PRODUCT MONOGRAPH

Pr OMNITROPE ®

somatropin [rDNA origin] for injection

Lyophilized Powder for solution: 5.8 mg/vial
Solution for Injection: 5 mg/1.5 mL, 10 mg/1.5 mL, 15 mg/1.5 mL

Pharmaceutical Standard: Ph.Eur./USP

Human Growth Hormone

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form/Strength	Clinically Relevant Nonmedicinal Ingredients
Subcutaneous injection	Lyophilized powder: 5.8 mg/vial	5.8 mg/vial: supplied with diluent containing 1.5% benzyl alcohol as preservative.*
Subcutaneous injection	Solution: 5 mg/1.5 mL (3.3 mg/mL), 10 mg/1.5 mL (6.7 mg/mL) and 15 mg/1.5 mL (10.0 mg/mL)	5 mg/1.5 mL: mannitol, benzyl alcohol (as preservative) 10 mg/1.5 mL: phenol (as preservative) 15 mg/1.5 mL: phenol (as preservative)

*For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING section.

DESCRIPTION

Omnitrope (somatropin for injection) is a polypeptide hormone of recombinant DNA origin. It has 191 amino acid residues and a molecular weight of 22,125 Daltons and an isoelectric point (pH) of 5.1. The amino acid sequence of the product is identical to that of human growth hormone of pituitary origin (somatropin). Omnitrope is synthesized in a strain of *Escherichia coli* which has been modified by the addition of the human growth hormone gene.

Omnitrope comes in two dosage forms: a sterile, white lyophilized powder and a clear, colourless, sterile solution both intended for subcutaneous injection.

The similarity between the SEB, Omnitrope, and the reference product was established in accordance with the *Guidance for Sponsors: Information and Submission Requirements for Subsequent Entry Biologics (SEBs).*

INDICATIONS AND CLINICAL USE

Comparability between Omnitrope and the reference product has been established based on comparative chemistry and manufacturing studies, comparative non-clinical studies, comparative PK studies and clinical safety and efficacy trials in pediatric patients with Growth Hormone Deficiency due to underlying hypothalamic or pituitary disease or who were growth hormone deficient during childhood. Indications in SGA (small for gestational age), TS (Turner Syndrome), ISS (idiopathic short stature) and GHD (growth hormone deficiency) in adults have been granted on the basis of demonstrated similarity between Omnitrope and the reference

product, in product quality, mechanism of action, disease pathophysiology, safety profile, dosage regimen and on clinical experience with the reference product.

Omnitrope (somatropin for injection) is indicated for:

Children
The long-term treatment of children, who have growth failure due to an inadequate secretion of endogenous growth hormone (growth hormone deficiency [GHD]). Other causes of short stature should be excluded.

SGA Indication
Omnitrope is indicated for the treatment of growth failure (current height standard deviation score [SDS] < - 2) in short children born SGA (birth weight and/or length below -2 SD) and who fail to achieve catch-up growth (height velocity SDS < 0 during the last year) by 2 to 4 years or later.

TS Indication
The treatment of short stature associated with Turner syndrome in patients whose epiphyses are not closed.

ISS Indication
The long-term treatment of idiopathic short stature (ISS), also called non-growth hormone-deficient short stature, defined by height standard deviation score (SDS) <-2.25, and associated with growth rates unlikely to permit attainment of adult height in the normal range, in pediatric patients for whom diagnostic evaluation excludes other causes associated with short stature that should be observed or treated by other means. Omnitrope treatment for ISS should be prescribed only for those patients whose epiphyses are not closed.

Adults
Omnitrope (somatropin [rDNA origin] for injection) is indicated for replacement of endogenous growth hormone in adults with growth hormone deficiency who meet either of the following two criteria:

Adult Onset (AO): Patients who have growth hormone deficiency, either alone or associated with multiple hormone deficiencies (hypopituitarism), as a result of pituitary disease, hypothalamic disease, surgery, radiation therapy, or trauma; or

Childhood Onset (CO): Patients who were growth hormone deficient during childhood as a result of congenital, genetic, acquired, or idiopathic causes.

Patients who were treated with somatropin for growth hormone deficiency in childhood and whose epiphyses are closed should be re-evaluated before continuation of somatropin therapy at the reduced dose level recommended for growth hormone deficient adults. According to current standards, confirmation of the diagnosis of adult growth hormone deficiency in both groups involves an appropriate growth hormone provocative test with two exceptions: (1) patients with multiple other pituitary hormone deficiencies due to organic disease; and (2) patients with congenital/genetic growth hormone deficiency.

Geriatrics: The safety and efficacy of Omnitrope in patients aged 65 and over have not been evaluated in clinical studies (see WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics).

CONTRAINDICATIONS

Omnitrope (somatropin for injection) should not be used when there is any evidence of **neoplastic activity**. Intracranial lesions must be inactive and antitumour therapy complete prior to the institution of therapy. Treatment with Omnitrope should be discontinued if there is evidence of tumour growth. Patients should be examined frequently for progression or recurrence of the underlying process.

Omnitrope should not be used for growth promotion in pediatric patients with **closed epiphyses**.

Omnitrope should not be initiated in patients with acute critical illness due to complications following cardiac or abdominal surgery, multiple accidental trauma, or to patients having acute respiratory failure. Clinical studies demonstrated that high doses of somatropin, were associated with a significantly increased morbidity and mortality in those patients (see WARNINGS AND PRECAUTIONS, General).

Somatropin is contraindicated in patients with Prader-Willi syndrome who are severely obese, have a history of upper airway obstruction or sleep apnea, or have severe respiratory impairment. There have been reports of sudden death when somatropin was used in such patients. Omnitrope is not indicated for the treatment of pediatric patients who have growth failure due to genetically confirmed Prader-Willi syndrome (see Serious Warnings and Precautions).

Growth Hormones have no effect on cartilaginous growth areas of the long bone. Treatment of paediatric growth disorders with growth hormones should be discontinued when the patient has reached satisfactory adult height, or the epiphyses are closed.

Antitumour therapy should be completed before growth hormone therapy with Omnitrope is initiated. Omnitrope should be discontinued if there is evidence of recurrent tumour growth.

Intracranial tumour shall be inactive and anti-malignancy treatment must be completed with evidence of remission prior to the institution of somatropin therapy. Patients should be examined frequently for progression or recurrence of the underlying process.

Omnitrope should not be administered in patients with proliferative or preproliferative diabetic retinopathy.

Omnitrope 5.8 mg/vial lyophilized powder when reconstituted with the diluent Bacteriostatic Water for Injection (benzyl alcohol preserved) and Omnitrope 5.0 mg/1.5 mL solution which also contains the preservative benzyl alcohol, should not be administered in newborns or in patients with a known sensitivity to benzyl alcohol (see WARNINGS AND PRECAUTIONS).

Omnitrope is contraindicated in patients who are hypersensitive to somatropin or to any ingredient in the formulations. For a complete listing, see DOSAGE FORMS, COMPOSITION AND PACKAGING section of the product monograph.

Treatment with Omnitrope should be discontinued at the time of renal transplantation.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- **There have been reports of fatalities associated with the use of growth hormone in pediatric patients with Prader-Willi syndrome who have one or more of the following risk factors: severe obesity, history of respiratory impairment or sleep apnea or unidentified [i.e., previously undiagnosed/mildly symptomatic] respiratory infections (see CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS – Congenital Disorders).**
- **A significant increase in mortality was reported among somatropin treated patients with acute critical illness in intensive care units due to complications following open-heart surgery, abdominal surgery, multiple accidental trauma or acute respiratory failure compared with those receiving placebo (see WARNINGS AND PRECAUTIONS - Perioperative Considerations).**
- Omnitrope shall only be used if, once reconstituted, the resulting solution is water-clear and devoid of particulate matter (see DOSAGE AND ADMINISTRATION, Administration).
- Benzyl alcohol, used as a preservative in Bacteriostatic Water for Injection, USP has been associated with toxicity in newborns. When administering Omnitrope to newborns, reconstitute with sterile water for injection USP. Only use one reconstituted dose per growth hormone vial and discard the unused portion.
- Treatment with somatropin should be directed by specialists experienced in the diagnosis and management of growth disorders.
- Any change in brand of somatropin products should be made cautiously and only under medical supervision (see WARNINGS AND PRECAUTIONS, Immune – Antibody Production).

General

Patients and caregivers who will administer Omnitrope in medically unsupervised situations should receive appropriate training and instruction on the proper use of Omnitrope from the physician or other suitably qualified health professionals.

If injected subcutaneously, the injection site should be rotated to minimize the risk of lipoatrophy occurring.

To avoid transmission of disease, cartridge and prefilled syringe shall not be used by more than one person.

Concomitant glucocorticoid therapy may inhibit the response to Growth hormone and should not exceed 10-15 mg hydrocortisone equivalent/m^2 body surface area during somatropin therapy.

Carcinogenesis and Mutagenesis
Mutagenicity or carcinogenicity studies have not been conducted with Omnitrope.

Leukemia has been reported in a small number of growth hormone deficient patients, treated with growth hormone. Based on the current evidence, experts cannot conclude that growth hormone therapy is responsible for these occurrences.

Treatment with growth hormone may have an increased risk of developing neoplasm.

Secondary Neoplasm in Survivors of Childhood Cancer
In childhood cancer survivors, an increased risk of a second neoplasm (benign and malignant) has been reported in patients treated with growth hormone. 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. However, in childhood cancer survivors, no increased risk of primary cancer recurrence has been reported in patients treated with growth hormones.

Congenital Disorders
There have been reports of fatalities associated with the use of growth hormone in pediatric patients with Prader-Willi syndrome who had one or more of the following risk factors: severe obesity, history of respiratory impairment or sleep apnea, or unidentified (i.e., previously undiagnosed/mildly symptomatic) respiratory infection. Another possible risk factor may be male gender (see CONTRAINDICATIONS).

Prader-Willi Syndrome
Patients with Prader-Willi syndrome should be evaluated for signs of upper airway obstruction and sleep apnea before initiation of treatment with somatropin.

If a somatropin treated patients shows signs of upper airway obstruction (including onset of or increased snoring), and/or new onset of sleep apnea, somatropin treatment should be interrupted and the patients should be treated for upper airway obstruction and/or sleep apnea.

All patients with Prader-Willi syndrome treated with somatropin should also have effective weight control and be monitored for signs of respiratory infection, which should be diagnosed as early as possible and treated aggressively (see CONTRAINDICATIONS).

Omnitrope is NOT indicated in Canada for the treatment of genetically confirmed growth failure due to Prader-Willi syndrome.

Turner's syndrome
Patients with Turner syndrome may be at increased risk for development of intracranial hypertension. Therefore, these patients should be evaluated for signs and symptoms of intracranial hypertension and, if present, this condition should be treated before initiation of treatment with somatropin.

Patients with Turner syndrome should be evaluated carefully for otitis media and other ear disorders before and during treatment with somatropin because these patients have an increased

risk of ear and hearing disorders (see ADVERSE REACTIONS).

Patients with Turner syndrome are at risk for cardiovascular disorders (e.g. hypertension, stroke, and aortic dilatation, aneurysm and dissection) and these patients should be monitored closely for development or worsening of these conditions before and during treatment with somatropin.

Patients with Turner syndrome have an inherently increased risk of developing autoimmune thyroid disease. Therefore, these patients should have periodic thyroid function tests performed and be treated appropriately (see Endocrine and Metabolism).

Note: Skeletal abnormalities including scoliosis are commonly seen in untreated patients with Turner syndrome.

Dependence/Tolerance:
Inappropriate use of somatropin by individuals who do not have indications for which growth hormone is approved, may result in clinically significant negative health consequences (see ADVERSE REACTIONS and OVERDOSAGE).

Somatropin is not a drug of dependence.

Endocrine and Metabolism
Patients with diabetes mellitus or glucose intolerance should be monitored closely during therapy with somatropin as an adjustment of their antidiabetic therapy may be required.

Treatment with somatropin may decrease insulin sensitivity, particularly at higher doses in patients with risk factors for diabetes mellitus, such as obesity, Turner syndrome, or a family history of diabetes mellitus, those receiving high dose corticosteroid therapy, and patients with impaired glucose tolerance or pre-existing diabetes mellitus. As a result, previously undiagnosed impaired glucose tolerance and overt diabetes mellitus may be unmasked during somatropin treatment. Therefore, patients who receive somatropin should be monitored for evidence of abnormal glucose metabolism and/or diabetes mellitus. New-onset type 2 diabetes mellitus has been reported in children and adults receiving somatropin.

In patients with hypopituitarism (multiple hormonal deficiencies) standard hormonal replacement therapy should be monitored closely when treatment with Omnitrope is administered.

Somatropin can increase the extrathyroidal conversion of thyroxine (T4) to triiodothyronine (T3) and may unmask incipient hypothyroidism. Because inadequate treatment of hypothyroidism may prevent optimal response to somatropin, thyroid function should be evaluated before starting somatropin therapy and should be monitored regularly during treatment, not less frequently than annually. If hypothyroidism is diagnosed in the course of growth hormone therapy, it should be corrected.

Notes Regarding Potential Effects of Somatropin on Glucocorticoid Metabolism: The microsomal enzyme 11β-hydroxysteroid dehydrogenase type 1 (11βHSD-1) is required for conversion of cortisone to its active metabolite, cortisol in hepatic and adipose tissue. Endogenous growth hormone and exogenous somatropin inhibit the activity of 11βHSD-1.

Therefore growth hormone deficiency is associated with a relative increase in 11βHSD-1 activity, which in turn results in a relative increase in serum cortisol. Somatropin treatment may inhibit 11βHSD-1, resulting in relative reduction of serum cortisol concentrations.

In addition, somatropin may enhance the activity of CYP3A4, a cytochrome P450 enzyme involved in glucocorticoid catabolism. Therefore, by increasing the activity of CYP3A4, somatropin could potentially decrease serum cortisol concentration. Because somatropin may both inhibit 11βHSD-1 (an enzyme required for production of cortisol) and induce activity of CYP3A4 (an enzyme involved in cortisol breakdown), careful monitoring of serum cortisol concentrations is required for all patients receiving concomitant glucocorticoid and somatropin therapy.

As a consequence of its actions on enzymes involved in cortisol metabolism, somatropin treatment may unmask previously undiagnosed central (secondary) hypoadrenalism, and glucocorticoid replacement may be required. In addition, patients treated with glucocorticoids for previously diagnosed hypoadrenalism (primary or secondary) may require adjustments of their maintenance or stress doses following initiation of somatropin treatment; this may be especially true for patients treated with cortisone acetate and prednisone, because conversion of these drugs to their biologically active metabolites is dependent on the activity of 11βHSD-1 (see Monitoring and Laboratory Tests).

Fluid Retention

Fluid retention during somatropin replacement therapy in adults may occur frequently. Clinical manifestations of fluid retention are usually transient and dose dependent.

Hematologic

Serum levels of inorganic phosphorous, alkaline phosphatase and Insulin-like Growth Factor 1 (IGF-1) may increase with growth hormone therapy. It is recommended that Insulin-like Growth Factor-I (IGF-I) concentrations be monitored regularly and maintained within the normal range for age and sex.

Immune

Local or systemic allergic reactions:

With growth hormone therapies patients may experience redness, swelling, pain, inflammation, or itching at the site of injection. Most of these minor reactions usually resolve in a few days to a few weeks. They may occur if the injection is not properly made (irritants in the skin cleansing agent or poor injection technique), or if the patient is allergic to the growth hormone or any excipients (see CONTRAINDICATIONS).

Rarely, SC administration of somatropin can result in lipoatrophy (depression in the skin) or lipohypertrophy (enlargement or thickening of tissue). Patients should be advised to consult their doctor if they notice any of these conditions. Continuous rotation of the injection site within a given area may help reduce or prevent these reactions. On rare occasion, injection site reactions may require discontinuation of therapy with somatropin.

Systemic allergic reactions:

Systemic allergic reactions have rarely occurred with growth hormone therapy. These reactions may be characterized by a generalized rash (with pruritus), shortness of breath, wheezing, angioneurotic edema and drop in blood pressure. Severe cases of generalized allergy including anaphylactic reaction may be life-threatening. If any serious hypersensitivity or allergic reactions occurs, somatropin therapy should be discontinued immediately and appropriate therapy initiated as per general guidelines.

Antibody production:
As with all protein pharmaceuticals, a small percentage of patients may develop antibodies during treatment with growth hormones. Patients who have demonstrated an allergic reaction to other growth hormone products may demonstrate an allergic reaction to somatropin. If growth deceleration is observed that is not attributable to another cause, the physician should consider testing the patient for antibodies to somatropin.

Musculoskeletal
Increased tissue turgor (non-edematous swelling, particularly in the hands and feet) and musculoskeletal discomfort (pain, swelling and/or stiffness) may occur during treatment with growth hormones. These symptoms may resolve spontaneously, with analgesic therapy, or after reducing the dosage. Carpal tunnel syndrome may occur during treatment with growth hormone. If the symptoms of carpal tunnel syndrome do not resolve by decreasing the dosage of growth hormone, it is recommended that treatment be discontinued.

Somatropin has not been shown to increase the incidence of scoliosis. Progression of **scoliosis** can occur in patients who experience rapid growth. Because growth hormone increases growth rate, patients with a history of scoliosis who are treated with growth hormone should be monitored for progression of scoliosis.

Slipped capital femoral epiphysis may occur more frequently in patients with endocrine disorders (including pediatric growth hormone deficiency, Turner syndrome and hypothyroidism) or in patients undergoing rapid growth. Any pediatric patient with the onset of a limp or complaints of hip or knee pain during somatropin therapy should be carefully evaluated (see Monitoring and Laboratory Tests).

Oral Estrogen:
Because oral estrogens may reduce the serum IGF-I response to somatropin treatment, girls and women receiving oral estrogen replacement may require greater somatropin dosages.

Pancreatitis
Cases of pancreatitis have been reported rarely in children and adults receiving somatropin treatment, with some evidence supporting a greater risk in children compared with adults. Pancreatitis should be considered in any somatropin treated patients, especially a child, who develops persistent severe abdominal pain.

Neurologic
Patients with growth hormone deficiency secondary to an **intracranial lesion** should be examined frequently for progression or recurrence of the underlying disease process.

Intracranial Hypertension (IH)
Intracranial hypertension (IH) with papilledema, visual changes, headache, nausea and/or vomiting has been reported in a small number of patients treated with growth hormone products. Symptoms usually occurred within the first eight (8) weeks of the initiation of growth hormone therapy. In all reported cases, IH-associated signs and symptoms resolved after discontinuation of therapy or a reduction of the growth hormone dose. Funduscopic examination of patients is recommended at the initiation, and periodically during the course of growth hormone therapy.

Perioperative Considerations
See CONTRAINDICATIONS for information on increased mortality in patients with **acute critical illnesses** in intensive care units due to complications following open heart or abdominal surgery, multiple accidental traumas, or with acute respiratory failure. The safety of continuing growth hormone treatment in patients receiving replacement doses for approved indications who concurrently develop these illnesses has not been established. Therefore, the potential benefit of treatment continuation with growth hormone in patients having acute critical illnesses should be weighed against the potential risk.

Reproduction Studies
No adequate and well-controlled studies with Omnitrope in reproduction studies have been performed.

Sensitivity/Resistance
Patients with known sensitivities to benzyl alcohol should not use either the Omnitrope 5.8 mg/vial reconstituted with the Bacteriostatic Water for Injection diluent or the Omnitrope 5.0 mg/1.5 mL as both formulations contain benzyl alcohol.

Sensitivity to Diluent: Benzyl alcohol has been associated with toxicity in newborns. The diluent, Bacteriostatic Water for Injection, for use with Omnitrope 5.8 mg/vial lyophilized powder contains benzyl alcohol as a preservative. Therefore, it should not be used in newborns.

Omnitrope 5.0 mg/1.5 mL solution also contains the ingredient benzyl alcohol as a preservative. It must not be used in newborns.

Special Populations
Pregnant Women: Reproduction studies have not been conducted with Omnitrope. It is also not known whether Omnitrope can cause fetal harm when administered to a pregnant woman or affect reproduction capacity. Omnitrope should only be given to a pregnant woman if the benefits outweigh the risks.

Nursing Women: It is not known whether this drug is excreted in human milk. There are no adequate and well-controlled studies in nursing women. Therefore, Omnitrope should be used with caution in nursing woman.

Pediatric Patients: (see INDICATIONS AND CLINICAL USE).

Pediatrics (< 3 years of age): Prudence is indicated for children under age of 3 years, when administering Omnitrope lyophilized powder reconstituted in Bacteriostatic Water for Injection (benzyl alcohol preserved) and Omnitrope 5.0 mg/1.5 mL solution (benzyl alcohol preserved);

although there is no information on the toxicity of benzyl alcohol for this age group, the toxic dose for premature neonates is in the range of 100 to 250 mg/kg per day.

Children, who have endocrine disorders, including growth hormone deficiency, may develop slipped capital femoral epiphyses more frequently than children in the general population. Any pediatric patient with onset of a limp or complaints of hip or knee pain during somatropin therapy should be evaluated.
Note: Some of the height gain obtained with somatropin treatment may be lost if treatment is stopped before final height is reached.

Turner Syndrome: see Congenital Disorders.

Idiopathic Short Stature: Other medical reasons or treatments that could explain growth disturbance should be ruled out before starting Omnitrope treatment for children with idiopathic short stature. Omnitrope treatment for idiopathic short stature should be prescribed only for those patients whose epiphyses are not closed and should be managed by physicians who have sufficient knowledge of idiopathic short stature and the efficacy/safety profile of somatropin.

Small for Gestational Age: In short children born small for gestational age (SGA) other medical reasons or treatments that could explain growth disturbance should be ruled out before starting treatment with somatropin (Omnitrope). Experience with SGA patients with Silver-Russell syndrome is limited, as is experience in initiating treatment in SGA patients near onset of puberty.

In short children born SGA, it is recommended that IGF-1 concentration should be measured before initiation of treatment and monitored every 6 months thereafter. If on repeated measurements IGF-1 concentrations exceed +2 SD compared to references for age and pubertal status, the IGF-1/IGFBP-3 ratio could be taken into account to consider dose adjustment.

Adult Patients: Patients with ephiphyseal closure who were treated with somatropin therapy in childhood should be re-evaluated according to the criteria provided in INDICATIONS AND CLINICAL USE before continuation of somatropin therapy at the reduced dose level required for growth hormone-deficient adults.

Experience with prolonged treatment in adults is limited. Adverse events such as peripheral edema, myalgia, arthralgia, and paresthesiae have been reported during post-marketing studies (see ADVERSE REACTIONS).

Growth hormone deficiency in the adult is a lifelong condition and should be treated accordingly. Experience with patients over sixty years of age is limited.

Note: Based on assessment of clinical trial data, post-marketing data, and spontaneous reports carpal tunnel syndrome appears to occur more frequently in patients over 40 years of age than in younger patients. In almost half of the reported cases the recommended maximum somatropin dose had been exceeded. In the majority of cases, the condition resolved spontaneously or with a

decrease in dosage, interruption of treatment, or discontinuation of treatment. The maximum recommended dosage should not be exceeded.

Geriatrics (>65 years of age): The safety and effectiveness of Omnitrope in patients aged 65 and over has not been evaluated in clinical studies. Elderly patients may be more sensitive to the action of Omnitrope and may be more prone to develop adverse reactions.

Obese Patients: Obese individuals are more likely to manifest adverse effects when treated with a weight-based regimen (see DOSAGE AND ADMINISTRATION).

Renal or Hepatic Impairment
No studies have been conducted with Omnitrope in these patient populations.

Monitoring and Laboratory Tests
Serum levels of inorganic phosphorus, alkaline phosphatase, parathyroid hormone (PTH) and IGF-1 may increase during somatropin therapy.

Adults: Adult patients, during GH treatment, should be monitored at 1- to 2-month intervals during dose titration and every 6 months thereafter with clinical assessment, evaluation for adverse effects, IGF-1 levels, and other parameters of GH response. Other laboratory testing should include a lipid profile and a fasting glucose. These should be assessed annually.

Patients with an intra- or extra-cranial neoplasm in remission who are receiving treatment with somatropin should be examined carefully and at regular intervals by the physician. In case of persistent edema or severe paraesthesia the dosage should be decreased in order to avoid the development of carpal tunnel syndrome (see ADVERSE REACTIONS).

Children: Children, during GH treatment, should be monitored every 3 to 6 months with measurement of IGF- 1/IGFBP-3 levels and clinical assessment expressed as increase in height (SD per year) and change in height velocity.

Bone age should be monitored periodically during somatropin administration.

Patients with an intra- or extra-cranial neoplasm in remission who are receiving treatment with somatropin should be examined carefully and at regular intervals by the physician.

In short children born SGA, it is recommended that IGF I concentration be measured before initiation of treatment and monitored every 6 months thereafter. If on repeated measurements IGF-1 concentrations exceed +2 SD compared to references for age and pubertal status, the IGF-1/IGFBP-3 ratio could be taken into account to consider dose adjustment.

ADVERSE REACTIONS

Adverse Drug Reaction Overview
Four serious adverse drug reactions (1%) on worsening of a pre-existing scoliosis were reported in one single patient in clinical trials with Omnitrope in the pediatric population.

Most frequent adverse drug reactions (experienced by ≥3% of patients) reported in clinical trials with Omnitrope Powder in the pediatric population were, eosinophilia (11 events in 9 patients (10%)), headache (8 events in 5 patients (5%)) and injection site haemorrhage (5 events in 5 patients (5%)).
Most frequent adverse drug reactions (experienced by ≥3% of patients) reported in clinical trials with Omnitrope Solution in the pediatric population were glycosylated hemoglobin A1c (HbA1c) increased 31 events in 25 patients (16%)), headache (19 events in 10 patients (6%)) and eosinophilia(19 events in 9 patients (6%)).

The highest normalized rates of adverse drug reactions for Omnitrope Powder in the pediatric population were recorded for eosinophilia (0.0477 events per patient-year), headache (0.0347 events per patient-year) and injection site haemorrhage (0.0217 events per patient year). The highest normalized rates of adverse drug reactions for Omnitrope Solution in the pediatric population were reported for glycosylated haemoglobin increased (0.0467 events per patient-year), headache (0.0286 events per patient-year), and eosinophilia (0.0286 events per patient-year).

The following events were observed in patients using somatropins (see also WARNINGS AND PRECAUTIONS section):

- Short-term local injection site reactions, such as pain, numbness, redness and swelling. The subcutaneous administration of growth hormone at the same injection site over a long period may result in local lipoatrophy.
- Disturbances in fluid balance (swelling), joint pain, muscle pain, stiffness of the hands and feet, numbness. In general, these undesirable effects occur at the beginning of therapy with growth hormones and also depend on the dose. They are common in adult patients, but uncommon in children.
- Carpal tunnel syndrome in adults.
- Benign intracranial hypertension, diabetes mellitus.

Due to the content of benzyl alcohol in Omnitrope, rare general hypersensitivity reactions are possible. No case was observed during the clinical trials.

Leukemia was reported in a small number of pediatric patients who were treated with growth hormone, including growth hormone of pituitary origin and recombinant growth hormone. The relationship, if any, between leukemia and growth hormone therapy is uncertain.

Clinical Trial Adverse Drug Reactions - Omnitrope

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

As with all protein drugs, a small number of patients may develop antibodies to the protein. Growth hormone antibody with binding capacity lower than 2 mg/L has not been associated with growth attenuation.

Preparations of Omnitrope contain a small amount of host cell *Escherichia coli* peptides (HCP). Anti-HCP antibodies are found in a small number of patients treated with Omnitrope, but these appear to be of no clinical significance.

The following events were observed during the Omnitrope clinical studies conducted in children with growth hormone deficiency (GHD):

Most Common Adverse Drug Reactions (≥ 1%) for Omnitrope and Genotropin®

Table 1a: Incidence of drug-related* adverse events occurring in pediatric patients with GHD (Studies EP2K-99-PhIII/EP2K-00-PhIIIFo).

	Omnitrope Lyophilizate COV[1] N=44	**Genotropin® N=45**
Preferred Term	**N (%)**	**N (%)**
Application site		
Injection site pain	0 (0%)	1 (2%)
Total events	0 (0%)	1 (2%)
Body as a whole		
Face oedema	1 (2%)	0 (0%)
Fever	1 (2%)	0 (0%)
Headache	3 (7%)	3 (7%)
Leg pain	1 (2%)	1 (2%)
Pain	1 (2%)	0 (0%)
Total events	7 (15%)	4 (9%)
Blood and lymphatic system disorders		
Anaemia	1 (2%)	0 (0%)
Elevated HbA1c	4 (9%)	3 (7%)
Eosinophilia	5 (11%)	3 (7%)
Total events	10 (22%)	6 (14%)
Cardiac disorders		
Heart murmur	1 (2%)	0 (0%)
Total events	1 (2%)	0 (0%)
Endocrine system		
Hypothyroidism	6 (14%)	2 (4%)
Total events	6 (14%)	2 (4%)
Eye disorders		
Conjunctivitis	0 (0%)	1 (2%)
Vision abnormal	0 (0%)	1 (2%)

Preferred Term	Omnitrope Lyophilizate COV[1] N=44 N (%)	Genotropin® N=45 N (%)
Total events	0 (0%)	2 (4%)
Gastro-intestinal system		
Abdominal pain	1 (2%)	0 (0%)
Total events	1 (2%)	0 (0%)
Infections and infestations		
Pharyngitis	0 (0%)	1 (2%)
Total events	0 (0%)	1 (2%)
Injury and procedural complications		
Haematoma	4 (9%)	5 (11%)
Total events	4 (9%)	5 (11%)
Abnormal hematologic and clinical chemistry findings		
SGOT increased	0 (0%)	1 (2%)
SGPT increased	0 (0%)	1 (2%)
T4 decreased	0 (0%)	1 (2%)
TSH decreased	0 (0%)	2 (4%)
Total events	0 (0%)	5 (10%)
Metabolic and nutritional		
Anorexia	1 (2%)	1 (2%)
Hypercholesterolaemia	1 (2%)	0 (0%)
Hyperglycaemia	1 (2%)	0 (0%)
Hypertriglyceridaemia	2 (5%)	2 (4%)
Total events	5 (11%)	3 (6%)
Musculo-skeletal system		
Arthralgia	1 (2%)	0 (0%)
Scoliosis	0 (0%)	1 (2%)
Total events	1 (2%)	1 (2%)
Nervous system		
Coma	1 (2%)	0 (0%)
Total events	1 (2%)	0 (0%)
Renal and urinary disorders		
Polyuria	0 (0%)	1 (2%)
Total events	0 (0%)	1 (2%)
Skin and subcutaneous tissue disorders		
Pruritus	1 (2%)	0 (0%)
Purpura	0 (0%)	1 (2%)
Total events	1 (2%)	1 (2%)

*Drug-related = possible, probable or unclassified relationship to study drug
N = number of patients
1=not marketed material

Table 1b: Incidence of drug-related* adverse events occurring in pediatric patients with GHD (Study EP2K-00-PhIIIAQ Part A)

Preferred Term	Omnitrope lyophilizate N=44 N (%)	Omnitrope liquid N=45 N (%)
Body as a whole		
Headache	2 (5%)	2 (4%)
Leg pain	1 (2%)	1 (2%)
Total events	3 (7%)	3 (6%)
Blood and lymphatic system disorders		
Elevated HbA1c	0 (0%)	3 (7%)
Eosinophilia	2 (5%)	3 (7%)
Total events	2 (5%)	6 (14%)
Endocrine system		
Hypothyroidism	0 (0%)	1 (2%)
Total events	0 (0%)	1 (2%)
Infections and infestations		
Bronchitis	0 (0%)	1 (2%)
Total events	0 (0%)	1 (2%)
Injury and procedural complications		
Haematoma	2 (5%)	1 (2%)
Total events	2 (5%)	1 (2%)
Metabolic and nutritional		
Hypertriglyceridaemia	1 (2%)	1 (2%)
Hypercholesterolaemia	1 (2%)	1 (2%)
Total events	2 (4%)	2 (4%)
Musculo-skeletal system		
Arthralgia	0 (0%)	1 (2%)
Scoliosis	0 (0%)	1 (2%)
Total events	0 (0%)	2 (4%)

*Drug-related = possible, probable or unclassified relationship to study drug.
N = number of patients.

Table1c: Incidence of drug-related* adverse events (coded by MedDRA preferred term) occurring in two or more pediatric patients with GHD (across all three consecutive studies EP2K-99-PhIII, EP2K-00-PhIIIFo, and EP2K-00-PhIIIAQ)**

	Omnitrope liquid N=89
Preferred Term	N (%)
Application site	
Injection site haematoma	12 (13.5%)
Total events	12 (13.5%)
Body as a whole	
Headache	14 (15.7%)
Pain in extremity	5 (5.6%)
Pyrexia	2 (2.2%)
Total events	21 (23.5%)
Blood and lymphatic system disorders	
Eosinophilia	11 (12.4%)
Leukopaenia	3 (3.4%)
Total events	14 (15.8%)
Endocrine system	
Goitre	2 (2.2%)
Hypothyroidism	13 (14.6%)
Total events	15 (16. 8%)
Eye disorders	
Myopia	2 (2.2%)
Total events	2 (2.2%)
Gastrointestinal system	
Vomiting	2 (2.2%)
Total events	2 (2.2%)
Infections and infestations	
Bronchitis	2 (2.2%)
Nasopharyngitis	4 (4.5%)
Total events	6 (6.7%)
Injury and procedural complications	3 (3.4%)
Haematoma	3 (3.4%)
Total events	
Abnormal hematologic and clinical chemistry findings	
Alanine aminotransferase increased	2 (2.2%)
Aspartate aminotransferase increased	2 (2.2%)
Blood alkaline phosphatase increased	11 (12.4%)
Blood bilirubin increased	2 (2.2%)
Blood thyroid stimulating hormone decreased	6 (6.7%)
Blood thyroid stimulating hormone increased	2 (2.2%)
Blood triglycerides increased	9 (10.1%)
Glycosylated haemoglobin increased	26 (29.2%)

Preferred Term	Omnitrope liquid N=89 N (%)
Insulin-like growth factor increased	2 (2.2%)
Red blood cell sedimentation rate increased	2 (2.2%)
Thrombocytopenia	2 (2.2%)
Thyroxine decreased	6 (6.7%)
Thyroxine free decreased	2 (2.2%)
Urine analysis abnormal	2 (2.2%)
White blood cells urine positive	2 (2.2%)
Total events	78 (87.1%)
Metabolic and nutritional	
Decreased appetite	2 (2.2%)
Hyperglycaemia	4 (4.5%)
Hypertriglyceridaemia	2 (2.2%)
Hypocholesterolaemia	4 (4.5%)
Total events	12 (13.4%)
Musculo-skeletal system	
Arthralgia	3 (3.4%)
Musculosceletal disorder	2 (2.2%)
Myalgia	2 (2.2%)
Scoliosis	7 (7.9%)
Total events	14 (15.7%)

*Drug-related = possible, probable or unclassified relationship to study drug.
**Drug-related adverse events occurring in individual patients only, are listed below.
N = number of patients.

Less Common drug-related Clinical Trial Adverse Drug Reactions in individual pediatric patients with GHD during the 84 months treatment period of the three consecutive studies EP2K-99-PhIII, EP2K-00-PhIIIFO, and EP2K-00-PhIIIAQ coded by MedDRA system organ class and preferred term

The following list provides the incidence of drug-related adverse events occurring in pediatric patients with GHD reported in individual patients during the 84 months treatment period of the three consecutive studies EP2K-99-PhIII, EP2K-00-PhIIIFO, and EP2K-00-PhIIIAQ coded by MedDRA system organ class and preferred term.

Investigations: blood calcium increased, blood cholesterol increased, blood pressure increased, cardiac murmur, eosinophil count increased, gamma-glutamyltransferase increased, insulin-like growth factor decreased, platelet count decreased, white blood cell count decreased.

Metabolism and nutrition disorders: body fat disorder, hyperphosphataemia, hyperuricaemia, hypoalbuminaemia, hypocholesterolaemia, hypoproteinaemia, metabolic acidosis.

General disorders and administration site condition: Injection site pain.

Nervous system disorders: epilepsy, sciatica, syncope.

Blood and lymphatic system disorders: monocytosis, neutrophilia.

Infections and infestations: pharyngitis, conjunctivitis, eye pain, eyelid oedema, visual disturbance.

Gastrointestinal disorders: abdominal pain, dyspepsia.

Psychiatric disorders: anxiety, attention deficit/hyperactive disorder, depression, tic.

Skin and subcutaneous tissue disorders: pruritius, rash, scar.
Ear and labyrinth disorders: hypoacusis.
Hepatobiliary disorders: hyperbilirubinaemia.
Injury, poisoning and procedural complications: contusion.
Renal and urinary disorders: polyuria.

Regarding the adverse drug reactions reported from somatropin products in adults, replacement therapy in growth hormone deficient adult patients is often accompanied by signs and symptoms of fluid retention, such as edema, arthralgia and paraesthesia. Musculo-skeletal pain and/or stiffness may also occur. These events usually have an early onset after initiation of treatment with a reduction in incidence and prevalence over time. In most cases the severity is mild or moderate. One patient developed diabetes mellitus during Genotropin® therapy, which was probably attributable to treatment. The following events were also reported infrequently: carpal tunnel syndrome; headache; back pain; myalgia; hypoesthesia.

Table 1d: Incidence of drug-related* adverse events (coded by MedDRA preferred term) occurring in pediatric patients with GHD (Studies EP2K-02-PhIII-Lyo and EP2K-00-PhIIIb-E)

	EP2K-02-PhIII-Lyo[1] N=51	**EP2K-00-PhIIIb-E[2] N=70**
Preferred Term	N (%)	N (%)
Application site		
Injection site erythema	1 (2.0%)	0 (0%)
Injection site haemorrhage	5 (9.8%)	0 (0%)
Injection site inflammation	1 (2.0%)	0 (0%)
Injection site oedema	1 (2.0%)	0 (0%)
Injection site pain	0 (0%)	1 (1.4%)
Injection site reaction	1 (2.0%)	0 (0%)
Total events	9 (17.8%)	1 (1.4%)
Body as a whole		
Fatigue	1 (2.0%)	0 (0%)
Headache	4 (7.8%)	1 (1.4%)
Migraine	0 (0%)	1 (1.4%)
Neck pain	1 (2.0%)	0 (0%)
Pain in extremity	1 (2.0%)	0 (0%)
Pyrexia	1 (2.0%)	0 (0%)
Total events	8 (15.8%)	2 (2.9%)
Blood and lymphatic system disorders		
Antibody test abnormal	0 (0%)	2 (2.9%)
Eosinophilia	6 (11.8%)	0 (0%)
Glycosylated haemoglobin increased	2 (3.9%)	0 (0%)
Total events	8 (15.7%)	2 (2.9%)
Cardiac disorders		

	EP2K-02-PhIII-Lyo[1] N=51	EP2K-00-PhIIIb-E[2] N=70
Preferred Term	N (%)	N (%)
Ventricular hypertrophy	1 (2.0%)	0 (0%)
Total events	1 (2.0%)	0 (0%)
Endocrine system		
Hypothyroidism	4 (7.8%)	0 (0%)
Total events	4 (7.8%)	0 (0%)
Eye disorders		
Fundoscopy abnormal	1 (2.0%)	0 (0%)
Myopia	2 (3.9%)	1 (1.4%)
Total events	3 (5.9%)	1 (1.4%)
Injury and procedural complications		
Contusion	1 (2.0%)	0 (0%)
Total events	1 (2.0%)	0 (0%)
Gastro-intestinal system		
Abdominal pain upper	1 (2.0%)	0 (0%)
Gastroenteritis	0 (0%)	1 (1.4%)
Vomitting	0 (0%)	1 (1.4%)
Total events	1 (2.0%)	2 (2.9%)
Infections and infestations		
Nasopharyngitis	1 (2.0%)	0 (0%)
Viral pharyngitis	0 (0%)	1 (1.4%)
Total events	1 (2.0%)	1 (1.4%)
Abnormal hematologic and clinical chemistry findings		
Blood alkaline phosphatase increased	1 (2.0%)	0 (0%)
Total events	1 (2.0%)	0 (0%)
Metabolic and nutritional		
Hyperglycaemia	0 (0%)	1 (1.4%)
Total events	0 (0%)	1 (1.4%)
Musculo-skeletal system		
Arthralgia	1 (2.0%)	0 (0%)
Scoliosis	4 (7.8%)	0 (0%)
Tendonitis	0 (0%)	1 (1.4%)
Total events	5 (9.8%)	1 (1.4%)
Skin and subcutaneous tissue disorders		
Dermatitis	0 (0%)	1 (1.4%)
Lipodystrophy acquired	1 (2.0%)	0 (0%)
Total events	1 (2.0%)	1 (1.4%)

N = number of patients;
[1] = covered treatment period: up to 48 months
[2] = covered treatment period: up to 60 months

Post market Adverse Drug Reactions
The post marketing data available for Omnitrope did not reveal any unexpected adverse drug reactions.

Adverse Drug Reaction Overview – Reference product[1]

Patients with growth hormone deficiency are characterized by extracellular volume deficit. When treatment with somatropin is started this deficit is rapidly corrected. In adult patients adverse effects related to fluid retention, such as peripheral edema, stiffness in the extremities, arthralgia, myalgia and paraesthesia are common. 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 patients, and possibly inversely related to the age of patients at the onset of growth hormone deficiency. In children such adverse effects are uncommon.

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 Omnitrope (somatropin for injection) therapy (see WARNINGS AND PRECAUTIONS, Endocrine and Metabolism).

Clinical Trial Adverse Drug Reactions - Reference product

> *Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

Children

Anti-hGH Antibodies
As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to somatropin with the incidence of antibodies to other products may be misleading. In the case of growth hormone, antibodies with binding capacities lower than 2 mg/mL have not been associated with growth attenuation. In a very small number of patients

[1] Description of Data Sources: The data described herein reflect the exposure to the reference product Genotropin® (for the indication SGA, TS, ISS and GHD in adults). A detailed discussion of the Adverse Drug Reactions for the reference product can be found in this section.

treated with somatropin, when binding capacity was greater than 2 mg/mL, interference with the growth response was observed.

In 419 pediatric patients evaluated in clinical studies with the reference product lyophilized powder, 244 had been treated previously with somatropin or other growth hormone preparations and 175 had received no previous growth hormone therapy. Antibodies to growth hormone (anti-hGH antibodies) were present in six previously treated patients at baseline. Three of the six became negative for antihGH antibodies during 6 to 12 months of treatment with somatropin. Of the remaining 413 patients, eight (1.9%) developed detectable anti-hGH antibodies during treatment with somatropin; none had an antibody binding capacity > 2 mg/L. There was no evidence that the growth response to somatropin was affected in these antibody-positive patients.

Clinical Trials in children with GHD

In clinical studies with the reference product in children, the following events were reported infrequently: injection site reactions, e.g. pain or burning associated with the injection, fibrosis, nodules, rash, inflammation, pigmentation; bleeding; lipoatrophy; headache; hematuria; hypothyroidism; mild hyperglycemia.

Clinical Trials in children with SGA

In clinical studies of 273 pediatric patients born small for gestational age treated with the reference product, the following clinically significant events were reported: mild transient hyperglycemia, one patient with benign intracranial hypertension, two patients with central precocious puberty, two patients with jaw prominence, and several patients with aggravation of preexisting scoliosis, injection site reactions, and self-limited progression of pigmented nevi. IGF-1 levels ranged from <20 ng/mL to 593 ng/mL.

Anti-GH antibodies were assessed at baseline, 12 and 24 months in somatropin -treated SGA children enrolled in a study with another somatropin. At 12 months, the study included 27 untreated SGA children, 59 SGA children treated with somatropin at a dose of 33 mcg/kg body weight/day and 51 short SGA children treated with somatropin at a dose of 67mcg/kg body weight/day. At 24 months, the study included 10 untreated SGA children, 62 short SGA children treated with somatropin at a dose of 33 mcg/kg body weight/day (including 9 children who received no treatment during the first 12 months of the study) and 56 SGA children treated with somatropin at a dose of 67 mcg/kg body weight/day (including 8 children who received no treatment during the first 12 months of the study). None of these patients were determined to be positive for anti-GH antibodies at baseline or at any time during the course of the 24 months of the study.

Table 2: Adverse events reported in ≥ 1% of children (baseline to month 12) - all causality

Body system / Preferred Term	Untreated N=76	0.033 mg/kg/day N=105	0.067 mg/kg/day N=117	0.1 mg/kg/day N=19
	n (%)	n (%)	n (%)	n (%)
Skin & Appendage				
Naevus	0	0	1(0.9)	2 (10.5)
Nail disorder	0	1(1.0)	0	0
Rash erythematous	0	1(1.0)	0	0
Skin disorder	0	1(1.0)	0	0
Urticaria acute	0	1(1.0)	0	0
Musculoskeletal				
Fracture	0	1(1.0)	1(0.9)	0
Skeletal malformation	0	0	0	1(5.3)
Tooth malformation	0	1(1.0)	0	0
Central & Peripheral Nervous System				
Convulsions	0	1(1.0)	0	0
Dysphonia	0	1(1.0)	0	0
Headache	0	1(1.0)	0	0
Vision				
Strabismus	1(1.3)	0	1(0.9)	0
Hearing & Vestibular system				
Ear disorder nos	0	1(1.0)	1(0.9)	0
Psychiatric				
Nervousness	0	1(1.0)	0	0
Personality disorder	1(1.3)	0	0	1(5.3)
Gastrointestinal				
Abdominal pain	0	0	1(0.9)	0
Anorexia	1(1.3)	2(1.9)	0	0
Anus disorder	1(1.3)	0	0	0
Enteritis	1(1.3)	0	0	0
Gastroenteritis	0	2(1.9)	2(1.7)	0
Hernia nos	1(1.3)	0	1(0.9)	0
Surgical intervention	0	1(1.0)	2(1.7)	0
Vomiting	2(2.6)	0	1(0.9)	0
Metabolism and Nutritional				
Hyperglycaemia	0	1(1.0)	0	0
Extra Cardiac				
Vein distended	0	1(1.0)	0	0
Respiratory Total				
Surgical intervention	1(1.3)	2(1.9)	4(3.4)	1(5.3)
Apnea	0	1(1.0)	0	0
Asthma	2(2.6)	0	3(2.6)	0
Bronchitis	0	5(4.8)	4(3.4)	0
Coughing	2(2.6)	0	4(3.4)	1(5.3)
Epistaxis	1(1.3)	0	0	0
Laryngitis	0	0	1(0.9)	1(5.3)
Pneumonia	0	2(1.9)	2(1.7)	1(5.3)
Rhinitis	1(1.3)	2(1.9)	6(5.1)	1(5.3)
Upper respiratory tract infection	1(1.3)	7(6.7)	7(6.0)	2(10.5)
Red Blood Cell				
Anemia	1(1.3)	0	0	0
White Cell				

Body system / Preferred Term	Untreated N=76	0.033 mg/kg/day N=105	0.067 mg/kg/day N=117	0.1 mg/kg/day N=19
	n (%)	n (%)	n (%)	n (%)
Lymphadenopathy	1(1.3)	0	0	0
Platelet/Bleed				
Purpura thrombocytopenic	0	1(1.0)	0	0
Thrombocytopenia	0	1(1.0)	0	0
Reproductive-Male				
Testis disorder	1(1.3)	1(1.0)	0	0
General Total				
Surgical intervention	0	1(1.0)	2(1.7)	0
Accident	0	0	0	1(5.3)
Allergic reaction	0	1(1.0)	0	0
Allergy	2(2.6)	0	1(0.9)	0
Fever	2(2.6)	0	1(0.9)	1(5.3)
Influenza-like symptoms	0	0	2(1.7)	0
Application Site				
Injection site reaction	0	1(1.0)	0	0
Tympanic membrane perforation	0	1(1.0)	0	0
Resistance Mechanism				
Herpes zoster	0	1(1.0)	1(0.9)	0
Infection	0	3(2.9)	3(2.6)	0
Infection bacterial	1(1.3)	3(2.9)	0	0
Infection fungal	0	1(1.0)	0	0
Infection viral	6(7.9)	7(6.7)	8(6.8)	0
Otitis media	1(1.3)	8(7.6)	8(6.8)	0
Pharyngitis	6(7.9)	5(4.8)	5(4.3)	0

Less Common Clinical Trial Adverse Drug Reactions (Baseline to Month 12)
Clinical trial adverse drug reactions with a frequency of less than 1% are presented in the following listing:
Skin & Appendage disorders: eczema
Musculoskeletal disorders: bone development abnormal, spine malformation
Central and Peripheral nervous system disorders: ataxia
Psychiatric disorders: aggressive reaction, concentration impaired
Gastrointestinal disorders: abdominal pain, malabsorption
Endocrine disorders: gynaecomastia, puberty precocious
Respiratory disorders: sinusitis
Urinary disorders: dysuria
General disorders: hepatomegaly

Table 3: Adverse events reported in ≥ 1% of children (12 to 24 month) - all causality

Body system / Preferred Term	Untreated N=53	0.033 mg/kg/day N=106	0.067 mg/kg/day N=118	0.1 mg/kg/day N=19
	n (%)	n (%)	n (%)	n (%)
Skin & Appendage				
Eczema	0	1(0.9)	2(1.7)	0
Skin discolouration	0	0	2(1.7)	0
Musculoskeletal				
Osteomyelitis	0	0	0	1(5.3)
Central & Peripheral Nervous System				
Convulsions	0	0	0	1(5.3)
Vision				
Myopia	0	0	1(0.8)	2(10.5)
Strabismus	0	0	0	1(5.3)
Vision abnormal	1(1.9)	0	0	0
Psychiatric				
Agitation	0	0	2(1.7)	0
Gastrointestinal				
Gastroenteritis	2(3.8)	1(0.9)	2(1.7)	0
Surgical intervention	1(1.9)	2(1.9)	4(3.4)	0
Respiratory				
Surgical intervention	0	4(3.8)	3(2.5)	1(5.3)
Asthma	0	2(1.9)	2(1.7)	0
Bronchitis	0	3(2.8)	3(2.5)	1(5.3)
Coughing	1(1.9)	4(3.8)	2(1.7)	0
Pneumonia	1(1.9)	1(0.9)	1(0.8)	1(5.3)
Rhinitis	1(1.9)	4(3.8)	4(3.4)	1(5.3)
Sinusitis	0	0	0	1(5.3)
Upper respiratory tract infection	2(3.8)	5(4.7)	2(1.7)	0
Urinary				
Urinary incontinence	1(1.9)	0	0	0
General				
Surgical intervention	2(3.8)	3(2.8)	5(4.2)	1(5.3)
Allergic reaction	1(1.9)	1(0.9)	0	0
Allergy	1(1.9)	1(0.9)	3(2.5)	0
Fever	0	1(0.9)	2(1.7)	0
Influenza-like symptoms	0	2(1.9)	4(3.4)	1(5.3)
Edema pharynx	1(1.9)	0	0	0
Pain	2(3.8)	0	1(0.8)	0
Resistance Mechanism				
Balanoposthitis	0	0	0	1(5.3)
Herpes simplex	0	1(0.9)	0	1(5.3)
Infection	0	1(0.9)	2(1.7)	0
Infection bacterial	2(3.8)	3(2.8)	0	0
Infection viral	3(5.7)	13(12.3)	5(4.2)	0
Otitis media	1(1.9)	7(6.6)	5(4.2)	4(21.1)
Pharyngitis	2(3.8)	8(7.5)	8(6.8)	0

Less Common Clinical Trial Adverse Drug Reactions (12 to 24 Month)

Clinical trial adverse drug reactions with a frequency of less than 1% are presented in the following listing:

Skin & Appendage disorders: acne, nail disorder, pruritus, skin dry, sweating increased, urticaria
Musculoskeletal disorders: arthralgia, fracture, spine malformation
Central and Peripheral nervous system disorders: absences, headaches
Vision: conjunctivitis
Hearing and Vestibular system disorders: earache
Gastrointestinal disorders: abdominal pain, anorexia, enteritis
Metabolism and nutritional system disorders: hypoglycemia
Endocrine disorders: puberty precocious
Extra cardiac: vein distended
Respiratory disorders: thyroid adenoma
Red blood cell: anemia
White blood cell: lymphadenopathy
Platelet/bleed disorder: purpura, thrombocytopenia
Urinary disorders: cystitis, urinary tract infection, urogenital malformation
Neoplasm disorder: neoplasm nos
General disorders: accident

Table 4: Most frequent adverse events (reported in ≥ 1% of children treated with somatropin continuously up to month 72) – 0-72 population

Body system / Preferred Term	0.033 mg/kg/day N=37	0.067 mg/kg/day N=25	Total N=62
	n (%)	n (%)	n (%)
Skin & Appendage			
Angioedema	1(2.7)	0	1(1.6)
Eczema	1(2.7)	0	1(1.6)
Fistula incomplete	0	1(4.0)	1(1.6)
Nail disorder	1(2.7)	0	1(1.6)
Pruritus	0	1(4.0)	1(1.6)
Rash erythematous	1(2.7)	0	1(1.6)
Skin disorder	3(8.1)	0	3(4.8)
Skin exfoliation	0	1(4.0)	1(1.6)
Sweating increased	1(2.7)	0	1(1.6)
Urticaria	1(2.7)	1(4.0)	2(3.2)
Verruca	0	1(4.0)	1(1.6)
Musculo-Skeletal			
Arthrosis	1(2.7)	0	1(1.6)
Fracture	3(8.1)	1(4.0)	4(6.5)
Joint malformation	1(2.7)	0	1(1.6)
Spine malformation	1(2.7)	0	1(1.6)
Tooth malformation	1(2.7)	0	1(1.6)
Central & Peripheral Nervous System			
Absences	1(2.7)	0	1(1.6)
Headache	2(5.4)	0	2(3.2)
Hyperkinesia	0	2(8.0)	2(3.2)
Muscle contractions involuntary	0	1(4.0)	1(1.6)
Neuritis	1(2.7)	0	1(1.6)
Paralysis	0	1(4.0)	1(1.6)
Vision			
Conjunctivitis	1(2.7)	1(4.0)	2(3.2)

Body system / Preferred Term	0.033 mg/kg/day N=37	0.067 mg/kg/day N=25	Total N=62
	n (%)	n (%)	n (%)
Hearing & Vestibular System			
Ear disorder nos	1(2.7)	1(4.0)	2(3.2)
Earache	1(2.7)	0	1(1.6)
Psychiatric			
Concentration impaired	1(2.7)	0	1(1.6)
Thinking abnormal	0	1(4.0)	1(1.6)
Gastro-Intestinal			
Abdominal pain	3(8.1)	1(4.0)	4(6.5)
Anorexia	1(2.7)	0	1(1.6)
Diarrhoea	1(2.7)	0	1(1.6)
Enteritis	1(2.7)	0	1(1.6)
Gastroenteritis	4(10.8)	6(24.0)	10(16.1)
Hernia nos	1(2.7)	0	1(1.6)
Intestinal obstruction	1(2.7)	0	1(1.6)
Stomatitis aphthous	1(2.7)	0	1(1.6)
Surgical intervention	1(2.7)	2(8.0)	3(4.8)
Tooth disorder	1(2.7)	0	1(1.6)
Vomiting	1(2.7)	0	1(1.6)
Metabolic & Nutritional			
Hypoglycaemia	0	1(4.0)	1(1.6)
Endocrine			
Osteomalacia	0	1(4.0)	1(1.6)
Puberty precocious	1(2.7)	1(4.0)	2(3.2)
Respiratory			
Surgical intervention	7(18.9)	4(16.0)	11(17.7)
Asthma	1(2.7)	1(4.0)	2(3.2)
Bronchitis	4(10.8)	5(20.0)	9(14.5)
Coughing	5(13.5)	2(8.0)	7(11.3)
Laryngitis	1(2.7)	1(4.0)	2(3.2)
Pneumonia	2(5.4)	1(4.0)	3(4.8)
Rhinitis	13(35.1)	6(24.0)	19(30.6)
Sinusitis	2(5.4)	0	2(3.2)
Upper respiratory tract infection	9(24.3)	9(36.0)	18(29.0)
Red blood cell			
Anaemia	0	1(4.0)	1(1.6)
White cell			
Lymphadenopathy	1(2.7)	1(4.0)	2(3.2)
Platelet/Bleed			
Haematoma	1(2.7)	0	1(1.6)
Urinary			
Cystitis	1(2.7)	0	1(1.6)
Urinary incontinence	1(2.7)	1(4.0)	2(3.2)
Urinary tract infection	0	1(4.0)	1(1.6)
Urogenital malformation	1(2.7)	0	1(1.6)
Reproductive-Male			
Penis disorder	0	1(4.0)	1(1.6)
Testis disorder	1(2.7)	0	1(1.6)
Neoplasms			
Neoplasm nos	1(2.7)	0	1(1.6)
General			
Surgical intervention	0	3(12.0)	3(4.8)

Body system / Preferred Term	0.033 mg/kg/day N=37	0.067 mg/kg/day N=25	Total N=62
	n (%)	n (%)	n (%)
Allergic reaction	3(8.1)	0	3(4.8)
Allergy	2(5.4)	0	2(3.2)
Deviating laboratory value	0	1(4.0)	1(1.6)
Fatigue	1(2.7)	0	1(1.6)
Fever	1(2.7)	2(8.0)	3(4.8)
Hepatomegaly	0	1(4.0)	1(1.6)
Hypothermia	1(2.7)	0	1(1.6)
Inflammatory reaction nos	0	1(4.0)	1(1.6)
Influenza-like symptoms	2(5.4)	2(8.0)	4(6.5)
Pain	1(2.7)	0	1(1.6)
Application Site			
Injection site atrophy	0	1(4.0)	1(1.6)
Injection site fibrosis	0	1(4.0)	1(1.6)
Injection site reaction	0	1(4.0)	1(1.6)
Otitis externa	0	1(4.0)	1(1.6)
Resistance Mechanism			
Abscess	0	1(4.0)	1(1.6)
Herpes ocular	0	1(4.0)	1(1.6)
Herpes simplex	2(5.4)	1(4.0)	3(4.8)
Infection	5(13.5)	6(24.0)	11(17.7)
Infection bacterial	6(16.2)	0	6(9.7)
Infection fungal	1(2.7)	0	1(1.6)
Infection viral	14(37.8)	3(12.0)	17(27.4)
Otitis media	9(24.3)	8(32.0)	17(27.4)
Pharyngitis	12(32.4)	7(28.0)	19(30.6)
Sepsis	0	1(4.0)	1(1.6)
Events			
Bite	2(5.4)	0	2(3.2)
Molluscum contagiosa	0	1(4.0)	1(1.6)

Adverse Events Leading to Termination of Treatment

Clinical trial adverse drug reactions with the reference product that lead to treatment termination are listed below by dose group:

0.033 mg/kg/day: Thrombocytopenic purpura

0.067 mg/kg/day: Aggressive reaction, Ataxia, Retinal dystrophy (2 patients)

Discontinuous therapy: Diabetes mellitus, Surgical intervention, Muscle malformation.

Respiratory Adverse Events in children with SGA

In the open- label SGA studies with the reference product, the percentage of respiratory adverse events for the 3 active treatment groups (16.2% in 0.033 mg/kg/day, 20.5% in 0.067 mg/kg/day and 26.3% in 0.1 mg/kg/day) were higher than in the untreated group (10.5%) between 0 - 12 months. Between 12 - 24 months, the incidence of respiratory events was also higher in the 3 active treatment groups (18.9% in 0.033 mg/kg/day; 13.6% in 0.067 mg/kg/day; 21.1% in 0.1 mg/kg/day) compared to 7.5% in the untreated control group. Respiratory adverse events included mostly upper respiratory tract infections. Adverse events classified as 'resistance mechanism' which included viral infection, otitis media, and pharyngitis occurred at a higher rate in 2 of the active treatment groups (21.9% in 0.033 mg/kg/day; 19.7% in 0.067 mg/kg/day; 0% in 0.1 mg/kg/day) compared to the untreated control group (15.8%) between 0 - 12 months.

Between 12 - 24 months, the incidence of resistance mechanism adverse events was higher in all 3 active treatment groups (25.5% in 0.033 mg/kg/day; 16.1% in 0.067 mg/kg/day; 31.6% in 0.1 mg/kg/day) compared to 13.2% in the untreated control group. However, none of the differences among the four study groups were evaluated for statistical significance.

The adverse events most frequently reported for the study periods were: viral infections, otitis media, pharyngitis, upper respiratory tract infections, and rhinitis. Overall, these events were consistent with the pattern of normal childhood illnesses in this age group. No evidence of a dose-related pattern was apparent. There were a higher number of patients in 2 of the somatropin-treated groups (0.033 mg/kg/day, n=105; 0.067 mg/kg/day, n=117) than in the untreated group (n=76); however the highest dose group (0.1 mg/kg/day) had only 19 patients. While, the investigators did not consider these events to be treatment-related, this cannot be ruled out.

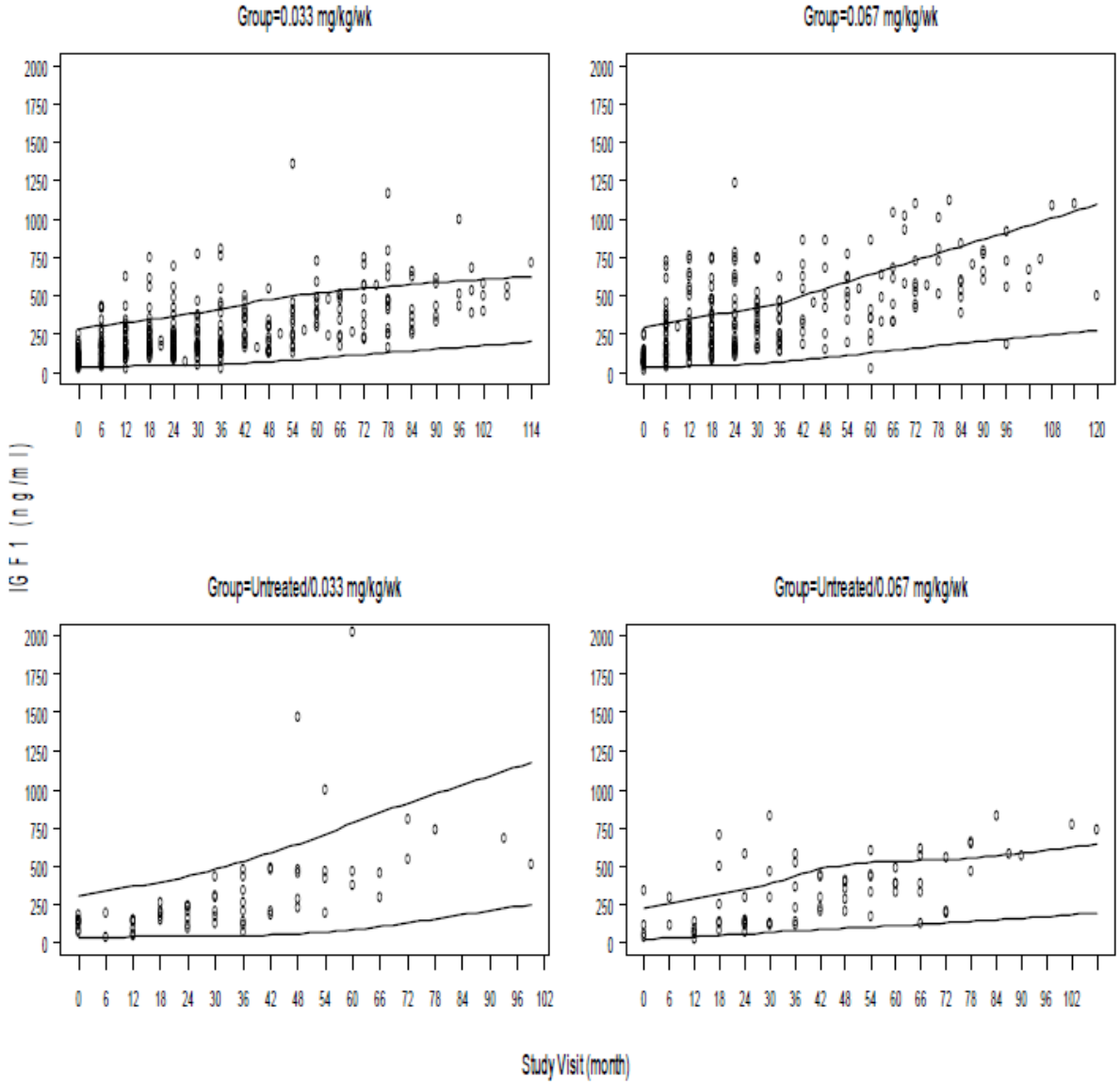
IGF-1 levels

Table 5 summarizes the frequencies of subjects with IGF-1 levels below/above or within normal range, organized for all treatment groups side-by-side and across all visits from a study with another somatropin. Subject groups Untreated/0.033 mg/kg/wk and Untreated/0.067 mg/kg/wk include subjects who served as untreated controls for 12 months or longer, and were subsequently treated with somatropin 0.033 mg/kg/wk or 0.067 mg/kg/wk, respectively. In Figure 1, the solid reference lines were created by averaging individual upper and lower limits of normal ranges across all subjects with observed IGF-1 levels at a given time-point. As such, the reference lines are for overall inference, as they represent an approximation of the exact normative values. As can be seen in the various graphs, IGF-1 levels generally ranged from <20 ng/mL to 593 ng/mL.

Table 5: Frequency of subjects with IGF-1 levels below/above or within normal range for all treatment groups and across all visits

Month	Treatment group																							
	0.033 mg/kg/wk						0.067 mg/kg/wk						Untreated/0.033 mg/kg/wk						Untreated/0.067 mg/kg/wk					
	IGF-I status						IGF-I status						IGF-I status						IGF-I status					
	Below		Normal		Above		Below		Normal		Above		Below		Normal		Above		Below		Normal		Above	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
0	1	2.5	38	95.0	1	2.5	1	3.2	30	96.8	-	-	-	-	7	87.5	1	12.5	-	-	4	100.0	-	-
6	-	-	24	85.7	4	14.3	3	11.1	20	74.1	4	14.8	-	-	2	100.0	-	-	-	-	2	100.0	-	-
12	2	5.4	31	83.8	4	10.8	2	5.7	22	62.9	11	31.4	2	33.3	4	66.7	-	-	2	40.0	3	60.0	-	-
18	1	3.4	23	79.3	5	17.2	3	10.7	17	60.7	8	28.6	-	-	4	80.0	1	20.0	-	-	5	83.3	1	16.7
24	4	10.8	27	73.0	6	16.2	3	11.1	14	51.9	10	37.0	1	14.3	6	85.7	-	-	-	-	6	85.7	1	14.3
30	1	4.3	18	78.3	4	17.4	-	-	12	70.6	5	29.4	-	-	6	100.0	-	-	-	-	5	83.3	1	16.7
36	3	11.5	17	65.4	6	23.1	-	-	10	66.7	5	33.3	1	12.5	6	75.0	1	12.5	-	-	6	100.0	-	-
42	-	-	8	53.3	7	46.7	-	-	3	37.5	5	62.5	-	-	4	100.0	-	-	-	-	3	60.0	2	40.0
48	1	7.1	11	78.6	2	14.3	-	-	4	66.7	2	33.3	-	-	3	60.0	2	40.0	-	-	4	80.0	1	20.0
54	1	8.3	8	66.7	3	25.0	-	-	5	62.5	3	37.5	-	-	2	40.0	3	60.0	-	-	4	80.0	1	20.0
60	-	-	6	60.0	4	40.0	1	14.3	5	71.4	1	14.3	-	-	2	66.7	1	33.3	-	-	2	50.0	2	50.0
66	-	-	6	75.0	2	25.0	-	-	5	83.3	1	16.7	-	-	2	66.7	1	33.3	-	-	3	60.0	2	40.0
72	-	-	6	66.7	3	33.3	-	-	5	62.5	3	37.5	-	-	2	100.0	-	-	-	-	2	66.7	1	33.3

FIGURE 1: IGF-I VALUES BY STUDY MONTH



Clinical Trials in children with Turner Syndrome

In two clinical studies with the reference product in pediatric patients with Turner syndrome, the most frequently reported adverse events were respiratory illnesses (influenza, tonsillitis, otitis, sinusitis), joint pain, and urinary tract infection. The only treatment-related adverse event that occurred in more than 1 patient was joint pain. In one study in children with TS, none of the 42 patients discontinued from the study early while in the second study, none of the patients discontinued before 18 months.

Table 6: Summary of adverse events (AE) that occurred in at least 1 patient - all causality

WHO Dictionary Term	Somatropin N= 22	Somatropin plus ethinyloestradiol N=20
Joint Pain	4 (18.2%)	3 (15.0%)
Epilepsy	1 (4.5%)	1 (5.0%)
Sinusitis	1 (4.5%)	1(5.0%)
Cellulitis	1 (4.5%)	0
Urinary Tract Infection	0	1 (5.0%)
Dysfunctional voiding	0	1 (5.0%)
Menarche	1 (4.5%)	0
Varicella	1 (4.5%)	0
Measles	1 (4.5%)	0
Herpes Zoster	1 (4.5%)	0
Total AEs	9(41.0%)	6 (30.0%)

Table 7: Summary of adverse events that occurred in at least 1 patient – all causality

WHO dictionary term	Somatropin N=17	Somatropin + oxandrolone N=17
Skin and appendage disorders		
Furonculosis	1 (5.9%)	0
Loss of hair	1 (5.9%)	0
Eczema	0	1 (5.9%)
Musculo-skeletal system disorders		
Joint Pain	1 (5.9%)	1 (5.9%)
Radius farcture	0	1 (5.9%)
Hearing and vestibular disorders		
Tympanic membrane	1 (5.9%)	0
Psychiatric disorders		
Nervousness	1 (5.9%)	0
Increased Appetite	0	2 (11.8 %)
Liver and biliary system		
Hepatitis A	1 (5.9%)	0
Hepatic injury	0	1 (5.9%)
Metabolic and nutritional disorders		
Insulin value increased	0	1 (5.9%)
Endocrine disorders		
Hypothyroidism	1 (5.9%)	0
Thyroiditis	1 (5.9%)	0
Vascular (extra cardiac) disorders		
Flushing	1 (5.9%)	0
Respiratory Infections		
Otitis	3 (17.6%)	1 (5.9%)
Tonsillitis	2 (11.8%)	3 (17.6%)
Rhinitis	1	0
Sinusitis	2 (11.8%)	1 (5.9%)
Influenza	1 (5.9%)	4 (23.5%)
Pneumonia	0	1 (5.9%)
Bronchitis	0	2 (11.8 %)

WHO dictionary term	Somatropin N=17	Somatropin + oxandrolone N=17
White cell and res disorders		
Neutropenia, chronic	1 (5.9%)	0
Platelet, bleeding and clotting disorders		
Epistaxis	2 (11.8%)	0
Hematoma	0	1 (5.9%)
Urinary system disorders		
Urinary Tract Infection	3 (17.6%)	0
Hematuria	1 (5.9%)	0
Enuresis	0	1 (5.9%)
Reproductive disorders		
Metrorrhagia	0	1 (5.9%)
Leukorrhea	0	1 (5.9%)
Spotting	0	1 (5.9%)
Hemorrhage	0	1 (5.9%)
Vaginitis	0	1 (5.9%)
Body as a whole – General disorders		
Car accident	0	1 (5.9 %)
Fatigue	0	1 (5.9%)
Voice alteration	0	1 (5.9%)

Clinical Trials in children with Turner's syndrome

In one study with the reference product with patients with TS, respiratory infections (otitis, tonsillitis, sinusitis, influenza, bronchitis) represented the majority of adverse events in children with TS with eight patients in the somatropin group and 11 patients in the somatropin and oxandrolone groups. The instances of the respiratory infections were assessed as unrelated to study drug. No patient discontinued treatment due to a treatment related adverse event. Younger patients, including patients with TS, treated or untreated, are known to have generally greater incidence of otitis media and ear problems.

In a second study with the reference product, one patient experienced sinusitis, orbital cellulitis and grand mal seizure. These events were considered to be unlikely related to the study drug as per the investigator and they were also low in frequency.

Clinical Trials in children with Idiopathic Short Stature

In two open-label clinical studies with the reference product in pediatric patients with ISS, the most commonly encountered adverse events include upper respiratory tract infections, influenza, tonsillitis, nasopharyngitis, gastroenteritis, headaches, increased appetite, pyrexia, fracture, altered mood, and arthralgia. In one of the two studies, during somatropin treatment, the mean IGF-1 standard deviation (SD) scores were maintained in the normal range. IGF-1 SD scores above +2 SD were observed as follows: 1 subject (3%), 10 subjects (30%) and 16 subjects (38%) in the untreated control, 0. 23 and the 0.47 mg/kg/week groups, respectively, had at least one measurement; while 0 subjects (0%), 2 subjects (7%) and 6 subjects (14%) had two or more consecutive IGF-1 measurements above +2 SD.

Table 8: Incidence of treatment-emergent adverse events that occurred in at least 1 patient

Body system / Preferred Term	Prepuberta			Pubertal		Somatropin 0.033 and 0.067 mg/kg/day N = 112	Untreated Controls[b] N = 61
	0.033 mg/kg/day N = 47	0.067 mg/kg/day N = 49	Untreated Controls N = 46	0.067 mg/kg/day N = 16	Untreated Controls N = 15		
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Blood and lymphatic system disorders							
Anaemia	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Eosinophilia	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Iron deficiency anaemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.7)	0 (0.0)	1 (1.6)
Lymphadenopathy	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Mononucleosis syndrome	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Congenital, familial and genetic disorders							
Epidermal naevus	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Pigmented naevus	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Skeleton dysplasia	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Ear and labyrinth disorders							
Motion sickness	0 (0.0)	0 (0.0)	1 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)
Vertigo	0 (0.0)	0 (0.0)	1 (2.2)	1 (6.3)	0 (0.0)	1 (0.9)	1 (1.6)
Endocrine disorders							
Delayed puberty	0 (0.0)	0 (0.0)	4 (8.7)	0 (0.0)	0 (0.0)	0 (0.0)	4 (6.6)
Goitre	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Pituitary cyst	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Precocious puberty	0 (0.0)	0 (0.0)	1 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)
Thyroid disorder	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Eye disorders							
Astigmatism	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Conjunctivitis	1 (2.1)	1 (2.0)	1 (2.2)	1 (6.3)	0 (0.0)	3 (2.7)	1 (1.6)
Conjunctivitis allergic	1 (2.1)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.8)	0 (0.0)
Eye inflammation	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	1 (0.9)	0 (0.0)
Eye redness	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	1 (0.9)	0 (0.0)
Visual disturbance	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Gastrointestinal disorders							
Abdominal pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.7)	0 (0.0)	1 (1.6)
Abdominal pain upper	1 (2.1)	4 (8.2)	0 (0.0)	0 (0.0)	0 (0.0)	5 (4.5)	0 (0.0)
Constipation	2 (4.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.8)	0 (0.0)
Nausea	0 (0.0)	2 (4.1)	1 (2.2)	0 (0.0)	0 (0.0)	2 (1.8)	1 (1.6)
Tooth disorder	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Vomiting	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
General disorders and administration site conditions							
Chest discomfort	1 (2.1)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.8)	0 (0.0)
Chest pain	1 (2.1)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.8)	0 (0.0)
Disease recurrence	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Fatigue	1 (2.1)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.8)	0 (0.0)
Hunger	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	1 (0.9)	0 (0.0)
Edema peripheral	1 (2.1)	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	2 (1.8)	0 (0.0)
Pain	0 (0.0)	0 (0.0)	1 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)
Pyrexia	8 (17.0)	4 (8.2)	2 (4.3)	1 (6.3)	0 (0.0)	13 (11.6)	2 (3.3)
Thirst	0 (0.0)	2 (4.1)	0 (0.0)	1 (6.3)	0 (0.0)	3 (2.7)	0 (0.0)
Immune system disorders							
Hypersensitivity	1 (2.1)	3 (6.1)	2 (4.3)	0 (0.0)	0 (0.0)	4 (3.6)	2 (3.3)
Seasonal allergy	1 (2.1)	3 (6.1)	1 (2.2)	1 (6.3)	1 (6.7)	5 (4.5)	2 (3.3)
Infections and infestations							
Appendicitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.7)	0 (0.0)	1 (1.6)
Borrelia infection	0 (0.0)	1 (2.0)	1 (2.2)	0 (0.0)	0 (0.0)	1 (0.9)	1 (1.6)
Ear infection	1 (2.1)	3 (6.1)	0 (0.0)	0 (0.0)	0 (0.0)	4 (3.6)	0 (0.0)
Eye infection	1 (2.1)	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	2 (1.8)	0 (0.0)
Gastroenteritis	7 (14.9)	4 (8.2)	0 (0.0)	1 (6.3)	1 (6.7)	12 (10.7)	1 (1.6)
Impetigo	1 (2.1)	2 (4.1)	0 (0.0)	0 (0.0)	0 (0.0)	3 (2.7)	0 (0.0)
Infectious mononucleosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.7)	0 (0.0)	1 (1.6)
Influenza	8 (17.0)	7 (14.3)	2 (4.3)	3 (18.8)	1 (6.7)	18 (16.1)	3 (4.9)

Body system / Preferred Term	Prepuberta			Pubertal		Somatropin 0.033 and 0.067 mg/kg/day N = 112	Untreated Controls[b] N = 61
	0.033 mg/kg/day N = 47	0.067 mg/kg/day N = 49	Untreated Controls N = 46	0.067 mg/kg/day N = 16	Untreated Controls N = 15		
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Mycoplasma infection	2 (4.3)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (2.7)	0 (0.0)
Nasopharyngitis	7 (14.9)	5 (10.2)	1 (2.2)	0 (0.0)	0 (0.0)	12 (10.7)	1 (1.6)
Orchitis	0 (0.0)	0 (0.0)	1 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)
Otitis media acute	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Parotitis	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Pertussis	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Pharyngitis	3 (6.4)	0 (0.0)	1 (2.2)	1 (6.3)	0 (0.0)	4 (3.6)	1 (1.6)
Pneumonia	1 (2.1)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.8)	0 (0.0)
Pyelonephritis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.7)	0 (0.0)	1 (1.6)
Respiratory tract infection	0 (0.0)	2 (4.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.8)	0 (0.0)
Rhinitis	1 (2.1)	2 (4.1)	0 (0.0)	0 (0.0)	0 (0.0)	3 (2.7)	0 (0.0)
Scarlet fever	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Sinusitis	0 (0.0)	1 (2.0)	1 (2.2)	0 (0.0)	0 (0.0)	1 (0.9)	1 (1.6)
Streptococcal infection	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Tonsillitis	7 (14.9)	5 (10.2)	2 (4.3)	1 (6.3)	1 (6.7)	13 (11.6)	3 (4.9)
Upper respiratory tract infection	14 (29.8)	20 (40.8)	5 (10.9)	2 (12.5)	2 (13.3)	36 (32.1)	7 (11.5)
Urinary tract infection	0 (0.0)	0 (0.0)	1 (2.2)	1 (6.3)	0 (0.0)	1 (0.9)	1 (1.6)
Varicella	1 (2.1)	0 (0.0)	2 (4.3)	1 (6.3)	0 (0.0)	2 (1.8)	2 (3.3)
Viral infection	0 (0.0)	0 (0.0)	0 (0.0)	2 (12.5)	0 (0.0)	2 (1.8)	0 (0.0)
Injury, poisoning and procedural complications							
Ankle fracture	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Clavicle fracture	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Concussion	2 (4.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.8)	0 (0.0)
Contusion	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Eye injury	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Fall	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Femur fracture	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Hand fracture	1 (2.1)	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	2 (1.8)	0 (0.0)
Head injury	0 (0.0)	0 (0.0)	1 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)
Joint dislocation	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.7)	1 (0.9)	1 (1.6)
Joint injury	2 (4.3)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (2.7)	0 (0.0)
Limb injury	1 (2.1)	1 (2.0)	1 (2.2)	0 (0.0)	1 (6.7)	2 (1.8)	2 (3.3)
Lower limb fracture	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Mouth injury	0 (0.0)	0 (0.0)	1 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)
Overdose	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Radius fracture	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Road traffic accident	1 (2.1)	1 (2.0)	1 (2.2)	0 (0.0)	1 (6.7)	2 (1.8)	2 (3.3)
Skull fracture	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.7)	0 (0.0)	1 (1.6)
Tibia fracture	1 (2.1)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.8)	0 (0.0)
Wound	2 (4.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.8)	0 (0.0)
Investigations							
Blood immunoglobulin G decreased	0 (0.0)	0 (0.0)	1 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)
Blood testosterone decreased	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Blood thyroid stimulating hormone decreased	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	1 (6.7)	1 (0.9)	1 (1.6)
Cardiac murmur	0 (0.0)	0 (0.0)	1 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)
Haemoglobin decreased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.7)	0 (0.0)	1 (1.6)
Heart rate irregular	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.7)	0 (0.0)	1 (1.6)
Heart sounds abnormal	0 (0.0)	0 (0.0)	1 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)
Thyroxine decreased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.7)	0 (0.0)	1 (1.6)
Thyroxine free decreased	0 (0.0)	2 (4.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.8)	0 (0.0)
Metabolism and nutrition disorders							
Appetite disorder	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Decreased appetite	2 (4.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.8)	0 (0.0)
Increased appetite	6 (12.8)	5 (10.2)	0 (0.0)	3 (18.8)	0 (0.0)	14 (12.5)	0 (0.0)
Lactose intolerance	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	1 (0.9)	0 (0.0)
Markedly reduced dietary intake	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Musculoskeletal and connective tissue disorders							

Body system / Preferred Term	Prepuberta			Pubertal		Somatropin 0.033 and 0.067 mg/kg/day N = 112	Untreated Controls[b] N = 61
	0.033 mg/kg/day N = 47	0.067 mg/kg/day N = 49	Untreated Controls N = 46	0.067 mg/kg/day N = 16	Untreated Controls N = 15		
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Arthralgia	2 (4.3)	5 (10.2)	1 (2.2)	0 (0.0)	1 (6.7)	7 (6.3)	2 (3.3)
Back disorder	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Back pain	0 (0.0)	5 (10.2)	1 (2.2)	0 (0.0)	2 (13.3)	5 (4.5)	3 (4.9)
Jaw disorder	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Limb discomfort	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Lower limb deformity	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Muscle cramp	0 (0.0)	0 (0.0)	1 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)
Neck pain	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Osteochondrosis	0 (0.0)	0 (0.0)	1 (2.2)	1 (6.3)	0 (0.0)	1 (0.9)	1 (1.6)
Pain in extremity	1 (2.1)	3 (6.1)	0 (0.0)	0 (0.0)	0 (0.0)	4 (3.6)	0 (0.0)
Patellofemoral pain syndrome	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Periostitis	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Scoliosis	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	1 (0.9)	0 (0.0)
Tendonitis	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Torticollis	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	1 (0.9)	0 (0.0)
Nervous system disorders							
Disturbance in attention	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Epilepsy	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Facial paresis	0 (0.0)	0 (0.0)	1 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)
Headache	5 (10.6)	9 (18.4)	5 (10.9)	2 (12.5)	0 (0.0)	16 (14.3)	5 (8.2)
Migraine	1 (2.1)	1 (2.0)	1 (2.2)	1 (6.3)	1 (6.7)	3 (2.7)	2 (3.3)
Movement disorder	0 (0.0)	0 (0.0)	1 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)
Nervous system disorder	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Paraesthesia	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	1 (0.9)	0 (0.0)
Petit mal epilepsy	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Psychomotor hyperactivity	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Syncope	2 (4.3)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (2.7)	0 (0.0)
Psychiatric disorders							
Aggression	3 (6.4)	3 (6.1)	0 (0.0)	0 (0.0)	0 (0.0)	6 (5.4)	0 (0.0)
Apathy	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Attention deficit/hyperactivity disorder	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Depressed mood	1 (2.1)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.8)	0 (0.0)
Depression	0 (0.0)	0 (0.0)	1 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)
Dissociative identity disorder	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Eating disorder	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Elevated mood	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Euphoric mood	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Impulse-control disorder	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Irritability	2 (4.3)	2 (4.1)	0 (0.0)	0 (0.0)	0 (0.0)	4 (3.6)	0 (0.0)
Mental disorder	1 (2.1)	0 (0.0)	2 (4.3)	0 (0.0)	0 (0.0)	1 (0.9)	2 (3.3)
Mood altered	3 (6.4)	7 (14.3)	0 (0.0)	2 (12.5)	0 (0.0)	12 (10.7)	0 (0.0)
Mood swings	3 (6.4)	3 (6.1)	1 (2.2)	0 (0.0)	0 (0.0)	6 (5.4)	1 (1.6)
Personality change	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
School refusal	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Sleep disorder	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Social phobia	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Stress symptoms	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Renal and urinary disorders							
Calculus bladder	0 (0.0)	0 (0.0)	1 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)
Reproductive system and breast disorders							
Dysmenorrhoea	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.7)	0 (0.0)	1 (1.6)
Gynaecomastia	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Hydrocele	0 (0.0)	1 (2.0)	1 (2.2)	0 (0.0)	0 (0.0)	1 (0.9)	1 (1.6)
Menorrhagia	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Phimosis	1 (2.1)	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	2 (1.8)	0 (0.0)
Testicular torsion	0 (0.0)	1 (2.0)	0 (0.0)	1 (6.3)	0 (0.0)	2 (1.8)	0 (0.0)
Respiratory, thoracic and mediastinal disorders							

Body system / Preferred Term	Prepuberta			Pubertal		Somatropin 0.033 and 0.067 mg/kg/day N = 112	Untreated Controls[b] N = 61
	0.033 mg/kg/day N = 47	0.067 mg/kg/day N = 49	Untreated Controls N = 46	0.067 mg/kg/day N = 16	Untreated Controls N = 15		
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Asthma	1 (2.1)	3 (6.1)	2 (4.3)	1 (6.3)	0 (0.0)	5 (4.5)	2 (3.3)
Cough	2 (4.3)	2 (4.1)	1 (2.2)	1 (6.3)	0 (0.0)	5 (4.5)	1 (1.6)
Dyspnoea	1 (2.1)	0 (0.0)	1 (2.2)	0 (0.0)	0 (0.0)	1 (0.9)	1 (1.6)
Nasal congestion	1 (2.1)	2 (4.1)	0 (0.0)	0 (0.0)	0 (0.0)	3 (2.7)	0 (0.0)
Pharyngolaryngeal pain	1 (2.1)	5 (10.2)	2 (4.3)	0 (0.0)	0 (0.0)	6 (5.4)	2 (3.3)
Rhinitis allergic	1 (2.1)	3 (6.1)	0 (0.0)	0 (0.0)	0 (0.0)	4 (3.6)	0 (0.0)
Skin and subcutaneous tissue disorders							
Cafe au lait spots	0 (0.0)	0 (0.0)	1 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)
Dermal cyst	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Dermatitis allergic	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	1 (0.9)	0 (0.0)
Eczema	2 (4.3)	1 (2.0)	1 (2.2)	0 (0.0)	0 (0.0)	3 (2.7)	1 (1.6)
Hyperhidrosis	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Ingrowing nail	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Pigmentation disorder	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	1 (0.9)	0 (0.0)
Prurigo	1 (2.1)	0 (0.0)	1 (2.2)	0 (0.0)	0 (0.0)	1 (0.9)	1 (1.6)
Psoriasis	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Skin disorder	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Urticaria	1 (2.1)	0 (0.0)	2 (4.3)	0 (0.0)	0 (0.0)	1 (0.9)	2 (3.3)
Social circumstances							
Corrective lens user	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Death of parent	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Death of relative	1 (2.1)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.8)	0 (0.0)
Death of sibling	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Divorced parents	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.7)	0 (0.0)	1 (1.6)
Physical assault	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Smoker	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Social problem	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Surgical and medical procedures							
Appendicectomy	1 (2.1)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.8)	0 (0.0)
Brain tumour operation	0 (0.0)	0 (0.0)	1 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)
Ear tube insertion	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Hernia repair	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Meniscus operation	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Skin neoplasm excision	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Surgery	1 (2.1)	0 (0.0)	1 (2.2)	1 (6.3)	0 (0.0)	2 (1.8)	1 (1.6)
Tonsillectomy	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Tooth extraction	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Vascular disorders							
Hypertension	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Hypotension	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)

Table 9: Treatment-related adverse events based on probable, possible, not assessable, and unknown definition and reported in ≥ 2% of somatropin treated subjects

Adverse Event	Somatropin 0.033 and 0.067 mg/kg/day N = 112		Untreated Controls[b] N = 61		Prepubertal						Pubertal			
					0.033 mg/kg/day N = 47		0.067 mg/kg/day N = 49		Untreated Controls N = 46		0.067 mg/kg/day N = 16		Untreated Controls N = 15	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Upper respiratory infection	15	13.4	2	3.3	8	17.0	6	12.2	2	4.3	1	6.3	0	0.0
Increased appetite	14	12.5	0	0.0	6	12.8	5	10.2	0	0.0	3	18.8	0	0.0
Mood altered	11	9.8	0	0.0	3	6.4	6	12.2	0	0.0	2	12.5	0	0.0
Headache	10	8.9	1	1.6	5	10.6	4	8.2	1	2.2	1	6.3	0	0.0
Influenza	9	8.0	0	0.0	5	10.6	3	6.1	0	0.0	1	6.3	0	0.0
Gastroenteritis	6	5.4	0	0.0	3	6.4	3	6.1	0	0.0	0	0.0	0	0.0
Nasopharyngitis	6	5.4	1	1.6	4	8.5	2	4.1	1	2.2	0	0.0	0	0.0
Aggression	5	4.5	0	0.0	3	6.4	2	4.1	0	0.0	0	0.0	0	0.0
Fracture[c]	4	3.6	0	0.0	2	4.2	2	4.1	0	0.0	0	0.0	0	0.0
Pharyngolaryngeal pain[a]	4	3.6	1	1.6	1	2.1	3	6.1	1	2.2	0	0.0	0	0.0
Rhinitis allergic	4	3.6	0	0.0	1	2.1	3	6.1	0	0.0	0	0.0	0	0.0
Mood swings	4	3.6	1	1.6	3	6.4	1	2.0	1	2.2	0	0.0	0	0.0
Ear infection	3	2.7	0	0.0	1	2.1	2	4.1	0	0.0	0	0.0	0	0.0
Tonsillitis	3	2.7	2	3.3	0	0.0	2	4.1	2	4.3	1	6.3	0	0.0
Cough	3	2.7	1	1.6	1	2.1	2	4.1	1	2.2	0	0.0	0	0.0

[a] Includes all somatropin Treated Subjects in the Safety Analysis Population.
B Includes all Untreated Controls in the Safety Analysis Population.
C Consists of: ankle fracture (n = 1 somatropin), clavicle fracture (n = 1 somatropin), radius fracture (n = 1 somatropin), tibia fracture (n = 2 somatropin).

Adverse Events Leading to Termination of Treatment

Clinical trial adverse drug reactions in the Study with the Reference product presented in Table 9 above that lead to treatment termination are listed below:
Dissociative identity disorder, pituitary cyst, mood swings and irritability.

Table 10: Incidence (%) of treatment-emergent adverse events reported in ≥ 1% of patients

Body system / Preferred Term	Somatropin 0.047 mg/kg/day N = 18		Control group N = 19	
	n	%	n	%
Endocrine Disorders				
Hypothyroidism	2	11.1	0	0.0
Infection	3	16.7	1	5.3
Eye Disorders				
Hypermetropia	1	5.6	0	0.0
General Disorders and Administration Site Conditions				
Influenza like illness	2	11.1	0	0.0
Injection site rash	1	5.6	0	0.0
Pyrexia	1	5.6	0	0.0
Investigations				
Increased alanine aminotransferase	1	5.6	0	0.0

Body system / Preferred Term	Somatropin 0.047 mg/kg/day N = 18		Control group N = 19	
	n	%	n	%
Increased aspartate aminotransferase	1	5.6	0	0.0
Increased blood insulin	1	5.6	0	0.0
Decreased blood thyroid stimulating hormone	1	5.6	0	0.0
Increased blood thyroid stimulating hormone	1	5.6	0	0.0
Increased tri-iodothyronine	1	5.6	0	0.0
Increased blood triglycerides	1	5.6	0	0.0
Eosinophil percentage increased	2	11.1	0	0.0
Decreased oestradiol	1	5.6	0	0.0
Metabolism and Nutrition Disorders				
Impaired glucose tolerance	1	5.6	0	0.0
Trace element deficiency	1	5.6	0	0.0
Ear and Labyrinth Disorders				
Middle ear effusion	1	5.6	0	0.0
Gastrointestinal Disorders				
Diarrhoea	1	5.6	1	5.3
Nausea	1	5.6	0	0.0
Umbilical hernia	1	5.6	0	0.0
Vomiting	2	11.1	1	5.3
Infections and Infestations				
Acute tonsillitis	4	22.2	0	0.0
Bronchitis	3	16.7	3	15.8
Ear infection	1	5.6	0	0.0
Febrile infection	2	11.1	1	5.3
Gastroenteritis	2	11.1	1	5.3
Measles	0	0.0	1	5.3
Nasopharyngitis	2	11.1	0	0.0
Otitis media	1	5.6	1	5.3
Otitis media acute	0	0.0	1	5.3
Rhinitis	2	11.1	0	0.0
Rubella	1	5.6	0	0.0
Scarlet fever	1	5.6	1	5.3
Sinusitis	1	5.6	0	0.0
Skin infection	1	5.6	0	0.0
Tonsillitis	3	16.7	0	0.0
Infections and Infestations				
Upper respiratory tract infection	2	11.1	1	5.3
Varicella	0	0.0	1	5.3
Viral infection	2	11.1	0	0.0
Viral upper respiratory tract infection	0	0.0	1	5.3
Injury, Poisoning and Procedural Complications				
Arthropod bite	1	5.6	0	0.0
Concussion	1	5.6	0	0.0
Fall	1	5.6	0	0.0
Foot fracture	1	5.6	0	0.0

Body system / Preferred Term	Somatropin 0.047 mg/kg/day N = 18		Control group N = 19	
	n	%	n	%
Skin injury	1	5.6	0	0.0
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	1	5.6	0	0.0
Nervous System Disorders				
Disturbance in attention	1	5.6	0	0.0
Dizziness	1	5.6	0	0.0
Headache	4	22.2	0	0.0
Mental impairment	1	5.6	0	0.0
Petit mal epilepsy	1	5.6	0	0.0
Renal and Urinary Disorders				
Leukocyturia	1	5.6	0	0.0
Reproductive System and Breast Disorders				
Balanitis	0	0.0	1	5.3
Breast induration	1	5.6	0	0.0
Breast swelling	1	5.6	0	0.0
Gynaecomastia	1	5.6	0	0.0
Respiratory, Thoracic and Mediastinal Disorders				
Asthma	0	0.0	1	5.3
Cough	1	5.6	0	0.0
Pharyngolaryngeal pain	1	5.6	0	0.0
Skin and Subcutaneous Tissue Disorders				
Dermatitis allergic	1	5.6	0	0.0
Dermatitis atopic	1	5.6	0	0.0
Eczema	1	5.6	0	0.0
Hyperhidrosis	1	5.6	0	0.0
Neurodermatitis	1	5.6	1	5.3
Pruritus	1	5.6	0	0.0
Psoriasis	1	5.6	0	0.0
Surgical and Medical Procedures				
Adenoidectomy	0	0.0	1	5.3
Adenotonsillectomy	0	0.0	1	5.3
Myringotomy	0	0.0	1	5.3
Nasal polypectomy	0	0.0	1	5.3
Umbilical hernia repair	1	5.6	0	0.0

Clinical Trials in children with Idiopathic Short Stature

In ISS studies with the reference product, the most frequently encountered respiratory adverse events, seen in ≥5 % of subjects, included infections and infestations (upper respiratory tract infections, influenza, tonsillitis, nasopharyngitis).

In the pivotal study with the reference product, eight of the 15 subjects with upper respiratory infection were in the lower dose somatropin treatment group (0.033 mg/kg/day; prepubertal) and seven received 0.067 mg/kg/day (six prepubertal and one pubertal).

Influenza occurred in four subjects that received 0.067 mg/kg/day (three prepubertal and one pubertal) and in five subjects that received 0.033 mg/kg/day. Nasopharyngitis was also reported only in prepubertal somatropin treated subjects (four at 0.033 mg/kg/day and two at 0.067 mg/kg/day).

Adults

Clinical Trials in adults with GHD

In clinical trials with the reference product recurrence of pituitary adenoma and of craniopharyngioma were reported in one case each. In these patient categories tumour recurrence is not uncommon, but it is as yet not possible to compare rates between patients on GH treatment and those without such substitution.

In clinical trials with the reference product in 1145 GHD adults, the majority of the adverse events consisted of mild to moderate symptoms of fluid retention, including peripheral swelling, arthralgia, pain and stiffness of the extremities, peripheral edema, myalgia, paresthesia, and hypoesthesia. These events were reported early during therapy, and tended to be transient and/or responsive to dosage reduction.

Table 11 displays the adverse events reported by 5 % or more of adult GHD patients in clinical trials after various durations of treatment with somatropin. Also presented are the corresponding incidence rates of these adverse events in placebo patients during the 6-month double-blind portion of the clinical trials.

Table 11: Adverse events reported by ≥ 5% of 1145 adult GHD patients during clinical trials of somatropin and placebo, grouped by duration of treatment

	Double Blind Phase		Open Label Phase Somatropin		
Adverse Event	**Placebo 0–6 mo. n = 572 % Patients**	**Somatropin 0–6 mo. n = 573 % Patients**	**6–12 mo. n = 504 % Patients**	**12–18 mo. n = 63 % Patients**	**18–24 mo. n = 60 % Patients**
Swelling, peripheral	5.1	17.5*	5.6	0	1.7
Arthralgia	4.2	17.3*	6.9	6.3	3.3
Upper respiratory infection	14.5	15.5	13.1	15.9	13.3
Pain, extremities	5.9	14.7*	6.7	1.6	3.3
Edema, peripheral	2.6	10.8*	3.0	0	0
Paresthesia	1.9	9.6*	2.2	3.2	0
Headache	7.7	9.9	6.2	0	0
Stiffness of extremities	1.6	7.9*	2.4	1.6	0
Fatigue	3.8	5.8	4.6	6.3	1.7
Myalgia	1.6	4.9*	2.0	4.8	6.7
Back pain	4.4	2.8	3.4	4.8	5.0

* Increased significantly when compared to placebo, P≤ 0.025: Fisher´s Exact Test (one-sided)
n = number of patients receiving treatment during the indicated period.
% = percentage of patients who reported the event during the indicated period.

Post-Trial Extension Studies in Adults
In expanded post-trial extension studies with the reference product, diabetes mellitus developed in 12 of 3031 patients (0.4%) during treatment with somatropin. All 12 patients had predisposing factors, e.g., elevated glycosylated hemoglobin levels and/or marked obesity, prior to receiving somatropin. Of the 3031 patients receiving somatropin, 61 (2%) developed symptoms of carpal tunnel syndrome, which lessened after dosage reduction or treatment interruption (52) or surgery (9). Other adverse events that have been reported include generalized edema and hypoesthesia.

Post Market Adverse Drug Reactions - Reference Product
Because these adverse events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. The adverse events reported during post-marketing surveillance do not differ from those listed/discussed above (see Clinical Trials Adverse Reactions) in children and adults.

Leukemia has been reported in a small number of GHD children treated with somatropin, somatrem (methionylated rhGH) and GH of pituitary origin. It is uncertain whether these cases of leukemia are related to GH therapy, the pathology of GHD itself, or other associated treatments such as radiation therapy. On the basis of current evidence, experts have not been able to conclude that GH therapy per se was responsible for these cases of leukemia. The risk for children with GHD, if any, remains to be established (see CONTRAINDICATIONS AND WARNINGS AND PRECAUTIONS).

The following additional adverse reactions have been observed during the appropriate use of somatropin: headaches (children and adults), gynecomastia (children), and pancreatitis (see WARNINGS AND PRECAUTIONS).

New-onset type 2 diabetes mellitus has been reported.

Slipped capital femoral epiphysis and Legg-Calve-Perthes disease have been reported in children treated with growth hormone. No causal relationship has been demonstrated with somatropin.

DRUG INTERACTIONS

Drug-Drug Interactions
No studies on the interaction of Omnitrope with other drugs have been performed.

Concomitant glucocorticoid treatment may inhibit the growth-promoting effect of human growth hormone. Pediatric growth hormone-deficient patients with glucocorticoid replacement for hypoadrenalism require vigilant assessment of their glucocorticoid replacement, and may require an increase in their maintenance doses when receiving growth hormone (see also WARNINGS AND PRECAUTIONS**,** Endocrine and Metabolism).

Limited published data indicate that growth hormone treatment increases cytochrome P450 (CP450) mediated antipyrine clearance in man. These data suggest that growth hormone

administration may alter the clearance of compounds known to be metabolized by CP450 liver enzymes (e.g. corticosteroids, sex steroids, anticonvulsants, cyclosporine). Careful monitoring is advisable when growth hormone is administered in combination with other drugs known to be metabolized by CP450 liver enzymes.

Table 12: Established or Potential Drug-Drug Interactions with Omnitrope

Therapeutic Class	Effect	Clinical Comment
Glucocorticoids	Concomitant glucocorticoid treatment may inhibit the growth promoting effect of human growth hormone.	Patients treated with glucocorticoid replacement for hypoadrenalism require vigilant assessment of their glucocorticoid replacement, and may require an increase in their maintenance doses when receiving growth hormone.
Cytochrome P450	Somatropin may be an inducer of CP450 3A4 when administered in combination with drugs known to be metabolized by CP450 liver enzymes.	Patients should be monitored for clinical effectiveness of such drugs.
Insulin and anti-hypoglycemic agents	Patients with diabetes mellitus who receive concomitant somatropin may require adjustment of their doses of insulin and/or other antihypoglycemic agents.	Because somatropin may induce a state of insulin resistance, patients who receive somatropin should be monitored for evidence of abnormal glucose metabolism and/or diabetes mellitus. New-onset type 2 diabetes mellitus has been reported in children and adults receiving somatropin.

Legend: ACTH = Adrenocorticotropic Hormone

Drug-Food Interactions
Interactions with food have not been established.

Drug-Herb Interactions
Interactions with herbal products have not been established.

Drug-Laboratory Test Interactions
Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Therapy with Omnitrope (somatropin for injection) should be supervised by a physician who is experienced in the diagnosis and management of pediatric patients with growth failure associated with growth hormone deficiency (GHD), Turner syndrome (TS), those who were born small for gestational age (SGA) or Idiopathic Short Stature (ISS), and adult patients with either childhood onset or adult onset GHD.

The Omnitrope dosage and administration schedule should be individualized based on the growth response of each patient.

Response to somatropin therapy in pediatric patients tends to decrease with time. However, in pediatric patients, the failure to increase growth rate, particularly during the first year of therapy, indicates the need for close assessment of compliance and evaluation for other causes of growth failure, such as hypothyroidism, undernutrition, advanced bone age and antibodies to recombinant human GH (rhGH).

Treatment with Omnitrope for short stature should be discontinued when the epiphyses are fused.

Recommended Dose and Dosage Adjustment

The recommended dosage of Omnitrope is:

Indication	Recommended Dose (mg/kg body weight)	Route [4]	Comments
Pediatric Growth Hormone Deficiency [1]	0.16 - 0.24 mg/kg body weight/week	SC	Divided into 6-7 doses diagnosis of GHD should be confirmed before Omnitrope is administered.
Adults Growth Hormone Deficiency	0.15 - 0.3 mg/day [2]	SC	
Turner Syndrome [1]	0.33 mg/kg body weight per week	SC	Divided into 6-7 doses
Idiopathic Short Stature [1]	UP TO 0.47 mg/kg body weight per week [3]	SC	Divided into 6-7 doses
Small for Gestational Age [1]	UP TO 0.48 mg/kg body weight per week	SC	Divided into 6-7 doses

[1] Omnitrope dosage must be adjusted for the individual patient.
[2] Final dose should be individually increased as required with respect to age and gender to a maximum daily maintenance dose of 1.33 mg. Women may require higher doses than men. As normal physiological growth hormone production decreases with age, dose requirements may be reduced.
[3] Treatment should stop when near adult height is achieved (height velocity < 2cm/yr and/or bone age >16 yr in boys and >14 yr in girls) or when height is in the normal adult range (above -2 SDS).
[4] Omnitrope may be administered in the thigh, buttocks or abdomen; the site of SC injections (administered preferably in the evenings) should be rotated daily to help prevent lipoatrophy.

Adults Growth hormone deficiency

Clinical response, side effects and determination of IGF-1 in serum may be used as guidance for dose titration. The level of IGF-1 should not exceed the upper limit of normal IGF-1 levels matched to age and sex.

It is recommended that IGF-1 concentrations be monitored regularly and GH dose be reduced in children with a plasma IGF-1 above + 2SD.

Small for Gestational Age

Recent literature has recommended initial treatment with larger doses of somatropin (e.g., 0.48 mg/kg/week), especially in very short children (i.e., height SDS <–3), and/or older/ pubertal children, and that a reduction in dosage (e.g., gradually towards 0.24 mg/kg/week) should be considered if substantial catch-up growth is observed during the first few years of therapy. On the other hand, in younger SGA children (e.g., approximately <4 years) with less severe short stature (i.e., baseline height SDS values between -2 and -3), consideration should be given to initiating treatment at a lower dose (e.g., 0.24 mg/kg/week), and titrating the dose as needed over time. In all children, clinicians should carefully monitor the growth response, and adjust the somatropin dose as necessary.

Dosing should continue until final height is reached (see DETAILED PHARMACOLOGY, Human Pharmacology, Pharmacodynamics). 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.

In short children born SGA, it is recommended that IGF I concentration be measured before initiation of treatment and monitored every 6 months thereafter. If on repeated measurements IGF-1 concentrations exceed +2 SD compared to references for age and pubertal status, the IGF-1/IGFBP-3 ratio could be taken into account to consider dose adjustment.

Missed Dose

For patients who miss a dose of Omnitrope, it is not recommended to double the next dose. Administer the regular dose at the next scheduled dosage time. Patients should contact their physician for instructions.

Administration

Omnitrope (somatropin for injection) – Vials of 5.8 mg:

Reconstitution

Omnitrope (somatropin for injection) lyophilized powder is dispensed in vials of 5.8 mg:

- A 5.8 mg vial of Omnitrope lyophilized powder should be reconstituted with 1.14 mL of Bacteriostatic Water for Injection (benzyl alcohol preserved). The concentration of the reconstituted solution is 5.0 mg/mL. After reconstitution, the solution may be refrigerated for a maximum of 28 days between 2 to 8°C.

To prepare the Omnitrope solution, first disinfect both, the rubber membrane of the vial, and the cartridge containing diluent with an alcohol swab. Then, slowly inject the Bacteriostatic Water for Injection from the cartridge into the Omnitrope vial using the transfer set. Follow the directions that came with the transfer set. Gently swirl the reconstituted vial until the content is completely dissolved. **Do not shake**. After reconstitution, the Omnitrope solution should be clear. If the solution is cloudy or contains particles, it should not be used. Transfer all of the dissolved solution back into the cartridge using the transfer set.

This presentation is intended for multiple use. It should only be administered with the Omnitrope Pen L, an injection device specifically developed for use with Omnitrope 5.0 mg/mL reconstituted solution for injection. The solutions must be administered using sterile, disposable pen needles. The solution must be clear. Do not inject if the solution is cloudy.

Patients and caregivers must receive appropriate training and instruction on the proper use of the Omnitrope vials, diluent cartridge, transfer set and pen from the physician or other qualified healthcare professional. After reconstitution and first injection, the diluent cartridge should remain in the Pen L and be refrigerated between 2 to 8 °C.

Omnitrope (somatropin for injection) – 5.0 mg/1.5 mL ; 10.0 mg/1.5 mL, 15.0 mg/1.5 mL Cartridges

Omnitrope 5.0 mg/1.5 mL,10.0 mg/1.5 mL and 15.0 mg/1.5 mL solutions for injection, are sterile, ready-to-use solutions filled in pen cartridges.

The presentations are indicated for multiple use. They should only be administered with the Omnitrope® Surepal 5, Omnitrope® Surepal 10 and Omnitrope® Surepal 15 pen injection devices specifically developed for use with Omnitrope 5.0 mg/1.5 mL, Omnitrope 10.0 mg/1.5 mL, and Omnitrope 15.0 mg/1.5 mL respectively. The solutions must be administered using sterile, disposable pen needles. The solution must be clear prior to insertion of the cartridge into the Pen. Do not inject if the solution is cloudy. Patients and caregivers have to receive appropriate training and instruction on the proper use of the Omnitrope cartridges and pens from the physician or other suitable qualified healthcare professionals.

After the first injection, the content of the cartridge must be used within 28 days. The cartridge should remain in the pen and be refrigerated between 2 and 8°C. Do not freeze. Protect from light.

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

Wash your hands.

1. Ensure that the solution in the cartridge is clear and colourless prior to inserting the cartridge into the Pen. Do not use if the solution is cloudy or contains particulate matter.
2. Disinfect the rubber membrane of the cartridge with an alcohol swab.
3. Insert the cartridge into the Omnitrope Pen following the instructions for use provided with the pen.
4. Clean the site of injection with an alcohol swab.
5. Administer the appropriate dose by subcutaneous injection using a sterile pen needle. The sites of injection should be rotated each time Omnitrope is administered to avoid lipoatrophy.
6. Remove the pen needle and dispose of it in accordance with local requirements.

OVERDOSAGE

There is little information on acute or chronic overdosage with Omnitrope. Intravenously administered growth hormone has been shown to result in an acute decrease in plasma glucose and subsequently to hyperglycemia. It is thought that the same effect might occur on rare occasions with high dosages of Omnitrope administered subcutaneously. Long-term overdosage may result in signs and symptoms of acromegaly, with resultant and considerable morbidity and mortality from cardiovascular complications and malignancy. Furthermore, overdose with somatropin is likely to cause fluid retention.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Omnitrope (somatropin for injection) is a human growth hormone (hGH) produced by recombinant DNA technology. The amino acid sequence of the somatropin protein is identical to that of the human growth hormone of pituitary origin.

In vitro, preclinical, and clinical tests have demonstrated that somatropins are therapeutically equivalent to human growth hormone of pituitary origin and achieve similar pharmacokinetic profiles in normal adults. In pediatric patients who have growth hormone deficiency (GHD), treatment with somatropin stimulates linear growth and normalizes concentrations of Insulin-like Growth Factor -I (IGF-I).
In adults with GHD, treatment with somatropin results in reduced fat mass, increased lean body mass, metabolic alterations that include beneficial changes in lipid metabolism, and normalization of IGF-I concentrations.

In addition, the following actions have been demonstrated for Omnitrope (somatropin for injection) and/or human growth hormone of pituitary origin.

Tissue Growth

- Skeletal Growth: Somatropin stimulates skeletal growth in children with growth failure due to inadequate secretion of endogenous growth hormone. The measurable increase in body length after administration of somatropin results from an effect on the epiphyseal plates of long bones. Concentrations of IGF-I, which may play a role in skeletal growth, are generally low in the serum of pediatric patients with growth hormone deficiency, but tend to increase during treatment with Omnitrope. Elevations in mean serum alkaline phosphatase concentration are also seen.

- Cell Growth: It has been shown that there are fewer skeletal muscle cells in short-statured children who lack endogenous growth hormone as compared with the normal pediatric population. Treatment with somatropin for injection results in an increase in both the number and size of skeletal muscle cells.

Protein Metabolism

Linear growth is facilitated in part by increased cellular protein synthesis. Nitrogen retention, as demonstrated by decreased urinary nitrogen excretion and serum urea nitrogen, follows the initiation of therapy with somatropin.

Carbohydrate Metabolism

Pediatric patients with hypopituitarism sometimes experience fasting hypoglycemia, which is improved by treatment with somatropin. Large doses of growth hormone may impair glucose tolerance.

Lipid Metabolism
In growth hormone-deficient patients, administration of recombinant somatropin has resulted in lipid mobilization, reduction in body fat stores, and increased plasma fatty acids.

Mineral Metabolism
Retention of sodium, potassium, and phosphorus is induced by pituitary growth hormone in children. Serum concentrations of inorganic phosphate are increased in patients with growth hormone deficiency after therapy with somatropin. Serum calcium is not significantly altered in patients treated with somatropin. Growth hormone could increase calciuria.

Body Composition
Adult growth hormone-deficient patients treated with somatropin at the recommended adult dose (see DOSAGE AND ADMINISTRATION) demonstrate a decrease in fat mass and an increase in lean body mass. When these alterations are coupled with the increase in total body water, the overall effect of somatropin is to modify body composition, an effect that is maintained with continued treatment.

Pharmacodynamics

Table 13: Pharmacodynamic Parameters after a Single SC Administration of 5 mg Omnitrope Powder for Solution for Injection (5.8mg/vial) and of 5 mg Omnitrope 10.0 mg/1.5 mL Solution for Injection

IGF-1	5 mg of Omnitrope powder for solution for injection; 5.8 mg/vial (N = 32)	5 mg of Omnitrope 10.0 mg/1.5 mL solution for injection (N = 32)
$AUEC_{last}$ [h·mcg/L]	20355 ± 5067	19829 ± 5107
E_{max} [mcg/L]	267 ± 64	265 ± 68
$t_{max,E}$ [h]	24* (16 - 48)	24* (16 - 24)

Results are presented as mean ± SD.
*median value (min - max) for $t_{max,E}$
Legend: IGF-1 = Insulin-like Growth Factor 1

IGFBP-3	5 mg of Omnitrope powder for solution for injection; 5.8 mg/vial (N = 32)	5 mg of Omnitrope 10.0 mg/1.5 mL solution for injection (N = 32)
$AUEC_{last}$ [h·mg/L]	471 ± 70	468 ± 67
E_{max} [mg/L]	5.4 ± 0.8	5.4 ± 0.8
$t_{max,E}$ [h]	48* (16 – 96)	48* (0 - 72)

Results are presented as mean ± SD.
*median value (min - max) for $t_{max,E}$

Legend: IGFBP = Insulin-like Growth Factor Binding Protein 3

NEFA	5 mg of Omnitrope powder for solution for injection; 5.8 mg/vial (N = 32)	5 mg of Omnitrope 10.0 mg/1.5 mL solution for injection (N = 32)
$AUEC_{last}$ [h·mmol/L]	13.1 ± 3.8	12.8 ± 3.7
E_{max} [mmol/L]	1.1 ± 0.3	1.1 ± 0.3
$t_{max,E}$ [h]	3* (1 - 16)	3* (2 - 16)

Results are presented as mean ± SD.
*median value (min - max) for $t_{max,E}$
Legend: NEFA = Nonesterified Fatty Acids

Table 14: Pharmacodynamic Parameters after a Single SC Administration of 5 mg Omnitrope Powder for Solution for Injection (5.8mg/vial) and of 5mg Omnitrope 5.0 mg/1.5 mL Solution for Injection

IGF-1	5 mg of Omnitrope powder for solution for injection; 5.8 mg/vial (N = 35)	5 mg of Omnitrope 5.0 mg/1.5 mL solution for injection (N = 35)
$AUEC_{last}$ [h·mcg/L]	16712 ± 3847	16295 ± 3664
E_{max} [mcg/L]	218 ± 56	213 ± 49
$t_{max,E}$ [h]	24* (12 - 48)	24* (12 - 48)

Results are presented as mean ± SD.
*median value (min - max) for $t_{max,E}$

IGFBP-3	5 mg of Omnitrope powder for solution for injection; 5.8 mg/vial (N = 35)	5 mg of Omnitrope 5.0 mg/1.5 mL solution for injection (N = 35)
$AUEC_{last}$ [h·mg/L]	430 ± 61	427 ± 56
E_{max} [mg/L]	4.9 ± 0.7	4.9 ± 0.6
$t_{max,E}$ [h]	48* (24 – 96)	48* (12 - 96)

Results are presented as mean ± SD.
*median value (min - max) for $t_{max,E}$

NEFA	5 mg of Omnitrope powder for solution for injection; 5.8 mg/vial (N = 35)	5 mg of Omnitrope 5.0 mg/1.5 mL solution for injection (N = 35)
$AUEC_{last}$ [h·mmol/L]	15.3 ± 4.9	14.8 ± 3.8

E_{max} [mmol/L]	1.3 ± 0.3	1.2 ± 0.3
$t_{max,E}$ [h]	2* (0 - 16)	2* (1 - 24)

Results are presented as mean ± SD.
*median value (min - max) for $t_{max,E}$

Table 15: Pharmacodynamic Parameters after a Single SC Administration of 5 mg Omnitrope Powder for Solution for Injection (5.8mg/vial) and of 5mg Omnitrope 15.0 mg/1.5 mL Solution for Injection

IGF-1	**5 mg of Omnitrope powder for solution for injection; 5.8 mg/vial (N = 33)**	**5 mg of Omnitrope 15.0 mg/1.5 mL solution for injection (N = 33)**
$AUEC_{last}$ [h·mcg/L]	27878.79 (7809.28)	28181.82 (8822.75)
E_{max} [mcg/L]	389.09 (106.14)	383.09 (115.23)
$t_{max,E}$ [h]*	24.02 [12.03; 48.03]*	24.03 [12.02; 48.03]*

Results are presented as mean ± SD.
*median value (min - max) for $t_{max,E}$

IGFBP-3	**5 mg of Omnitrope powder for solution for injection; 5.8 mg/vial (N = 33)**	**5 mg of Omnitrope 15.0 mg/1.5 mL solution for injection (N = 33)**
$AUEC_{last}$ [h·mg/L]	497.77 (62.87)	489.304 (68.01)
E_{max} [mg/L]	5.67 (0.71)	5.584(0.72)
$t_{max,E}$ [h]*	48.03 [12.03; 96.03]*	48.03 [12.02; 72.17]*

Results are presented as mean ± SD.
*median value (min - max) for $t_{max,E}$

NEFA	**5 mg of Omnitrope powder for solution for injection; 5.8 mg/vial (N = 33)**	**5 mg of Omnitrope 15.0 mg/1.5 mL solution for injection (N = 33)**
$AUEC_{last}$ [h·mmol/L]	13.13 (3.77)	13.56 (4.78)
E_{max} [mmol/L]	1.17 (0.19)	1.13 (0.39)
$t_{max,E}$ [h]*	3.00 [1.02; 16.03]*	3.03 [1.03; 16.03]*

Results are presented as mean ± SD.
*median value (min - max) for $t_{max,E}$

Pharmacokinetics

Table 16: Pharmacokinetic Parameters After a Single SC Administration of 5 mg of Omnitrope Powder for Solution for Injection (5.8mg/vial) and 5 mg of Omnitrope 10.0 mg/1.5 mL Solution for Injection

	5 mg of Omnitrope powder for solution for injection; 5.8 mg/vial (N = 32)	5 mg of Omnitrope 10.0 mg/1.5 mL solution for injection (N = 32)
AUC_T [h·mcg/L]	550 ± 96	558 ± 115
AUC_I [h·mcg/L]	555 ± 96	561 ± 114
C_{max} [mcg/L]	69 ± 16	74 ± 22
t_{max} [h]	4.0* (2.0 - 6.0)	4.0* (2.0 - 6.0)
$t_{1/2}$ [h]	2.9 ± 0.5	2.5 ± 0.7

Results are presented as mean ± SD .
*median value (min - max)

Table 17: Pharmacokinetic Parameters After a Single SC Administration of 5 mg of Omnitrope Powder for Solution for Injection (5.8 mg/vial) and 5 mg of Omnitrope 5.0 mg/1.5 mL Solution for Injection

	5 mg of Omnitrope powder for solution for injection; 5.8 mg/vial (N = 35)	5 mg of Omnitrope 5.0 mg/1.5 mL solution for injection (N = 35)
AUC_T [h·mcg/L]	559 ± 148	542 ± 141
AUC_I [h·mcg/L]	566 ± 147	546 ± 140
C_{max} [mcg/L]	71 ± 24	72 ± 28
t_{max} [h]	4.0* (2.0 -6.0)	4.0* (2.0 -8.0)
$t_{1/2}$ [h]	3.2 ± 0.7	2.8 ± 0.7

Results are presented as mean ± SD (n=35).
* median value (min - max)

Table 18: Pharmacokinetic Parameters After a Single SC Administration of 5 mg of Omnitrope Powder for Solution for Injection (5.8mg/vial) and 5 mg of Omnitrope 15.0 mg/1.5 mL Solution for Injection

	5 mg of Omnitrope powder for solution for injection; 5.8 mg/vial (N = 33)	5 mg of Omnitrope 5.0 mg/1.5 mL solution for injection (N = 33)
AUC_T [h·mcg/L]	419.16 (112.34)	391.51 (100.47)
AUC_I [h·mcg/L]	424.31 (109.40)	394.60 (98.58)
C_{max} [mcg/L]	55.22 (21.50)	52.89 (19.09)

t_{max} [h]*	4.03 [2.02; 6.03]*	4.02 [2.02; 6.03]*
$t_{1/2}$ [h]	3.24 (0.91)	2.76 (0.84)

Results are presented as mean ± SD.
* median value (min - max)

For additional information on comparative pharmacokinetic and pharmacodynamic studies please refer to "CLINICAL TRIALS" of PART II.

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 (5.0 mg/1.5 mL Solution for Injection) in healthy adults results in plasma C_{max} and t_{max} values of 72 ± 28 mcg/L and 4.0 ± 2.0 hours, respectively. Following SC injection, maximum serum growth hormone concentrations are reached approximately 4 hours (range 2 to 8 hours) and growth hormone serum concentrations return to baseline within 24 hours.

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 in healthy adults, a half-life of approximately 3 hours is estimated. The longer half-life observed after subcutaneous administration is an example of 'flip-flop' pharmacokinetics, such that the estimated elimination rate is actually the absorption rate from the site of administration. The mean metabolic clearance of Omnitrope, subcutaneously administered in healthy adults, is 0.14 (± 0.04) L/h·kg.

Metabolism
Extensive metabolism studies have not been conducted. The metabolic fate of somatropin involves classical protein catabolism in both the liver and kidneys.

Subpopulations
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 pediatric populations, in different races and in patients with renal, hepatic or cardiac insufficiency is either lacking or incomplete.

Special Populations and Conditions
Pediatrics: No studies to estimate recombinant human Growth Hormone (rhGH) clearance have been conducted with Omnitrope in these patient populations.

Gender: No gender studies have been performed in pediatric patients; however, following a subcutaneous injection of 5 mg Omnitrope to healthy adult volunteers, gender had no effect on the pharmacokinetic parameters of Omnitrope (C_{max} and t_{max}).

Race: No studies have been conducted with Omnitrope to assess pharmacokinetic differences among races.

Elderly, Renal, Hepatic or Cardiac Insufficiency: No studies have been conducted with Omnitrope in these patient populations.

STORAGE AND STABILITY

Omnitrope (somatropin for injection) 5.8 mg/vial:
Before Reconstitution*:* Vials of Omnitrope (somatropin for injection) and the supplied diluent for Omnitrope are stable when stored at 2 to 8 °C. Avoid freezing the diluent for Omnitrope. Expiration dates are stated on the labels.

After Reconstitution:
Omnitrope 5.8 mg/vial is supplied with the diluent, Bacteriostatic Water for Injection containing 1.5% benzyl alcohol as a preservative. After reconstitution, the contents of the vial must be used within 28 days and refrigerated between 2 and 8°C. The cartridge containing the reconstituted Omnitrope solution should remain in the Pen L and also refrigerated between 2 and 8°C.

Refrigerate Omnitrope between 2 and 8°C. Do not freeze. Omnitrope is light sensitive and should be stored in the carton.

Omnitrope (somatropin for injection) 5.0 mg/ 1.5 mL, 10.0 mg/1.5 mL, 15.0 mg/1.5 mL:
Omnitrope pen cartridges for use with Surepal 5, Surepal 10 and Surepal 15.

- Keep out of reach and sight of children.
- Store in the original package in order to protect from light.
- Store between 2 and 8°C (in a refrigerator). Do not freeze.
- Use a cool box for transporting the package(s) if you are travelling.
- After the first injection, the cartridge should remain in the pen injector and has to be kept in a refrigerator between 2°C to 8°C for a maximum of 28 days (see Instructions for Use of the pen injector).
- Do not use after the expiry date stated on the label and carton.
- Do not use Omnitrope if it was frozen or subject to high temperatures.
- Do not use Omnitrope if you notice that the solution is cloudy or contains particles.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Form and Composition

Omnitrope (somatropin for injection) is a sterile lyophilized powder in vials for reconstitution:

- **5.8 mg Vial:** Each vial contains 5.8 mg somatropin (approximately 17.4 IU), 27.6 mg glycine, 2.09 mg disodium hydrogen phosphate heptahydrate and 0.56 mg sodium dihydrogen phosphate dihydrate.

- **Diluent:** The 5.8 mg vial is supplied with a cartridge containing 1.14 mL of diluent (Bacteriostatic Water for Injection containing 1.5% benzyl alcohol as a preservative). After reconstitution, the solution has a concentration of 5.0 mg/mL (approximately 15 IU/mL).

Omnitrope Pen Cartridges contain somatropin solution for injection:

- **5.0 mg/1.5 mL Cartridge:** Each 1.5 mL pen cartridge contains: 5.0 mg of somatropin (15 IU/1.5 mL), 1.3 mg disodium hydrogen phosphate heptahydrate, 1.6 mg sodium dihydrogen phosphate dihydrate, 3.0 mg poloxamer 188, 13.5 mg benzyl alcohol, 52.5 mg mannitol and water for injection. Phosphoric acid and/or sodium hydroxide may have been used to adjust pH.

- **10.0 mg/1.5 mL Cartridge:** Each 1.5 mL pen cartridge contains: 10.0 mg of somatropin (30.0 IU/1.5 mL), 1.70 mg disodium hydrogen phosphate heptahydrate, 1.35 mg sodium dihydrogen phosphate dihydrate, 3.0 mg poloxamer 188, 4.5 mg phenol, 27.75 mg glycine and water for injection. Phosphoric acid and/or sodium hydroxide may have been used to adjust pH.

- **15.0 mg/1.5 mL Cartridge:** Each 1.5 mL pen cartridge contains: 15.0 mg of somatropin (45.0 IU/1.5 mL), 0.29 mg disodium hydrogen phosphate heptahydrate, 2.17 mg sodium dihydrogen phosphate dihydrate, 4.5 mg poloxamer 188, 4.5 mg phenol, 10.5 mg sodium chloride and water for injection. Phosphoric acid and/or sodium hydroxide may have been used to adjust pH.

Packaging

Omnitrope Lyophilized Powder is supplied as:

Omnitrope 5.8 mg/vial:
Carton contains 8 vials of Omnitrope 5.8 mg and 8 cartridges of diluent (Bacteriostatic Water for Injection containing 1.5% benzyl alcohol as a preservative).

Omnitrope Pen Cartridge is supplied as:

Omnitrope 5.0 mg/1.5 mL is supplied in the following pack sizes:
- One cartridge per carton
- Five cartridges per carton
- Ten cartridges per carton

Omnitrope 10.0 mg/1.5 mL is supplied in the following pack sizes:
- One cartridge per carton
- Five cartridges per carton
- Ten cartridges per carton

Omnitrope 15.0 mg/1.5 mL is supplied in the following pack sizes:

- One cartridge per carton
- Five cartridges per carton

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

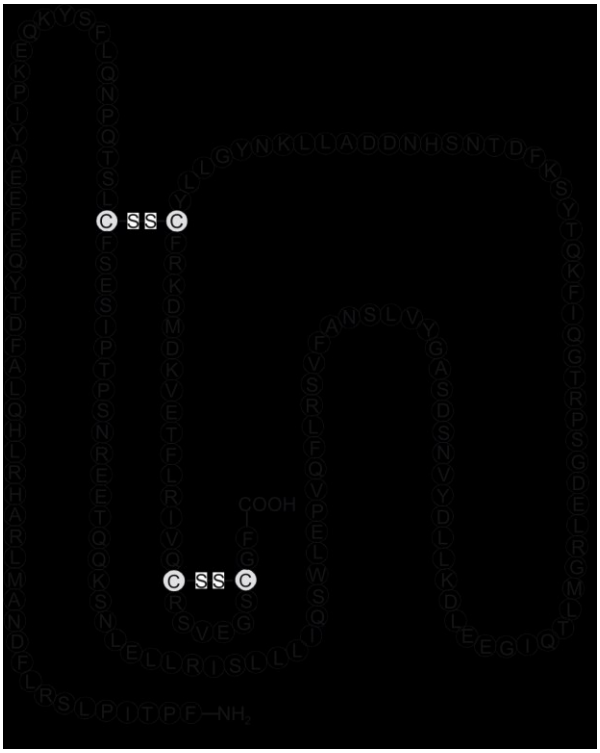
Proper name: Somatropin

Common name: recombinant human growth hormone (rhGH)

Molecular formula: $C_{990}H_{1528}N_{262}O_{300}S_7$ (191 amino acid residues)

Molecular mass: 22,125 Daltons

Structural formula:



Physicochemical properties:

Biological Activity: The biological activity of growth hormone is approximately 3.0 international units/1 mg.

CLINICAL TRIALS

Omnitrope is a subsequent entry biologic.

Comparative Pharmacokinetic and Pharmacodynamic Studies with Omnitrope
During the clinical development of the lyophilized powder and the liquid formulations of Omnitrope, six clinical pharmacology studies, EP2K-99-PhISUSA, EP2K-99-PhIUSA EP2K-00-PhI^{AQ}, EP00-104, EP00-105 and EP00-107, were performed in healthy volunteers after a single subcutaneous dose of 5 mg. Five of these Phase I studies were comparative bioavailability studies.

Pharmacokinetics
The results for the pharmacokinetic parameters of the Growth Hormone (GH) concentrations determined during the four comparative Phase I studies are summarized in the tables below.

Table 19: Pharmacokinetic Parameters after a Single SC Administration of 5 mg Omnitrope Powder for Solution for Injection (5.8 mg/vial) and of 5 mg Genotropin® 5 mg/mL Powder for Solution for Injection – Study EP2K-99-PhIUSA

	5 mg of Omnitrope powder for solution for injection; 5.8 mg/vial (N = 24)	5 mg of Genotropin® 5 mg/mL powder for solution for injection (N = 24)	Ratio and 90% confidence interval [%] (N = 24)
AUC_T [h·mcg/L]	413 ± 111	396 ± 106	104.18 [99.97 ; 108.58]
AUC_I [h·mcg/L]	416 ± 110	400 ± 105	104.00 [99.90 ; 108.27]
C_{max} [mcg/L]	52 ± 21	48 ± 20	106.96 [97.96 ; 116.78]
t_{max}* [h]	4 (2 - 8)	4 (2 - 10)	
$t_{1/2}$ [h]	2.7 ± 0.6	2.9 ± 0.6	

Results are presented as mean ± SD.
*median value (min - max) for t_{max}

Table 20: Pharmacokinetic Parameters after a Single SC Administration of 5 mg Omnitrope 5 mg/1.5 mL Solution for Injection and of 5 mg Omnitrope Powder for Solution for Injection (5.8 mg/vial) – Study EP2K-00-PhI^{AQ}

	5 mg of Omnitrope 5 mg/1.5 mL solution for injection (N = 24)	5 mg of Omnitrope powder for solution for injection; 5.8 mg/vial (N = 24)	Ratio and 90% confidence interval [%] (N = 24)

	5 mg of Omnitrope 5 mg/1.5 mL solution for injection (N = 24)	5 mg of Omnitrope powder for solution for injection; 5.8 mg/vial (N = 24)	Ratio and 90% confidence interval [%] (N = 24)
AUC_T [h·mcg/L]	422 ± 45	453 ± 43	93.13 [89.89 ; 96.48]
AUC_I [h·mcg/L]	426 ± 45	456 ± 44	93.32 [90.10 ; 96.65]
C_{max} [mcg/L]	52 ± 10	55 ± 13	94.76 [90.29 ; 99.45]
t_{max}* [h]	3 (2 - 8)	3 (2 - 10)	
$t_{1/2}$ [h]	2.4 ± 0.7	2.4 ± 0.6	

Results are presented as mean ± SD.
*median value (min - max) for t_{max}

Table 21: Pharmacokinetic Parameters after a Single SC Administration of 5 mg Omnitrope 5 mg/1.5 mL Solution for Injection, of 5 mg Omnitrope Powder for Solution for Injection (5.8 mg/vial), and of 5 mg Genotropin® 5 mg/mL Powder for Solution for Injection – Study EP00-104

	5 mg of Omnitrope powder for solution for injection; 5.8 mg/vial (N = 35)	5 mg of Omnitrope 5.0 mg/1.5 mL solution for injection (N = 35)	5 mg of Genotropin® 5 mg/mL powder for solution for injection (N = 35)
AUC_T [h·mcg/L]	559 ± 148	542 ± 141	588 ± 133
AUC_I [h·mcg/L]	566 ± 147	546 ± 140	592 ± 131
C_{max} [mcg/L]	71 ± 24	72 ± 28	78 ± 27
t_{max}* [h]	4 (2 - 6)	4 (2 - 8)	4 (2 - 8)
$t_{1/2}$ [h]	3.2 ± 0.7	2.8 ± 0.7	2.6 ± 0.7
Ratio of LS-Means and 90% CI [%]	AUC_T: 103.58 [98.86 ; 108.52] AUC_I: 103.90 [99.23 ; 108.78] C_{max}: 102.15 [94.28 ; 110.68]		
	AUC_T: 94.20 [89.90 ; 98.69] AUC_I: 94.67 [90.42 ; 99.12] C_{max}: 91.57 [84.51 ; 99.22]		
	AUC_T: 90.94 [86.80 ; 95.29] AUC_I: 91.12[87.03 ; 95.40] C_{max}: 89.64 [82.73 ; 97.12]		

Results are presented as mean ± SD.
*median value (min - max) for t_{max}

Table 22: Pharmacokinetic Parameters after a Single SC Administration of 5 mg Omnitrope 10 mg/1.5 mL Solution for Injection, of 5 mg Omnitrope Powder for Solution for Injection (5.8 mg/vial), and of 5 mg Genotropin® 5 mg/mL Powder for Solution for Injection – Study EP00-105

	5 mg of Omnitrope powder for solution for injection; 5.8 mg/vial (N = 32)	**5 mg of Omnitrope 10 mg/1.5 mL solution for injection (N = 32)**	**5 mg of Genotropin® 5 mg/mL powder for solution for injection (N = 32)**
AUC_T [h·mcg/L]	550 ± 96	558 ± 115	537 ± 110
AUC_I [h·mcg/L]	555 ± 96	561 ± 114	540 ± 110
C_{max} [mcg/L]	69 ± 16	74 ± 22	73 ± 20
t_{max}* [h]	4 (2 - 6)	4 (2 - 6)	4 (2 - 6)
$t_{1/2}$ [h]	2.9 ± 0.5	2.5 ± 0.7	2.5 ± 0.7
Ratio of LS-Means and 90% CI [%]	AUC_T: 98.70 [95.54 ; 101.96] AUC_I: 98.81 [95.64 ; 102.09] C_{max}: 95.28 [90.59 ; 100.22]		
	AUCT: 102.27 [99.03 ; 105.62] AUC_I: 102.28 [99.03 ; 105.64] C_{max}: 95.89 [91.22 ; 100.81]		
	AUC_T: 103.62 [100.34 ; 107.01] AUC_I: 103.51 [100.22 ; 106.91] C_{max}: 100.64 [95.74 ; 105.80]		

Results are presented as mean ± SD.
*median value (min - max) for t_{max}

Table 23: Pharmacokinetic Parameters after a Single SC Administration of 5 mg Omnitrope 15 mg/1.5 mL Solution for Injection, of 5 mg Omnitrope Powder for Solution for Injection (5.8 mg/vial), and of 5 mg Genotropin® 5 mg/mL Powder for Solution for Injection – Study EP00-107

	5 mg of Omnitrope powder for solution for injection; 5.8 mg/vial (N = 33)	**5 mg of Omnitrope 15 mg/1.5 mL solution for injection (N = 33)**	**5 mg of Genotropin® 5 mg/mL powder for solution for injection (N = 33)**
AUC_T [h·mcg/L]	424.31 (109.40)	394.60 (98.58)	407.00 (114.27)
AUC_I [h·mcg/L]	419.16 (112.34)	391.51 (100.47)	403.86 (115.79)
C_{max} [mcg/L]	55.22 (21.50)	52.89 (19.09)	53.64 (20.33)
t_{max}* [h]		4.02 [2.02; 6.03]	4.03 [2.02; 6.03]
$t_{1/2}$ [h]	3.24 (0.91)	2.76 (0.85)	2.75 (0.82)
Ratio of LS-Means and 90% CI [%]		AUC_T: 1.06 [1.03 ; 1.10] AUC_I: 1.070 C_{max}: 1.03 [0.96 ; 1.10]	
		AUC_T: 1.04 [1.01 ; 1.07] AUC_I: 1.05 C_{max}: 1.02 [0.95 ; 1.09]	
		AUC_T: 0.98 [0.95 ; 1.01] AUC_I: 0.98 C_{max}: 0.99 [0.93 ; 1.06]	

Results are presented as mean ± SD.
*median value (min - max) for t_{max}

After single doses of 5 mg of Omnitrope are administered via SC route, bioequivalence was demonstrated among the different formulations and strengths of Omnitrope products. Bioavailability of Omnitrope lyophilized powder 5.8 mg/Vial, solution for injection 5 mg/1.5 mL 10 mg/1.5mL and 15 mg/1.5mL are comparable to that of Genotropin® 5.8 mg (5 mg/mL) at the same dose administered via the same route in adult healthy volunteers.

Pharmacodynamics

The results for the pharmacodynamic parameters IGF-1, IGFBP-3, and NEFA determined during the five comparative Phase I studies are summarized in the tables below.

Table 24: Pharmacodynamic Parameters after a Single SC Administration of 5 mg Omnitrope Powder for Solution for Injection (5.8mg/vial) and of 5 mg Genotropin® 5 mg/mL Powder for Solution for Injection – Study EP2K-99-PhIUSA

		5 mg of Omnitrope powder for solution for injection; 5.8 mg/vial (N = 24)	5 mg of Genotropin® 5 mg/mL powder for solution for injection (N = 24)	Ratio and 95% confidence interval [%] (N = 24)
IGF-1	AUEC [h·mcg/L]	31974 ± 10766	29893 ± 9569	106.11 [97.18; 115.86]
	E_{max} [mcg/L]	458 ± 159	428 ± 152	106.58 [92.51; 122.80]
	$t_{max,E}$* [h]	24 (12 - 97)	24 (12 - 96)	
IGFBP-3	AUEC [h·mg/L]	420 ± 124	431 ± 148	98.55 [90.72; 107.06]
	E_{max} [mg/L]	5.6 ± 2.1	5.3 ± 1.9	103.83 [94.99; 113.49]
	$t_{max,E}$* [h]	24 (0 - 97)	48 (0 - 97)	
NEFA	AUEC [h·mmol/L]	10.4 ± 4.2	10.7 ± 4.0	97.44 [84.00; 113.04]
	E_{max} [mmol/L]	1.0 ± 0.2	1.0 ± 0.3	102.02 [89.50; 116.30]
	$t_{max,E}$* [h]	4 (3 - 8)	4 (3 - 12)	

Results are presented as mean ± SD.
*median value (min - max) for $t_{max,E}$

Table 25: Pharmacodynamic Parameters after a Single SC Administration of 5 mg Omnitrope 5 mg/1.5 mL Solution for Injection and of 5 mg Omnitrope Powder for Solution for Injection (5.8 mg/vial) – Study EP2K-00-PhI[AQ]

		5 mg of Omnitrope 5 mg/1.5 mL solution for injection (N = 24)	5 mg of Omnitrope powder for solution for injection; 5.8 mg/vial (N = 24)	Ratio and 95% confidence interval [%] (N = 24)
IGF-1	AUEC [h·mcg/L]	19087 ± 4684	18806 ± 4381	101.50 [96.62; 106.62]
	E_{max} [mcg/L]	264 ± 58	260 ± 53	101.44 [95.78; 107.45]
	$t_{max,E}$* [h]	24 (12 - 24)	24 (12 - 48)	
IGFBP-3	AUEC [h·mg/L]	358 ± 69	362 ± 71	98.91 [94.87; 103.13]
	E_{max} [mg/L]	4.3 ± 0.9	4.4 ± 0.8	97.01 [90.87; 103.57]
	$t_{max,E}$* [h]	24 (12 - 24)	24 (12 - 48)	
NEFA	AUEC [h·mmol/L]	10.7 ± 4.1	10.8 ± 4.1	99.39 [86.37; 114.37]
	E_{max} [mmol/L]	0.9 ± 0.3	0.8 ± 0.3	109.20 [95.30; 125.11]
	$t_{max,E}$* [h]	3 (2 - 8)	3 (2 - 10)	

Results are presented as mean ± SD.
*median value (min - max) for t_{max}

Table 26: Pharmacodynamic Parameters after a Single SC Administration of 5 mg Omnitrope, 5 mg/1.5 mL Solution for Injection and of 5 mg Omnitrope 5 mg/mL Powder for Solution for Injection (5.8 mg/vial), and of 5 mg Genotropin® 5 mg/mL Powder for Solution for Injection – Study EP00-104

IGF-1	**5 mg of Omnitrope powder for solution for injection; 5.8 mg/vial (N = 35)**	**5 mg of Omnitrope 5.0 mg/1.5 mL solution for injection (N = 35)**	**5 mg of Genotropin® 5 mg/mL powder for solution for injection (N = 35)**
AUEC [h·mcg/L]	16712 ± 3847	16295 ± 3664	15960 ± 3557
E_{max} [mcg/L]	218 ± 56	213 ± 49	209 ± 49
$t_{max,E}$* [h]	24 (12 - 48)	24 (12 - 48)	24 (12 - 48)
Ratio of LS-Means and 95% CI [%]	X	X	
	AUEC: 102.35 [98.70 ; 106.13]		
	E_{max}: 102.15 [94.28 ; 110.68]		
	X		X
	AUEC: 104.51 [100.78 ; 108.37]		
	E_{max}:104.08 [99.34 ; 109.04]		
		X	X
		AUEC: 102.11 [98.47 ; 105.89]	
		E_{max}: 102.19 [97.53 ; 107.06]	

Results are presented as mean ± SD.
*median value (min - max) for $t_{max,E}$

IGFBP-3	**5 mg of Omnitrope powder for solution for injection; 5.8 mg/vial (N = 35)**	**5 mg of Omnitrope 5.0 mg/1.5 mL solution for injection (N = 35)**	**5 mg of Genotropin® 5 mg/mL powder for solution for injection (N = 35)**
AUEC [h·mg/L]	430 ± 61	427 ± 56	424 ± 57
E_{max} [mg/L]	4.9 ± 0.7	4.9 ± 0.6	4.9 ± 0.7
$t_{max,E}$* [h]	48 (24 - 96)	48 (12 - 96)	48 (16 - 72)
Ratio of LS-Means and 95% CI [%]	X	X	
	AUEC: 100.49 [98.74 ; 102.27]		
	E_{max}: 100.58 [97.90 ; 103.34]		
	X		X
	AUEC: 101.23 [99.47 ; 103.02]		
	E_{max}: 101.12 [98.42 ; 103.89]		
		X	X
		AUEC: 100.73 [98.98 ; 102.52]	
		E_{max}: 100.53 [97.85 ; 103.28]	

Results are presented as mean ± SD.
*median value (min - max) for $t_{max,E}$

NEFA	**5 mg of Omnitrope powder for solution for injection; 5.8 mg/vial (N = 35)**	**5 mg of Omnitrope 5.0 mg/1.5 mL solution for injection (N = 35)**	**5 mg of Genotropin® 5 mg/mL powder for solution for injection (N = 35)**
AUEC [h·mmol/L]	11.8 ± 3.8	11.5 ± 3.0	12.5 ± 3.8
E_{max} [mmol/L]	1.0 ± 0.3	0.9 ± 0.3	1.0 ± 0.3
$t_{max,E}$* [h]	2 (0 - 16)	2 (1 - 24)	3 (1 - 16)
Ratio of LS-Means and 95% CI [%]	X	X	
	AUEC: 101.96 [92.26 ; 112.67]		
	E_{max}: 102.64 [94.65 ; 111.30]		
	X		X
	AUEC: 94.03 [85.09 ; 103.91]		
	E_{max}:95.27 [87.85 ; 103.31]		
		X	X
		AUEC: 92.23 [83.46 ; 101.92]	
		E_{max}: 92.92 [95.60 ; 100.65]	

Results are presented as mean ± SD.
*median value (min - max) for $t_{max,E}$

Table 27: Pharmacodynamic Parameters after a Single SC Administration of 5 mg Omnitrope 10 mg/1.5 mL Solution for Injection, of 5 mg Omnitrope Powder for Solution for Injection (5.8 mg/vial), and of 5 mg Genotropin® 5 mg/mL Powder for Solution for Injection – Study EP00-105

IGF-1	**5 mg of Omnitrope powder for solution for injection; 5.8 mg/vial (N = 32)**	**5 mg of Omnitrope 10.0 mg/1.5 mL solution for injection (N = 32)**	**5 mg of Genotropin® 5 mg/mL powder for solution for injection (N = 32)**
AUEC [h·mcg/L]	20355 ± 5067	19829 ± 5107	19126 ± 5072
E_{max} [mcg/L]	267 ± 64	265 ± 68	252 ± 67
$t_{max,E}$* [h]	24 (16 - 48)	24 (16 - 24)	24 (12 - 24)
Ratio of LS-Means and 95% CI [%]	X	X	
	AUEC: 100.04 [93.47 ; 107.07]		
	E_{max}: 100.42 [96.66 ; 104.32]		
	X		X
	AUEC: 108.71 [101.57 ; 116.36]		
	E_{max}:105.90 [101.93 ; 110.02]		
		X	X
		AUEC: 108.67 [101.61 ; 116.22]	
		E_{max}: 105.46 [101.55 ; 109.52]	

Results are presented as mean ± SD.
*median value (min - max) for $t_{max,E}$

IGFBP-3	**5 mg of Omnitrope powder for solution for injection; 5.8 mg/vial (N = 32)**	**5 mg of Omnitrope 10.0 mg/1.5 mL solution for injection (N = 32)**	**5 mg of Genotropin® 5 mg/mL powder for solution for injection (N = 32)**
AUEC [h·mg/L]	471 ± 70	468 ± 67	459 ±66
E_{max} [mg/L]	5.4 ± 0.8	5.4 ± 0.8	5.3 ± 0.7
$t_{max,E}$* [h]	48 (16 - 96)	48 (0 - 72)	48 (24 - 72)
Ratio of LS-Means and 95% CI [%]	X	X	
	AUEC: 98.21 [91.82 ; 105.04]		
	E_{max}: 99.49 [96.67 ; 102.40]		
	X		X
	AUEC: 104.79 [97.97 ; 112.08]		
	E_{max}: 102.14 [99.24 ; 105.12]		
		X	X
		AUEC: 106.70 [99.83 ; 114.04]	
		E_{max}: 102.66 [99.78 ; 105.62]	

Results are presented as mean ± SD.

*median value (min - max) for $t_{max,E}$

NEFA	5 mg of Omnitrope powder for solution for injection; 5.8 mg/vial (N = 32)	5 mg of Omnitrope 10.0 mg/1.5 mL solution for injection (N = 32)	5 mg of Genotropin® 5 mg/mL powder for solution for injection (N = 32)
AUEC [h·mmol/L]	13.1 ± 3.8	12.8 ± 3.7	12.0 ± 4.2
E_{max} [mmol/L]	1.1 ± 0.3	1.1 ± 0.3	1.0 ± 0.3
$t_{max,E}$* [h]	3 (1 - 16)	3 (2 - 16)	3 (1 - 20)
Ratio of LS-Means and 95% CI [%]	X	X	
	AUEC: 103.25 [94.53 ; 112.78]		
	E_{max}: 96.87 [88.35 ; 106.21]		
	X		X
	AUEC: 113.01 [103.56 ; 123.33]		
	E_{max}:111.81 [102.07 ; 122.48]		
		X	X
		AUEC: 109.46 [100.30 ; 119.45]	
		E_{max}: 115.43 [105.37 ; 126.44]	

Results are presented as mean ± SD.
*median value (min - max) for $t_{max,E}$

Table 28: Pharmacodynamic Parameters after a Single SC Administration of 5 mg Omnitrope 15.0 mg/1.5 mL Solution for Injection, of 5 mg Omnitrope 5 mg/mL Powder for Solution for Injection (5.8 mg/vial), and of 5 mg Genotropin® 5 mg/mL Powder for Solution for Injection – Study EP00-107

IGF-1	**5 mg of Omnitrope powder for solution for injection; 5.8 mg/vial (N = 33)**	**5 mg of Omnitrope 15.0 mg/1.5 mL solution for injection (N = 33)**	**5 mg of Genotropin® 5 mg/mL powder for solution for injection (N = 33)**
AUEC [h·mcg/L]	27878.79 (7809.28)	28181.82 (8822.75)	28757.58 (8996.63)
E_{max} [mcg/L]	389.09 (106.14)	383.09 (115.23)	387.76 (118.75)
$t_{max,E}$* [h]	24.02 [12.03; 48.03]	24.03 [12.02; 48.03]	24.017 [12.00; 24.03]
Ratio of LS-Means and 95% CI [%]	X 1.01 [0.93 ; 1.10] 1.03 [0.970 ; 1.09]	X	
	X 0.99 [0.91; 1.08] 1.02 [0.96 ; 1.08]		X
		X 0.98 [0.90 ; 1.07] 0.99 [0.94 ; 1.05]	X

Results are presented as mean ± SD.
*median value (min - max) for $t_{max,E}$

IGFBP-3	**5 mg of Omnitrope powder for solution for injection; 5.8 mg/vial (N = 33)**	**5 mg of Omnitrope 15.0 mg/1.5 mL solution for injection (N = 33)**	**5 mg of Genotropin® 5 mg/mL powder for solution for injection (N = 33)**
AUEC [h·mg/L]	497.77 (62.87)	489.30 (68.01)	498.79 (69.10)
E_{max} [mg/L]	5.67 (0.71)	5.58 (0.72)	5.719 (0.79)
$t_{max,E}$* [h]	48.03 [12.03; 96.03]	48.03 [12.02; 72.17]	48.03 [12.02; 96.02]
Ratio of LS-Means and 95% CI [%]	X 1.02 [1.00 ; 1.00] 1.02 [0.99; 1.04]	X	
	X 0.999 [0.98 ; 1.02] 0.992 [0.97 ; 1.02]		X
		X	X 0.98 [0.96 ; 1.00]

IGFBP-3	5 mg of Omnitrope powder for solution for injection; 5.8 mg/vial (N = 33)	5 mg of Omnitrope 15.0 mg/1.5 mL solution for injection (N = 33)	5 mg of Genotropin® 5 mg/mL powder for solution for injection (N = 33)
			0.98 [0.95 ; 1.00]

Results are presented as mean ± SD.
*median value (min - max) for $t_{max,E}$

NEFA	5 mg of Omnitrope powder for solution for injection; 5.8 mg/vial (N = 33)	5 mg of Omnitrope 15.0 mg/1.5 mL solution for injection (N = 33)	5 mg of Genotropin® 5 mg/mL powder for solution for injection (N = 33)
AUEC [h·mmol/L]	13.13 (3.77)	13.56 (4.78)	13.23 (3.83)
E_{max} [mmol/L]	1.17 (0.19)	1.13 (0.39)	1.13 (0.24)
$t_{max,E}$* [h]	3.00 [1.02; 16.03]	3.033 [1.03; 16.03]	3.00 [0.00; 16.03]
Ratio of LS-Means and 95% CI [%]	X	X	
	1.00 [0.92 ; 1.08]		
	1.07 [0.99 ; 1.17]		
	X		X
	0.99 [0.91 ; 1.08]		
	1.05 [0.96 ; 1.14]		
		X	X
		1.00 [0.92 ; 1.09]	
		0.98 [0.90 ; 1.06]	

Results are presented as mean ± SD.
*median value (min - max) for $t_{max,E}$

Conclusion:
The pharmacodynamic responses in terms of IGF-1, IGFBP-3, and NEFA were highly comparable after single doses of 5 mg of the different strengths and formulations of Omnitrope and of Genotropin®.

Clinical Efficacy and Safety Studies with Omnitrope

Pediatric Growth Hormone Deficiency (GHD)

Five Phase III studies were performed in a total of 190 pediatric patients who have growth failure due to an inadequate secretion of endogenous growth hormone (See Table 29).

Table 29: Study Demographics and Trial Design for Phase III Trials

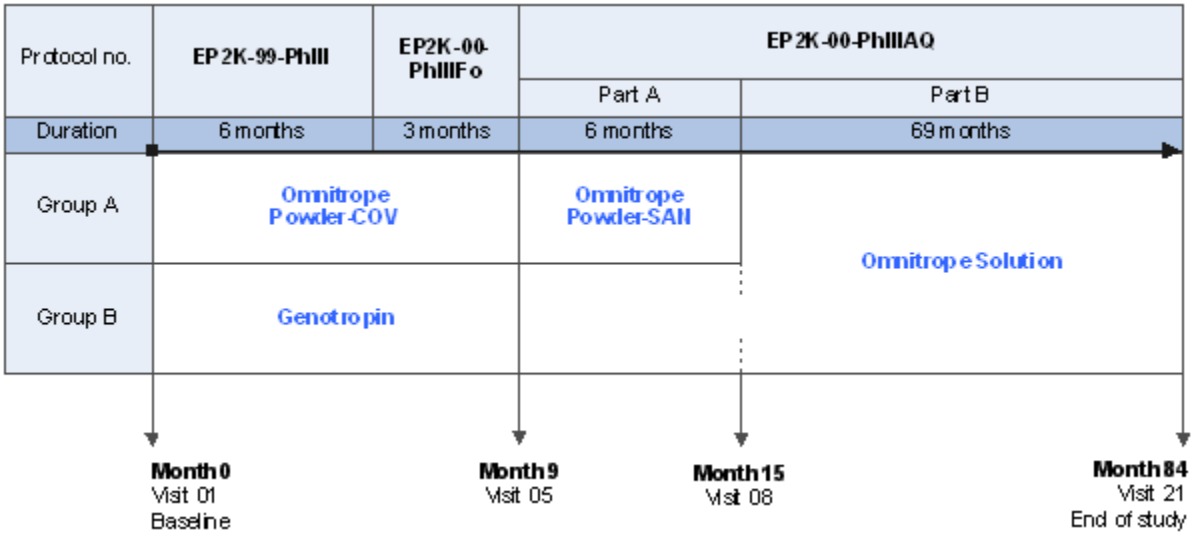
Study Number	Length of Study	Trial Design	Dosage, Route of Administration and Duration	Study Subjects (N)	Gender, Mean Age (Range)
EP2K-99-PhIII	6 months	Phase III, randomized, open, multicentre, controlled, parallel two-group study of Omnitrope lyophilizate and Genotropin® in GHD children with growth failure	S: Omnitrope powder for solution for injection; 5.8 mg/vial C: Genotropin® 5mg/mL powder 0.03 mg/kg SC, once daily	89	S: 28M, 16F 7.8 yrs (3-13 yrs) C: 21M, 24F 7.4 yrs (2-14 yrs)
EP2K-00-PhIIIFo	3 months				
EP2K-00-PhIII^{AQ} Part A	6 months (from months 9 to 15 of overall GH therapy)	Phase III, open, multicentre, comparative, parallel two-group study of Omnitrope lyophilizate and Omnitrope liquid.	S1: Omnitrope powder for solution for injection; 5.8 mg/vial S2: Omnitrope 5mg/1,5mL solution for injection 0.03 mg/kg SC, once daily	86	S1: 27M, 15F 8.8 yrs (4-14 yrs) S2: 20M, 24F 8.1 yrs (3-14 yrs)
EP2K-00-PhIII^{AQ} Part B	69 months, (from months 16 - 84 of overall GH therapy)	Phase III, open, multicentre, non-comparative follow-up study of Omnitrope liquid.	Omnitrope 5mg/1,5mL solution for injection 0.03 mg/kg SC, once daily	86	47M, 39F 9.4 yrs (4-15 yrs)
EP2K-00-PhIIIb-E	60 months,	Phase III, open, multicentre study to demonstrate the efficacy and safety of Omnitrope liquid 5.0 mg/1.5 mL in the treatment of growth-deficient children due to GHD.	Omnitrope 5mg/1,5mL solution for injection 0.03 mg/kg SC, once daily	50	44M, 26F 8.7 yrs (4-12 yrs)
EP2K-02-PhIII-Lyo	48 months, (up to 54 months)	Phase III, open, multicentre study to demonstrate the efficacy and safety of Omnitrope lyophilizate 5.8 mg in the treatment of growth-deficient children due to GHD.	Omnitrope powder for solution for injection; 5.8 mg/vial 0.03 mg/kg SC, once daily	51	30M, 21F 7.6 yrs (2-14 yrs)

C: Comparator
S: Omnitrope lyophilize powder with active ingredient from Covance Biotechnology, USA (not available on the market).
S1: Omnitrope lyophilize powder with active ingredient from Sandoz, Austria.
S2: Omnitrope solution for injection with active ingredient from Sandoz, Austria.

The efficacy and safety of Omnitrope was compared with Genotropin®, a somatropin product authorized for treatment of growth hormone deficiency (GHD) in pediatric patients. In a randomized clinical trial involving a total of 89 GHD children, 44 patients received Omnitrope powder for solution for injection (5.8 mg/vial) and 45 patients received Genotropin® for 9 months. In both groups, somatropin was administered as a daily subcutaneous injection at a dose of 0.03 mg/kg. Subsequently, after 9 months of treatment, patients who had received Genotropin® switched to Omnitrope Solution (5.0 mg/mL). Omnitrope Powder was continued beyond 9 months on the same treatment and dose. After 15 months of treatment, all patients were switched

to Omnitrope Solution (5.0 mg/mL) to collect long-term efficacy and safety data for Omnitrope Solution. The route of administration, dose and duration was the same for Omnitrope Powder and Omnitrope Solution.

Figure 2: Design of the three consecutive Phase III studies EP2K-99-PhIII/ EP2K-00-PhIIIFo/EP2K-00-PhIII[AQ]



Omnitrope powder-COV: active ingredient from Covance Biotechnology, USA (not available on the market).
Omnitrope powder-SAN: lyophilize powder with active ingredient from Sandoz, Austria.

The efficacy results of treatment with Omnitrope lyophilized powder, Omnitrope Solution and the Genotropin® are summarized in Table 30, Table 31 and Table 32.

Table 30: Key primary endpoints in Phase III Studies EP2K-99-PhIII/EP2K-00-PhIIIFo (mean ± SD)

	Omnitrope lyophilizate N=44 Mean (SD)	**Genotropin®** N=45 Mean (SD)	**Treatment effect** Mean (95% CI)
Height Velocity (cm/yr)			
Pre-treatment	3.8 (1.2)	3.9 (0.8)	
Month 9	10.7 (2.6)	10.7 (2.9)	
Change from pre-treatment to Month 9	6.9 (3.1)	6.8 (3.2)	-0.1 (-1.5;1.3)
Height velocity SDS			
Pre-treatment	-2.3 (1.3)	-2.3 (0.9)	
Month 9	5.9 (3.4)	5.0 (2.9)	
Change from pre-treatment to Month 9	8.2 (4.0)	7.4 (3.2)	-0.9 (-2.4;0.7)
Height SDS			
Pre-treatment	-3.0 (0.7)	-3.1 (0.9)	
Month 9	-2.3 (0.7)	-2.5 (0.7)	
Change from pre-treatment to Month 9	0.8 (0.4)	0.7 (0.5)	-0.1 (-0.3;0.1)
IGF-1			
Pre-treatment	158.6 (92.0)	157.7 (43.0)	
Month 9	291.1 (174.0)	301.9 (182.9)	
IGFBP-3			

Pre-treatment	3.5 (1.3)	3.5 (1.0)	
Month 9	4.6 (3.0)	4.0 (1.5)	

Table 31: Key primary endpoints in Phase III Study EP2K-00-PhIII[AQ] Part A (mean ± SD)

	Omnitrope lyophilizate N=42 Mean (SD)	**Omnitrope liquid** N=44 Mean (SD)	**Treatment effect** Mean (95% CI)
Height Velocity (cm/yr)			
Month 9	10.7 (2.6)	10.7 (2.9)	
Month 15	9.3 (1.7)	9.4 (2.2)	
Change from Month 9 to Month 15	-1.4 (1.4)	-1.4 (1.3)	0.0 (-0.6;0.6)
Height velocity SDS			
Month 9	5.9 (3.4)	5.0 (2.9)	
Month 15	4.4 (2.9)	3.6 (2.2)	
Change from Month 9 to Month 15	-1.5 (1.7)	-1.4 (1.4)	0.1 (-0.6;0.7)
Height SDS			
Month 9	-2.3 (0.7)	-2.5 (0.7)	
Month 15	-2.0 (0.7)	-2.2 (0.7)	
Change from Month 9 to Month 15	0.3 (0.2)	0.3 (0.2)	0.0 (-0.1;0.1)
IGF-1			
Month 9	291 (174)	302 (183)	
Month 15	300 (225)	323 (189)	
IGFBP-3			
Month 9	4.6 (3.0)	4.0 (1.5)	
Month 15	4.6 (1.3)	4.9 (1.4)	

Table 32: Key primary endpoints in Phase III Study EP2K-00-PhIII[AQ] Part B (mean ± SD)

		Omnitrope liquid N=86	
Height velocity (cm/yr)	N	Mean	SD
Month 15	86	9.32	1.95
Month 24	80	7.69	1.58
Month 36	75	7.06	2.04
Month 48	69	6.58	1.60
Month 60	65	6.07	2.08
Month 72	59	5.69	2.33
Month 84	49	5.53	2.34
Height velocity SDS			
Month 15	86	4.01	2.64
Month 24	79	2.17	2.18
Month 36	75	1.82	2.50
Month 48	66	1.58	1.94
Month 60	59	0.87	1.91
Month 72	53	0.26	1.92
Month 84	47	–0.02	2.68
Height SDS			
Month 15	85	–2.10	0.73
Month 24	80	–1.86	0.80
Month 36	75	–1.59	0.89

		Omnitrope liquid N=86	
Month 48	69	–1.31	0.89
Month 60	64	–1.16	0.97
Month 72	58	–0.97	0.87
Month 84	49	–0.91	0.97
IGF-1			
Month 15	86	296.1	209.9
Month 24	80	330.8	168.6
Month 36	75	443.1	230.3
Month 48	69	467.7	218.2
Month 60	65	403.4	167.1
Month 72	59	447.3	154.9
Month 84	49	395.1	132.7
IGFBP-3			
Month 15	86	6.66	1.89
Month 24	80	8.52	2.27
Month 36	75	6.54	1.76
Month 48	69	6.35	1.23
Month 60	65	5.76	0.95
Month 72	59	6.09	1.11
Month 84	49	5.72	1.43

Height velocity SDS: peak centered

The three sequential Phase III studies EP2K-99-PhIII, EP2K-00-PhIIIFo, and EP2K-00-PhIII^{AQ} in the same group of patients have demonstrated the following:

- Omnitrope has a clinical efficacy and safety profile in the treatment of GHD children which is comparable to Genotropin®.
- The lyophilized powder and liquid formulations of Omnitrope have comparable clinical efficacy and safety profiles in the treatment of children with GHD.
- Omnitrope given to GHD children up to 84 months, was shown to be efficacious.

Results from studies EP2K-02-PhIII-Lyo and EP2K-00-PhIIIb-E

Two additional open-label Phase III studies, EP2K-02-PhIII-Lyo and EP2K-00-PhIIIb-E, were initiated to further investigate the efficacy and safety of Omnitrope lyophilized powder for solution for injection (5.8 mg/vial) and Omnitrope Solution (5.0 mg/1.5 mL solution for injection), respectively, in somatropin treatment-naïve prepubertal children with growth hormone deficiency and to confirm the low immunogenicity of both products. The studies provided long-term efficacy and safety data, with EP2K-02-PhIII-Lyo covering up to 48 months and EP2K-00 PhIIIb-E covering up to 60 months studies of GH treatment.

Growth of the children treated with Omnitrope liquid and Omnitrope powder was comparable. The small differences in growth parameters between the studies can be explained by the average higher age of the children in study EP2K-00-PhIIIb-E.

The efficacy results were consistent with the results obtained in previous studies with Omnitrope and as expected with regard to the results obtained with other rhGH products in the treatment of

GHD children. With regard to secondary efficacy results, synthesis of IGF-1 and the corresponding binding protein IGFBP-3 was directly stimulated by Omnitrope. The safety profile of Omnitrope is consistent with the profile for rhGH treatment of previously untreated GHD children and confirmed the low immunogenicity of Omnitrope. In summary, safety and efficacy of rhGH treatment with Omnitrope liquid and Omnitrope powder were confirmed.

Table 33: Baseline Growth Characteristics and Effect of OMNITROPE® in Phase III Studies (mean ± SD)

	EP2K-02-PhIII-Lyo Omnitrope powder for solution for injection; 5.8 mg/vial N=51 Mean (SD)	**EP2K-00-PhIIIb-E Omnitrope 5.0 mg/1.5 mL solution for injection** N=50 Mean (SD)
Height Velocity (cm/yr)		
Month 0	3.72 (1.40)	3.86 (1.25)
Month 12	10.39 (2.50)	9.39 (2.23)
Month 24	7.58 (1.63)	7.91 (2.09)
Month 36	6.69 (2.15)	6.75 (1.59)
Month 48	6.27 (1.91)	6.17 (1.71)
Month 60		7.58 (1.80)
Height velocity SDS (Peak centered, Tanner)		
Month 0	-2.25 (1.68)	-2.08 (1.47)
Month 12	5.22 (2.96)	4.19 (2.86)
Month 24	2.09 (2.25)	1.77 (2.40)
Month 30	1.12 (2.74)	0.92 (2.14)
Month 48	0.94 (2.30)	1.35 (2.03)
Month 60		2.66 (2.43)
Height SDS (National)		
Month 0	-2.97 (0.87)	-2.98 (0.60)
Month 12	-2.15 (0.74)	-2.17 (0.57)
Month 24	-1.76 (0.75)	-1.73 (0.66)
Month 36	-1.50 (0.88)	-1.56 (0.70)
Month 48	-1.38 (1.12)	-1.25 (0.67)
Month 60		-1.12 (0.42)
IGF-1 (ng/mL)		
Month 0	78.8 (46.9)	127.2 (73.7)
Month 12	208.4 (105.9)	244.5 (123.6)
Month 24	208.8 (92.7)	300.7 (152.5)
Month 30	254.5 (116.0)	342.1 (129.6)
Month 48	259.5 (115.4)	379.3 (144.2)
Month 60		387.3 (96.7)
IGFBP-3 (ng/mL)		
Month 0	2733.9 (1025.5)	2959.7 (756.4)
Month 12	365 (878.5)	3989.4 (850.8)
Month 24	389 (860.1)	3713.8 (866.7)
Month 30	3518.7 (787.7)	3986.6 (823.6)
Month 48	4009.1 (961.8)	3793.0 (793.4)
Month 60		3711.3 (69.9)

Small for gestational age (SGA), Turner Syndrome (TS), Idiopathic Short Stature (ISS) and Growth Hormone Deficiency (GHD) in adults:
The indications for small for gestational age (SGA), with Turner Syndrome (TS), Idiopathic Short Stature (ISS) or Growth Hormone Deficiency (GHD) in adults have been granted on the basis of demonstrated similarity between Omnitrope and the reference product, Genotropin, and on the basis of the similarity of mechanism of action and disease pathophysiology of these indications and GHD in children. Thus, although there were no clinical trials conducted with Omnitrope in patients small for gestational age (SGA), with Turner Syndrome (TS) or Idiopathic Short Stature (ISS), as in the case for adults with growth hormone deficiency (GHD), granting of these pediatric indications also involved data extrapolation. Omnitrope and the reference product Genotropin were demonstrated to be highly similar in comparative physico-chemical and biological studies, comparative non-clinical, comparative human pharmacokinetic/pharmacodynamic and comparative clinical efficacy and safety studies in children which demonstrated comparable clinical profiles between Omnitrope and the reference product. The dosage regimen as well as the safety profile and clinical experience with the reference product were also factors considered.

DETAILED PHARMACOLOGY

Animal Pharmacology

Pharmacodynamics
The efficacy of recombinant human growth hormone has been measured by different methods, mostly in the rat. Growth hormone is an anabolic hormone, and exerts a wide spectrum of actions *in vivo* and *in vitro*. Some of these important effects are as follows: stimulation of postnatal somatic growth; insulin-like effects; lipolytic.

The pharmacodynamic properties of Omnitrope were evaluated in rat weight gain bioassays and a rat tibial width assay.

Rat Weight Gain Bioassay
When a growing rat is hypophysectomized, it stops gaining weight and growing in length. Since somatropin promotes growth of skeletal and soft tissue and influences the metabolism of carbohydrate, fat, and protein, it leads to weight gain in the rats.

The rat weight gain bioassays were performed to compare the efficacy of different formulations of human growth hormone to that of international standards when administered to hypophysectomized male Wistar rats. Groups of 10 male rats were given Omnitrope drug substances, Omnitrope drug products, reference somatropin, vehicle or an international standard at 5 or 10 mcg/animal daily, for 10 consecutive days by subcutaneous injections.

The results from the comparative biological assays showed the comparability of different batches of Omnitrope drug substances and Omnitrope drug products, the marketed reference somatropin and two international reference standards of human somatropin regarding their specific action on

body weight gain. The results confirm that Omnitrope is an authentic human growth hormone with the same quantitative activity as international standards and the marketed reference somatropin.

Rat Tibial Width Assay
The rat tibial width assay was performed to compare the potency of different human growth hormone products, each with a high and low content of product-related substances, by determining their effect on the increase of the width of the proximal epiphysis of the tibia in immature hypophysectomized rats with that of a standard preparation. The different formulations of human GH were administered by daily subcutaneous injections to rats for 10 consecutive days. Groups of 8 male rats were given Omnitrope liquid 5.0 mg/1.5 mL and Omnitrope lyophilizate 5.8 mg, marketed reference somatropins, vehicle or the standard at 6.7 or 53.3 mcg/animal/day.

The pharmacodynamic effects on the increase of the width of proximal epiphysis of the tibia in immature hypophysectomized rats were comparable for the different human growth hormone products tested (Omnitrope, marketed recombinant preparations, each with a high and low content of product-related substances) and were similar to the potency of the international standard of human somatropin.

Human Pharmacology
Pharmacodynamics
In clinical trials with the reference product in short children born SGA doses of 0.24 mg/kg/wk (0.033 and 0.067 mg/kg/day) have been used for treatment until final height. A dose of 0.10 mg/kg/day has also been used for treatment but was associated with serious adverse events within a 24 month study period.

Pharmacokinetics
In a study with the reference product, the comparison of pharmacokinetic (pK) profiles in short children born small for gestational age (SGA) were assessed before (at baseline) and after 6 months of continuous somatropin treatment. Eighteen short (median height = - 3.5 SDS) SGA children (7 females) with a median age of 7.6 years (range: 3.9 - 11.5 years) at study start were included in this portion of the study. All patients were prepubertal at the time of both tests, which were performed at baseline and after 180 days (range 144 to 259 days) of somatropin treatment at a dose of treatment at a dose of 67 mcg/kg body weight/day.

For the pK studies, a somatropin dose of 67 mcg/kg was administered at baseline (before somatropin therapy was started) and 24 hours after the last somatropin dose. Blood samples were collected hourly for the first 6 hours, every two hours up to 16 hours and at 20 and 24 hours. Descriptive statistics were calculated for the pharmacokinetic parameters AUC, C_{max}, and t_{max} at baseline and after 6 months of treatment. One child was excluded from the pharmacokinetic evaluation due to incorrect dosing.

The GH serum concentration vs. time profiles varied between the patients. The disposition of the serum GH was characterized by a slow absorption phase, with maximum concentration reached after about 3 hours (range 1.9 - 6.0 for both profiles). At baseline, the given dose resulted in a median C_{max} at baseline of 33.9 mcg/L (range: 23.1 - 60.4). After 6 months of somatropin therapy

the median C_{max} was comparable at 32.6 mcg/L (range: 17.7 - 66.9). There were no significant differences between median values for the other pharmacokinetic profiles at baseline and after 6 months of somatropin therapy. However, despite the similarity between the two overall pK profiles, there was considerable intra-individual variation in the serum concentrations of GH with respect to the variables AUC, C_{max} and t_{max}.

The results indicated that there was no accumulation of GH in SGA children following 6 months of daily somatropin treatment and that there was no tendency towards an increase or decrease with respect to the parameters studied.

TOXICOLOGY

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.

Repeat Dose Toxicity

14 Day SC Toxicity Test in the Rat

Groups of 10 male and 10 female Sprague-Dawley rats were given Omnitrope bulk solution at 0, 2 or 8 mg/kg/day SC for 14 days in a full conventional subacute toxicity test, including pharmacokinetic analyses on days 1, 7 and 14.

There were no abnormal clinical signs during the study and no relevant adverse reactions were seen at the injection sites.

Treated females showed a dose-related increase in weight gain, accompanied by increased food consumption, but weight gain and food consumption of males were the same as that of the controls. Also, abnormal hematological results were not found.

Clinical chemistry tests in males were normal. In females there were decreases in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) and an increase in alkaline phosphatase (ALP), as well as a decrease in serum albumin. The changes in ALT and AST were

small, although significant. The increase in ALP is very likely due to increased growth activity. The change in albumin level is insignificant. Small changes are also described in triglyceride levels that are likely due to the metabolic effects of treatment. There were small increases in relative heart and kidney weight in females but no effect on organ weight in males. Also, histopathological abnormalities were not observed.

Omnitrope had no toxic effect and the changes observed in the female animals likely represented its specific pharmacodynamic action.

Subchronic Toxicity
Similar conclusions were reached in studies comparing the subchronic toxicity of biosynthetic human growth hormone in rats and monkeys. In these studies, somatropin was injected subcutaneously in 120 Wistar rats (60 males, 60 females) for 90 days and in cynomolgus monkeys for 30 days. The daily doses were 0.16, 1.1, 3.3 mg/kg, respectively in rats and 0.05 and 5 mg/kg, respectively in monkeys. Somatropin was well tolerated in both rats and monkeys. No drug related deaths occurred and all animals appeared to be normal and also behaved normally throughout the dosing period. Increased body weight gain, increased food consumption and increased organ weights were seen in rats in the high and intermediate dose groups. The treatment related findings may be explained as direct or secondary manifestations of exaggerated pharmacological effects of growth hormone.

Toxicokinetics
As part of the 14-day repeat-dose toxicity study in rats, serum was collected from selected animals in all groups on days 1, 7 and 14 at 0, 2, 4, 6 and 10 hours post dosing. The hGH concentration was measured by an immunoradiometric assay using an anti-human somatropin antibody.

There was slight accumulation of GH over the 14 days of treatment indicated by small increases in the predating levels on days 7 and 14 in the high-dose group. Furthermore, the circulating level of hGH had not returned to baseline (0) 10 hours post dosing on day 14 in the 2 mg/kg group and on days 1, 7 and 14 in the 8 mg/kg animals.

As the dose of hGH was increased there was a subproportional increase in C_{max} and AUC, resulting in apparently similar drug exposure in the 2 dosage groups. Release from the injection sites appeared slower on day 14 than day 1. Total body exposure to Omnitrope appeared lower on day 14 than on day 1. In fact, the relatively small numbers of sampled animals resulted in some uncertainty about the values cited.

Local Tolerance
Three local tolerance studies were performed in rabbits. In the first study, two formulations of Omnitrope (liquid and lyophilized powder), as well as their vehicles, were administered daily for 7 days to groups of 4 male and 4 female rabbits by intramuscular (IM), intravenous (IV) or subcutaneous (SC) injections at a dose of 5 mg/animal. There were signs of mechanical injection trauma in all groups.

Omnitrope liquid and its vehicle were associated with slight erythema at the sites of the IV injections and some local induration. The SC injection sites in all groups showed small hemorrhages attributed to mechanical trauma and minimal edema and erythema, slightly more marked after the administration of Omnitrope lyophilizate, and some induration after the administration of the vehicle of that formulation.

The results showed that both formulations had a slight local effect after IV or SC administrations, but not after repeated IM injection. The intensity of the local reactions observed did not suggest severe local intolerance to either formulation.

In the second study, Omnitrope liquid 10.0 mg/1.5 mL (low and high content of product-related substances), Omnitrope lyophilized powder 5.8 mg, Genotropin® 5 mg and 0.9% saline were administered by a single injection to groups of 6 males by IM, IV, intra-arterial (IA), perivenous (PV) or SC injections at a dose of 5 mg/animal.

Following the administration of Omnitrope liquid 10.0 mg/1.5 mL (low and high content of product-related substances), Omnitrope lyophilized powder 5.8 mg and Genotropin® 5 mg, macroscopic changes were not observed at the injection sites over the period of study in any of the animals. Furthermore, histopathological examination showed that all the formulations tested were tolerated as well as the saline control.

In the third study, Omnitrope liquid 15.0 mg/1.5 mL, Omnitrope lyophilized powder (reconstituted to 5 mg/mL), Genotropin® lyophilized powder (reconstituted to 5 mg/mL) and 0.9% saline were administered by a single injection to groups of 6 males by IM, IV, intra-arterial (IA), perivenous (PV) or SC injections at a dose of 5 mg/animal. This dose corresponds approximately to the maximum dose per single injection that would be applied to humans based on a mg/kg body weight basis. Half of this dose (2.5 mg in 0.25 and 0.5 mL injection volume, respectively) was administered by the IM and PV route in order to avoid major mechanical injection injury at the injection site related to limited distribution space.

Following the administration of Omnitrope liquid 15.0 mg/1.5 mL, reconstituted Omnitrope or Genotropin® , macroscopic changes were not observed at the injection sites over the period of study in any of the animals. For the unintended IM route of exposure, 0.5 mL of the reconstituted Omnitrope resulted in mild leucoytic infiltration, mild necrosis of muscle cells and mild increase of macrophages. Furthermore, histopathological examination showed that all products and remaining routes tested were tolerated as well as the saline control.

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PART III: CONSUMER INFORMATION (Lyophilized Powder)

PrOMNITROPE®
AWM nee trope
(Somatropin for Injection)
Lyophilized powder: 5.8 mg/vial

This leaflet is part III of a three-part "Product Monograph" published when Omnitrope was approved for sale in Canada and is designed specifically for consumers. This leaflet is a summary and will not tell you everything about Omnitrope. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
In children, Omnitrope is used to treat the following growth problems:

- If you are not growing properly and you do not have enough of your own growth hormone.
- If you have Turner syndrome. Turner syndrome is a chromosomal error in girls that can affect growth - your doctor will have told you if you have this.
- If you were small or too light at birth. Growth hormone may help you grow taller if you have not been able to catch up or maintain normal growth by two years of age or later.
- If you have idiopathic (unknown cause) short stature.

In adults, Omnitrope is used to treat persons with pronounced growth hormone deficiency. This can start during adult life, or it can continue from childhood.

If you have been treated with Omnitrope for growth hormone deficiency during childhood, your growth hormone status will be retested after completion of growth. If severe growth hormone deficiency is confirmed, your doctor will propose continuation of Omnitrope treatment.

What it does:
Omnitrope is used to increase growth hormone levels in children and adults unable to produce adequate amounts naturally.
Omnitrope may produce bone growth in children where the ends of the long bones have not yet hardened. In both adults and children requiring growth hormone replacement, Omnitrope helps in the development of muscles and causes fat to be used for energy. In adults with growth hormone deficiency, Omnitrope plays an important role in maintaining an improved ratio of body fat to lean mass.

When it should <u>not</u> be used:

- You are allergic (hypersensitive) to somatropin or any of the other ingredients of Omnitrope.
- You have an active tumour. Tumours must be inactive and you must have finished your anti-tumour treatment before you start using Omnitrope.
- You are seriously ill (for example, complications following open heart surgery, abdominal surgery, acute respiratory failure, accidental trauma or similar conditions). If you are about to have, or have had, a major operation, or go into hospital for any reason, tell your doctor and remind the other doctors you are seeing that you use growth hormone.
- Omnitrope has been prescribed to stimulate growth but you have already stopped growing (the growth plates on your long bones are closed).
- In patients with Prader-Willi syndrome who are very obese or have severe breathing problems. There have been reports of deaths in children with Prader-Willi syndrome who were treated with growth hormone and had one or more of the following risk factors: severe obesity, breathing problems, colds or lung infections.
- In patients with diabetic retinopathy, a complication of diabetes that results from damage to the blood vessels of the light-sensitive tissue at the back of the eye (retina).
- If you or your child are allergic to benzyl alcohol.

What the medicinal ingredient is:
Somatropin (recombinant human growth hormone)

What the important non-medicinal ingredients are:
Omnitrope Lyophilized Powder:
Glycine, disodium hydrogen phosphate, sodium dihydrogen phosphate.

Diluent Cartridge:
Bacteriostatic Water for Injection USP (benzyl alcohol preserved)

What dosage forms it comes in:
Omnitrope (somatropin for injection) is supplied as follows:
Lyophilized powder: 5.8 mg/vial

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- **Patients with acute critical illness suffering complications following open-heart surgery, abdominal surgery, multiple accidental trauma, acute respiratory failure or similar conditions should not be treated with somatropin** (See WARNINGS AND PRECAUTIONS - perioperative considerations).
- **There have been reports of deaths in children with Prader-Willi syndrome who were treated with growth hormone and had one or more of the following risk factors: severely obese, breathing problems, or colds and lung infections** (See WARNINGS AND PRECAUTIONS Congenital Disorders).

Omnitrope therapy should be carried out under the regular guidance of a doctor who is experienced in the diagnosis and management of patients with growth hormone deficiency.

BEFORE you use Omnitrope talk to your doctor or pharmacist:

- If the patient is at risk of developing diabetes, the doctor will need to monitor their blood sugar level during treatment with Omnitrope.
- If the patient has diabetes, they should closely monitor their blood sugar level during treatment with Omnitrope and discuss the results with their doctor to determine whether they need to change the dose of their medicines to treat diabetes.
- If the patient is receiving treatment with thyroid hormones it may be necessary to adjust their thyroid hormone dose.
- If the patient is taking growth hormone to stimulate growth and walk with a limp or if they start to limp during their growth hormone treatment due to pain in their hip, they should inform their doctor.
- If the patient develops a strong headache, visual disturbances or vomiting they should inform their doctor about it.
- If the patient is receiving Omnitrope for growth hormone deficiency following a previous tumour, they should be examined regularly for recurrence of the tumour.
- If the patient is a survivor of childhood cancer.
- If the patient, especially a child, develops severe abdominal pain (inflammation of the pancreas).
- If the patient is, or plans to become pregnant or is breastfeeding.
- If the patient develop a limp while being treated with Omnitrope.
- If the patient has Turner syndrome and develops an ear infection or headaches her doctor should be told about these problems.
- If the patient has hypopituitarism and is receiving standard hormone replacement therapy, the doctor should monitor the hormone replacement therapy closely during omnitrope treatment.
- If you or your child are allergic to benzyl alcohol. Omnitrope 5.8 mg/vial Lyophilized Powder requires reconstitution with a diluent that contains benzyl alcohol.

After starting Omnitrope treatment some patients may need to start thyroid hormone replacement.

Progression of pre-existing scoliosis (curvature of the spine) can occur in children who have rapid growth.

The patient should not use Omnitrope if they are pregnant or are trying to become pregnant.

INTERACTIONS WITH THIS MEDICATION

Steroid hormones (Glucocorticoids) such as cortisone or prednisone may decrease the effects of Omnitrope. If you or your child are receiving concomitant glucocorticoid (steroid) therapy contact your doctor. Steroid doses may need to be adjusted.

Omnitrope may affect your or your child's body's response to insulin, and blood sugar levels may increase. Contact your doctor if you/your child have diabetes. It may be necessary to adjust the dosage of diabetes medications.

You should tell the doctor or nurse about all medicines that you/your child are taking, even those obtained without a doctor's prescription.

PROPER USE OF THIS MEDICATION

Recommended dosage
The dose depends on your size, the condition for which you are being treated and how well growth hormone works for you. Everyone is different. Your doctor will advise you about your individualized dose of Omnitrope in milligrams (mg) from either your body weight in kilograms (kg), as well as your treatment schedule. Do not change the dosage and treatment schedule without consulting your doctor.

Children with growth hormone deficiency:
0.16-0.24 mg/kg body weight per week. Higher doses can be used. When growth hormone deficiency continues into adolescence, Omnitrope should be continued until completion of physical development.

Children with Turner syndrome:
0.33 mg/kg body weight per week.

Children with idiopathic short stature:
UP TO 0.47 mg/kg body weight per week

Children born smaller or lighter than expected and with growth disturbance:
UP TO 0.48 mg/kg body weight per week. Your doctor will determine the most appropriate dose and length of treatment. Treatment should be discontinued if: i) after the first year if you are not responding or ii) if you have reached your final height and stopped growing.

Adults with growth hormone deficiency:
You should start with 0.15-0.3 mg per day.
This dosage should be gradually increased or decreased according to blood test results as well as clinical response and side effects.

Follow the instructions given to you by your doctor

Injecting Omnitrope
Omnitrope is intended for subcutaneous use. This means that it is injected through a short injection needle into the fatty tissue just under your skin. Your doctor should have already shown you how to use Omnitrope. Always inject Omnitrope exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

If you use more Omnitrope than you should
If you inject much more than you should, contact your doctor or pharmacist as soon as possible. Your blood sugar level could fall too low and later rise too high. You might feel shaky, sweaty, sleepy or "not yourself", and you might faint.

If you forget to use Omnitrope
Do not use a double dose to make up for a forgotten dose. It is best to use your growth hormone regularly. If you forget to use a dose, have your next injection at the usual time the next day. Keep a note of any missed injections and tell your doctor at your next check-up.

If you stop using Omnitrope
Ask for advice from your doctor before you stop using Omnitrope.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

Overdosage:
Call your doctor immediately if you or your child take more than the amount of Omnitrope prescribed by your doctor.

Over-dosing growth hormone for several months or years may cause a disease called acromegaly, which causes bones to over-grow and can be fatal. Never share your medication

In case of drug overdose, contact a healthcare practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
Missing injections can interfere with the effectiveness of the medication. Talk to your doctor if this should happen. Do not try to make up for missed injections by "doubling up" on injections.

Note: Do not reconstitute Omnitrope or inject it, until you have been taught the proper technique by your healthcare provider and you understand the instructions. Ask your healthcare provider or pharmacist if you have any questions about injecting OMNITROPE.

INSTRUCTIONS FOR OMNITROPE 5.8 MG/VIAL

The dosage of Omnitrope must be adjusted for the individual patient. The weekly dose should be divided into daily subcutaneous (just under the skin) injections (administered preferably in the evening). Omnitrope may be given in the thigh, buttocks, or abdomen; the site of SC injections should be rotated daily to help prevent lipoatrophy.

The following instructions explain how to inject Omnitrope 5.8 mg/vial:

Do not inject Omnitrope yourself until you have been taught the proper technique by your healthcare provider and you understand the instructions.

- Omnitrope 5.8 mg/vial is for multiple use.
- The concentration of Omnitrope after reconstitution is 5.0 mg/mL.
- After reconstitution, Omnitrope solution contains a preservative and should not be used in newborns.
- Omnitrope solution is for subcutaneous (just under the skin) injection.
- The injection sites should be rotated daily to help prevent lipoatrophy (local reduction of fatty tissue under the skin).

Preparation
Collect necessary items before you begin:

- a vial with 5.8 mg Omnitrope powder for solution for injection.
- a cartridge with diluent (Bacteriostatic Water for Injection containing benzyl alcohol as preservative).
- a transfer set for mixing and transferring the reconstituted solution back into the cartridge.
- the Omnitrope Pen L, an injection device specifically developed for use with Omnitrope 5.0 mg/mL reconstituted solution for injection (not supplied in the pack; see Instructions for Use of the transfer set and of the injection device).
- 2 alcohol swabs (not supplied in the pack).

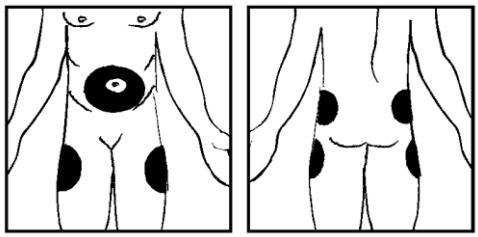
Wash your hands before you start with the next steps.

Reconstituting Omnitrope 5.8 mg/vial
- Remove the protective cap from the vial. With one alcohol swab, disinfect both the rubber membrane of the vial with powder and the cartridge containing diluent.

- Use the transfer set to transfer all of the diluent from the cartridge into the vial. Follow the directions that come with the transfer set.
- Gently swirl the reconstituted vial until the content is completely dissolved. **Do not shake**.
- If the solution is cloudy or contains particles, it should not be used. The solution must be clear and colourless after mixing.
- Transfer all of the dissolved solution back into the cartridge using the transfer set.

Injecting Omnitrope 5.8 mg/vial

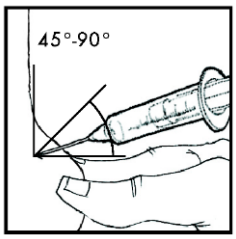
- Put the cartridge with the Omnitrope solution into the Pen L for injection. Follow the Instructions for Use of the Pen Injector.
- Eliminate any air bubbles.
- Select the site of injection. The best sites of injection are tissues with a layer of fat between skin and muscle, such as the thigh, buttocks, or abdomen as in the pictures shown below. **Do not inject near your belly button (navel) or waistline.**



- Make sure you rotate the injection sites on your body. Inject at least 1 cm from your last injection site and change the places on your body where you inject, as you have been taught.
- Before you make an injection, clean your skin well with an alcohol swab. Wait for the area to air dry.

- Insert the needle into the skin the way your doctor has taught you.

- With one hand, pinch a fold of loose skin at the injection site. With your other hand, hold the Pen L as you would a pencil. Insert the needle into the pinched skin straight in or at a slight angle (an angle of 45° to 90°).



- Pull the needle straight out of the skin. After injection, press the injection site with a small bandage or sterile gauze if needed for bleeding, for several seconds. Do not massage or rub the injection site.

After Injecting Omnitrope 5.8 mg/vial

- After injection, press the injection site with a small bandage or sterile gauze for several seconds. Do not massage the injection site.
- Remove the needle from the pen using the outer needle cap and discard the needle. This will keep Omnitrope sterile and prevent leaking. It will also stop air from going back into the pen and the needle clogging up. Do not share your needles. Do not share your pen.
- Leave the cartridge in the pen, replace the pen cap and store in a refrigerator (at 2-8°C) and discard any unused solution 28 days after reconstitution.
- The solution should be clear after removal from the refrigerator. **Do not use if the solution is cloudy or contains particles.**

  Do not inject Omnitrope yourself until you have been taught the proper technique by your healthcare provider and you understand the instructions.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, Omnitrope can cause side effects, although not everybody experiences them. Please ask your doctor for advice when you experience any of the symptoms described below.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom/effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common	General disorders and reactions at the injection site. In children: temporary local skin reactions.		✓	
	Musculoskeletal system, connective tissues, bones. In adults: stiffness of the limbs, joints and muscle pain.		✓	
	Nervous System. In adults: numbness, tingling or pain in arms, legs or face, or trouble		✓	

	with vision.			
	Increased blood sugar. In adults: mild edema (tissue swelling).		✓	
	Disorders of the immune system such as development of antibodies.		✓	
Uncommon	Musculoskeletal system, connective tissues, bones. In children: stiffness of the limbs, joints and muscle pain.		✓	
	Nervous System. -In children: numbness, tingling or pain in arms, legs or face, or trouble with vision -In adults: carpal tunnel syndrome		✓	
	Increased blood sugar, in children: mild edema (tissue swelling).		✓	
Rare	Nervous System such as: benign intracranial hypertension.		✓	
	Increased blood sugar such as: Diabetes mellitus.		✓	
	Allergic reactions		✓	
Very Rare	Leukemia – Benign and malignant cancers.		✓	

Slipped capital femoral epiphysis and Legg-Calve-Perthes disease may be considered by your doctor if discomfort or pain in the hip or knee is experienced whilst being treated with Omnitrope.

This is not a complete list of side effects. For any unexpected effects while taking Omnitrope, contact your doctor or pharmacist.

HOW TO STORE IT

- Omnitrope **must** be refrigerated between 2 - 8°C, both in powder form and after reconstitution.
- Discard any unused solution 28 days after reconstitution.
- Do NOT freeze.
- Omnitrope is light sensitive and should be stored in the original package.
- Do NOT use after the expiry date on the label and carton.
- Do NOT use Omnitrope if the solution is cloudy or contains particles.
- Keep out of reach and sight of children.

Reporting Suspected Side Effects

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

Report online at www.healthcanada.gc.ca/medeffect
Call toll-free at 1-866-234-2345
Complete a Canada Vigilance Reporting Form and:
Fax toll-free to 1-866-678-6789, or
Mail to:
Canada Vigilance Program
Health Canada
Postal Locator 0701E
Ottawa, Ontario
K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document, plus the full Product Monograph prepared for health professionals, can be obtained at www.sandoz.ca or by contacting the sponsor, Sandoz Canada Inc., at: 1-800-361-3062 or

by written request at:

Sandoz Canada Inc.

145, Jules-Léger

Boucherville, (Québec), Canada

J4B 7K8

or by e-mail at :
medinfo@sandoz.com

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Questions or Concerns: 1-800-361-3062

Last revised: May 8, 2015

PART III: CONSUMER INFORMATION (Solution for Injection)

PrOMNITROPE®
AWM nee trope
(Somatropin for Injection)
Solution for Injection: 5.0 mg/1.5 mL, 10 mg/1.5 mL and 15 mg/1.5 mL

This leaflet is part III of a three-part "Product Monograph" published when Omnitrope was approved for sale in Canada and is designed specifically for consumers. This leaflet is a summary and will not tell you everything about Omnitrope. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

In children, Omnitrope is used to treat the following growth problems:

- If you are not growing properly and you do not have enough of your own growth hormone.
- If you have Turner syndrome. Turner syndrome is a chromosomal error in girls that can affect growth - your doctor will have told you if you have this.
- If you were small or too light at birth. Growth hormone may help you grow taller if you have not been able to catch up or maintain normal growth by two years of age or later.
- If you have idiopathic (unknown cause) short stature.

In adults, Omnitrope is used to treat persons with pronounced growth hormone deficiency. This can start during adult life, or it can continue from childhood.

If you have been treated with Omnitrope for growth hormone deficiency during childhood, your growth hormone status will be retested after completion of growth. If severe growth hormone deficiency is confirmed, your doctor will propose continuation of Omnitrope treatment.

What it does:
Omnitrope is used to increase growth hormone levels in children and adults unable to produce adequate amounts naturally.

Omnitrope may produce bone growth in children where the ends of the long bones have not yet hardened. In both adults and children requiring growth hormone replacement, Omnitrope helps in the development of muscles and causes fat to be used for energy. In adults with growth hormone deficiency, Omnitrope plays an important role in maintaining an improved ratio of body fat to lean mass.

When it should <u>not</u> be used:

- You are allergic (hypersensitive) to somatropin or any of the other ingredients of Omnitrope.
- You have an active tumour. Tumours must be inactive and you must have finished your anti-tumour treatment before you start using Omnitrope.
- You are seriously ill (for example, complications following open heart surgery, abdominal surgery, acute respiratory failure, accidental trauma or similar conditions). If you are about to have, or have had, a major operation, or go into hospital for any reason, tell your doctor and remind the other doctors you are seeing that you use growth hormone.
- Omnitrope has been prescribed to stimulate growth but you have already stopped growing (the growth plates on your long bones are closed).
- In patients with Prader-Willi syndrome who are very obese or have severe breathing problems. There have been reports of deaths in children with Prader-Willi syndrome who were treated with growth hormone and had one or more of the following risk factors: severe obesity, breathing problems, colds or lung infections.
- In patients with diabetic retinopathy, a complication of diabetes that results from damage to the blood vessels of the light-sensitive tissue at the back of the eye (retina).
- If you or your child are allergic to benzyl alcohol.

What the medicinal ingredient is:
Somatropin (recombinant human growth hormone)

What the important non - medicinal ingredients are:
5.0 mg/1.5 mL cartridge contains: disodium hydrogen phosphate heptahydrate, sodium dihydrogen phosphate dihydrate, mannitol, poloxamer 188, benzyl alcohol, water for injection.

10.0 mg/1.5 mL cartridge contains: disodium hydrogen phosphate heptahydrate, sodium dihydrogen phosphate dihydrate, glycine, poloxamer 188, phenol, water for injection.

15.0 mg/1.5 mL cartridge contains: disodium hydrogen phosphate heptahydrate, sodium dihydrogen phosphate dihydrate, soduium chloride, poloxamer 188, phenol, water for injection.

What dosage forms it comes in:
Omnitrope (somatropin for injection) is supplied as a solution: 5.0 mg/1.5 mL cartridge, 10 mg/1.5 mL cartridge and 15 mg/1.5 mL cartridge.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- **Patients with acute critical illness suffering complications following open-heart surgery, abdominal surgery, multiple accidental trauma, acute respiratory failure or similar conditions should not be treated with somatropin** (See WARNINGS AND PRECAUTIONS - perioperative considerations**)**.
- **There have been reports of deaths in children with Prader-Willi syndrome who were treated with growth hormone and had one or more of the following risk**

factors: severely obese, breathing problems, or colds and lung infections (See WARNINGS AND PRECAUTIONS Congenital Disorders).

Omnitrope therapy should be carried out under the regular guidance of a doctor who is experienced in the diagnosis and management of patients with growth hormone deficiency.

BEFORE you use Omnitrope talk to your doctor or pharmacist:

- If the patient is at risk of developing diabetes, the doctor will need to monitor their blood sugar level during treatment with Omnitrope.
- If the patient has diabetes, they should closely monitor their blood sugar level during treatment with Omnitrope and discuss the results with their doctor to determine whether they need to change the dose of their medicines to treat diabetes.
- If the patient is receiving treatment with thyroid hormones it may be necessary to adjust their thyroid hormone dose.
- If the patient is taking growth hormone to stimulate growth and walk with a limp or if they start to limp during their growth hormone treatment due to pain in their hip, they should inform their doctor.
- If the patient develops a strong headache, visual disturbances or vomiting they should inform their doctor about it.
- If the patient is receiving Omnitrope for growth hormone deficiency following a previous tumour, they should be examined regularly for recurrence of the tumour.
- If the patient is a survivor of childhood cancer.
- If the patient, especially a child, develops severe abdominal pain (inflammation of the pancreas).
- If the patient is, or plans to become pregnant or is breastfeeding.
- If the patient develop a limp while being treated with Omnitrope.
- If the patient has Turner syndrome and develops an ear infection or headaches her doctor should be told about these problems.
- If the patient has hypopituitarism and is receiving standard hormone replacement therapy, the doctor should monitor the hormone replacement therapy closely during omnitrope treatment.
- If you or your child are allergic to benzyl alcohol.

After starting Omnitrope treatment some patients may need to start thyroid hormone replacement.

Progression of pre-existing scoliosis (curvature of the spine) can occur in children who have rapid growth.

The patient should not use Omnitrope if they are pregnant or are trying to become pregnant.

INTERACTIONS WITH THIS MEDICATION

Steroid hormones (Glucocorticoids) such as cortisone or prednisone may decrease the effects of Omnitrope. If you/your child are receiving concomitant glucocorticoid (steroid) therapy contact your doctor. Steroid doses may need to be adjusted.

Omnitrope may affect your or your child's body's response to insulin, and blood sugar levels may increase. Contact your doctor if you/your child have diabetes. It may be necessary to adjust the dosage of diabetes medications.

You should tell the doctor or nurse about all medicines that the patient is taking, even those obtained without a doctor's prescription.

PROPER USE OF THIS MEDICATION

Recommended dosage
The dose depends on your size, the condition for which you are being treated and how well growth hormone works for you. Everyone is different. Your doctor will advise you about your individualized dose of Omnitrope in milligrams (mg) from either your body weight in kilograms (kg), as well as your treatment schedule. Do not change the dosage and treatment schedule without consulting your doctor.

Children with growth hormone deficiency:
0.16-0.24 mg/kg body weight per week. Higher doses can be used. When growth hormone deficiency continues into adolescence, Omnitrope should be continued until completion of physical development.

Children with Turner syndrome:
0.33 mg/kg body weight per week.

Children with idiopathic short stature:
UP TO 0.47 mg/kg body weight per week

Children born smaller or lighter than expected and with growth disturbance:
UP TO 0.48 mg/kg body weight per week. Your doctor will determine the most appropriate dose and length of treatment. Treatment should be discontinued: i) if after the first year if you are not responding or ii) if you have reached your final height and stopped growing.

Adults with growth hormone deficiency:
You should start with 0.15-0.3 mg per day.
This dosage should be gradually increased or decreased according to blood test results as well as clinical response and side effects. Follow the instructions given to you by your doctor

Injecting Omnitrope
Omnitrope is intended for subcutaneous use. This means that it is injected through a short injection needle into the fatty tissue just under your skin. Your doctor should have already shown you how to use Omnitrope. Always inject Omnitrope exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

If you use more Omnitrope than you should
If you inject much more than you should, contact your doctor or pharmacist as soon as possible. Your blood sugar level could fall too low and later rise too high. You might feel shaky, sweaty, sleepy or "not yourself", and you might faint.

If you forget to use Omnitrope
Do not use a double dose to make up for a forgotten dose. It is best to use your growth hormone regularly. If you forget to use a dose, have your next injection at the usual time the next day. Keep a note of any missed injections and tell your doctor at your next check-up.

If you stop using Omnitrope
Ask for advice from your doctor before you stop using Omnitrope.

Overdose:
Call your doctor **immediately** if you/your child take more than the amount of Omnitrope prescribed by your doctor.

Over-dosing growth hormone for several months or years may cause a disease called acromegaly, which causes bones to over-grow and can be fatal. Never share your medication

In case of drug overdose, contact a healthcare practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
Missing injections can interfere with the effectiveness of the medication. Talk to your doctor if this should happen. Do not try to make up for missed injections by "doubling up" on injections.

INSTRUCTIONS FOR USE OMNITROPE 5.0 mg/1.5mL (somatropin for injection)

How to inject Omnitrope 5.0 mg/1.5 mL
The following instructions explain how to inject Omnitrope 5.0 mg/1.5 mL yourself. Please read the instructions carefully and follow them step by step. Your doctor or other suitably qualified healthcare professionals will show you how to inject Omnitrope. Do not attempt to inject unless you are sure you understand the procedure and requirements for injection.

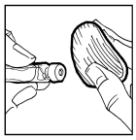
- Omnitrope is given as a subcutaneous (just under the skin) injection.
- Carefully inspect the solution before injecting it and use only if clear and colourless.
- Change the injection sites to minimize the risk of local lipoatrophy (local reduction of fatty tissue under the skin).

Preparation
Collect necessary items before you begin:

- a cartridge with Omnitrope 5.0 mg/1.5 mL solution for injection.
- the Omnitrope® Surepal 5, an injection device specifically developed for use with Omnitrope 5.0 mg/1.5 mL solution for injection (not supplied in the pack; see Instructions for Use provided with the Omnitrope® Surepal 5).
- a pen needle for subcutaneous (just under the skin) injection.
- 2 alcohol swabs (not supplied in the pack).

Wash your hands before you continue with the next steps.

Injecting Omnitrope
- With an alcohol swab, disinfect the rubber membrane of the cartridge.
- The contents must be clear and colourless.



- Insert the cartridge into the pen for injection. Follow the Instructions for Use of the pen injector. To set up the pen dial the dose.
- Select the site of injection. The best sites for injection are tissues with a layer of fat between skin and muscle, such as the thigh, buttocks, or abdomen (except the navel or waistline).
- Make sure you inject at least 1 cm from your last injection site and that you change the places where you inject, as you have been taught.
- Before you make an injection, clean your skin well with an alcohol swab. Wait for the area to dry.

- Insert the needle into the skin in the way your doctor has taught you.

After Injecting
- After injection, press the injection site with a small bandage or sterile gauze for several seconds. Do not massage the injection site.
- Take the needle off the pen using the outer needle cap, and discard the needle. This will keep the Omnitrope solution sterile and prevent leaking. It will also stop air going back into the pen and the needle clogging up. Do not share your needles. Do not share your pen.

- Leave the cartridge in the pen, put the cap on the pen, and store it in the refrigerator.
- The solution should be clear after removal from the refrigerator. **Do not use if the solution is cloudy or contains particles.**
- After the first injection, the cartridge should remain in the pen injector in a refrigerator between 2°C to 8°C for a maximum of 28 days.

INSTRUCTIONS FOR USE OMNITROPE 10.0 mg/1.5 mL (somatropin for injection)

How to inject Omnitrope 10.0 mg/1.5 mL
The following instructions explain how to inject Omnitrope 10.0 mg/1.5 mL yourself. Please read the instructions carefully and follow them step by step. Your doctor or other suitably qualified healthcare professionals will show you how to inject Omnitrope. Do not attempt to inject unless you are sure you understand the procedure and requirements for injection.

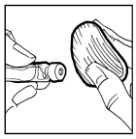
- Omnitrope is given as a subcutaneous (just under the skin) injection.
- Carefully inspect the solution before injecting it and use only if clear and colourless.
- Change the injection sites to minimise the risk of local lipoatrophy (local reduction of fatty tissue under the skin).

Preparation
Collect necessary items before you begin:

- a cartridge with Omnitrope 10.0 mg/1.5 mL solution for injection.
- the Omnitrope® Surepal 10, an injection device specifically developed for use with Omnitrope 10.0 mg/1.5 mL solution for injection (not supplied in the pack; see Instructions for Use provided with the Omnitrope® Surepal 10).
- a pen needle for subcutaneous (just under the skin) injection.
- 2 alcohol swabs (not supplied in the pack).

Wash your hands before you continue with the next steps.

Injecting Omnitrope
- With an alcohol swab, disinfect the rubber membrane of the cartridge.
- The contents must be clear and colourless.



- Insert the cartridge into the pen for injection. Follow the Instructions for Use of the pen injector. To set up the pen, dial the dose.
- Select the site of injection. The best sites for injection are tissues with a layer of fat between skin and muscle, such as the thigh, buttocks, or abdomen (except the navel or waistline).
- Make sure you inject at least 1 cm from your last injection site and that you change the places where you inject, as you have been taught.
- Before you make an injection, clean your skin well with an alcohol swab. Wait for the area to dry.

- Insert the needle into the skin in the way your doctor has taught you.

After Injecting
- After injection, press the injection site with a small bandage or sterile gauze for several seconds. Do not massage the injection site.
- Take the needle off the pen using the outer needle cap, and discard the needle. This will keep the Omnitrope solution sterile and prevent leaking. It will also stop air going back into the pen and the needle clogging up. Do not share your needles. Do not share your pen.
- Leave the cartridge in the pen, put the cap on the pen, and store it in the refrigerator.
- The solution should be clear after removal from the refrigerator. **Do not use if the solution is cloudy or contains particles.**
- After the first injection, the cartridge should remain in the pen injector in a refrigerator between 2°C to 8°C for a maximum of 28 days.

INSTRUCTIONS FOR USE OMNITROPE 15.0 mg/1.5 mL (somatropin for injection)

How to inject Omnitrope 15.0 mg/1.5 mL
The following instructions explain how to inject Omnitrope 15.0 mg/1.5 mL yourself. Please read the instructions carefully and follow them step by step. Your doctor or other suitably qualified healthcare professionals will show you how to inject Omnitrope. Do not attempt to inject unless you are sure you understand the procedure and requirements for injection.

- Omnitrope is given as a subcutaneous (just under the skin) injection.
- Carefully inspect the solution before injecting it and use only if clear and colourless.
- Change the injection sites to minimise the risk of local lipoatrophy (local reduction of fatty tissue under the skin).

Preparation

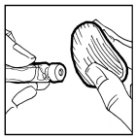
Collect necessary items before you begin:

- a cartridge with Omnitrope 15.0 mg/1.5 mL solution for injection.
- the Omnitrope® Surepal 15, an injection device specifically developed for use with Omnitrope 15.0 mg/1.5 mL solution for injection (not supplied in the pack; see Instructions for Use provided with the Omnitrope® Surepal 15).
- a pen needle for subcutaneous (just under the skin) injection.
- 2 alcohol swabs (not supplied in the pack).

Wash your hands before you continue with the next steps.

Injecting Omnitrope

- With an alcohol swab, disinfect the rubber membrane of the cartridge.
- The contents must be clear and colourless.



- Insert the cartridge into the pen for injection. Follow the Instructions for Use of the pen injector. To set up the pen, dial the dose.
- Select the site of injection. The best sites for injection are tissues with a layer of fat between skin and muscle, such as the thigh, buttocks, or abdomen (except the navel or waistline).
- Make sure you inject at least 1 cm from your last injection site and that you change the places where you inject, as you have been taught.
- Before you make an injection, clean your skin well with an alcohol swab. Wait for the area to dry.

- Insert the needle into the skin in the way your doctor has taught you.

After Injecting

- After injection, press the injection site with a small bandage or sterile gauze for several seconds. Do not massage the injection site.
- Take the needle off the pen using the outer needle cap, and discard the needle. This will keep the Omnitrope solution sterile and prevent leaking. It will also stop air going back into the pen and the needle clogging up. Do not share your needles. Do not share your pen.
- Leave the cartridge in the pen, put the cap on the pen, and store it in the refrigerator.
- The solution should be clear after removal from the refrigerator. **Do not use if the solution is cloudy or contains particles.**
- After the first injection, the cartridge should remain in the pen injector in a refrigerator between 2°C to 8°C for a maximum of 28 days.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, Omnitrope can cause side effects, although not everybody experiences them. Please ask your doctor for advice when you experience any of the symptoms described below.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom/effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common	General disorders and reactions at the injection site. In children: temporary local skin reactions.		✓	
	Musculoskeletal system, connective tissues, bones. In adults: stiffness of the limbs, joints and muscle pain.		✓	
	Nervous System. In adults: numbness, tingling or pain in arms, legs or face, or trouble with vision.		✓	
	Increased blood sugar. In adults: mild edema (tissue swelling).		✓	
	Disorders of the immune system such as development of antibodies.		✓	
Uncommon	Musculoskeletal system, connective tissues, bones. In children: stiffness of the limbs, joints and muscle pain.		✓	
	Nervous System. In children: numbness, tingling or pain in arms, legs or face, or trouble with vision In adults: carpal tunnel syndrome		✓	
	Increased blood sugar. In children: mild edema (tissue swelling) .		✓	

Rare	Nervous System such as: benign intracranial hypertension.		✓	
	Increased blood sugar such as: Diabetes mellitus.		✓	
	Allergic reactions		✓	
Very Rare	Leukemia – Benign and malignant cancers.		✓	

Slipped capital femoral epiphysis and Legg-Calve-Perthes disease may be considered by your doctor if discomfort or pain in the hip or knee is experienced whilst being treated with Omnitrope.

This is not a complete list of side effects. For any unexpected effects while taking Omnitrope, contact your doctor or pharmacist.

HOW TO STORE IT

- Omnitrope **must** be refrigerated between 2 and 8°C.
- Omnitrope solution must be used within 28 days after the first injection.
- Do NOT freeze.
- Omnitrope is light sensitive and should be stored in the original package.
- Do NOT use after the expiry date on the label and carton.
- Do NOT use Omnitrope if the solution is cloudy or contains particles.
- After the first injection, the cartridge should remain in the pen injector and must be kept in a refrigerator between 2 and 8°C (see Instructions for Use of the pen injector).
- Keep out of reach and sight of children.

Reporting Suspected Side Effects

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

Report online at www.healthcanada.gc.ca/medeffect
Call toll-free at 1-866-234-2345
Complete a Canada Vigilance Reporting Form and:
Fax toll-free to 1-866-678-6789, or
Mail to:
Canada Vigilance Program
Health Canada
Postal Locator 1908CE
Ottawa, Ontario
K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document, plus the full Product Monograph prepared for health professionals, can be obtained at www.sandoz.ca or by contacting the sponsor, Sandoz Canada Inc., at: 1-800-361-3062 or

by written request at:

Sandoz Canada Inc.

145, Jules-Léger

Boucherville, (Québec), Canada

J4B 7K8

or by e-mail at :

medinfo@sandoz.com

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Questions or Concerns: 1-800-361-3062

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