

SciTropin A™

Somatropin (rbe) (recombinant human growth hormone, r-hGH) Solution for Injection in cartridge 5 mg/1.5 mL (15 IU) and 10 mg/1.5 mL (30 IU)

DESCRIPTION

SciTropin A™ is produced using recombinant DNA technology. The active substance somatropin (biosynthetic human growth hormone, rDNA-derived human growth hormone [r-hGH]) is produced in cell culture by Escherichia coli cells bearing the gene for human growth hormone.

SciTropin A™ Solution for Injection is a clear, colourless solution. SciTropin A™ is a biosimilar product of Genotropin ®. SciTropin A™ has been shown to have a comparable quality, safety and efficacy profile to Genotropin ®.

COMPOSITION

SciTropin A™ 5 mg/1.5mL (15 IU) Solution for Injection

Each cartridge (1.5 mL) contains 10 mg recombinant somatropin. Other ingredients: sodium phosphate dibasic heptahydrate 1.34 mg, sodium phosphate monobasic dihydrate 1.56 mg, poloxamer 188 3.0 mg, phenol 4.50 mg, glycine 27.75 mg and water for injection ad 1.5 mL.

SciTropin A™ 10 mg/1.5mL (30 IU) Solution for Injection

Each cartridge (1.5 mL) contains 10 mg recombinant somatropin. Other ingredients: sodium phosphate dibasic heptahydrate 1.34 mg, sodium phosphate monobasic dihydrate 1.56 mg, poloxamer 188 3.0 mg, phenol 4.50 mg, glycine 27.75 mg and water for injection ad 1.5 mL.

CLINICAL TRIAL DATA FOR THE BIOSIMILAR DESCRIBING CLINICAL SIMILARITY TO THE REFERENCE PRODUCT

In three sequential clinical trials, involving a total of previously untreated 89 GHD children the efficacy and safety of SciTropin A™ were compared with another somatropin (Genotropin ®) product approved for growth hormone deficiency (GHD) in pediatric patients.

44 patients received SciTropin A™ powder for solution for injection (p.f.s.f.i.) 5.8 mg/ vial and 45 patients received Genotropin ® for 9 months. After 9 months of treatment patients who had received Genotropin ® product were switched to SciTropin A™ solution for injection (s.f.i.) 5 mg/1.5 mL. After 15 months of treatment, all patients were switched to SciTropin A™ s.f.i. to collect long-term efficacy and safety data.

In both groups, somatropin was administered as a daily subcutaneous injection at a dose of 0.03 mg/kg. Similar effects on growth were observed between SciTropin A™ p.f.s.f.i. and Genotropin ® during the initial 9 months of treatment.

The efficacy results after 9 months of treatment (SciTropin A™ p.f.s.f.i. vs. Genotropin ® and after 15 months (SciTropin A™ s.f.i.) are summarized in Table 1. The table also shows the long-term efficacy results for both treatment groups.

Table 1 Baseline growth characteristics and effect of SciTropin A™ after 9 and 15, and 84 months of treatment

Treatment Duration	Treatment Group A	Treatment Group B
0 - 9 months	SciTropin A™ p.f.s.f.i. (n=44)	Genotropin ® (n=45)
9 - 15 months	SciTropin A™ p.f.s.f.i. (n=42)	SciTropin A™ s.f.i. (n=44)
15 - 84 months	SciTropin A™ s.f.i. (n=42)b	SciTropin A™ s.f.i. (n=44)b
Treatment Parameter	Mean (SD)	Mean (SD)
Height velocity (cm/yr)		
Pre-treatment	3.8 (1.2)	3.9 (0.8)
Month 9	10.7 (2.6)	10.7 (2.9)
Month 15	9.3 (1.7)	9.4 (2.1)
Month 84	5.5 (1.6)	5.5 (2.9)
Height velocity SDS		
Pre-treatment	-2.3 (1.2)	-2.3 (0.9)
Month 9	5.9 (3.4)	5.0 (2.9)
Month 15	4.4 (2.9)	3.6 (2.2)
Month 84	-0.2 (2.5)	0.1 (2.8)
Height SDS		
Pre-treatment	-2.9 (0.7)	-3.1 (0.9)
Month 9	-2.2 (0.7)	-2.4 (0.7)
Month 15	-1.9 (0.7)	-2.2 (0.7)
Month 84	-0.8 (0.8)	-1.0 (1.1)
IGF-1* (ng/mL)		
Pre-treatment	96 (84)	94 (64)
Month 9	250 (184)	267 (192)
Month 15	282 (227)	310 (194)
Month 84	389 (109)	400 (151)
IGFBP-3* (µg/mL)		
Pre-treatment	3.2 (1.5)	2.9 (1.4)
Month 9	4.4 (3.0)	3.9 (1.6)
Month 15	4.6 (1.3)	4.9 (1.4)
Month 84	4.2 (0.6)	4.0 (1.3)

Values below the limit of detection (LOD) were set to LOD/2 n= Number of patients at the beginning of the study

The results of three consecutive multicenter studies demonstrated equivalent therapeutic efficacy and clinical comparability between SciTropin A™ p.f.s.f.i. and Genotropin ® and between SciTropin A™ p.f.s.f.i. and SciTropin A™ s.f.i.

Because clinical trials are conducted under varying conditions, adverse reaction rates observed during the clinical trials performed with one somatropin formulation cannot always be directly compared to the rates observed during the clinical trials performed with a second somatropin formulation, and may not reflect the adverse reaction rates observed in practice.

The following events were observed during the clinical study with SciTropin A™ p.f.s.f.i.

Table 2 Incidence of Adverse Reactions reported in ≥ 5% pediatric patients with GHD during treatment with SciTropin A™ p.f.s.f.i. over a treatment period of nine months (N=44)

Adverse Event	n (%)
Hypothyroidism	7 (16%)
Eosinophilia	5 (11%)
Glycosylated hemoglobin increased	4 (9%)
Hematoma	4 (9%)
Headache	3 (7%)
Blood triglycerides increased	2 (5%)
Pain in extremity	2 (5%)

N = number of patients receiving treatment

n = number of patients who reported the event during study period

% = percentage of patients who reported the event during study period

The following events were observed during the clinical studies with SciTropin A™ s.f.i.

Table 3 Incidence of Adverse Reactions reported in ≥ 5% pediatric patients with GHD during treatment with SciTropin A™ s.f.i. over a treatment period of up to 75 months (N=86)

Adverse Event	n (%)
Glycosylated hemoglobin increased	26 (30%)
Blood alkaline phosphatase increase	11 (13%)
Hypothyroidism	9 (10%)
Headache	9 (10%)
Eosinophilia	9 (10%)
Scoliosis	7 (8%)
Blood triglycerides increased	6 (7%)
Thyroxine decreased	6 (7%)
Injection site hematoma	6 (7%)
Blood thyroid stimulating hormone decreased	5 (6%)
Pain in extremity	4 (5%)

N = number of patients receiving treatment

n = number of patients who reported the event during study period

% = percentage of patients who reported the event during study period

As with all protein drugs, a small percentage of patients may develop antibodies to the protein. Additional efficacy analyses carried out revealed that the presence of anti-hGH antibodies did not affect the growth parameters of the patients with a positive anti-rhGH and anti-HCP test. The safety profiles were similar and as expected from experience with established rhGH preparations.

The long-term safety of SciTropin A™ solution in the treatment of children with GHD was demonstrated.

PHARMACOLOGY

Pharmacodynamics

Pharmacotherapeutic group: Pituitary and hypothalamic hormones and analogues, anterior pituitary lobe hormones and analogues, ATC code: H01AC01.

Somatropin is a potent metabolic hormone of importance for the metabolism of lipids, carbohydrates and proteins. In children with inadequate endogenous growth hormone, somatropin stimulates linear growth and increases growth rate. In adults as well as in children, somatropin maintains a normal body composition by increasing nitrogen retention and stimulation of skeletal muscle growth, and by mobilization of body fat. Visceral adipose tissue is particularly responsive to somatropin. In addition to enhanced lipolysis, somatropin decreases the uptake of triglycerides into body fat stores.

Serum concentrations of IGF-I (Insulin-like Growth Factor-I) and 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 reduction in serum LDL and apolipoprotein B. A reduction in serum total cholesterol may also be observed.

Carbohydrate metabolism:

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

Water and mineral metabolism:

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

Bone metabolism:

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

Physical capacity:

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

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.

Pharmacokinetics

Absorption

The bioavailability of subcutaneously administered somatropin is approximately 80% in both healthy subjects and growth hormone deficient patients. A subcutaneous dose of 5 mg of SciTropin A 5mg/1.5mL Solution for Injection in healthy adults results in plasma Cmax and tmax values of 72±28 µg/L and 4.0±2.0 hours, respectively. A subcutaneous dose of 5mg of SciTropin A 10mg/1.5mL Solution for Injection in healthy adults results in plasma Cmax and tmax values of 74±22µg/L and 3.9±1.2 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 of SciTropin A™, a half-life of 3 hours is 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 subcutaneous 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.

INDICATIONS

Infants, children & adolescents

- Growth disturbance due to insufficient secretion of growth hormone (Growth Hormone Deficiency, GHD)
- Growth disturbance associated with Turner syndrome
- Growth disturbance associated with chronic renal insufficiency
- Growth disturbance (current height standard deviation score (SDS) < -2.5 and parental adjusted height SDS < -1) in short children born small for gestational age (SGA), with a birth weight and/or length below -2 standard deviation (SD), who fail to show catch-up growth (height velocity (HV) SDS < 0 during the last year) by 4 years of age or later.
- Prader-Willi syndrome (PWS), for improvement of growth and body composition in children. The diagnosis of PWS should be confirmed by appropriate genetic testing.

Adults

Replacement therapy in adults with pronounced growth hormone deficiency. Patients with severe growth hormone deficiency in adulthood are defined as patients with known hypothalamic pituitary pathology and at least one known deficiency of pituitary hormone not being prolactin. These patients should undergo a single dynamic test in order to diagnose or exclude a growth hormone deficiency. In patients with childhood onset isolated GH deficiency (no evidence of hypothalamic-pituitary disease or cranial irradiation), two dynamic tests should be recommended, except for those having low IGF-I concentrations (SDS < -2) who may be considered for one test. The cut-off point of the dynamic test should be strict.

DOSAGE AND ADMINISTRATION

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

The dosage and administration schedule should be individualized.

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

Paediatric population

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

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 2.7 mg should not be exceeded. Treatment should not be used in paediatric patients with a growth velocity less than 1 cm per year and near closure of epiphyses

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

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

Growth disturbance in short children born small for gestational age (SGA): A dose of 0.035 mg/kg body weight per day (1.0 mg/m2 body surface area per day) is usually recommended until final height is reached. Treatment should be discontinued after the first year of treatment if the height velocity SDS is below +1. Treatment should be discontinued if height velocity is < 2 cm/year and, if is required, bone age is > 14 years (girls) or > 16 years (boys), corresponding to epiphyseal closure.

Patients with epiphyseal closure who were treated with Somatropin replacement therapy in childhood should be re-evaluated before continuation of somatropin therapy at the reduced dose level recommended for GH deficient adults.

Indication	mg/kg body weight dose per day	mg/m ² body surface
Growth hormone deficiency in children	0.025-0.035	0.7-1.0
Prader-Willi syndrome in children	0.035	1.0
Turner syndrome	0.045-0.050	1.4
Chronic renal insufficiency	0.045-0.050	1.4
Children born small for gestational age (SGA)	0.035	1.0

Treatment should not be used in children with a growth velocity less than 1 cm per year and near closure of epiphyses.

Growth hormone deficient adult patients

Therapy should start with a low dose, 0.15 - 0.3 mg per day. The dose should be gradually increased according to individual patient requirements as determined by the IGF-I concentration. Treatment goal should be insulin-like growth factor (IGF-I) concentrations within 2 SDS from the age corrected mean of healthy adults. Patients with normal IGF-I concentrations at the start of the treatment should be administered growth hormone up to an IGF-I level into upper range of normal, not exceeding the 2 SDS. Clinical response and side effects may also be used as guidance for dose titration. The daily maintenance dose seldom exceeds 1.0 mg per day. Woman may require higher dose than men, while men showing an increasing IGF-I sensitivity over time. This means that there is a risk that women, especially those on oral oestrogen replacement are under-treated while men are over-treated. The accuracy of the growth hormone dose should therefore be controlled every 6 months. As normal physiological growth hormone production decreases with age, dose requirements may be reduced. The minimum effective dose should be used.

CONTRAINDICATIONS

- Hypersensitivity to somatropin or to any of the excipients
- Somatropin must not be used when there is any evidence of activity of a tumour. Intracranial tumours must be inactive and anti-tumour therapy must be completed prior to starting GH therapy. Treatment should be discontinued if there is evidence of tumour growth.
- Somatropin should not be used for growth promotion in children with closed epiphyses.
- Somatropin should not be used in children with PWS and a corresponding severe respiratory disorder or severe obesity.
- Patients with acute critical illness suffering complications following open heart surgery, abdominal surgery, multiple accidental trauma, acute respiratory failure or similar conditions should not be treated with somatropin
- The 5mg/1.5ml presentation contains benzyl alcohol, its use should be avoided in children under two years of age. Not to be used in Neonates.

WARNINGS AND PRECAUTIONS

The maximum recommended daily dose should not be exceeded (see Dosage and Administration).

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded

Intravenous administration of benzyl alcohol has been associated with serious adverse events and death in neonates ("gasping syndrome"). The minimum amount of benzyl alcohol at which toxicity may occur is not known.

Hypoadrenalism

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

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.

Insulin Sensitivity

Somatropin may induce a state of insulin resistance and in some patients,hyperglycaemia. Therefore patients should be observed for evidence of glucose intolerance. In rare cases the diagnostic criteria (including obese PWS patients), familie history, steroid treatment, or pre-existing impaired glucose tolerance have been present in most cases where this occurred. In patients with an already manifest diabetes mellitus, the anti-diabetic therapy might require adjustment when somatropin is instituted.

Thyroid Function

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 general, the peripheral thyroid hormone levels have remained within the reference ranges for healthy subjects. The effects of somatropin on thyroid hormone levels may be of clinical relevance in patients with central subclinical hypothyroidism in whom hypothyroidism theoretically may develop. 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.

Neoplasms

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

Slipped capital femoral epiphysis

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 (IH)

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

Leukaemia

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

Antibodies

A small percentage of patients may develop antibodies to SciTropin A™. SciTropin A™ 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.

Pancreatitis

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

Scoliosis

Scoliosis is known to be more frequent in some of the patient groups treated with somatropin. In addition, rapid growth in any child can cause progression of scoliosis. Somatropin has not been shown to increase the incidence or severity of scoliosis. Signs of scoliosis should be monitored during treatment.

Acute Critical Illness

The effects of somatropin on recovery were studied in two placebo controlled trials involving 522 critically ill adult patients suffering complications following open heart surgery, abdominal surgery, multiple accidental trauma or acute respiratory failure. Mortality was higher in patients treated with 5.3 or 8 mg somatropin daily compared to patients receiving placebo, 42% vs. 19%. Based on this information, these types of patients should not be treated with somatropin. As there is no information available on the safety of growth hormone substitution therapy in acutely critically ill patients, the benefits of continued treatment in this situation should be weighed against the potential risks involved. In all patients developing other or similar acute critical illness, the possible benefit of treatment with somatropin must be weighed against the potential risk involved.

Elderly patients

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

Prader-Willi syndrome (PWS)

In patients with PWS, 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 paediatric patients with PWS 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 PWS and one or more of these risk factors may be at greater risk.

Patients with PWS should be evaluated for upper airway obstruction, sleep apnoea or respiratory infections before initiation of treatment with somatropin. 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 examined by representative methods like polysomnographia or oxymetria during the night before initiation of growth hormone therapy and patients should be monitored if necessary. All patients with PWS should be evaluated for sleep apnoea and monitored if sleep apnoea is suspected.

All patients with PWS should be monitored for signs of respiratory infections which should be diagnosed as early as possible and treated aggressively.

In patients with severe respiratory disorder treatment with somatropin is contraindicated. 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 assessment for upper airway obstruction performed.

All patients with PWS should have effective weight control before and during treatment with somatropin.

Experience with prolonged treatment in adults and in patients with PWS is limited.

Patients born SGA

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 (CRI), 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 SciTropin A™ are available.

Benzyl Alcohol

Because of the presence of benzyl alcohol in SciTropin A™ 5mg/1.5mL, the product must not be given to premature babies or neonates. It may cause toxic reactions and anaphylactoid reactions in infants and children up to 2 years old.

INTERCHANGEABILITY/ SUBSTITUTION

Switching of one Somatropin product with another during treatment increases the risk of immunogenic reactions. If such switching is deemed necessary, it should be done with caution under strict medical supervision. No automatic substitution.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Concomitant treatment with glucocorticoids inhibits the growth-promoting effects of SciTropin A™. Patients with ACTH deficiency should have their glucocorticoid replacement therapy carefully adjusted to avoid any inhibitory effect 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.In women on oral oestrogen replacement, a higher dose of growth hormone may be required to achieve the treatment goal.

Data from an interaction study performed in growth hormone deficient adults suggests that somatropin administration may increase the clearance of compounds known to be metabolized by cytochrome P450 isoenzymes. The clearance of compounds metabolized by cytochrome P450 3A4 (e.g. sex steroids, corticosteroids, anticonvulsants and cyclosporin) may be especially increased resulting in lower plasma levels of these compounds. The clinical significance of this is unknown. Also see section on "Warnings and Precautions" for statements regarding diabetes

mellitus and thyroid disorders and section on "Dosage and Administration" for statement on oral estrogen replacement therapy

FERTILITY, PREGNANCY AND LACTATION Pregnancy

There are no or limited amount of data from the use of somatropin in pregnant women. Animal studies are insufficient with respect to reproductive toxicity. Somatropin is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breastfeeding

There have been no clinical studies conducted with somatropin containing products in breast-feeding women. It is not known if somatropin is excreted into breast milk,

but absorption of intact protein from the gastrointestinal tract of the infant is extremely unlikely. Therefore caution should be exercised when is administered to nursing women.

Fertility

Fertility studies with SciTropin A™ have not been performed.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

SciTropin A™ has no or negligible influence on the ability to drive and use machines.

ADVERSE REACTIONS

Summary of the safety profile
Patients with growth hormone deficiency are characterised by extracellular volume deficit. When treatment with somatropin is started this deficit is rapidly corrected. In adults patients adverse reactions related to fluid retention, such as peripheral oedema, face oedema, musculoskeletal stiffness, arthralgia, myalgia and paraesthesia are common. In general these adverse reactions are mild to moderate, arise within the first months of treatment and subside spontaneously or with dose-reduction. The incidence of these adverse reactions 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 reactions are uncommon.

SciTropin A™ 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 WARNINGS AND PRECAUTIONS).

Tabulated list of adverse reactions

Table 1 shows 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

System Organ Class	Frequency
Neoplasms Benign, Malignant and Unspecified (including cysts and polyps)	Uncommon: Leukaemia ^{1†} Not known: Leukaemia ^{2,3,4,5}
Endocrine disorders	Not known: Hypothyroidism ^{**}
Metabolism and Nutrition Disorders	Not known: Type II diabetes mellitus
Nervous System Disorders	Common: Paraesthesia*, Benign intracranial hypertension †, Carpal Tunnel Syndrome6 Not known: Benign intracranial hypertension ^{1,2,3,4,6} Not known: Headache ^{**}
Skin and Subcutaneous Tissues disorders	Common: Rash ^{**} , Urticaria ^{**} Uncommon: Pruritus ^{**}
Musculoskeletal, Connective Tissue and Bone Disorders	Very common: Arthralgia* Common: Myalgia*, Musculoskeletal stiffness*
Reproductive system and breast disorders	Uncommon: Gynaecomastia ^{**}
General Disorders and Administration Site Conditions	Very common: Injection site reaction\$, Oedema peripheral [†] Not known: Face oedema*
Investigations	Not known: Blood cortisol decreased [†]

- 1 Clinical trials in children with GHD
- 2 Clinical trials in children with Turner syndrome
- 3 Clinical trials in children with chronic renal insufficiency
- 4 Clinical trials in children with SGA
- 5 Clinical trials in PWS
- 6 Clinical trials in adults with GHD

*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 reaction (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. Description of selected adverse reactions

Somatropin has been reported to reduce serum cortisol levels, possibly by affecting carrier proteins or by increasing hepatic clearance. The clinical relevance of these findings may be limited. Nevertheless, corticosteroid replacement therapy should be optimised before initiation of therapy.

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.

PRECLINICAL SAFETY DATA

In studies with SciTropin A regarding subacute toxicity and local tolerance, no clinically relevant effects have been observed.

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

With somatropins, 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 medicinal product bleomycin. The clinical significance of this finding is unclear.

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

OVERDOSE AND TREATMENT

Acute overdose could lead initially to hypoglycaemia and subsequently to hyperglycaemia.

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

INCOMPATIBILITIES

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

SHELF LIFE AND STORAGE CONDITIONS

SciTropin A™ 5mg/1.5mL (15 IU) and 10mg/1.5 mL (30 IU) Solution for Injection Both solutions for injection (5 mg/1.5 mL and 10mg/1.5 mL) should be stored and transported at 2°C to 8°C in a refrigerator. Do not freeze. If unopened, the contents should be stored in the original package in order to protect from light. The 5mg/1.5 mL is stable for 24 months whereas the 10mg/1.5 mL is stable for 18 months.

After the first injection, the contents of the cartridge must be used within 28 days and the cartridge should remain in the pen, and kept at 2°C to 8°C (in a refrigerator) protected from light.

PRESENTATION

The solutions for injection (15 IU and 30 IU) contain less than 1 mmol sodium (23 mg) per mL, i.e. essentially 'sodium free'.

SciTropin A™ 5mg/1.5 mL (15 IU) Solution for Injection

Each pack contains 1 or 2 cartridges of the solution.

This is a ready-to-use solution which is filled in a glass cartridge and intended for multiple-use with a pen device. The pen is intended for use by a single patient only

SciTropin A™ 10mg/1.5 mL (30 IU) Solution for Injection

Each pack contains 1 cartridge of the solution.

This is a ready-to-use solution which is filled in a glass cartridge and intended for multiple-use with a pen device. The pen is intended for use by a single patient only

INSTRUCTIONS FOR USE AND HANDLING

SciTropin A™ 5mg/1.5mL (15IU) & 10mg/1.5mL (30IU) Solution for injection is a sterile, ready-to-use solution for subcutaneous injection filled in a glass cartridge.

The presentations are intended for multiple-use. A pen compatible with SciTropin ATM is specifically developed for use with the SciTropin ATM solution. It has to be administered using sterile, disposable pen needles. Patients and caregivers have to receive appropriate training and instruction on the proper use of the SciTropin A™ cartridges and the pen from the physician or other suitable qualified health professionals.

The following is a general description of the administration process. The manufacturer's instructions with each pen must be followed for loading the cartridge, attaching the injection needle and for the administration.

1. Hands should be washed.
2. If the solution is cloudy or contains particulate matter, it should not be used. The content must be clear and colourless.
3. Disinfect the rubber membrane of the cartridge with a cleansing swab
4. Insert the cartridge into the Pen, following the instructions for use provided with the pen.
5. Clean the site of injection with an alcohol swab.
6. Administer the appropriate dose by subcutaneous injection using a sterile pen needle.

Remove the pen needle and dispose of it in accordance with local requirements
Any unused product or waste material should be disposed of in accordance with local requirements.

Manufactured by

Novartis Pharmaceutical Manufacturing
GmbH Biochemiestraße 10
6336 Langkampfen, Austria.

For

SciGen Pte. Ltd.
150 Beach Road, #32-05/08 Gateway West, Singapore 189720

Product Registration Holder

DKSH Malaysia Sdn Bhd
B-11-01, The Ascent, Paradigm, No. 1
Jalan SS7/26A, Kelana Jaya,
47301 Petaling Jaya Selangor

Date of Preparation:

21 May 2025

Teckwah Value Chain Pte Ltd			
Product Information (INSERT)		Colours	
Customer:	SciGen Pte. Ltd.	1C x 1C: Black	
Item:	06HI1GJF09		
Item Description:	MYS Scitropin A PI (5mg & 10mg)		
Material:	50gsm Woodfree		
Open Size:	175mm x 360mm		
Fold Size:	43.75mm x 60mm		
Changes Required			
Date	Version	Remark	
07 Mar 2025	V01	Initial Release	
21 May 2025	V02	Remove text, change month on pg2	
Done By		Approved By	
Date	21 May 2025	Date	
Name	Huiling	Signature	