SCHEDULING STATUS: S5

1. NAME OF MEDICINE

GENOTROPIN® 16 IU (5,3 mg) lyophilised powder and solvent for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

GENOTROPIN 16 IU (5,3 mg) is a two-compartment cartridge containing the dry lyophilised powder in the front compartment and the solvent in the rear compartment. The powder is reconstituted when inserted into the Genotropin Pen administering device.

After reconstitution, the solution contains per mL:

Recombinant somatropin corresponding to somatropin 16 IU (5,3 mg) and M-cresol 0,3 % m/v.

Excipient with known effect

Contains 41 mg mannitol per mL.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Lyophilised powder and solvent for injection.

GENOTROPIN 16 IU (5,3 mg) is a two-compartment cartridge with a dry, white powder in the front compartment and clear solvent in the rear compartment.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

  Growth hormone deficiency should be verified before GENOTROPIN is administered. This requires a thorough investigation of the pituitary function, including proper provocation tests.
- Short stature in gonadal dysgenesis (Turner's Syndrome).
- Growth disturbance in prepubertal children with chronic renal insufficiency.

4.2 Posology and method of administration

Posology

The weekly dose should be divided into six to seven subcutaneous injections. The injection site should be varied to prevent lipoatrophy.

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

The dosage is according to individual requirements. Generally, a dose of 0,5 - 0,7 IU/kg body weight per week or approximately 14 - 20 IU/m^2 body surface area per week is recommended.

Turner's Syndrome

Generally, a dose of 1,0 IU/kg body weight per week is recommended, or 28 IU/m^2 body surface area per 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.

Chronic renal insufficiency

A dose of 30 IU/m^2 body surface area per week (approximately 1 IU/kg body weight per week) is recommended. Higher doses may be needed if growth velocity is too low. A dose correction may be needed after 6 months of treatment.

Method of administration

GENOTROPIN 16 IU (5,3 mg) is intended to be used with the GENOTROPIN Pen injection device. The two-compartment cartridge is fitted into the GENOTROPIN Pen causing reconstitution to take place. Instructions for use are enclosed with the Genotropin Pen package.

Missed dose

If a dose is missed one day, continue according to the prescription on the next day. Do not inject two prescribed doses on the same day.

Treatment interruption

There are no withdrawal effects described if treatment with GENOTROPIN is stopped from one day to another.

4.3 Contraindications

- Hypersensitivity to somatropin, m-cresol or to any of the excipients of GENOTROPIN (listed in section 6.1).
- Pregnancy and breastfeeding (see section 4.6).
- GENOTROPIN should not be used when there is evidence of activity of a tumour. Intracranial lesions must be inactive and anti-tumour therapy completed prior to starting therapy.
- GENOTROPIN should not be used for growth promotion in children with closed epiphyses.

4.4 Special warnings and precautions for use

The diagnosis should be confirmed before treatment starts. Therapy with GENOTROPIN should be directed by suitably qualified medical practitioners.

Hypothyroidism may occur and thyroid function should be monitored during GENOTROPIN treatment. Patients substituted with L-thyroxine should be monitored for thyroid hormone levels including measurement of triiodothyronine (T3) and thyroxine (T4).

Hypoglycaemia may occur initially and again after cessation of GENOTROPIN therapy. Hyperglycaemia may occur during therapy.

In diabetes mellitus, the dose of insulin might require adjustment when treatment with GENOTROPIN is instituted.

Introduction of GENOTROPIN treatment may result in inhibition of 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD-1) and reduced serum cortisol concentrations. In patients treated with GENOTROPIN, 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 GENOTROPIN treatment (see section 4.5).

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

In patients with (pan) hypopituitarism, GENOTROPIN therapy has to be monitored closely.

In chronic renal insufficiency, the renal function should have decreased below 50 % of the norm before institution of GENOTROPIN therapy. To verify the growth disturbance, the growth should have been followed for a year preceding institution of GENOTROPIN therapy. Conservative treatment for the renal insufficiency should have been established and should be maintained during treatment. GENOTROPIN treatment should be discontinued after renal transplant.

Patients with growth hormone deficiency secondary to an intracranial lesion should be frequently examined for progression or recurrence of the underlying disease process.

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 GENOTROPIN treatment should be discontinued.

In patients with endocrine disorders, including growth hormone deficiency, slipped epiphyses of the hip may occur more frequently. Each child limping during treatment with GENOTROPIN should be examined clinically.

Resistance to the therapeutic effect may occur.

Excipients with known effect

GENOTROPIN contains mannitol and may have a mild laxative effect.

4.5 Interaction with other medicines and other forms of interaction

Concomitant treatment with glucocorticoids inhibits the growth-promoting effects of somatropin containing medicines. 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).

Administration of GENOTROPIN may increase the clearance of compounds metabolised by cytochrome P450 3A4 (e.g. sex steroids, corticosteroids, anticonvulsants, and ciclosporin).

In women on oral oestrogen replacement, a higher dose of growth hormone may be required to achieve the treatment goal (see section 4.4).

The clinical significance of this potential interaction is unknown.

4.6 Fertility, pregnancy and lactation

GENOTROPIN is contraindicated during pregnancy and lactation (see section 4.3).

Safety and efficacy of GENOTROPIN use during pregnancy has not been established.

4.7 Effects on ability to drive and use machines

No effects on the ability to drive and use machines have been observed.

4.8 Undesirable effects

Tabulated list of adverse reactions

Tables 1 - 3 show the adverse reactions ranked under headings of system organ class and frequency 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) for each of the indicated conditions.

Table 1: Clinical trials in children with GHD

Long-term treatment of children with growth disturbance due to insufficient secretion of growth hormone		
System organ class	**Frequency**	**Adverse event**

Neoplasms benign, malignant, and unspecified (including cysts and polyps)	Uncommon	Leukaemia†
Metabolism and nutrition disorders	Unknown	Type 2 diabetes
Nervous system disorders	Unknown	Paraesthesia*, benign intracranial hypertension
Musculoskeletal, connective tissue, and bone disorders	Uncommon	Arthralgia*
	Unknown	Myalgia*, musculoskeletal stiffness*
General disorders and administration site conditions	Very common	Injection site reaction[$]
	Unknown	Peripheral oedema, face oedema*
Investigations	Unknown	Decreased blood cortisol

*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.

$ Transient injection site reactions in children are common have been reported.

‡ Clinical significance is unknown.

† Reported in growth hormone deficient children treated with GENOTROPIN, but the incidence appears to be similar to that in children without growth hormone deficiency.

Post- marketing side effects in children with GHD

System organ class	**Side effect**
Skin and subcutaneous tissue disorders	Rash, pruritus, urticaria

Table 2: Clinical trials in children with Turner syndrome

Long-term treatment of children with growth disturbance due to Turner syndrome		
System organ class	**Frequency**	**Adverse event**
Neoplasms benign, malignant, and unspecified	Unknown	Leukaemia†

(including cysts and polyps)		
Metabolism and nutrition disorders	Unknown	Type 2 diabetes
Nervous system disorders	Unknown	Paraesthesia*, benign intracranial hypertension
Musculoskeletal, connective tissue, and bone disorders	Very common	Arthralgia*
	Unknown	Myalgia*, musculoskeletal stiffness*
General disorders and administration site conditions	Unknown	Peripheral oedema, face oedema*, injection site reaction[$]
Investigations	Unknown	Decreased blood cortisol

*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.

$ Transient injection site reactions in children have been reported.

‡ Clinical significance is unknown.

† Reported in growth hormone deficient children treated with GENOTROPIN, but the incidence appears to be similar to that in children without growth hormone deficiency.

Post- marketing side effects in children with Turner syndrome

System organ class	**Side effect**
Skin and subcutaneous tissue disorders	Rash, pruritus, urticaria

Table 3: Clinical trials in children with chronic renal insufficiency

Long-term treatment of children with growth disturbance due to chronic renal insufficiency		
System organ class	**Frequency**	**Adverse event**
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	Unknown	Leukaemia†
Metabolism and nutrition disorders	Unknown	Type 2 diabetes
Nervous system disorders	Unknown	Paraesthesia*, benign intracranial hypertension
Musculoskeletal, connective tissue, and bone disorders	Unknown	Arthralgia*, myalgia*, musculoskeletal stiffness*
	Common	Injection site reaction[$]

General disorders and administration site conditions	Unknown	Peripheral oedema, face oedema*
Investigations	Unknown	Decreased blood cortisol

*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.

$ Transient injection site reactions in children have been reported.

‡ Clinical significance is unknown.

† Reported in growth hormone deficient children treated with GENOTROPIN, but the incidence appears to be similar to that in children without growth hormone deficiency.

Post- marketing side effects in children with chronic renal insufficiency

System organ class	**Side effect**
Skin and subcutaneous tissue disorders	Rash, pruritus, urticaria

Local skin reactions may occur which may be due to the m-cresol.

Transient local skin reactions at the injection site in children are common (> 1 and > 1/10).

Allergic reactions may occur and may necessitate discontinuation of therapy.

Antibodies towards growth hormone are formed in some patients treated with human growth hormone. The frequency of such antibody formation is low. Antibody binding capacity is negligible and without clinical significance.

Hyperlipidaemia, haematuria, hypocalcaemia and albuminuria may occur.

Cases of benign intracranial hypertension and Type II diabetes mellitus have been reported.

In vitro chromosome aberrations have been reported during growth hormone therapy; the clinical significance is unknown.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care professionals are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

Acute overdosage could lead initially to hypoglycaemia and subsequently to hyperglycaemia. Long-term overdosage could result in signs and symptoms consistent with the effects of human growth hormone excess (see section 4.8).

Treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

Somatropin is produced by recombinant DNA technology; it is synthesised in bacteria, namely *Escherichia coli*.

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anterior pituitary lobe hormones and analogues. ATC Code: H01AC01

Somatropin stimulates linear growth and increases growth rate in children who lack adequate endogenous growth hormone.

In addition, the following actions have been demonstrated for somatropin:

Tissue growth

Stimulation of skeletal muscle growth in patients with growth hormone deficiency (GHD), as well as increase in number and size of muscle cells.

Protein metabolism

Nitrogen retention demonstrated by decreased urinary nitrogen excretion and increased serum urea.

Carbohydrate metabolism

Children with hypopituitarism sometimes experience fasting hypoglycaemia that is improved by treatment with somatropin. Large doses of human growth hormone may impair glucose tolerance.

Lipid metabolism

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

Mineral metabolism

Retention of sodium, potassium and phosphorous is induced by somatropin. Serum concentrations of inorganic phosphate are increased in patients with growth hormone deficiency after treatment with somatropin. Serum calcium is not significantly altered.

5.2 Pharmacokinetic properties

Approximately 80 % of somatropin is absorbed following subcutaneous injection and maximum serum concentrations are achieved after 3 - 4 hours.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder:

Disodium phosphate anhydrous

Glycine

Mannitol

Sodium dihydrogen phosphate anhydrous

Water for injection

Solvent:

Mannitol

Water for injection

Metacresol (preservative)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Unreconstituted medicine (Lyophilised powder)

36 months at 2 °C – 8 °C protected from light

1 month room temperature (up to 25 °C)

Reconstituted solution

28 days at 2 °C – 8 °C protected from light

6.4 Special precautions for storage

Lyophilised powder

Store between 2 °C and 8 °C (refrigerated). Protect from light.

Stable for 1 month at room temperature (at or below 25 °C).

Reconstituted solution

Stable for 28 days at 2 °C to 8 °C protected from light.

Frozen solution should not be used.

The GENOTROPIN Pen needs no maintenance. The exterior can be cleaned by wiping with a damp cloth.

The GENOTROPIN Pen is provided in a specially designed pen-case. Keep the GENOTROPIN Pen in the pen-case where it is protected against dirt and damage.

6.5 Nature and content of container

Packs of 1 x 1 mL two-compartment cartridge or 5 x 1 mL two-compartment cartridges.

GENOTROPIN Pen administering device.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Pfizer Laboratories (Pty) Ltd

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Sandton 2196

South Africa

Tel: +27(0)11 320 6000 / 0860 734 937 (toll free South Africa)

8. REGISTRATION NUMBER

X/21.10/214

9. DATE OF FIRST AUTHORISATION

20 June 1991

10. DATE OF REVISION OF THE TEXT

20 May 2025