GoQuick Pen, or reconstitution device, Genotropin GoQuick Mixer or sealed in a disposable multidose pre-filled pen, GoQuick. The Genotropin GoQuick Pens are colour coded, and must be used with the matching colour coded Genotropin GoQuick two-chamber cartridge to give the correct dose. The Genotropin GoQuick Pen 12 (purple) must be used with Genotropin GoQuick 12 mg cartridge (purple). The 12 mg pre-filled pen Genotropin GoQuick is colour coded purple.

8.4. Storage and Handling Instructions

Storage

Store Genotropin GoQuick under refrigeration at 2°C to 8°C. Do not freeze. Protect from light. Storage for one month can take place at room temperature. Reconstituted Genotropin GoQuick with preservative may be stored under refrigeration (2°C to 8°C) for up to 4 weeks protected from light.

Instructions for Use/Handling

Two-chamber cartridge: The solution is prepared by screwing the reconstitution device or injection device (Genotropin GoQuick Pen) together so that the solvent will be mixed with the powder in the two-chamber cartridge. Gently dissolve the drug with a slow, swirling motion. Do not shake vigorously; this might cause denaturation of the active ingredient.

Genotropin GoQuick Pen: The two-chamber cartridge is fitted into the device. Screwing the pen together will cause reconstitution to take place. The injection needle should be screwed on Genotropin GoQuick Pen before reconstitution.

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

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.

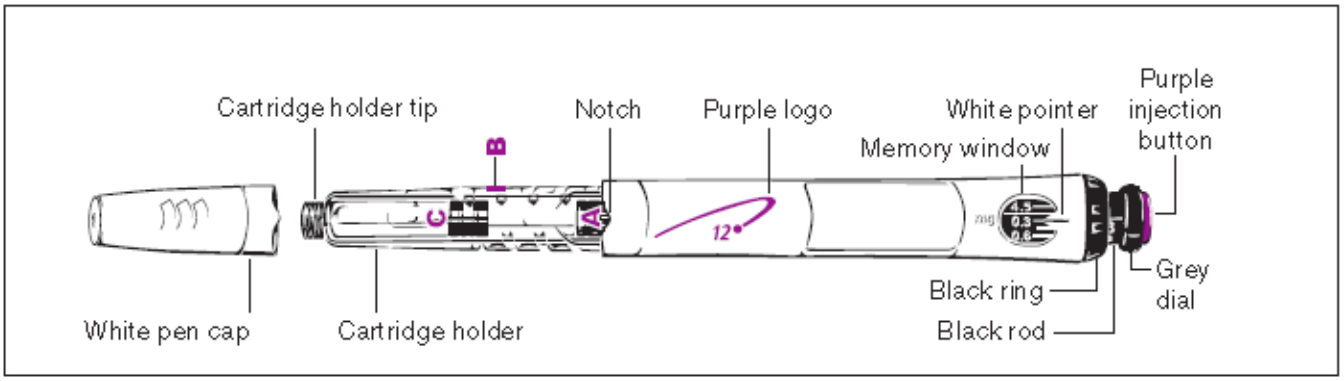
About GoQuick

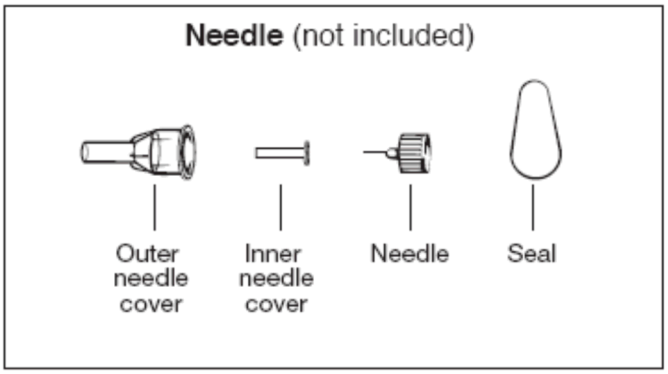
GoQuick is a prefilled, multidose, disposable injection pen that holds 12 mg of somatropin. The Genotropin in the pen is mixed only once, when you start a new pen. A single pen can be used up to 28 days after mixing. You never have to change cartridges. When the pen is empty, you just start a new pen.

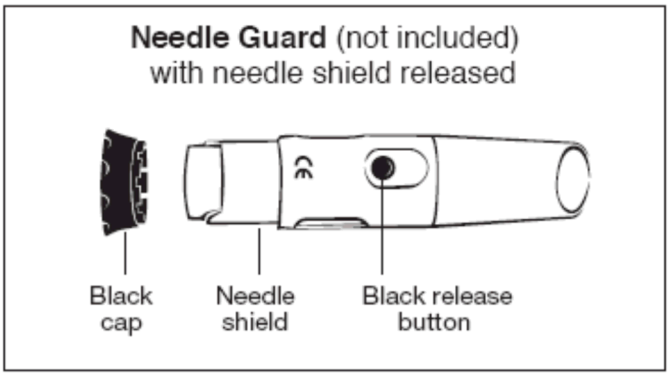
The pen has dose memory. The dose is set once on a new pen. The pen then gives the same dose for each injection. You can use the pen with or without the optional needle guard.

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 purple injection button.
- Wash your hands.

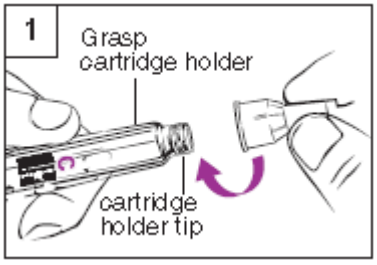






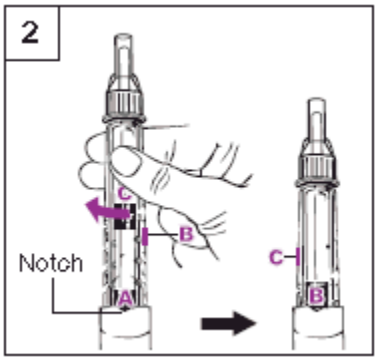
Step 1. Attach the Needle

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.



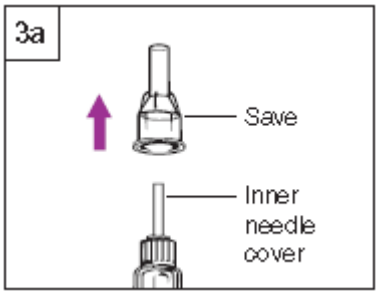
Step 2. Mix the Genotropin GoQuick

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.

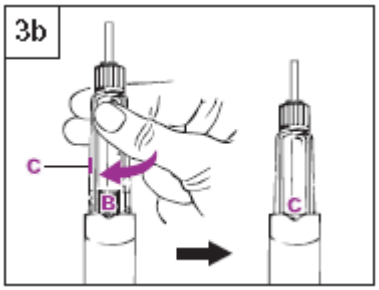


Step 3. Remove the Air

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

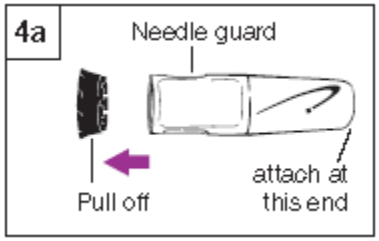


c. Hold the pen with the needle-end pointing up. (Figure 3b)
d. Tap the cartridge holder gently to help any trapped air move to the top.
e. **Firmly,** twist the cartridge holder into the pen until **C** clicks into the notch.
   - Some liquid may appear around the inner needle cover.

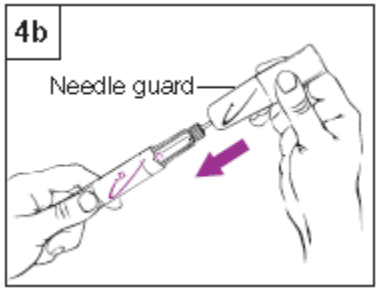


Step 4. Attach the Needle Guard (Optional)

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.

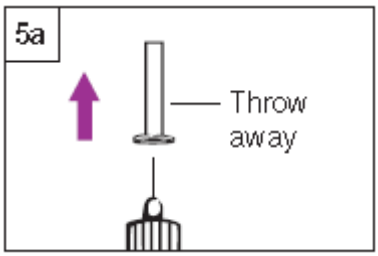


b. Hold the pen in one hand below the purple logo. With the other hand, hold the needle guard below the needle shield. (Figure 4b)
c. Line up the black logo on the needle guard with the purple logo on the pen. Carefully push the needle guard onto the pen until it snaps into place.

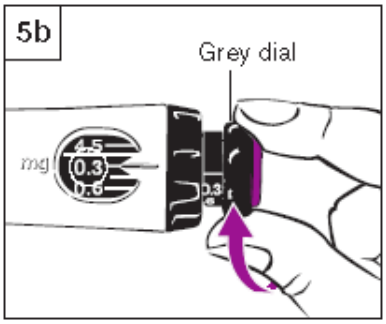


Step 5. Prime the Pen

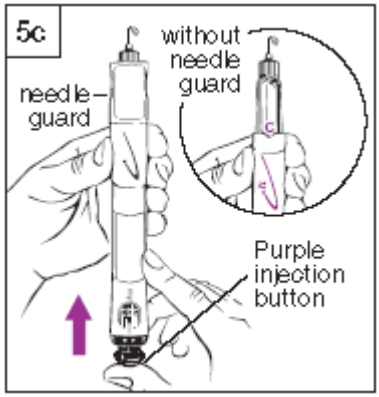
a. Pull the inner needle cover off. Throw it away. (Figure 5a)



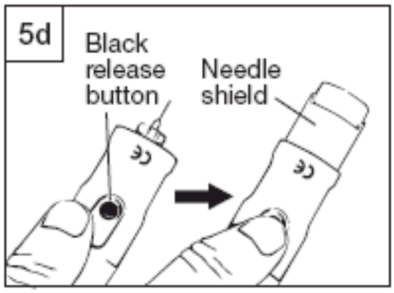
b. Check that 0.3 mg is set in the memory window.
c. Turn the grey dial in the direction of the arrows until it stops clicking. (Figure 5b)



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)

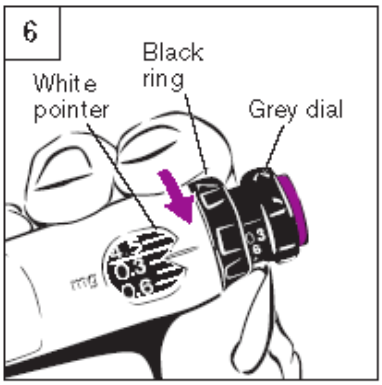


Step 6. Set the Dose

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

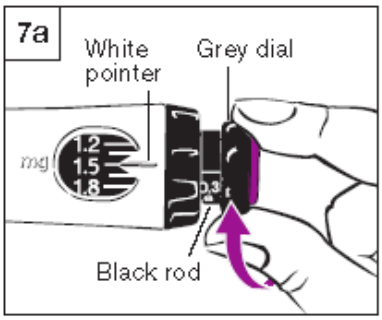
a. Hold the black ring as shown in Figure 6.
b. Turn the black ring until your dose lines up with the white pointer. Your doctor or nurse has told you your dose.
c. If you turn your dose past the white pointer, just turn the black ring back to set the correct dose.
d. Once you have set your dose, do 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).

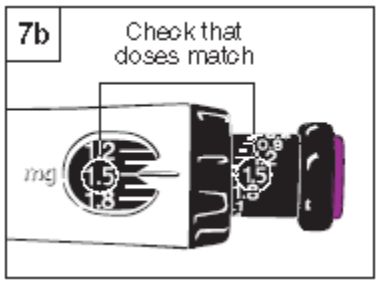


Step 7. Draw Up a Dose

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.

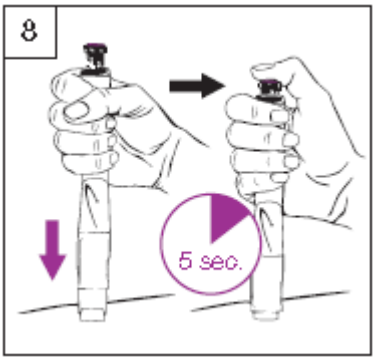


c. Check that the dose you drew up on the black rod is the same as the dose you set in the memory window. Figure 7b shows an example.
d. If the doses do not match, make sure you have turned the grey dial in the direction of the arrow until it does not click anymore.



Step 8. Give the Injection

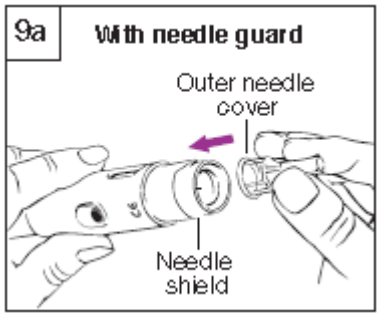
a. Prepare an injection site as your doctor or nurse has told you.
b. Hold the pen over the injection site.
c. Push the pen down to insert the needle into the skin.
d. Using your thumb, push the purple injection button down until it stops clicking. (Figure 8)
    - Count for 5 seconds before you pull 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

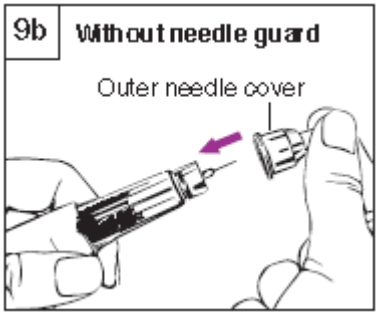
Step 9a: With needle guard

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.



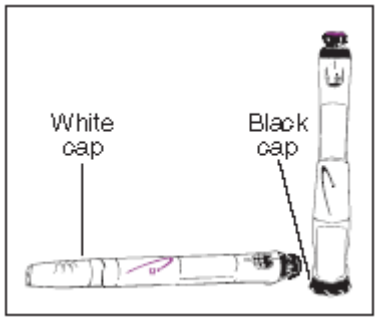
Step 9b: Without needle guard

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.

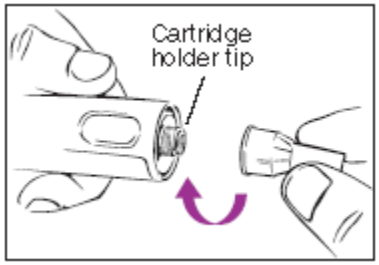


Routine Use of GoQuick

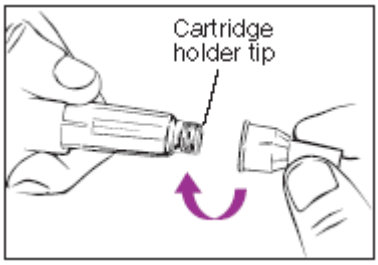
1. Pull the black cap from the needle guard or the white cap from the pen.



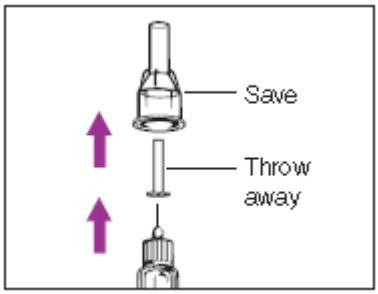
2. Attach a new needle.
   - With the needle guard:
     - If the needle shield releases, push it back into place.
     - Attach a new needle to the cartridge holder tip.



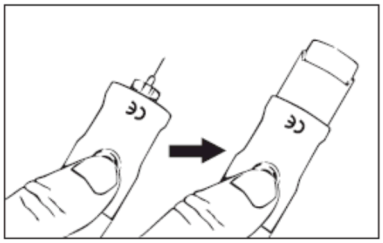
- Without the needle guard:
  - Attach a new needle to the cartridge holder tip.



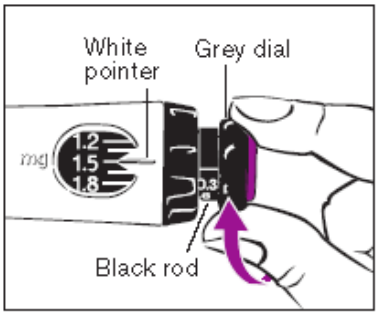
3. Remove both needle covers. Save the outer needle cover.



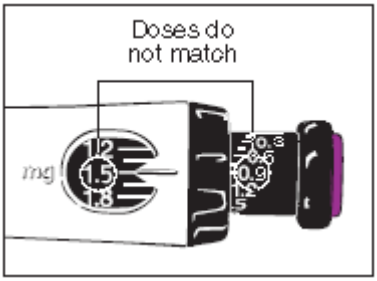
4. If you use the needle guard, press the black release button to extend the needle shield.



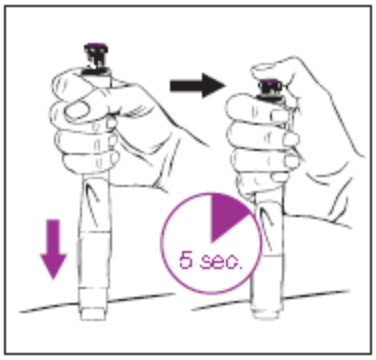
5. To draw up the dose, turn the grey dial until it stops clicking.



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.

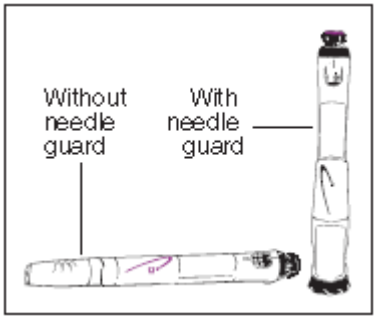


7. Prepare an injection site as your doctor or nurse has told you.



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 beginning of section **8.4 Storage and Handling instructions** above 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.

Question 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.

9. PATIENT COUNSELLING INFORMATION

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

Advise patient to connect their health care provider if they develop discomfort at the injection site, joint pain, swelling in parts of body, skin irritation and redness, injection site discomfort, abnormal sensations, increased pressure in the skull, joint and muscle pain, swelling in parts of body, numbness and tingling in the hand and arm, muscle stiffness (see section **4.8 Undesirable Effects**).

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

Genotropin GoQuick is supplied in a two-chamber cartridge, with the lyophilized powder in the front chamber and a diluent in the rear chamber. The two-chamber cartridge is sealed in a disposable multidose pre-filled pen, GoQuick. The 12 mg pre-filled pen GoQuick is colour coded purple. The two-chamber cartridge contains overfill in order to deliver the stated amount of somatropin.

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

Please see section **8.4 Storage and Handling Instructions** for directions for use of the reconstitution and/or delivery device.

10. DETAILS OF MANUFACTURER

M/s. Pfizer manufacturing Belgium NV, Rijksweg 12, 2870, Purrs, Belgium

Imported by:

Pfizer Products India Pvt. Ltd., The Capital-B wing, 1802,18th Floor, Plot No. C-70, G Block, Bandra Kurla Complex, Bandra (East), Mumbai, India

11. DETAILS OF PERMISSION OR LICENSE NUMBER WITH DATE

4-84/00-DC dated 23/11/2001

12. DATE OF REVISION

July 2022