SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Omnitrope 5 mg/1.5 ml solution for injection in cartridge

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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 9 mg benzyl alcohol in each ml.
Benzyl alcohol may cause allergic reactions.

* produced in Escherichia coli by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection in a cartridge for SurePal 5.
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 (growth hormone deficiency, GHD).
- Growth disturbance associated with Turner syndrome.
- Growth disturbance associated with chronic renal insufficiency.

- Growth disturbance (current height standard deviation score (SDS) < -2.5 and parental adjusted height SDS < -1) in short children/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.
- *Adult onset:* Patients who have severe growth hormone deficiency associated with multiple hormone deficiencies as a result of known hypothalamic or pituitary pathology, and who have at least one known deficiency of a pituitary hormone not being prolactin. These patients should undergo an appropriate dynamic test in order to diagnose or exclude a growth hormone deficiency.
- *Childhood onset:* Patients who were growth hormone deficient during childhood as a result of congenital, genetic, acquired, or idiopathic causes. Patients with childhood onset GHD should be re-evaluated for growth hormone secretory capacity after completion of longitudinal growth. In patients with a high likelihood for persistent GHD, i.e. a congenital cause or GHD secondary to a hypothalamic-pituitary disease or insult, an insulin-like growth factor-I (IGF-I) SDS < -2 off growth hormone treatment for at least 4 weeks should be considered sufficient evidence of profound GHD.

All other patients will require IGF-I assay and one growth hormone stimulation test.

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 growth disorders.

Posology

Paediatric population
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/m^2 body surface area per day is recommended. Even higher doses have been used.

Where childhood onset GHD persists into adolescence, treatment should be continued to achieve full somatic development (e.g. body composition, bone mass). For monitoring, the attainment of a normal peak bone mass defined as a T score > -1 (i.e. standardized to average adult peak bone mass measured by dual energy X-ray absorptiometry taking into account sex and ethnicity) is one of the therapeutic objectives during the transition period. For guidance on dosing see adult section below.

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/m^2 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/m^2 body surface area per day is recommended.

Growth disturbance in chronic renal insufficiency
A dose of 0.045 - 0.050 mg/kg body weight per day (1.4 mg/m^2 body surface area per day) is recommended. Higher doses may be needed if growth velocity is too low. A dose correction can 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/m^2 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 closure of the epiphyseal growth plates.

Dose recommendations in 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
In patients who continue growth hormone therapy after childhood GHD, the recommended dose to restart is 0.2 – 0.5 mg per day. The dose should be gradually increased or decreased according to individual patient requirements as determined by the IGF-I concentration.

In adults with adult-onset GHD, 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.

In both cases treatment goal should be insulin-like growth factor (IGF-I) concentrations within 2 SDS from the age corrected mean. 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 side effects may also be used as guidance for dose titration. It is recognized that there are patients with GHD who do not normalize IGF-I levels despite a good clinical response, and thus do not require dose escalation. The maintenance dose rarely exceeds 1.0 mg per day. Women may require higher doses than men, with 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.

Special populations

Elderly
In patients above 60 years, therapy should start with a dose of 0.1 - 0.2 mg per day and should be slowly increased according to individual patient requirements. The minimum effective dose should be used. The maintenance dose in these patients seldom exceeds 0.5 mg per day.

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.

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 (regarding patients undergoing substitution therapy, see section 4.4).

4.4 Special warnings and precautions for use

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

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.

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 reduce insulin sensitivity. For patients with diabetes mellitus, the insulin dose may require adjustment after somatropin therapy is instituted. Patients with diabetes, glucose intolerance, or additional risk factors for diabetes should be monitored closely during somatropin therapy.

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 the 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 Omnitrope. Omnitrope has given rise to the formation of antibodies in approximately 1% of patients. The binding capacity of these antibodies is low and there is no effect on growth rate. Testing for antibodies to somatropin should be carried out in any patient with otherwise unexplained lack of response.

Pancreatitis

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

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

Acute critical illness

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

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

Prader-Willi syndrome

In patients with PWS, treatment should always be in combination with a calorie-restricted diet.

There have been reports of fatalities associated with the use of growth hormone in paediatric patients with PWS who had one or more of the following risk factors: severe obesity (those patients exceeding a weight/height of 200%), history of respiratory impairment or sleep apnoea or unidentified respiratory infection. Patients with PWS and one or more of these risk factors may be at greater risk.

Before initiation of treatment with somatropin patients with PWS should be evaluated for upper airway obstruction, sleep apnoea or respiratory infections should be assessed.

If during the evaluation of upper airway obstruction, pathological findings are observed, the child should be referred to an Ear, nose and throat (ENT) specialist for treatment and resolution of the respiratory disorder prior to initiating growth hormone treatment.

Sleep apnoea should be 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.

Patients 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 growth hormone treatment.

Scoliosis is common in patients with Prader-Willi syndrome. Scoliosis may progress in any child during rapid growth. Signs of scoliosis should be monitored during treatment.

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

Small for gestational age

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.

Chronic renal insufficiency

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.

Omnitrope 5 mg/1.5 ml solution for injection contains benzyl alcohol:
This medicine contains 9 mg 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.

Advise pregnant or breast feeding patients that large amounts of benzyl alcohol can be build up in their body and may cause sides effects (called “metabolic acidosis”).

Advise patients who have a liver or kidney disease that large amounts of benzyl alcohol can be build up in their body and may cause sides effects (called “metabolic acidosis”).

Sodium content
This medicine 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

Concomitant treatment with glucocorticoids inhibits the growth-promoting effects of Omnitrope. Patients with Adrenocorticotropic hormone (ACTH) deficiency should have their glucocorticoid replacement therapy carefully adjusted to avoid any inhibitory effect on growth. Therefore, patients treated with glucocorticoids should have their growth monitored carefully to assess the potential impact of glucocorticoid treatment on growth.

Growth hormone decreases the conversion of cortisone to cortisol and may unmask previously undiscovered central hypoadrenalism or render low glucocorticoid replacement doses ineffective (see section 4.4).

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 metabolised by cytochrome P450 isoenzymes. The clearance of compounds metabolised by cytochrome P450 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 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 Omnitrope is administered to breast-feeding women.

Fertility

Fertility studies with Omnitrope have not been performed.

4.7 Effects on ability to drive and use machines

Omnitrope 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.

Omnitrope 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

Table 1 shows the adverse reactions ranked under headings of System Organ Class and frequency using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data) for each of the indicated conditions.

Table 1

System Organ Class	Frequency
Neoplasms Benign, Malignant and Unspecified (including cysts and polyps)	Uncommon: Leukaemia†[1] Not known: Leukaemia†[2,3,4,5]
Endocrine disorders	Not known: Hypothyroidism**
Metabolism and Nutrition Disorders	Not known: Type II diabetes mellitus
Nervous System Disorders	Common: Paraesthesia*, Benign intracranial hypertension [5], Carpal Tunnel Syndrome[6] Not known: Benign intracranial hypertension [1,2,3,4,6] 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 children with chronic renal insufficiency
[4] Clinical trials in children with SGA
[5] Clinical trials in PWS
[6] Clinical trials in adults with GHD

*In general, these adverse effects are mild to moderate, arise within the first months of treatment, and subside spontaneously or with dose-reduction. The incidence of these adverse effects is related to the administered dose, the age of the patients, and possibly inversely related to the age of the patients at the onset of growth hormone deficiency.
**Adverse drug reaction (ADR) identified post-marketing.

$ Transient injection site reactions in children have been reported.

‡ Clinical significance is unknown

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

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, although no causal relationship has been demonstrated.

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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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

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

Omnitrope is a biosimilar medicinal product. Detailed information is available on the website of the European Medicines Agency http://www.ema.europa.eu

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 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.

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 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.

Clinical efficacy and safety

In clinical trials in short children/adolescents born SGA doses of 0.033 and 0.067 mg/kg body weight per day have been used for treatment until final height is reached. In 56 patients who were continuously treated and have reached (near) final height, the mean change from height at start of treatment was +1.90 SDS (0.033 mg/kg body weight per day) and +2.19 SDS (0.067 mg/kg body weight per day). Literature data from untreated SGA children/adolescents without early spontaneous catch-up suggest a late growth of 0.5 SDS.

Post-marketing study experience:

An international, non-interventional, non-controlled, longitudinal, open and multicenter, voluntary category 3 PASS designed to record the safety and effectiveness data of 7359 pediatric patients treated with Omnitrope in various indications was conducted by Sandoz between 2006 and 2020 in 11 European countries, in North America, Canada, Australia and Taiwan.
The main pediatric indications were: GHD (57.9%), SGA (26.6%), TS (4.9%), ISS (3.3%), PWS (3.2%) and CRI (1.0%). Most patients were naïve of previous rhGH treatment (86.0%). Across all indications, the most frequent AEs with a suspected causal relationship to Omnitrope treatment in patients were headache (1.6%), injection site pain (1.1%), injection site hematoma (1.1%) and arthralgia (0.6%), assessed in 7359 pediatric patients (SAF). The

majority of AEs assessed as related to Omnitrope treatment were expected based on the SmPC and as known for this type of class of molecule (GH). The intensity of most AEs was mild or moderate.
The effectiveness results, assessed in 6589 pediatric patients (EFF consisting of 5671 naïve, 915 rhGH pretreated and 3 patients with missing pre-treatment information), show that Omnitrope treatment was effective and resulted in a substantial catch-up growth which are consistent with those reported in observational studies of other approved rhGH medicines: the median H SDS increased effectively from -2.64 at baseline to -1.97 after 1 year and to -0.98 after 5 years of treatment in naïve patients, and a median H SDS increased from -1.49 to -1.21 after 1 year and to -0.98 after 5 years of Omnitrope treatment in pre-treated patients. 1628/6589 (24.7%) patients of the EFF reached final height according to physician's opinion (naïve: 1289/5671, 22.7%); rhGH pretreated: 338/915, 36.9%). Median (range) final H SDS in naïve patients -1.51 (-9.3 to 2.7) and -1.43 (-8.7 to 2.1) in pre-treated patients.

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 5 mg/1.5 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 5 mg/1.5 ml, a half-life of 3 hours is achieved. The observed difference is likely due to slow absorption from the injection site following subcutaneous administration.

Special 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 drug 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 and a blue ring (for Omnitrope 15 mg/1.5 ml solution for injection only) on one side (siliconised bromobutyl), a disc (bromobutyl) and a cap (aluminium) on the other side. The glass cartridge is irreversibly integrated in a transparent container and assembled to a plastic mechanism with a threaded rod at one extremity.
Pack sizes of 1, 5 and 10.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Omnitrope 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 SurePal 5, an injection device specifically developed for use with Omnitrope 5 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 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 SurePal 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.

7 MARKETING AUTHORISATION HOLDER

Sandoz GmbH
Biochemiestr. 10
A-6250 Kundl
Austria

8 MARKETING AUTHORISATION NUMBER(S)

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