Recombinant Somatropin for Injection I.P. Genotropin®

1. GENERIC NAME

Recombinant Somatropin for Injection I.P.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Recombinant Somatotropin I.P. (Sterile, Lyophilized Powder) for solution for subcutaneous Injection; 5.3 mg (16IU) and 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. 5.3 mg (16IU) and 12 mg (36IU).

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Somatropin 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.

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

Myositis is a very rare adverse event that may be related to the preservative metacresol. In the case of myalgia or disproportionate pain at injection site, myositis should be considered and if confirmed, a somatropin 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 somatropin. Somatropin 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 somatropin, and therefore may be more prone to develop adverse reactions.

Acute critical illness
The effects of somatropin 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 somatropin daily compared to patients receiving placebo, 42% vs. 19%. Based on this information, these types of patients should not be treated with somatropin. 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 somatropin 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 somatropin 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

Somatropin 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.

Somatropin 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 somatropin 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

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
5.3 mg and 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 Pen, or reconstitution device, Genotropin Mixer. The Genotropin Pens are colour coded, and must be used with the matching colour coded Genotropin two-chamber cartridge to give the correct dose. The Genotropin Pen 5.3 (blue) must be used with Genotropin 5.3 mg cartridge (blue). The Genotropin Pen 12 (purple) must be used with Genotropin 12 mg cartridge (purple). The Genotropin Pens are colour coded, and must be used with the matching colour coded Genotropin two-chamber cartridge to give the correct dose.

8.4 Storage and Handling Instructions

Store Genotropin 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 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 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.

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.

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 is supplied in a two-chamber cartridge, with the lyophilized powder in the front chamber and a diluent in the rear chamber. A reconstitution device is used to mix the diluent and powder. The two-chamber cartridge contains overfill in order to deliver the stated amount of somatropin.

The Genotropin 5.3 mg and 12 mg cartridges are color-coded to help ensure proper use with the Genotropin Pen delivery device. The Genotropin Pen 5.3 (blue) must be used with Genotropin 5.3 mg cartridge (blue). The Genotropin Pen 12 (purple) must be used with Genotropin 12 mg cartridge (purple).

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