

1. NAME OF THE MEDICINAL PRODUCT

GENOTROPIN 5.3 mg,
GENOTROPIN 12 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

GENOTROPIN 5.3 mg powder and solvent for solution for injection, with preservative. One cartridge contains 5.3 mg somatropin*. After reconstitution the concentration of somatropin is 5.3 mg/ml.

GENOTROPIN 12 mg powder and solvent for solution for injection, with preservative. One cartridge contains 12 mg somatropin*. After reconstitution the concentration of somatropin is 12 mg/ml.

* produced in *Escherichia coli* cells by recombinant DNA technology

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Children:

Short stature due to inadequate or failed secretion of pituitary growth hormone or Turner's syndrome.

Short stature in children with chronic renal insufficiency.

Growth disturbance (height SDS < -2.5 and parental adjusted height SDS < -1) in short children born SGA (SGA – small for gestational age, i.e. born small in relation to the length of the fetus development), with a birth weight and/or length < -2 SD, who failed to show catch up growth (HV SDS < 0 during the last year) by 4 years of age or later. In Prader-Willi syndrome (PWS) to improve growth and body composition.

The diagnosis of PWS should be confirmed by genetic analysis.

Adults:

For adults who have suffered from growth-hormone deficiency since childhood.

For adults who have acquired growth hormone deficiency due to a pituitary pathology causing hypopituitarism.

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 lipodatrophy.

- 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.
- Prader Willi Syndrome, 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/m² body surface area per day is recommended. Daily doses of 2.7mg should not be exceeded. Treatment should not be used in children with growth velocity less than 1cm 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 1.4 mg/m² body surface area per day (0.045-0.050 mg/kg body weight per day) is recommended. Higher doses may be needed if growth velocity is too low. A dose correction may be needed after six months of treatment. Factor (IGF-I) in serum should be used as guidance for dose titration. The minimum effective dose should be used and dose requirements may decline with increasing age.
- In growth disturbances in short children born SGA is usually a dose of 0.035mg/kg body weight per day (1mg/m² body surface area per day) is recommended, until final height is reached (see Pharmacodynamic properties section). Treatment should be discontinued after 1 year if the height velocity SDS is below +1. The treatment should be discontinued if height velocity is < 2 cm/year and, if confirmation is required, bone age > 14 years (girls) or > 16 years (boys), corresponding to the closure of the epiphyseal growth plates.

Dosage Recommendations:

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

<i>Indication</i>	Daily Dose			
	mg/kg body weight	IU/kg body weight	mg/m² body surface area	IU/m² body surface area
Growth hormone deficiency	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	0.035	0.10	1.0	3.0
Small for gestational age	0.035 – 0.067	0.10 – 0.20	1.0 – 2.0	3.0 - 6.0

- *Growth hormone deficient adult patients:* Therapy should start with a low dose, 0.15-0.3mg (0.45 to 0.90 IU) per day. The final dose should be gradually increased according to individual patient requirements as determined by the IGF-I concentration with respect to age and gender. Treatment goal should be insulin-like growth factor (IGF-1) 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 be used as guidance for dose titration.

The daily maintenance dose seldom exceeds 1.3 mg (4 IU) 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 decreased with age, dose requirements may be reduced. Clinical response, side effects, and

determination of IGF-I in serum may be used as guidance for dose titration. The minimum effective dose should be used.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1

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 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 (regarding patients undergoing substitution therapy, see section 4.4). Somatropin is contraindicated in patients with Prader-Willi syndrome who are severely obese or have severe respiratory impairment (see Warnings and precautions).

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

4.4 Special warnings and precautions for use

Diagnosis and therapy with GENOTROPIN 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 preparation without metacresol should be used.

The maximum recommended daily dose should not be exceeded (see section 4.2).

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 11 β HSD-1 and reduced serum cortisol concentrations. In patients treated with somatropin, previously undiagnosed central (secondary) hypoadrenalism may be unmasked and glucocorticoid replacement may be required. In addition, patients treated with glucocorticoid replacement therapy for previously diagnosed hypoadrenalism

may require an increase in their maintenance or stress doses, following initiation of somatropin treatment (see section 4.5).

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).

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 funduscopy 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. GENOTROPIN 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 60 years is limited. Elderly patients may be more sensitive to the action of GENOTROPIN, and therefore may be more prone to develop adverse reactions.

Acute critical illness

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 5.3 or 8 mg GENOTROPIN daily compared to patients receiving placebo, 42% vs. 19%. Based on this information, these types of patients should not be treated with GENOTROPIN. 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 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.

Small for gestational age

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 chronic renal insufficiency, renal function should be below 50 percent 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 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 Interaction with other medicinal products and other forms of interaction

Concomitant treatment with glucocorticoids inhibits the growth-promoting effects of somatropin containing products. Patients with Adrenocorticotrophic 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).

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 P 450 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 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).

4.6 Pregnancy and lactation

Pregnancy

Animal studies are insufficient with regard to effects on pregnancy, embryofetal development, parturition or postnatal development (See section 5.3). 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.

Breast-feeding

There have been no clinical studies conducted with somatotropin containing products in breast-feeding women. It is not known whether somatotropin 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 somatotropin containing products are administered to breast-feeding women.

4.7 Effects on ability to drive and use machines

GENOTROPIN 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 somatotropin 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 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.

Tabulated list of adverse reactions

Tables 1-6 show the adverse reactions ranked under headings of System Organ Class and frequency using the following convention: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$); not known (cannot be estimated from the available data) for each of the indicated conditions.

Clinical Trials in Children with GHD**Table 1****Long-term Treatment of Children with Growth Disturbance due to insufficient secretion of growth hormone**

System Organ Class	Very Common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1,000 to <1/100	Rare ≥1/10,000 to <1/1,000	Very Rare <1/10,000	Not Known (cannot be estimated from available data)
Neoplasms Benign, Malignant and Unspecified (including cysts and polyps)			Leukaemia†			
Metabolism and Nutrition Disorders						Type 2 diabetes mellitus
Nervous System Disorders						Paraesthesia* Benign intracranial hypertension
Skin and Subcutaneous Tissue Disorders			Rash** Pruritus** Urticaria**			
Musculoskeletal, Connective Tissue and Bone Disorders			Arthralgia*			Myalgia* Musculoskeletal stiffness*
Reproductive System and Breast Disorders			Gynaecomastia			
General Disorders and Administration Site Conditions	Injection site reaction§					Oedema peripheral* Face oedema*
Investigations						Blood cortisol decreased‡

*In general, these adverse effects are mild to moderate, arise within the first months of treatment, and subside spontaneously or with dose-reduction. The incidence of these adverse effects is related to the administered dose, the age of the patients, and possibly inversely related to the age of the patients at the onset of growth hormone deficiency.

** 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.

Clinical Trials in children with Turner Syndrome**Table 2****Long-term Treatment of Children with Growth Disturbance due to Turner syndrome**

System Organ Class	Very Common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1,000 to <1/100	Rare ≥1/10,000 to <1/1,000	Very Rare <1/10,000	Not Known (cannot be estimated from available data)
Neoplasms Benign, Malignant and Unspecified (including cysts and polyps)						Leukaemia†
Metabolism and Nutrition Disorders						Type 2 diabetes mellitus
Nervous System Disorders						Paraesthesia* Benign intracranial hypertension
Skin and Subcutaneous Tissue Disorders						Rash** Pruritus** Urticaria**
Musculoskeletal, Connective Tissue and Bone Disorders	Arthralgia*					Myalgia* Musculoskeletal stiffness*
Reproductive System and Breast Disorders			Gynaecomasia			
General Disorders and Administration Site Conditions						Oedema peripheral* Face oedema*
Investigations						Injection site reaction [§] 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.

Clinical Trials in Children with Chronic Renal Insufficiency**Table 3****Long-Term Treatment of Children with Growth Disturbance due to Chronic Renal Insufficiency**

System Organ Class	Very Common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1000 to <1/100	Rare ≥1/10,000 to <1/1000	Very Rare <1/10,000	Not Known (cannot be estimated from available data)
Neoplasms Benign, Malignant, and Unspecified (including cysts and polyps)						Leukaemia†
Metabolism and Nutrition Disorders						Type 2 diabetes mellitus
Nervous System Disorders						Paraesthesia* Benign intracranial hypertension
Skin and Subcutaneous Tissue Disorders		Rash**				Pruritus** Urticaria**
Musculoskeletal, Connective Tissue, and Bone Disorders						Arthralgia* Myalgia* Musculoskeletal stiffness*
Reproductive System and Breast Disorders			Gynaecomast ia			
General Disorders and Administration Site Conditions		Injection site reaction [§]				Oedema peripheral* Face oedema*
Investigations						Blood cortisol decreased‡

*In general, these adverse effects are mild to moderate, arise within the first months of treatment, and subside spontaneously or with dose-reduction. The incidence of these adverse effects is related to the administered dose, the age of the patients, and possibly inversely related to the age of the patients at the onset of growth hormone deficiency.

** 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.

Clinical Trials in children with SGA**Table 4****Long-term Treatment of Children with Growth Disturbance due to Born Small for Gestational Age**

System Organ Class	Very Common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1,000 to <1/100	Rare ≥1/10,000 to <1/1,000	Very Rare <1/10,000	Not Known (cannot be estimated from available data)
Neoplasms Benign, Malignant and Unspecified (including cysts and polyps)						Leukaemia†
Metabolism and Nutrition Disorders						Type 2 diabetes mellitus
Nervous System Disorders						Paraesthesia* Benign intracranial hypertension
Skin and Subcutaneous Tissue Disorders		Rash** Urticaria **	Pruritus**			
Reproductive System and Breast Disorders			Gynaecomasia			
Musculoskeletal, Connective Tissue and Bone Disorders			Arthralgia*			Myalgia* Musculoskeletal stiffness*
General Disorders and Administration Site Conditions		Injection site reaction [§]				Oedema peripheral* Face oedema*
Investigations						Blood cortisol decreased‡

*In general, these adverse effects are mild to moderate, arise within the first months of treatment, and subside spontaneously or with dose-reduction. The incidence of these adverse effects is related to the administered dose, the age of the patients, and possibly inversely related to the age of the patients at the onset of growth hormone deficiency.

** 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.

Clinical Trials in PWS**Table 5****Long-term Treatment and Improvement of Body Composition of Children with Growth Disturbance due to Prader-Willi Syndrome**

System Organ Class	Very Common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1,000 to <1/100	Rare ≥1/10,000 to <1/1,000	Very Rare <1/10,000	Not Known (cannot be estimated from available data)
Neoplasms Benign, Malignant and Unspecified (including cysts and polyps)						Leukaemia†
Metabolism and Nutrition Disorders						Type 2 diabetes mellitus
Nervous System Disorders		Paraesthesia*				
		Benign intracranial hypertension				
		Rash**				Pruritus**
Skin and Subcutaneous Tissue Disorders						Urticaria**
Musculoskeletal, Connective Tissue and Bone Disorders		Arthralgia* Myalgia*				Musculoskeletal stiffness*
Reproductive System and Breast Disorders			Gynaecomastia			
General Disorders and Administration Site Conditions		Oedema peripheral*				Face oedema* Injection site reaction [§]
Investigations						Blood cortisol decreased‡

*In general, these adverse effects are mild to moderate, arise within the first months of treatment, and subside spontaneously or with dose-reduction. The incidence of these adverse effects is related to the administered dose, the age of the patients, and possibly inversely related to the age of the patients at the onset of growth hormone deficiency.

** 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.

Clinical Trials in Adults with GHD

Table 6
Replacement Therapy in Adults with Growth Hormone Deficiency

System Organ Class	Very Common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1,000 to <1/100	Rare ≥1/10,000 to <1/1,000	Very Rare <1/10,000	Not Known (cannot be estimated from available data)
Metabolism and Nutrition Disorders						Type 2 diabetes mellitus
Nervous System Disorders		Paraesthesia* Carpal Tunnel Syndrome				Benign intracranial hypertension
Skin and Subcutaneous Tissue Disorders						Rash** Pruritus** Urticaria**
Musculoskeletal, Connective Tissue and Bone Disorders	Arthralgia*	Myalgia* Musculoskeletal stiffness*				
Reproductive System and Breast Disorders			Gynaecomastia			
General Disorders and Administration Site Conditions	Oedema peripheral*					Face oedema* Injection site reaction [§]
Investigations						Blood cortisol decreased [‡]

*In general, these adverse effects are mild to moderate, arise within the first months of treatment, and subside spontaneously or with dose-reduction. The incidence of these adverse effects is related to the administered dose, the age of the patients, and possibly inversely related to the age of the patients at the onset of growth hormone deficiency.

** Adverse Drug Reactions (ADR) identified post-marketing.

§ Transient injection site reactions in children have been reported.

‡ Clinical significance is unknown

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 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 (rare or very rare) 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 GH. 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 2 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. any suspected adverse events **should be reported** to the Ministry of Health according to the National Regulation by using an online form <https://sideeffects.health.gov.il/>

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 Pharmacodynamic properties

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

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 and IGFBP3 (Insulin-like Growth Factor Binding Protein 3) are increased by somatropin. In addition, the following actions have been demonstrated:

- **Lipid metabolism:** Somatropin induces hepatic LDL cholesterol receptors, and affects the profile of serum lipids and lipoproteins. In general, administration of somatropin to growth hormone deficient patients results in reductions in serum LDL and apolipoprotein B. A reduction in serum total cholesterol may also be observed.
- **Carbohydrate metabolism:** Somatropin increases insulin but fasting blood glucose is commonly unchanged. Children with hypopituitarism may experience fasting hypoglycemia. This condition is reversed by somatropin.
- **Water and mineral metabolism:** Growth hormone deficiency is associated with decreased plasma and extracellular volumes. Both are rapidly increased after treatment with somatropin. Somatropin induces the retention of sodium, potassium and phosphorus.
- **Bone metabolism:** Somatropin stimulates the turnover of skeletal bone. Long-term administration of somatropin to growth hormone deficient patients with osteopenia results in an increase in bone mineral content and density at weight-bearing sites.
- **Physical capacity:** Muscle strength and physical exercise capacity are improved after long-term treatment with somatropin. Somatropin also increases cardiac output, but the mechanism has yet to be clarified. A decrease in peripheral vascular resistance may contribute to this effect.

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.

5.2 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.

5.3 Preclinical safety data

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

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

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

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder: Front compartment	Solvent: Rear compartment
Glycine , Sodium dihydrogen phosphate anhydrous, Disodium phosphate anhydrous, Mannitol	Water for injections, Metacresol, Mannitol

6.2 Incompatibilities

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

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Before reconstitution:

Store in a refrigerator (2°C – 8°C) or for a maximum of 1 month at or below 25°C. Keep the two-chamber cartridge/pre-filled pen in the outer carton in order to protect from light.

After reconstitution:

Reconstituted Genotropin can be stored, protected from light, at 2°C-8°C for up to 28 days. Alternatively, reconstituted Genotropin can be stored, protected from light, at room temperature conditions (up to 25°C) for up to 2 hours per day, and within 28 days from reconstitution, during the approved shelf-life. not freeze.

6.5 Nature and contents of container

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

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).

6.6 Special precautions for disposal and other handling

Only reconstitute the powder with the solvent supplied.

Two-chamber cartridge: The solution is prepared by screwing the reconstitution device or injection device together so that the solvent will be mixed with the powder in the two chamber cartridge. Gently dissolve the powder with a slow, swirling motion. Do not shake vigorously, this might cause denaturation of the active substance. The reconstituted solution is almost colourless or slightly opalescent. The reconstituted solution for injection is to be inspected prior to use and only clear solutions without particles should be used.

When using an injection device the injection needle should be screwed on before reconstitution.

Disposal instructions: Any unused product or waste material should be disposed of in accordance with local requirements.

License Holder:

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