NAME OF THE MEDICINAL PRODUCT
ZOMACTON® 4 mg, powder and solvent for solution for injection

QUALITATIVE AND QUANTITATIVE COMPOSITION
One vial of powder contains: Somatropin* 4 mg
(corresponding to a concentration of 1.3 mg/ml or 3.3 mg/ml after reconstitution)

* Produced in *Escherichia coli* cells using recombinant DNA technology

List of excipients:
Powder: Mannitol
Solvent: Sodium chloride, benzyl alcohol, water for injections

PHARMACEUTICAL FORM
Powder and solvent for solution for injection, 4 mg

ZOMACTON® is a white to off-white lyophilised powder.
The solvent in ampoule is clear and colourless.

THERAPEUTIC INDICATIONS
ZOMACTON® is indicated for:
- the long-term treatment of children who have growth failure due to inadequate secretion of growth hormone
- the long-term treatment of growth retardation due to Turner's Syndrome confirmed by chromosome analysis.

POSOLOGY AND METHOD OF ADMINISTRATION
Posology
ZOMACTON® therapy should be initiated and monitored by physicians who are appropriately qualified and experienced in the management of patients with growth hormone deficiency.

The dosage and schedule of administration of ZOMACTON® should be individualised for each patient.

The duration of treatment, usually a period of several years, will depend on maximum achievable therapeutic benefit.

Growth Hormone Deficiency
Generally a dose of 0.17 - 0.23 mg/kg bodyweight (approximating to 4.9 mg/m^2 – 6.9 mg/m^2 body surface area) per week divided into 6 - 7 s.c. injections is recommended (corresponding to a daily injection of 0.02 – 0.03 mg/kg bodyweight or 0.7 - 1.0 mg/m^2 body surface area).

The total weekly dose of 0.27 mg/kg or 8 mg/m^2 body surface area should not be exceeded (corresponding to daily injections of up to about 0.04 mg/kg).

Turner's Syndrome
Generally a dose of 0.33 mg/kg bodyweight (approximating to 9.86 mg/m^2 body surface area) per week divided into 6 - 7 s.c. injections are recommended (corresponding to daily injection of 0.05 mg/kg bodyweight or 1.40 - 1.63 mg/m^2 body surface area).

Somatropin therapy should be continued in children and adolescents until their epiphysis are closed.

Patients with childhood onset Growth Hormone Deficiency should be re-evaluated for growth hormone secretory capacity after growth completion

Method of administration
The solution for injection should be administered subcutaneously. The injection site should be varied to prevent lipoatrophy.

For instructions for use and handling of the medicinal product, see section Instruction for use and handling and special precautions for disposal.

The required dose of ZOMACTON® 4 mg is administered with an ordinary syringe.

CONTRAINDICATIONS
Hypersensitivity to somatropin or to any of the excipients.

ZOMACTON® must not be used when there is any evidence of activity of a tumour. Intracranial tumours must be inactive and antitumor therapy must be completed prior to starting GH therapy. Treatment should be discontinued if there is evidence of tumour growth.

ZOMACTON® should not be used for growth promotion in children with closed epiphysis.

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 ZOMACTON® (see section Special warnings and precautions for use).

In children with chronic renal disease, treatment with ZOMACTON® should be discontinued at renal transplantation.

ZOMACTON® 4 mg must not be given to premature babies or neonates as the solvent contains benzyl alcohol.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE
The maximum recommended daily dose should not be exceeded (see section Posology and method of administration).

Due to the presence of benzyl alcohol as excipient, ZOMACTON® 4 mg may cause toxic reactions and anaphylactoid reactions in infants and children up to 3 years old and must not be given to premature babies or neonates.

Prader-Willi syndrome
ZOMACTON® is not indicated for the long term treatment of paediatric patients who have growth failure due to genetically confirmed Prader-Willi syndrome, unless they also have a diagnosis of GH deficiency. There have been reports of sleep apnoea and sudden death after initiating therapy with growth hormone in paediatric patients with Prader-Willi syndrome who had one or more of the following risk factors: severe obesity, history of upper airway obstruction or sleep apnoea or unidentified respiratory infection.

Intracranial hypertension
Rare cases of benign intra-cranial hypertension have been reported. In the event of severe or recurring headache, visual problems, and nausea/vomiting, a funduscopy for papilloedema is recommended. If papilloedema is confirmed, diagnosis of benign intra-cranial hypertension should be considered and if appropriate growth hormone treatment should be discontinued (see also section Undesirable effects).

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.

Leukaemia
Leukaemia has been reported in a small number of growth hormone deficient patients treated with somatropin as well as in untreated patients. However, there is no evidence that leukaemia incidence is increased in growth hormone recipients without predisposition factors.

Antibodies
As with all somatropin containing products, a small percentage of patients may develop antibodies to somatropin. 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 who fails to respond to therapy.

Thyroid function
Growth hormone increases the extrathyroidal conversion of T4 to T3 and may, as such, unmask incipient hypothyroidism. Monitoring of thyroid function should therefore be conducted in all patients. In patients with hypopituitarism, standard replacement therapy must be closely monitored when somatropin therapy is administered.

Insulin sensitivity
Because somatropin may reduce insulin sensitivity, patients should be monitored for evidence of glucose intolerance. For patients with diabetes mellitus, the insulin dose may require adjustment after somatropin containing product therapy is initiated. Patients with diabetes or glucose intolerance should be monitored closely during somatropin therapy. ZOMACTON® should also be used with caution in patients with a family history predisposition for the disease.

Intra-cranial lesions or other active neoplasms
In patients with growth hormone deficiency secondary to an intra-cranial lesion, frequent monitoring for progression or recurrence of the underlying disease process is advised. 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.

Discontinue ZOMACTON® therapy if progression or recurrence of the lesion occurs.

In patients with previous malignant diseases special attention should be given to signs and symptoms of relapse.

Scoliosis
Scoliosis may progress in any child during rapid growth. Signs of scoliosis should be monitored during somatropin treatment.

Slipped capital femoral epiphysis
Slipped capital femoral epiphysis may occur more frequently in patients with endocrine disorders. A patient treated with ZOMACTON® who develops a limp or complains of hip or knee pain should be evaluated by a physician.

Complications following surgery
The effects of treatment with growth hormone 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 (42 % vs. 19 %) among patients treated with growth hormones (doses 5.3 to 8 mg/day) compared to those receiving placebo. Based on this information, such patients should not be treated with growth hormones. 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.

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

In all patients developing other or similar acute critical illness, the possible benefit of treatment with growth hormone must be weighed against the possible risk involved.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION
Concomitant treatment with glucocorticoids inhibits the growth-promoting effects of somatropin containing products. Patients with ACTH deficiency should have their glucocorticoid replacement therapy carefully adjusted to avoid any inhibitory effect on growth hormone.

High doses of androgens, oestrogens, or anabolic steroids can accelerate bone maturation and may, therefore, diminish gain in final height.

Because somatropin can induce a state of insulin resistance, insulin dose may have to be adjusted in diabetic patients receiving concomitant ZOMACTON®.

Data from an interaction study performed in GH deficient adults suggests that somatropin administration may increase the clearance of compounds known to be metabolised by cytochrome P450 isoenzymes. The clearance of compounds metabolised by cytochrome P450 3A4 (e.g. sex steroids, corticosteroids, anticonvulsants and cyclosporine) may be especially increased resulting in lower plasma levels of these compounds. The clinical significance of this is unknown.

FERTILITY, PREGNANCY AND LACTATION
For ZOMACTON®, no clinical data on exposed pregnancies are available. There is no data from the use of ZOMACTON® during pregnancy in animals. Therefore, ZOMACTON® is not recommended during pregnancy and in woman of childbearing potential not using contraception.

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

Therefore caution should be exercised when somatropin containing products are administered to breast-feeding women.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
ZOMACTON® has no or negligible influence on the ability to drive and use machines.

UNDESIRABLE EFFECTS
The subcutaneous administration of growth hormone may lead to loss or increase of adipose tissue at the injection site. On rare occasion patients have developed pain and an itchy rash at the site of injection.

System Organ Class	Very common (≥1/10)	Common (≥1/100, <1/10)	Uncommon (≥1/1,000, <1/100)	Rare (≥1/10,000, <1/1,000)	Very rare (<1/10,000)
Blood and lymphatic system disorders			anemia		
Cardiac disorders			tachycardia, (adults) hypertension	(children) hypertension	
Ear and labyrinth disorders			vertigo		
Endocrine disorders		hypothyroidism			
Eye disorders			papilloedema, diplopia		
Gastro-intestinal disorders			vomiting, abdominal pain, flatulence, nausea	diarrhoea	
General disorders and administration site conditions	(adults) oedema, (adults) peripheral oedema	(children) oedema, (children) peripheral oedema, injection site reactions, asthenia	weakness, injection site atrophy, injection site haemorrhage, injection site mass, hypertrophy		
Immune system disorders		antibody building			
Investigations				renal function test abnormal	
Metabolism and nutrition disorders	(adults) mild hyper-glycaemia	(children) glucose tolerance impaired	hypoglycaemia, hyperphosphatemia	diabetes mellitus type II	
Musculoskeletal and connective tissue disorders	(adults) arthralgia, (adults) myalgia	(children) arthralgia, (children) myalgia, (adults) stiffness in the extremities	muscle atrophy, bone pain, carpal tunnel syndrome, (children) stiffness in the extremities		
Neoplasms benign, malignant and unspecified			neoplasm malignant, neoplasm		(children) leukaemia
Nervous system disorders	(adults) headache, (adults) paresthesia	headache, hypertonia, (adult) insomnia	somnolence, nystagmus	neuropathy, intracranial pressure increased, (children) insomnia, (children) paresthesia	
Psychiatric disorders			personality disorders		
Renal and urinary disorders			urinary incontinence, haematuria, polyuria, urine frequency / pollakiuria, urine abnormality		
Reproductive system and breast disorders			genital discharge, gynecomastia		
Skin and subcutaneous tissue disorders			lipodystrophy, skin atrophy, dermatitis exfoliative, urticaria, hirsutism, skin hypertrophy		

If adult/child is not specified in the table then applicable for all ages.

Antibodies anti-somatropin: the protein somatropin may give rise to the formation of antibodies. Depending on the concerned product, these antibodies have been identified in a definite percentage of the treated population. Their binding capacity and their titres are generally low with no clinical consequence. However, testing for antibodies to somatropin should be performed in case of absence of response to somatropin therapy.

Leukaemia: cases of leukaemia (very rare) have been reported in children with a GH deficiency, some of them being treated with somatropin and included in the post-marketing experience. However, there is no evidence of an increased risk of leukaemia without predisposition factors.

Slipped capital femoral epiphysis and Legg-Calve-Perthes disease have been reported in children treated with GH. Slipped capital femoral epiphysis occurs more frequently in case of endocrine disorders and Legg-Calve-Perthes is more frequent in case of short stature. But, it is unknown if these 2 pathologies are more frequent or not while treated with somatropin. A discomfort, a pain in the hip and/or the knee must evocate their diagnosis.

Other adverse drug reactions may be considered as class effect, as the hyperglycaemia due to the decrease in insulin-sensitivity, the decreased of free thyroxin level and the possible development of a benign intra-cranial hypertension.

Pancreatitis has been reported post-marketing during GH therapy (frequency unknown).

OVERDOSE
The recommended dose of ZOMACTON® should not be exceeded.

Single overdosage may lead to low blood glucose levels initially, followed by compensatory hyperglycaemia.

The effects of long-term, repeated use of ZOMACTON® in doses exceeding those recommended, are unknown. However, it is possible that such use might produce signs and symptoms consistent with the known effects of excess human growth hormone (e.g. acromegaly).

PHARMACODYNAMIC PROPERTIES
Pharmacotherapeutic group: Somatropin and somatropin agonists
ATC code: H 01 AC 01

ZOMACTON® contains somatropin, which is human growth hormone produced by recombinant DNA-technology. Somatropin is a potent metabolic hormone of importance for the metabolism of lipids, carbohydrates and proteins.

<u>Pharmacodynamic properties</u>
Identical to pituitary derived human growth hormone (pit-hGH) in amino acid sequence, chain length (191 amino acids) and pharmacokinetic profile. ZOMACTON® can be expected to produce the same pharmacological effects as the endogenous hormone.

<u>Skeletal system</u>
ZOMACTON® treatment stimulates growth of the skeletal bone in paediatric patients with confirmed deficiency of endogenous hGH.

The measurable increase in height after administration of ZOMACTON® results from an effect on the epiphyseal plates of long bones. In children who lack adequate amounts of endogenous hGH, ZOMACTON® produces increased growth rates and increased IGF 1

(Insulin like Growth Factor/Somatomedin-C) concentrations that are similar to those seen after therapy with endogenous hGH. Elevations in mean serum alkaline phosphatase concentrations are also involved.

Other organs and tissues
An increase in size, proportional to total increase in body weight, occurs in other tissues in response to growth hormone, as well. Changes include: increased growth of connective tissues, skin and appendages; enlargement of skeletal muscle with increase in number and size of cells; growth of the thymus; liver enlargement with increased cellular proliferation; and a slight enlargement of the gonads, adrenals, and thyroid.

Disproportionate growth of the skin and flat bones, and accelerated sexual maturation have not been reported in association with the growth hormone replacement therapy.

Protein, carbohydrate and lipid metabolism
Growth hormone exerts a nitrogen retaining effect and increases the transport of amino acids into tissue. Both processes augment the synthesis of protein. Carbohydrate use and lipogenesis are depressed by growth hormone. With large doses or in the absence of insulin, growth hormone acts as a diabetogenic agent, producing effects seen typically during fasting (i.e. intolerance to carbohydrate, inhibition of lipogenesis, mobilisation of fat and ketosis).

Mineral metabolism
Conservation of sodium, potassium, and phosphorous occurs after treatment with growth hormone. Increased calcium loss by the kidney is offset by increased absorption in the gut. Serum calcium concentrations are not significantly altered in patients treated with ZOMACTON® or with pit-hGH. Increased serum concentrations of inorganic phosphates have been shown to occur both after ZOMACTON® and pit-hGH. Accumulation of these minerals signals an increased demand during tissue synthesis.

PHARMACOKINETIC PROPERTIES
Eight healthy subjects received 0.1 mg somatropin/kg body weight. Peak plasma levels of about 64 ng/ml were found 6 hours after administration.

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

SHELF LIFE
3 years.

After reconstitution, the solution may be stored for a maximum of 14 days in a refrigerator (2°C - 8°C). Store the vial in an upright position.

SPECIAL PRECAUTIONS FOR STORAGE
Store in a refrigerator (2°C - 8°C); keep in the outer carton in order to protect from light.
For storage conditions after reconstitution of the medicinal product, see section Shelf life.

NATURE AND CONTENTS OF CONTAINER
Powder in vial (type I glass) with a stopper (grey halobutyl rubber), a seal and a “flip-off” top + 3.5 ml solvent in ampoule (type I glass).

Packs: 1, 5 and 10

Not all pack sizes may be marketed.

INSTRUCTIONS FOR USE AND HANDLING AND SPECIAL PRECAUTIONS FOR DISPOSAL

Reconstitution

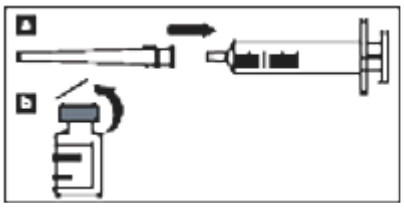
The powder should only be dissolved with the solvent provided.
Two concentrations can be prepared depending on the volume of solvent used:

- for administration using a syringe, use 1.3 ml of solvent for a concentration of 3.3 mg/ml (taking into account the whole content of the vial which is greater than 4 mg)
- use 3.2 ml of solvent for a concentration of 1.3 mg/ml (taking into account the whole content of the vial which is greater than 4 mg)

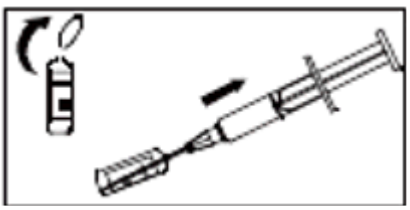
Reconstitution of the powder with the solvent, and administration of the solution for injection should be undertaken using syringe and needle.

Reconstitution should be performed in accordance with good practice rules, particularly in the respect of asepsis.

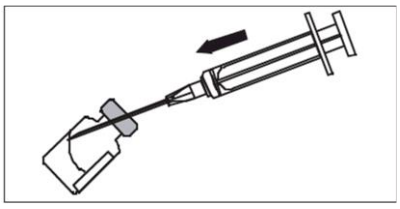
1. Hands should be washed.



2. Fit the needle into the graduated syringe. Remove the plastic top on the vial. The top of the vial should be wiped with an alcohol swab to prevent contamination of the content. Do not touch the rubber stopper after cleaning.



3. Snap off the top of the solvent ampoule. Remove the plastic cover on the needle. Make sure that the plunger is completely pushed in before introducing the needle into the ampoule.
4. Slowly draw up the required volume in the syringe.
5. Place the needle into the centre of the clean rubber stopper and into the vial and inject the solvent slowly into the vial aiming the stream of liquid against the glass wall in order to avoid foam.



6. Throw away the syringe and needle into a sharps disposal container.

7. The vial must then be swirled with a gentle rotary motion until the contents are completely dissolved in order to obtain a clear and colorless solution.

Since the powder mainly contains proteins, shaking or vigorous mixing is not recommended. If after mixing, the solution is cloudy or contains particles, the vial and its contents should be disposed of.

In case of cloudiness after refrigeration, the solution should be allowed to warm up to room temperature (25°C). If cloudiness still persist or coloration appears, dispose of the vial and its contents.

The solution should be used within 14 days after reconstitution if stored in a refrigerator. Any unused solution in the vial should be disposed of at the end of the 14-day storage period.

MANUFACTURER
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