

1. NAME OF THE MEDICINAL PRODUCT

Omnitrope 3.3 mg/ml solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Somatropin* 3.3 mg (corresponding to 10 IU)/ ml.

One cartridge contains 1.5 ml corresponding to 5 mg Somatropin* (15 IU).

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

Excipients:

One ml contains 9 mg benzyl alcohol.

For a 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

Infants, children and adolescents

- Growth disturbance due to insufficient secretion of growth hormone (GH).
- 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 SDS < -1) in short children/adolescents born small for gestational age (SGA), with a birth weight and/or length below -2 standard deviation (SD), who failed 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. 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 a 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 somatotropin should be initiated and monitored by physicians who are appropriately qualified and experienced in the diagnosis and management of patients with growth disorders.

The posology and administration schedule should be individualised.

Growth disturbance due to insufficient secretion of growth hormone in paediatric patients:

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 paediatric patients:

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 may be needed if growth velocity is too low. A dose correction may be needed after six months of treatment (see section 4.4).

Growth disturbance in short children/adolescents born small for gestational age (SGA):

A dose of 0.035 mg/kg body weight per day (1 mg/m² body surface area per day) is usually recommended until final height is reached (see section 5.1). 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 confirmation is required, bone age is > 14 years (girls) or > 16 years (boys), corresponding to epiphyseal closure.

Dose recommendations for paediatric patients

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

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 the upper range of normal, not exceeding the 2 SDS. Clinical response and undesirable effects may also be used as guidance for dose titration. The daily maintenance dose rarely exceeds 1.0 mg per day. Women may require higher doses than men, while men show 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.

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 somatropin or to any of the excipients.
- Somatropin must not be used when there is any evidence of tumour activity and anti-tumour therapy must be completed prior to starting therapy.
- Somatropin must not be used for growth promotion in patients with closed epiphyses.
- 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. With regard to patients undergoing substitution therapy, see section 4.4.

4.4 Special warnings and precautions for use

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 already manifested diabetes mellitus, the anti-diabetic therapy might require adjustment when somatropin is instituted.

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. Conversely, in patients receiving replacement therapy with thyroxin mild hyperthyroidism may occur. It is therefore particularly advisable to test thyroid function after starting treatment with somatropin and after dose adjustments.

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 Omnitrope therapy.

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

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.

In case of severe or recurrent headache, visual problems, nausea and/or vomiting, a funduscopy 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. However, clinical experience has shown that reinstatement of the therapy is often possible without recurrence of the intracranial hypertension. If growth hormone treatment is restarted, careful monitoring for symptoms of intracranial hypertension is necessary.

Experience in patients above 60 years is limited.

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, history of respiratory impairment, 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.

In case of signs of upper airway obstruction, the problem should be solved by a specialist before starting treatment with somatropin.

Sleep apnoea should be assessed before onset of growth hormone treatment by recognised methods such as polysomnography or overnight oxymetry, and monitored if sleep apnoea is suspected.

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 ENT assessment performed.

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.

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

Scoliosis is common in patients with PWS. Scoliosis may progress in any child during rapid growth. Signs of scoliosis should be monitored during treatment. However, growth hormone treatment has not been shown to increase the incidence or severity of scoliosis.

Experience with long term treatment in adults and in patients with PWS is limited.

In short children/adolescents born SGA, other medical reasons or treatments that could explain growth disturbance should be ruled out before starting treatment.

In SGA children/adolescents 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/adolescents 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/adolescents born SGA with growth hormone may be lost if treatment is stopped before final height is reached.

In chronic renal insufficiency, 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 Omnitrope are available.

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.

This medicinal product contains less than 1 mmol sodium (23 mg) per ml, i.e. essentially 'sodium-free'.

Because of the presence of benzyl alcohol the medicinal product must not be given to premature babies or neonates. It may cause toxic reactions and anaphylactoid reactions in infants and children up to 3 years old.

4.5 Interaction with other medicinal products and other forms of interaction

Data from an interaction study performed in growth hormone 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 P 450 3A4 (e.g. sex steroids, corticosteroids, anticonvulsants and ciclosporin) 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 disorder and section 4.2 for statement on oral oestrogen replacement therapy.

4.6 Pregnancy and lactation

For Omnitrope no clinical data on exposed pregnancies are available. Animal experimental data on reproductive toxicity of Omnitrope are not available. Treatment with Omnitrope should be interrupted if pregnancy occurs.

During normal pregnancy levels of pituitary growth hormone fall markedly after 20 gestation weeks, being replaced almost entirely by placental growth hormone by 30 weeks. In view of this, it is unlikely that continued replacement therapy with somatropin would be necessary in growth hormone deficient women in the third trimester of pregnancy.

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.

Caution should be exercised when Omnitrope is administered to breast-feeding women.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Within the organ system classes, adverse reactions are listed under headings of frequency (number of patients expected to experience the reaction), using the following categories: very common ($\geq 1/10$); common ($\geq 1/100, < 1/10$); uncommon ($\geq 1/1,000, < 1/100$); rare ($\geq 1/10,000, < 1/1,000$); very rare ($< 1/10,000$).

Patients with growth hormone deficiency are characterised by extracellular volume deficit. When treatment with somatropin is started this deficit is rapidly corrected. In adult patients, adverse reactions related to fluid retention, such as peripheral oedema, stiffness in the extremities, 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 undesirable effects 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 paediatric patients such undesirable effects are uncommon.

Neoplasms benign, malignant and unspecified (incl cysts and polyps)

Very rare: Leukemia. Very rare cases of leukaemia have been reported in growth hormone deficient paediatric patients treated with somatropin, but the incidence appears to be similar to that in the paediatric subjects without growth hormone deficiency.

Immune system disorders

Common: Formation of antibodies. Somatropin 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.

Endocrine disorders

Rare: Diabetes mellitus type II

Nervous system disorders

Common: In adults: paraesthesia
Uncommon: In adults: carpal tunnel syndrome; In paediatric patients: paraesthesia
Rare: Benign intracranial hypertension

Musculoskeletal and connective tissue disorders

Common: In adults: stiffness in the extremities, arthralgia, myalgia
Uncommon: In paediatric patients: stiffness in the extremities, arthralgia, myalgia

General disorders and administration site conditions

Common: In adults: peripheral oedema; In paediatric patients: transient local skin reactions at the injection site
Uncommon: In paediatric patients: peripheral oedema

4.9 Overdose

No case of overdose has been reported.

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

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: 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 mobilisation 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/adolescents born SGA doses of 0.033 and 0.067 mg somatropin/kg body weight per day have been used for treatment until final height is reached. In 56 patients who are 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/adolescents without early spontaneous catch-up suggest a late growth of 0.5 SDS. Long-term safety data are still limited.

5.2 Pharmacokinetic 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 Omnitrope 3.3 mg/ml 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.

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 Omnitrope 3.3 mg/ml solution for injection, 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.

5.3 Preclinical safety data

In studies with Omnitrope 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

disodium hydrogen phosphate heptahydrate
sodium dihydrogen phosphate dihydrate
mannitol
poloxamer 188
benzyl alcohol
water for injections

6.2 Incompatibilities

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

6.3 Shelf life

2 years.

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, 5 and 10.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Omnitrope 3.3 mg/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 the Omnitrope Pen 5, an injection device specifically developed for use with Omnitrope 3.3 mg/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 Omnitrope 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 Omnitrope Pen 5 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.

7. MARKETING AUTHORISATION HOLDER

Sandoz GmbH
Biochemiestrasse 10
A-6250 Kundl
Austria

8. MARKETING AUTHORISATION NUMBERS

EU/1/06/332/004
EU/1/06/332/005
EU/1/06/332/006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12 April 2006

10. DATE OF REVISION OF THE TEXT

18 March 2008

1. NAME OF THE MEDICINAL PRODUCT

Omnitrope 6.7 mg/ml solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Somatropin* 6.7 mg (corresponding to 20 IU)/ ml.

One cartridge contains 1.5 ml corresponding to 10 mg Somatropin* (30 IU).

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

For a 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

Infants, children and adolescents

- Growth disturbance due to insufficient secretion of growth hormone (GH).
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- Growth disturbance associated with chronic renal insufficiency.
- Growth disturbance (current height standard deviation score (SDS) < -2.5 and parental adjusted SDS < -1) in short children/adolescents born small for gestational age (SGA), with a birth weight and/or length below -2 standard deviation (SD), who failed 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. 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 a 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.

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The posology and administration schedule should be individualised.

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Prader-Willi syndrome, for improvement of growth and body composition in paediatric patients:
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 may be needed if growth velocity is too low. A dose correction may be needed after six months of treatment (see section 4.4).

Growth disturbance in short children/adolescents born small for gestational age (SGA):
A dose of 0.035 mg/kg body weight per day (1 mg/m² body surface area per day) is usually recommended until final height is reached (see section 5.1). 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 confirmation is required, bone age is > 14 years (girls) or > 16 years (boys), corresponding to epiphyseal closure.

Dose recommendations for paediatric patients

Indication	mg/kg body weight dose per day	mg/m² body surface area dose per day
Growth hormone deficiency	0.025 - 0.035	0.7 - 1.0
Prader-Willi syndrome	0.035	1.0
Turner syndrome	0.045 - 0.050	1.4
Chronic renal insufficiency	0.045 - 0.050	1.4
Children/adolescents born small for gestational age (SGA)	0.035	1.0

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 the upper range of normal, not exceeding the 2 SDS. Clinical response and undesirable effects may also be used as guidance for dose titration. The daily maintenance dose rarely exceeds 1.0 mg per day. Women may require higher doses than men, while men show 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.

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

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- Hypersensitivity to somatropin or to any of the excipients.
- Somatropin must not be used when there is any evidence of tumour activity and anti-tumour therapy must be completed prior to starting therapy.
- Somatropin must not be used for growth promotion in patients with closed epiphyses.
- 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. With regard to patients undergoing substitution therapy, see section 4.4.

4.4 Special warnings and precautions for use

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 already manifested diabetes mellitus, the anti-diabetic therapy might require adjustment when somatropin is instituted.

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. Conversely, in patients receiving replacement therapy with thyroxin mild hyperthyroidism may occur. It is therefore particularly advisable to test thyroid function after starting treatment with somatropin and after dose adjustments.

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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. However, clinical experience has shown that reinstatement of the therapy is often possible without recurrence of the intracranial hypertension. If growth hormone treatment is restarted, careful monitoring for symptoms of intracranial hypertension is necessary.

Experience in patients above 60 years is limited.

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, history of respiratory impairment, 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.

In case of signs of upper airway obstruction, the problem should be solved by a specialist before starting treatment with somatropin.

Sleep apnoea should be assessed before onset of growth hormone treatment by recognised methods such as polysomnography or overnight oxymetry, and monitored if sleep apnoea is suspected.

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 ENT assessment performed.

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.

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

Scoliosis is common in patients with PWS. Scoliosis may progress in any child during rapid growth. Signs of scoliosis should be monitored during treatment. However, growth hormone treatment has not been shown to increase the incidence or severity of scoliosis.

Experience with long term treatment in adults and in patients with PWS is limited.

In short children/adolescents born SGA, other medical reasons or treatments that could explain growth disturbance should be ruled out before starting treatment.

In SGA children/adolescents 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/adolescents 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/adolescents born SGA with growth hormone may be lost if treatment is stopped before final height is reached.

In chronic renal insufficiency, 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 Omnitrope are available.

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.

This medicinal product contains less than 1 mmol sodium (23 mg) per ml, i.e. essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Data from an interaction study performed in growth hormone 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 P 450 3A4 (e.g. sex steroids, corticosteroids, anticonvulsants and ciclosporin) 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 disorder and section 4.2 for statement on oral oestrogen replacement therapy.

4.6 Pregnancy and lactation

For Omnitrope no clinical data on exposed pregnancies are available. Animal experimental data on reproductive toxicity of Omnitrope are not available. Treatment with Omnitrope should be interrupted if pregnancy occurs.

During normal pregnancy levels of pituitary growth hormone fall markedly after 20 gestation weeks, being replaced almost entirely by placental growth hormone by 30 weeks. In view of this, it is unlikely that continued replacement therapy with somatropin would be necessary in growth hormone deficient women in the third trimester of pregnancy.

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.

Caution should be exercised when Omnitrope is administered to breast-feeding women.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Within the organ system classes, adverse reactions are listed under headings of frequency (number of patients expected to experience the reaction), using the following categories: very common ($\geq 1/10$); common ($\geq 1/100, < 1/10$); uncommon ($\geq 1/1,000, < 1/100$); rare ($\geq 1/10,000, < 1/1,000$); very rare ($< 1/10,000$).

Patients with growth hormone deficiency are characterised by extracellular volume deficit. When treatment with somatropin is started this deficit is rapidly corrected. In adult patients, adverse reactions related to fluid retention, such as peripheral oedema, stiffness in the extremities, 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 undesirable effects 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 paediatric patients such undesirable effects are uncommon.

Neoplasms benign, malignant and unspecified (incl cysts and polyps)

Very rare: Leukemia. Very rare cases of leukaemia have been reported in growth hormone deficient paediatric patients treated with somatropin, but the incidence appears to be similar to that in the paediatric subjects without growth hormone deficiency.

Immune system disorders

Common: Formation of antibodies. Somatropin 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.

Endocrine disorders

Rare: Diabetes mellitus type II

Nervous system disorders

Common: In adults: paraesthesia
Uncommon: In adults: carpal tunnel syndrome; In paediatric patients: paraesthesia
Rare: Benign intracranial hypertension

Musculoskeletal and connective tissue disorders

Common: In adults: stiffness in the extremities, arthralgia, myalgia
Uncommon: In paediatric patients: stiffness in the extremities, arthralgia, myalgia

General disorders and administration site conditions

Common: In adults: peripheral oedema; In paediatric patients: transient local skin reactions at the injection site
Uncommon: In paediatric patients: peripheral oedema

4.9 Overdose

No case of overdose has been reported.

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

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: 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 mobilisation 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/adolescents born SGA doses of 0.033 and 0.067 mg somatropin/kg body weight per day have been used for treatment until final height is reached. In 56 patients who are 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/adolescents without early spontaneous catch-up suggest a late growth of 0.5 SDS. Long-term safety data are still limited.

5.2 Pharmacokinetic 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 Omnitrope 6.7 mg/ml solution for injection in healthy adults results in plasma C_{max} and t_{max} values of 74 ± 22 µg/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 Omnitrope 6.7 mg/ml solution for injection, 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.

5.3 Preclinical safety data

In studies with Omnitrope 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

disodium hydrogen phosphate heptahydrate
sodium dihydrogen phosphate dihydrate
glycine
poloxamer 188
phenol
water for injections

6.2 Incompatibilities

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

6.3 Shelf life

18 months.

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, 5 and 10.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Omnitrope 6.7 mg/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 the Omnitrope Pen 10, an injection device specifically developed for use with Omnitrope 6.7 mg/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 Omnitrope 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 Omnitrope Pen 10 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.

7. MARKETING AUTHORISATION HOLDER

Sandoz GmbH
Biochemiestrasse 10
A-6250 Kundl
Austria

8. MARKETING AUTHORISATION NUMBERS

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10. DATE OF REVISION OF THE TEXT

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