SciTropin A™

1. NAME OF THE MEDICINAL PRODUCT
SciTropin A Solution for Injection 5 mg/1.5 ml
SciTropin A Solution for Injection 10 mg/1.5 ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
SciTropin A Solution for Injection 5 mg/1.5 ml
Each ml of solution contains 3.3 mg of somatropin* (corresponding to 10 IU)
One cartridge contains 1.5 ml corresponding to 5 mg somatropin* (15 IU).

Excipient(s) with known effect:
This medicine contains 9mg benzyl alcohol in each ml. Benzyl alcohol may cause allergic reactions.
SciTropin A Solution for Injection 10 mg/1.5 ml
Each ml of solution contains 6.7 mg of somatropin* (corresponding to 20 IU)
One cartridge contains 1.5 ml corresponding to 10 mg somatropin* (30 IU).

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Solution for injection.
The solution is clear and colourless.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications
Children
Growth disturbance due to insufficient secretion of growth hormone (growth hormone deficiency, GHD)
Growth disturbance associated with Turner syndrome

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.

4.2 Posology and method of 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.

Posology
Paediatric population
The posology and administration schedule should be individualized.
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.
Growth disturbance due to Turner syndrome: A dose of 0.045 - 0.050 mg/kg body weight per day or 1.4mg/ m2 body surface area per day is recommended.

Dosage recommendations for Paediatric Patients

Indication	mg/kg body weight dose per day	mg/m² body surface area dose per day
Growth hormone deficiency in children	0.025-0.035	0.7-1.0
Turner syndrome	0.045-0.050	1.4

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.

Method of administration
The injection should be given subcutaneously and the site varied to prevent lipoatrophy.
For instructions for use and handling see section 6.6.

4.3 Contraindications
Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Somatropin must not be used when there is any evidence of activity of a tumour.
Intracranial tumours must be inactive and anti-tumour therapy must be completed prior to starting GH therapy. Treatment should be discontinued if there is evidence of tumour growth.
Somatropin must 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 must not be treated with somatropin.
In new-borns, SciTropin A 5mg/1.5mL Solution for Injection should not be used because of the presence of the preservative, benzyl alcohol.

4.4 Special warnings and precautions for use

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.

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

Hypoadrenalism
Introduction of somatropin treatment may result in inhibition of 11βHSD-1 and reduced serum cortisol concentrations. In patients treated with somatropin, previously undiagnosed central (secondary) hypoadrenalism may be unmasked and glucocorticoid replacement may be required. In addition, patients treated with glucocorticoid replacement therapy for previously diagnosed hypoadrenalism may require an increase in their maintenance or stress doses, following initiation of somatropin treatment (see section 4.5).

Use with oral oestrogen therapy
If a woman taking somatropin begins oral oestrogen therapy, the dose of somatropin may need to be increased to maintain the serum IGF-1 levels within the normal age-appropriate range. Conversely, if a woman on somatropin discontinues oral oestrogen therapy, the dose of somatropin may need to be reduced to avoid excess of growth hormone and/or side effects (see section 4.5).

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 for diabetes mellitus type II may be fulfilled as a result of the somatropin 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 occurred. In patients with an already manifest diabetes mellitus, the anti-diabetic therapy might require adjustment when somatropin is instituted.

Thyroid function
Growth hormone increases the extrathyroidal conversion of T4 to T3 which may result in a reduction in serum T4 and an increase in serum T3 concentrations. Whereas peripheral thyroid hormone levels have remained within the reference ranges for healthy subjects, hypothyroidism theoretically may develop in subjects with subclinical hypothyroidism. Consequently, monitoring of thyroid function should therefore be conducted in all patients. In patients with hypopituitarism on standard replacement therapy, the potential effect of growth hormone treatment on thyroid function must be closely monitored.

Neoplasms
In growth hormone deficiency secondary to treatment of malignant disease, it is recommended to pay attention to signs of relapse of the malignancy. In childhood cancer survivors, an increased risk of a second neoplasm has been reported in patients treated with somatropin after their first neoplasm. Intracranial tumours, in particular meningiomas, in patients treated with radiation to the head for their first neoplasm, were the most common of these second neoplasms.

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. Patients limping during treatment with somatropin should be examined clinically.

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

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

Antibodies
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.

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

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

Carcinogenesis, mutagenesis, impairment of fertility
Somatropin raises the serum levels of IGF-1. Associations between elevated serum IGF-1 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 somatropin who do not have growth hormone deficiency and who are treated for prolonged periods, is not known. Serum IGF-1 levels can be affected by factors other than growth hormone status including nutrition.

Switching of product during therapy
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 and under strict medical supervision.

Paediatric population
Pancreatitis in children
Children treated with somatropin have an increased risk of developing pancreatitis compared to adults treated with somatropin. Although rare, pancreatitis should be considered in somatropin-treated children who develop abdominal pain.

Benzyl alcohol
SciTropin A Solution for Injection 5 mg/1.5 ml contains 9mg of benzyl alcohol in each ml.
Benzyl alcohol may cause allergic reactions.
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.
Advise the parents or legal guardian to not use more than a week in young children (less than 3 years old) without a physician or pharmacist permission.

4.5 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 (see section 4.4).
In women on oral oestrogen replacement, a higher dose of growth hormone may be required to achieve the treatment goal (see section 4.4).
Data from an interaction study performed in growth hormone deficient adults suggests that somatropin administration may increase the clearance of compounds known to be 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 4.4 for statements regarding diabetes mellitus and thyroid disorders and section 4.2 for statement on oral estrogen replacement therapy.

4.6 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 (see section 5.3). Somatropin is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding
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 breast-feeding women.

Fertility
Fertility studies with SciTropin A have not been performed.

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

4.8 Undesirable effects
a. 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. Adverse reactions related to fluid retention, such as peripheral oedema and arthralgia are very common; musculoskeletal stiffness, 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 4.4).

b. Tabulated list of adverse reactions

Tables 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, <1/10); uncommon (≥1/1000, <1/100); rare (≥1/10,000, <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]
Endocrine disorders	Not known: Hypothyroidism**
Metabolism and Nutrition Disorders	Not known: Type II diabetes mellitus
Nervous System Disorders	Common: Paraesthesia*, Carpal Tunnel Syndrome[3] Not known: Benign intracranial hypertension[1,2,3] Not known: Headache**
Skin and Subcutaneaous 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 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.

c. Description of selected adverse reactions

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

Prader-Willi syndrome
In the post-marketing experience rare cases of sudden death have been reported in patients affected by Prader-Willi syndrome treated with somatropin.

Leukaemia
Cases of leukaemia (rare or very rare) have been reported in growth hormone deficient children treated with somatropin and included in the post-marketing experience. However, there is no evidence of an increased risk of leukaemia without predisposition factors, such as radiation to the brain or head.

Slipped capital femoral epiphysis and Legg-Calvé-Perthes disease
Slipped capital femoral epiphysis and Legg-Calvé-Perthes disease have been reported in children treated with GH. Slipped capital femoral epiphysis occurs more frequently in case of endocrine disorders and Legg-Calvé-Perthes is more frequent in case of short stature. But it is unknown if these 2 pathologies are more frequent or not while treated with somatropin. Their diagnosis should be considered in a child with a discomfort or pain in the hip or knee.

Other adverse drug reactions
Other adverse drug reactions may be considered somatropin class effects, such as possible hyperglycaemia caused by decreased insulin sensitivity, decreased free thyroxin level and benign intra-cranial hypertension.

Very rare occurrence of uneven or lumpy skin around the injection area if injection site does not vary.

4.9 Overdose

Symptoms:
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.

5. PHARMACOLOGICAL PROPERTIES

5.1Pharmacodynamics

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

Mechanism of action
Somatropin is a potent metabolic hormone of importance for the metabolism of lipids, carbohydrates and proteins. In children with inadequate endogenous growth hormone, somatropin stimulates linear growth and increases growth rate. In adults as well as in children, somatropin maintains a normal body composition by increasing nitrogen retention and stimulation of skeletal muscle growth, and by mobilization of body fat. Visceral adipose tissue is particularly responsive to somatropin. In addition to enhanced lipolysis, somatropin decreases the uptake of triglycerides into body fat stores. Serum concentrations of IGF-I (Insulin-like Growth Factor-I) and IGFBP3 (Insulin-like Growth Factor Binding Protein 3) are increased by somatropin. In addition, the following actions have been demonstrated.

Pharmacodynamic effects
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 phosphorous.

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

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

5.2 Pharmacokinetics properties

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 C_{max} and T_{max} 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 C_{max} and T_{max} 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

SciTropin A Solution for Injection 5 mg/1.5 ml
disodium hydrogen phosphate heptahydrate, sodium dihydrogen phosphate dihydrate, mannitol, phosphoric acid, poloxamer 188, sodium hydroxide, benzyl alcohol, water for injections

SciTropin A Solution for Injection 10 mg/1.5 ml
disodium hydrogen phosphate heptahydrate, sodium dihydrogen phosphate dihydrate, glycine, phosphoric acid, poloxamer 188, sodium hydroxide, phenol, water for injections

6.2 Incompatibilities

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

6.3 Shelf life after first use

After first use the cartridge should remain in the pen and has to be kept in a refrigerator (2°C - 8°C) for a maximum of 28 days. Store and transport refrigerated (2°C - 8°C). Do not freeze. Store in the original pen in order to protect from light.

6.4 Special precautions for storage

Unopened cartridge
Store and transport refrigerated (2°C - 8°C). Do not freeze. Store in the original package in order to protect from light.
For storage conditions of the in-use medicinal product, see section 6.3.

6.5 Nature and contents of container

1.5 ml of solution in a cartridge (colourless type I glass) with plunger on one side (siliconised bromobutyl), a disc (bromobutyl) and a cap (aluminium) on the other side. Pack sizes of 1 or 2. Not all presentations are marketed.

6.6 Special precautions for disposal and other handling

SciTropin A 5mg/1.5ml (15IU) Solution for Injection
SciTropin A 5 mg/1.5 ml solution for injection is a sterile, ready-to-use solution for subcutaneous injection filled in a glass cartridge.
This presentation is intended for multiple use. It should only be administered with a compatible injection pen device specifically developed for use with SciTropin A 5 mg/1.5 ml solution for injection. It has to be administered using sterile, disposable pen needles.

SciTropin A 10mg/1.5ml (30IU) Solution for Injection
SciTropin A 10 mg/1.5 ml solution for injection is a sterile, ready-to-use solution for subcutaneous injection filled in a glass cartridge.
This presentation is intended for multiple use. It should only be administered with a compatible injector pen device specifically developed for use with SciTropin A 10 mg/1.5 ml solution for injection. 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 injector pen device 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 injection pen device 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.

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