

AUSTRALIAN PRODUCT INFORMATION

GENOTROPIN[®] and GENOTROPIN *GoQuick*[®] powder for injection with diluent (with preservative)

GENOTROPIN MiniQuick[®] powder for injection with diluent (single dose syringes)

1. NAME OF THE MEDICINE

Somatropin (rbe).

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

After reconstitution, GENOTROPIN and GENOTROPIN *GoQuick* 5 mg with preservative, two-compartment cartridge contains somatropin (rbe) 5 mg/mL.

After reconstitution, GENOTROPIN and GENOTROPIN *GoQuick* 5.3 mg with preservative, two-compartment cartridge contains somatropin (rbe) 5.3 mg/mL.

After reconstitution, GENOTROPIN and GENOTROPIN *GoQuick* 12 mg with preservative, two-compartment cartridge contains somatropin (rbe) 12 mg/mL.

After reconstitution, GENOTROPIN MiniQuick, two-compartment cartridge contains somatropin (rbe) 0.2 mg, 0.4 mg, 0.6 mg, 0.8 mg, 1.0 mg, 1.2 mg, 1.4 mg, 1.6 mg, 1.8 mg or 2.0 mg in 0.25 mL.

Reconstituted solution has an osmolality of approximately 300 mOsm/kg and pH approximately 6.7.

Excipient(s) with known effect

- Mannitol

For the full list of excipients, see Section 6.1 - List of excipients.

3. PHARMACEUTICAL FORM

Powder for injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Short stature due to decreased or failed secretion of pituitary growth hormone.

Treatment of adults with severe growth hormone deficiency as diagnosed in the insulin tolerance test for growth hormone deficiency and defined by peak growth hormone concentrations of less than 2.5 nanogram/mL.

Growth disturbances associated with gonadal dysgenesis (Turner syndrome).

Improvement of body composition and treatment of short stature associated with Prader-Willi syndrome (PWS) in paediatric patients.

For treatment of growth disturbance in children with chronic renal insufficiency whose height is on or less than twenty-fifth percentile and whose growth velocity is on or less than twenty-fifth percentile for bone age. Chronic renal insufficiency is defined as glomerular filtration rate of less than 50 mL/min/1.73 m².

4.2 Dose and method of administration

GENOTROPIN is administered by subcutaneous injection. The injection site should be varied in an attempt to prevent lipoatrophy. The weekly dose should be given in divided doses, 6 to 7 times per week.

Children with growth hormone deficiency: The diagnosis of growth hormone deficiency should be verified before the preparation is administered. This requires a thorough investigation of the pituitary function, including proper provocation tests. The dosage is individual and gradually titrated, but generally an initial dose of 0.175 to 0.245 mg/kg body weight per week is recommended.

Turner syndrome: A dose of 0.3 to 0.35 mg/kg body weight per week is recommended.

Prader-Willi syndrome: The diagnosis of PWS should be confirmed by appropriate genetic testing. Generally a dose of 0.245 to 0.35 mg/kg body weight per week is recommended.

Chronic renal insufficiency: A dose of 0.3 to 0.35 mg/kg body weight per week is recommended.

Adults with growth hormone deficiency: The recommended dosage at the start of therapy is 0.04 mg/kg/week divided into 7 daily subcutaneous injections. This dose should be gradually increased according to individual patient requirements to a maximum of 0.08 mg/kg/week. Women may require higher doses than men. This means that there is a risk that women, especially those on oral oestrogen replacement may be under-treated. Dose titration is based on the development of side effects and determination of serum levels of insulin-like growth factor-I (IGF-I). Dose requirements may decline with increasing age.

Bioequivalence has not been demonstrated for GENOTROPIN 5 mg or GENOTROPIN 12 mg administered in the GENOTROPIN Pen injection devices and GENOTROPIN MiniQuick.

It is recommended that regular monitoring of growth rate and measurement of biochemical markers, such as IGF-I levels, be undertaken to ensure adequate delivery of growth hormone and compliance with therapy.

Handling

The solution is prepared by screwing the reconstitution device or administration device or *GoQuick* pre-filled pen sections together so that the diluent will be mixed with the powder in the two-compartment cartridge. Gently dissolve the drug with a slow swirling motion. Do not shake vigorously as this might cause denaturation of the active ingredient. When using an administration device or the *GoQuick* pre-filled pen the injection needle should be screwed on before reconstitution.

GENOTROPIN 5 mg, 5.3 mg and 12 mg

GENOTROPIN is dispensed in a special glass ampoule, a so-called two-compartment cartridge, with the active substance in one compartment and diluent in the other. GENOTROPIN cartridges are supplied for use in a re-usable Pfizer administration device (GENOTROPIN Pen), or sealed in a disposable multidose pre-filled pen (GENOTROPIN *GoQuick*).

The GENOTROPIN Pens are colour coded, and **must** be used with the matching colour coded GENOTROPIN cartridge to give the correct dose: GENOTROPIN Pen 5 (green) **must** be used with GENOTROPIN 5 mg cartridge (green); GENOTROPIN Pen 5.3 (blue) **must** be used with GENOTROPIN 5.3 mg cartridge (blue); GENOTROPIN Pen 12 (purple) **must** be used with GENOTROPIN 12 mg cartridge (purple).

The GENOTROPIN 5 mg *GoQuick* pen is colour coded green. The GENOTROPIN 5.3 mg *GoQuick* pen is colour coded blue. The GENOTROPIN 12 mg *GoQuick* pen is colour coded purple.

Empty GENOTROPIN *GoQuick* pens should never be refilled and must be disposed of properly.

GENOTROPIN MiniQuick 0.2 mg to 2.0 mg

GENOTROPIN MiniQuick is dispensed in a special glass ampoule, a so called two-compartment cartridge, with the active substance in one compartment and diluent in the other. Use in one patient on one occasion only. Contains no antimicrobial preservative.

4.3 Contraindications

GENOTROPIN should not be used in patients with active tumours or evidence of tumour growth. Anti-tumour therapy must be completed prior to starting therapy with GENOTROPIN.

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

Known hypersensitivity to metacresol is a contraindication for GENOTROPIN formulations with preservative as they contain metacresol in the supplied diluent.

Patients with acute critical illness suffering complications following open heart surgery, abdominal surgery, multiple accident trauma, extensive burns or acute respiratory failure should not be treated with GENOTROPIN (refer to section 4.4 – Special warnings and precautions for use regarding acutely critically ill patients on substitution therapy with GENOTROPIN).

Somatropin is contraindicated in patients with Prader-Willi syndrome who are severely obese or have severe respiratory impairment (see section 4.4 – Special warnings and precautions for use).

4.4 Special warnings and precautions for use

There have been reports of fatalities associated with the use of growth hormone in paediatric patients with Prader-Willi syndrome who had one or more of the following risk factors: severe obesity, history of respiratory impairment or sleep apnoea, or unidentified respiratory infection. Another possible risk factor may be male gender. Patients with Prader-Willi syndrome should be evaluated for upper airway obstruction before initiation of treatment with somatropin. If during treatment with somatropin patients show signs of upper airway obstruction (including onset of or increased snoring), treatment should be interrupted. All patients with Prader-Willi syndrome should be evaluated for sleep apnoea and monitored if sleep apnoea is suspected. These patients should also have effective weight control and be monitored for signs of respiratory infections, which should be diagnosed as early as possible and treated aggressively (see section 4.3 - Contraindications).

In patients with Prader-Willi syndrome, treatment should always be in combination with a calorie restricted diet. Experience with prolonged treatment in patients with PWS is limited.

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

Somatropin reduces insulin sensitivity and therefore patients should be observed for evidence of glucose intolerance. In rare cases the diagnostic criteria for type 2 diabetes mellitus may be fulfilled as a result of growth hormone therapy but risk factors such as obesity (including obese PWS patients), family history, steroid treatment or pre-existing impaired glucose tolerance have been present in most cases where this has occurred. Growth hormone can be used in patients with already manifest diabetes mellitus, however, its use requires special care and the dose of anti-diabetic therapy may require adjustment.

Introduction of somatropin treatment may result in inhibition of 11 β -hydroxysteroid dehydrogenase type 1 (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 - Interaction with other medicines and other forms of interactions).

If a woman taking somatropin begins oral oestrogen therapy, the dose of somatropin may need to be increased to maintain the serum IGF-I levels within the normal age-appropriate range. Conversely, if a woman on somatropin discontinues oral 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 - Interaction with other medicines and other forms of interaction).

In growth hormone deficiency secondary to treatment of a malignant disease it is recommended to pay attention to signs of relapse of the malignancy.

Newly diagnosed and recurrent cases of leukaemia have been reported in growth hormone deficient children treated with somatropin. These children had other risk factors for leukaemia. A causal association with somatropin has not been identified.

Treatment in adults should be attempted only after a definitive treatment of pituitary tumour (if present) is completed, and after all other pituitary hormone deficiencies are corrected as clinically indicated.

During treatment with somatropin an enhanced T4 to T3 conversion has been found which may result in a reduction in serum T4 and an increase in serum T3 concentrations. In patients receiving replacement therapy with thyroid hormone mild hyperthyroidism may occur. It is therefore advisable to test thyroid function after starting treatment with somatropin and after dose adjustments.

In some patients hypothyroidism might develop during growth hormone treatment. Since untreated hypothyroidism may interfere with the response to somatropin, patients should have a periodic thyroid function test and should be treated with thyroid hormone when indicated.

In patients with endocrine disorders, including growth hormone deficiency, hypopituitarism and renal osteodystrophy, slipped epiphysis of the hip may occur more frequently than in the general population. Patients administered growth hormone should be observed for signs of limping as this may indicate development of slipped capital femoral epiphysis (see Section 4.8 – Adverse effects (undesirable effects), Post-marketing experience).

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

Large doses of glucocorticoids may inhibit the growth promoting effect of growth hormone. Patients with co-existing ACTH deficiencies should have their glucocorticoid replacement doses carefully adjusted.

Somatropin has been reported to reduce serum cortisol levels, possibly by affecting carrier proteins. Changes to serum levels of unbound serum cortisol have not been reported. The clinical relevance of these findings seems limited.

Patients with pan hypopituitarism are at risk of adrenal insufficiency after treatment with growth hormone is commenced, particularly if this has not previously been recognised or the patients are on inadequate replacement.

In patients with (pan) hypopituitarism, standard replacement therapy should be closely monitored.

Growth hormone treatment of patients with renal allograft may represent an increased risk for acute rejection in patients with two or more rejection episodes in their background history.

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 guide clinical decision making in patients with resolved intracranial hypertension. If growth hormone treatment is restarted, careful monitoring for symptoms of intracranial hypertension is necessary.

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 mg or 8 mg GENOTROPIN daily compared to patients receiving placebo (41.9% versus 19.3%). These types of patients should not be treated with GENOTROPIN (refer to section 4.3 - Contraindications). 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 benefits of treatment with GENOTROPIN must be weighed against the potential risk involved.

Patients with childhood growth hormone deficiency should be retested for growth hormone deficiency before commencing treatment as adults.

Experience with prolonged therapy in adults is lacking.

Experience with patients over 60 years is lacking.

In chronic renal insufficiency, growth should be followed for a year preceding institution of therapy, to verify growth disturbance. Conservative treatment for renal insufficiency should have been established and should be maintained during treatment. The treatment should be discontinued at renal transplantation.

GENOTROPIN should be administered by physicians who are experienced in the diagnosis and management of patients with growth hormone deficiency.

Use in the Elderly

No data available.

Paediatric Use

No data available.

Effects on Laboratory Tests

No data available.

4.5 Interactions with other medicines and other forms of interactions

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 - Special warnings and precautions for use).

Data from an interaction study conducted in growth hormone deficient adults, suggest that somatropin administration may increase the clearance of compounds known to be metabolised by cytochrome P450 3A4 (e.g. sex steroids, corticosteroids, anticonvulsants and ciclosporin). The clinical significance of this is unknown.

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).

See also statements under Section 4.4 – Special warnings and precautions for use regarding diabetes mellitus, thyroid disorder and ACTH deficiencies.

4.6 Fertility, pregnancy and lactation

Effects on Fertility

Reproduction was inhibited in male and female rats at somatropin doses of 1 mg/kg/day or more, with reduced copulation and conception rates, lengthened or absent oestrus cycles and at 3.3 mg/kg/day, a lack of responsiveness of females to males, and slight reductions in sperm motility and survival. Rat reproduction was unaffected by 0.3 mg/kg/day somatropin, which resulted in a systemic exposure (based on body surface area) of approximately twice that anticipated at maximal clinical dose.

Use in Pregnancy – Pregnancy Category B2

Somatropin was not teratogenic and did not affect fetal growth at subcutaneous maternal doses up to 3.3 mg/kg/day in rats or 1.3 mg/kg/day in rabbits, which resulted in systemic exposures based on body surface area of approximately 40-fold the anticipated maximum clinical exposure.

There is no experience with somatropin during pregnancy, nor has the need for such use been established.

Use in Lactation

No information as to whether peptide hormones pass into the breast milk is available, but absorption of the intact protein in the gastrointestinal tract of the infant is extremely unlikely.

4.7 Effects on ability to drive and use machines

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 Adverse effects (undesirable effects)

Adverse effects have been noted in approximately 10% of the patients participating in clinical trials in children with short stature.

In clinical trials in adults, adverse effects have been noted in 30 – 40% of patients, primarily related to symptoms of fluid retention, in both active and placebo treated groups. Dosage reduction reduced symptoms in some patients. Adverse effects rarely influenced daily activities.

In general, in adult patients, adverse effects related to fluid retention, such as peripheral oedema, face oedema, musculoskeletal stiffness, arthralgia, myalgia and paraesthesia 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.

The adverse effects for adults and children are presented 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).

	Very Common $\geq 1/10$	Common $>1/100, <1/10$	Uncommon $>1/1000, <1/100$	Rare $>1/10,000, <1/1000$	Very Rare $<1/10,000$	Frequency Not Known (Cannot be estimated from the available data)
Neoplasms benign, malignant and unspecified (including cysts and polyps)					<i>Children</i> Leukaemia	
Immune system disorders		Formation of antibodies				
Metabolism and nutrition disorders				Type 2 diabetes mellitus		
Nervous system disorders		<i>Adults</i> Paraesthesia	<i>Adults</i> Carpal Tunnel syndrome <i>Children</i> Paraesthesia	Benign intracranial hypertension		
Musculoskeletal and connective tissue disorders	<i>Adults</i> Arthralgia	<i>Adults</i> Musculoskeletal stiffness Myalgia	<i>Children</i> Musculoskeletal stiffness Arthralgia Myalgia			
General disorders and administration site conditions	<i>Adults</i> Oedema peripheral	<i>Children</i> Injection-site reactions	<i>Children</i> Oedema peripheral			<i>Adults and Children</i> Face oedema

In a series of 230 GENOTROPIN treated children, anti-hGH antibodies were detectable in only four children at 12 months (1.7%). The binding capacities of these antibodies have been low and without

clinical significance, however, determination of antibody titre may be considered in those children who fail to respond to GENOTROPIN therapy.

After long term application of somatropin, an increased chromosome fragility has in one study been observed in lymphocytes from treated patients following *in vitro* addition of the radiomimetic drug bleomycin. The clinical significance of this finding is unclear.

Note: Some cases of leukaemia have been reported in growth hormone deficient children treated with somatropin, but the incidence appears to be similar to that in children without growth hormone deficiency (see Section 4.4 – Special warnings and precautions for use).

Post-marketing experience

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

Slipped capital femoral epiphysis and Legg-Calve-Perthes disease have been reported in children treated with growth hormone.

Rash, pruritus and urticaria have been reported in both adult patients (frequency not known) and paediatric patients (frequency uncommon).

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 Overdose

Signs and 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 somatropin excess.

Recommended Treatment

Treatment is symptomatic and supportive. There is no antidote for somatropin overdose. It is recommended to monitor thyroid function following an overdose.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of Action

In vitro, preclinical and clinical tests have demonstrated that GENOTROPIN is therapeutically equivalent to human growth hormone of pituitary origin and achieves similar pharmacokinetic profiles in normal adults. In paediatric patients who have growth hormone deficiency or Prader-Willi Syndrome (PWS), treatment with GENOTROPIN stimulates linear growth and normalises

concentrations of IGF-I. In adults with growth hormone deficiency, treatment with GENOTROPIN results in reduced fat mass, increased lean body mass, metabolic alterations that include beneficial changes in lipid metabolism and normalisation of IGF-I concentrations.

In addition, the following actions have been demonstrated:

Tissue Growth

Skeletal growth: GENOTROPIN stimulates skeletal growth in paediatric patients with growth hormone deficiency or PWS. The measurable increase in body length after administration results from an effect on the epiphyseal plates of long bones. Concentrations of IGF-I, which may play a role in skeletal growth, are generally low in the serum of paediatric patients with growth hormone deficiency or PWS but tend to increase during treatment with GENOTROPIN. Elevations in mean serum alkaline phosphatase concentration are also seen.

Cell growth: It has been shown that there are fewer skeletal muscle cells in short-statured paediatric patients who lack endogenous hormone as compared with the normal paediatric population. Treatment with somatotropin results in an increase in both the number and size of muscle cells.

Protein metabolism

Linear growth is facilitated in part by increased cellular protein synthesis. Nitrogen retention, as demonstrated by decreased urinary nitrogen excretion and serum urea nitrogen, follows the initiation of therapy with GENOTROPIN.

Carbohydrate metabolism

Paediatric patients with hypopituitarism sometimes experience fasting hypoglycaemia that is improved by treatment with GENOTROPIN. Large doses of hormone may impair glucose tolerance.

Lipid metabolism

In growth hormone deficient patients, administration of somatotropin has resulted in lipid mobilisation, reduction in body fat stores and increased plasma fatty acids.

Mineral metabolism

Somatropin induces retention of sodium, potassium and phosphorus. Serum concentrations of inorganic phosphate are increased in patients with growth hormone deficiency after therapy with GENOTROPIN. Serum calcium is not significantly altered by GENOTROPIN. Growth hormone could increase calciuria.

Body composition

Adult growth hormone deficient patients treated with GENOTROPIN at the recommended adult dose demonstrate a decrease in fat mass and an increase in lean body mass. When these alterations are coupled with the increase in total body water, the overall effect is to modify body composition, an effect that is maintained with continued treatment.

Pharmacodynamics

Most growth hormone deficient children have subnormal serum levels of IGF-I which increase during growth hormone treatment. After GENOTROPIN administration an increase of IGF-I levels has been shown both in healthy volunteers and in growth hormone deficient children.

Clinical Trials

Turner Syndrome

Final height data are available on approximately 900 patients with Turner syndrome from 14 studies worldwide. The Kabi International Growth Study (KIGS; now the Pfizer International Growth Database) has contributed the largest number of patients at 168 with data collected from 28 countries. Other large series include USA, France and Australia with 166, 117 and 114 patients respectively. All 14 studies were uncontrolled and utilised historical control data and the method devised by Lyon of projected adult height for comparison with actual adult height in determining therapeutic efficacy.

A variety of adjunctive treatments including oestrogen replacement therapy and androgen therapy were used in the different studies. Age at introduction of concomitant oestrogen therapy varied. In one study with somatropin, concomitant oestrogen therapy commenced after age 15 years was associated with a 3.3 cm improvement in height compared with oestrogen therapy commenced after 12 years ($p = 0.003$). Androgen therapy was not shown to be of benefit in terms of increasing adult height.

The mean age at onset of somatropin therapy was relatively advanced, ranging from 9.2 to 13.1 years with 75% having a mean age of onset greater than 12 years. The estimated final height gain averaged across all studies (unweighted for the number of patients included in each study) was 5.4 cm, range 0 - 9.3 cm. Efficacy was demonstrated at doses of 0.160 to 0.375 mg/kg/week.

Prader-Willi Syndrome

The safety and efficacy of GENOTROPIN were evaluated in paediatric patients with Prader-Willi syndrome in two, non-blinded, randomised controlled clinical trials. Patients received either GENOTROPIN or they did not receive any treatment for the first year of the studies, while all patients received GENOTROPIN during the second year. GENOTROPIN was administered as a daily sc injection, and the dose was re-calculated at three month intervals for every patient. In study 1, the treatment group ($n = 15$) received GENOTROPIN at a dose of 0.24 mg/kg/week during the entire study. During the second year, the control group ($n = 12$) received GENOTROPIN at a dose of 0.48 mg/kg/week. In study 2, the treatment group received GENOTROPIN at a dose of 0.36 mg/kg/week during the entire study. During the second year, the control group received GENOTROPIN at a dose of 0.36 mg/kg/week. This study was not conducted beyond 24 months.

Patients who received GENOTROPIN showed significant increases in linear growth during the first year of study compared with patients who received no treatment (Table 1). Linear growth continued to increase in the second year, when both groups received treatment with GENOTROPIN. Final height data are not available from these studies.

Table 1: Efficacy of GENOTROPIN in Paediatric Patients with Prader-Willi Syndrome (Mean + SD)

	Study 1		Study 2	
	GENOTROPIN (0.24 mg/kg/week) n=15	Control n=12	GENOTROPIN (0.36 mg/kg/week) n=7	Control n=9
Linear Growth (cm)				
Baseline height	112.7 ± 14.9	109.5 ± 12.0	120.3 ± 17.5	120.5 ± 11.2
Growth from months 0 to 12	11.6 ± 2.3 (p≤0.001)	5.0 ± 1.2	10.7 ± 2.3 (p≤0.001)	4.3 ± 1.5
Height Standard Deviation Score (SDS) for Age				
Baseline SDS	-1.6 ± 1.3	-1.8 ± 1.5	-2.6 ± 1.7	-2.1 ± 1.4
SDS change from 0 to 12 months	-0.5 ± 1.3 (p≤0.0001)	-1.9 ± 1.4	-1.4 ± 1.5 (p≤0.0015)	-2.2 ± 1.4

Changes in body composition were also observed in patients receiving GENOTROPIN in the first year of study compared with patients who did not receive any treatment. Available results for subjects in Study 1 are present in Table 2. These changes included a decrease in the amount of fat mass and increases in the amount of lean body mass and the ratio of lean-to-fat tissue, while changes in body weight were similar. Treatment with GENOTROPIN did not accelerate bone age, compared with patients who did not receive any treatment. Data to confirm the relationship between body composition changes due to growth hormone treatment and health outcomes in Prader-Willi syndrome patients are not yet available.

Table 2: Effect of GENOTROPIN on Body Composition in Paediatric Patients with Prader-Willi Syndrome (Mean ± SD)

	GENOTROPIN (n=14)	Control (n=10)
Fat mass (kg)		
Baseline	12.3 ± 6.8	9.4 ± 4.9
Change from 0 months to 12	-0.9 ± 2.2 (p≤0.0045)	2.3 ± 2.4
Lean body mass (kg)		
Baseline	15.6 ± 5.7	14.3 ± 4.0
Change from 0 months to 12	4.7 ± 1.9 (p≤0.009)	0.7 ± 2.4
Lean body mass/Fat mass		
Baseline	1.4 ± 0.4	1.8 ± 0.8
Change from 0 months to 12	1.0 ± 1.4 (p≤0.0026)	-0.1 ± 0.6
Body weight (kg)[#]		
Baseline	27.2 ± 12.0	23.2 ± 7.0
Change from 0 months to 12	3.7 ± 2.0 (p=0.57)	3.5 ± 1.9

[#] n=15 for the group receiving GENOTROPIN; n=12 for the Control group

Adult Replacement Therapy

The effects of GENOTROPIN on growth hormone deficient adults were compared to placebo in 12 randomised clinical trials conducted in Europe and one multicentre study conducted in Australia. Each

study included a six month, double blind period followed by a six month open label treatment period where all patients received GENOTROPIN.

The largest multicentre trial (n=163) included 55 patients with childhood onset growth hormone deficiency, and was designed to assess the effects of replacement therapy with GENOTROPIN. The primary objective was to determine the effects of long term use of GENOTROPIN on quality of life, using the Nottingham Health Profile (NHP). (The NHP is a general health related quality of life questionnaire.) Secondary objectives were to compare the effects of GENOTROPIN and placebo on body composition.

83 patients received GENOTROPIN and 80 received placebo for six months, followed by six months of active treatment. The GENOTROPIN dosage for the first month of therapy was 0.04 mg/kg/week, followed by 0.08 mg/kg/week, divided into 7 daily doses.

Body fat mass and fat free mass were determined by anthropometry and bioelectrical impedance analysis (BIA), and by dual X-ray absorptiometry (DEXA) in a subset of patients. Bone mineral density, total body potassium and total body protein were also measured, as well as waist to hip ratio, lipid profile, blood glucose and blood pressure.

Compared to placebo, GENOTROPIN treated patients experienced a decrease in peripheral and truncal skin fold thickness (p=0.02, p<0.001 respectively) after 6 months, with the majority of this effect seen in the first 3 months. Fat mass by DEXA was significantly reduced in the GENOTROPIN treated group compared to placebo (p<0.001) at 6 months and this was maintained at 12 months. Fat free mass (BIA) was significantly increased in the GENOTROPIN group at 6 months (from 50.6 kg to 53.6 kg ± 0.3 kg) but was unchanged for the placebo group (p<0.001). Again, the majority of this increase occurred in the first 3 months of treatment. Similar results were seen with DEXA measurements. Total body protein increased after 6 months treatment, from 9.8 kg to 10.4 kg ± 0.2 kg, but was not changed for the placebo group (p<0.001). There was no further increase at 12 months.

A significant decrease in the waist/hip ratio was seen in the treated group at 6 months (0.894 to 0.87 ± 0.003) compared to placebo (0.892 to 0.894 ± 0.002) (p=0.001). For the group receiving 6 months placebo, waist to hip ratio was significantly decreased at the 9 and 12 month measurements. Total cholesterol decreased after six months of treatment compared to placebo (p<0.05) but this difference was not maintained at 12 months. However, the lower LDL levels observed at 6 months (from 3.8 mmol/L to 3.3 mmol/L ± 0.1) were maintained at 12 months.

At 6 months there were no statistically significant differences between GENOTROPIN and placebo with respect to physical activity at work or leisure, days of sick leave, satisfaction with social life, and occurrence of significant life events. Overall changes in the NHP scales were small.

Chronic Renal Insufficiency

Four open-label uncontrolled, multicentre studies evaluated the efficacy and safety of GENOTROPIN therapy in short pre-pubertal and pubertal children with chronic renal insufficiency (glomerular filtration rate of less than 50 mL/min/1.73 m²) on conservative treatment or on dialysis (peritoneal dialysis and haemodialysis). Dosage of GENOTROPIN in all studies was equivalent to 1.43 mg/m²/day, given as daily subcutaneous injections. The primary efficacy variable was growth rate calculated as cm/year. Height was measured every 3 months, and change in height determined annually.

A total of 161 patients with chronic renal insufficiency and 101 on dialysis were studied. Following GENOTROPIN treatment growth velocity doubled in patients during the first year of treatment, and remained above baseline during the study observation period of up to 4 years for both pre-pubertal and

pubertal patients (Table 3). This resulted in an improvement of height standard deviation score over the 4-year period.

Table 3: Height velocity, cm/year, in pre-pubertal and pubertal short children with chronic renal insufficiency before and during treatment with GENOTROPIN (Mean ± SD)

Study group	n	Pre-treatment	n	1 st year	n	2 nd year	n	3 rd year	n	4 th year
Pre-pubertal group										
96 10 834*	44	4.6 ± 1.8	44	8.8 ± 2.4	17	6.5 ± 2.2	7	6.5 ± 2.3	-	-
96 10 835**	16	3.0 ± 1.9	16	6.2 ± 3.4	6	5.6 ± 2.4	3	5.9 ± 2.2	-	-
97 10 028*	42	5.7 ± 2.8	42	9.9 ± 2.4	28	7.9 ± 1.6	19	7.3 ± 1.5	9	6.5 ± 1.2
97 10 087**	22	3.3 ± 2.4	22	7.1 ± 2.4	11	7.1 ± 1.2	7	5.6 ± 1.2	-	-
Pubertal group										
96 10 834*	14	4.7 ± 2.3	14	8.2 ± 2.6	8	7.0 ± 3.4	2	8.1 ± 3.4	-	-
96 10 835**	16	3.4 ± 2.4	16	7.4 ± 3.1	3	6.4 ± 1.8	-	-	-	-
97 10 028*	17	4.9 ± 1.8	17	8.1 ± 2.7	9	7.5 ± 2.1	4	5.9 ± 2.8	-	-
97 10 087**	19	3.5 ± 2.1	19	6.8 ± 3.0	13	5.9 ± 1.9	5	5.6 ± 3.0	-	-

* Study included patients with chronic renal insufficiency (glomerular filtration rate of less than 50 mL/min/1.73 m²).

** Study included patients with chronic renal insufficiency undergoing peritoneal dialysis or haemodialysis

There was no difference in the incidence of adverse events compared with studies of GENOTROPIN in growth hormone deficient patients and in Turner Syndrome.

GENOTROPIN MiniQuick Range

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

Only AUC was used to test for bioequivalence which is appropriate as this parameter gives the best measurement of the total amount of substance delivered by injection. Both strengths of GENOTROPIN MiniQuick met the standard criterion for bioequivalence with GENOTROPIN in that the 90% confidence interval (CI) for ratio between test and reference preparations was between 0.80 and 1.25. The AUC ratio for 0.4 mg MiniQuick/GENOTROPIN was 0.894 (90% CI, 0.802 – 0.996) and for 2.0 mg MiniQuick/GENOTROPIN was 0.890 (90% CI, 0.809 – 0.978).

GENOTROPIN 5.3 mg and GENOTROPIN 12 mg

The bioequivalence of GENOTROPIN when a dose of 5.3 mg was administered from two different formulations, 5.3 mg and 12 mg, was investigated in a cross over design study in healthy male volunteers. GENOTROPIN 5.3 mg was found to be bioequivalent to GENOTROPIN 12 mg, in that the 90% confidence interval (CI) for ratio between test and reference preparations was between 0.80 and 1.25. The ratios for AUC_∞ and AUC₀₋₂₄ of GENOTROPIN 12 mg to GENOTROPIN 5.3 mg were 1.06 (90% CI: 1.02-1.09) and 1.05 (90% CI: 1.01-1.09), respectively.

5.2 Pharmacokinetic properties

Approximately 80% is absorbed following subcutaneous (sc) injection. Maximum serum concentrations are achieved around 5 hours following injection and the elimination half life is about 4 hours. GENOTROPIN is metabolised in both the liver and kidneys via protein catabolism.

The pharmacokinetic profile after an intramuscular injection (im) is similar to sc injection. No significant differences have been noted in t_{max} , C_{max} or area under the curve (AUC) between these two routes of administration. Moreover, biological effects on increasing non-esterified fatty acid and IGF-1 do not differ.

No significant difference has been noted in positive growth responses to growth hormone administration by either the im or sc route where the frequency of dosing is the same.

5.3 Preclinical safety data

Carcinogenicity and Mutagenicity

Associations between elevated serum IGF-I concentrations and risks of certain cancers have been reported in epidemiological studies. Causality has not been demonstrated. The clinical significance of these associations, especially for subjects treated with somatotropin who do not have growth hormone deficiency and who are treated for prolonged periods, is not known. Serum IGF-I levels can be affected by factors other than growth hormone status including nutrition. There was no evidence for somatotropin genotoxicity in assays for gene mutation in bacteria and mouse lymphoma cells or chromosomal damage in human lymphocytes and rat bone marrow cells.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

After reconstitution, GENOTROPIN 5 mg with preservative, two-compartment cartridge contains:

- glycine 2 mg
- mannitol 41 mg
- monobasic sodium phosphate 280 µg
- dibasic sodium phosphate 270 µg
- metacresol 3 mg
- water for injections to 1 mL

After reconstitution, GENOTROPIN 5.3 mg with preservative, two-compartment cartridge contains:

- glycine 2 mg
- mannitol 41 mg
- monobasic sodium phosphate 290 µg
- dibasic sodium phosphate 280 µg
- metacresol 3 mg
- water for injections to 1 mL

After reconstitution, GENOTROPIN 12 mg with preservative, two-compartment cartridge contains:

- glycine 2 mg
- mannitol 40 mg
- monobasic sodium phosphate 410 µg
- dibasic sodium phosphate 400 µg
- metacresol 3 mg
- water for injections to 1 mL

After reconstitution, GENOTROPIN MiniQuick, two-compartment cartridge contains:

- glycine 0.21 mg
- mannitol 12.5 mg
- monobasic sodium phosphate 45 µg
- dibasic sodium phosphate 25 µg
- water for injections to 0.25 mL

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

GENOTROPIN and GENOTROPIN GoQuick 5 mg, 5.3 mg and 12 mg

Store at 2 - 8°C (refrigerate, do not freeze). Protect from light. Once reconstituted, the re-usable Pfizer administration device and the *GoQuick* pre-filled pen with cartridge in use can be stored in the refrigerator for 28 days. They should not be carried in the shirt pocket or in a school bag but should be kept in the refrigerator at 2 - 8°C. Storage under 25°C for 1 month is possible within the proposed shelf life, prior to reconstitution.

GENOTROPIN MiniQuick 0.2 mg to 2.0 mg

Store at 2 - 8°C (refrigerate, do not freeze). Protect from light. If necessary, the product may be stored at or below 25°C by the end-user for a single period of not more than 6 months. During and/or at the end of the 6 month period the product must be used or discarded. It should not be put back in the refrigerator. The reconstituted solution should be used immediately but can be stored at 2 - 8°C protected from light for up to 24 hours.

6.5 Nature and contents of container

GENOTROPIN / GENOTROPIN *GoQuick* 5 mg powder for injection with diluent (1 mL): 1s, 5s.

GENOTROPIN / GENOTROPIN *GoQuick* 5.3 mg powder for injection with diluent (1 mL): 1s, 5s.

GENOTROPIN / GENOTROPIN *GoQuick* 12 mg powder for injection with diluent (1 mL): 1s, 5s.

GENOTROPIN MiniQuick powder for injection with diluent (0.25 mL) in strengths of 0.2 mg, 0.4 mg, 0.6 mg, 0.8 mg, 1.0 mg, 1.2 mg, 1.4 mg, 1.6 mg, 1.8 mg or 2.0 mg: 7s.

Not all presentations and/or pack sizes may be marketed.

6.6 Special precautions for disposal

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 Physicochemical properties

Chemical Structure

No data available.

Description

GENOTROPIN is produced using recombinant DNA technology; it is synthesised in bacteria, *Escherichia coli* K12 containing a modified pBR322 plasmid which expresses the gene for a prohormone consisting of the 191 amino acids of human growth hormone preceded by a 23 amino acid signal peptide. The signal peptide is removed by a specific signal peptidase located in the bacterial plasma membrane. The authentic human growth hormone is then harvested through careful disruption of the outer wall of the bacterium. The inner cell wall remains in principle intact. The subsequent purification process guarantees a pure final product with a content and sequence of amino acids identical with endogenous human pituitary growth hormone.

CAS Number

No data available.

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 - Prescription Only Medicine.

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
Sydney NSW 2000
Toll Free Number: 1800 675 229
www.pfizer.com.au

9. DATE OF FIRST APPROVAL

2 December 1991.

10. DATE OF REVISION

26 February 2020

Date of AAT Consent Order: 26 November 2001 (on the decision to register the above mentioned products for the treatment of adults with severe growth hormone deficiency as diagnosed in the insulin tolerance test for growth hormone deficiency and defined by peak growth hormone concentrations of less than 2.5 nanogram/mL).

® Registered trademark

Summary Table of Changes

Section changed	Summary of new information
4.8	Add face oedema as a manifestation of fluid retention. Add new post-marketing ADRs of rash, pruritis and urticaria.
4.3, 4.4, 4.5 & 6.1	Align excipient names to IHIN
2, 4.2, 4.4, 4.8, 5.1 & 5.3	Editorial changes