PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr **OMNITROPE®**

Somatropin for injection

produced in *Escherichia coli* cells by recombinant DNA technology

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

Sandoz Canada Inc.

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Boucherville, Québec

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Date of Initial Authorization:
April 20, 2009

Date of Revision:
November 1, 2022

Submission Control Number: 256693

RECENT MAJOR LABEL CHANGES

TABLE OF CONTENTS

Omnitrope® (somatropin for injection) is a biosimilar biologic drug (biosimilar) to Genotropin®.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Indications have been granted on the basis of similarity between Omnitrope and the reference biologic drug Genotropin.

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.

1.1 Pediatrics

Based on the data submitted and reviewed by Health Canada, the efficacy and safety of Omnitrope in pediatric patients has been established. Therefore Health Canada has authorized indications for pediatric use (see 1 INDICATIONS, 14 CLINICAL TRIALS).

1.2 Geriatrics

The safety and efficacy of Omnitrope in patients aged 65 and over have not been evaluated in clinical studies (see 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.4 Geriatrics).

2 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.

Growth hormone should not be used for growth promotion in children with fused epiphyses.

Somatropin is contraindicated in patients with active proliferative or severe non-proliferative diabetic retinopathy.

Omnitrope is contraindicated in patients with acute critical illness due to complications following open heart or abdominal surgery, multiple accidental trauma, or acute respiratory failure. (see 7 WARNINGS AND PRECAUTIONS)

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 7 WARNINGS AND PRECAUTIONS).

Omnitrope is contraindicated in patients with a history of hypersensitivity to any of its components.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- Therapy with somatropin should be supervised by a physician who is experienced in the diagnosis and management of patients with growth hormone deficiency and that any change in brand of somatropin products should be made cautiously and only under medical supervision.
- Reconstutued Omnitrope must only be used if the solution is water-clear and contains no particles (see 4 DOSAGE AND ADMINISTRATION, 4.3 Reconstitution).
- 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.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

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.

4.2 Recommended Dose and Dosage Adjustment

The recommended dosage of Omnitrope is:

Table 1: The recommended dosage of Omnitrope

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	Divided into 6-7 doses
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. This means that there is a risk that women, especially those on oral estrogen replacement may be under-treated. 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 < 2 cm/ 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. 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.

No studies with somatropin have been carried out in geriatric patients or in patients with hepatic or renal impairment.

4.3 Reconstitution

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

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 (see 11 STORAGE, STABILITY AND DISPOSAL).

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.

Table 2: Reconstitution Table

Vial Size	Volume of Diluent to be Added to Vial	Approximate Available Volume	Concentration per mL
2 ml	1.14 mL	2 mL	5.0 mg/mL.

4.4 Administration

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

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 (see 11 STORAGE, STABILITY AND DISPOSAL).

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 (see 11 STORAGE, STABILITY AND DISPOSAL).

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.

4.5 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.

5 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 immediately.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

To help ensure the traceability of biologic products, including biosimilars, health professionals should recognise the importance of recording both the brand name and the non-proprietary (active ingredient) name as well as other product-specific identifiers such as the Drug Identification Number (DIN) and the batch/lot number of the product supplied.

Table 3: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Subcutaneous injection	Lyophilized powder: 5.8 mg/vial Each vial contains 5.8 mg somatropin (approximately 17.4 IU)	Each vial contains: disodium hydrogen phosphate heptahydrate, glycine and 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).

Subcutaneous injection	Solution: Omnitrope Pen Cartridges contain somatropin solution for injection:	
	5 mg/1.5 mL (3.3 mg/mL): Each 1.5 mL pen cartridge contains: 5.0 mg of somatropin (15 IU/1.5 mL)	Each 1.5 mL pen cartridge contains: benzyl alcohol as preservative, disodium hydrogen phosphate heptahydrate, mannitol, poloxamer 188, sodium dihydrogen phosphate dihydrate and water for injection. Phosphoric acid and/or sodium hydroxide may have been used to adjust pH
	10 mg/1.5 mL (6.7 mg/mL): Each 1.5 mL pen cartridge contains: 10.0 mg of somatropin (30.0 IU/1.5 mL)	Each 1.5 mL pen cartridge contains: disodium hydrogen phosphate heptahydrate, glycine, phenol as preservative, poloxamer 188, sodium dihydrogen phosphate dihydrate and water for injection. Phosphoric acid and/or sodium hydroxide may have been used to adjust pH
	and 15 mg/1.5 mL (10.0 mg/mL): Each 1.5 mL pen cartridge contains: 15.0 mg of somatropin (45.0 IU/1.5 mL)	Each 1.5 mL pen cartridge contains: disodium hydrogen phosphate heptahydrate, phenol as preservative, poloxamer 188, sodium chloride, sodium dihydrogen phosphate dihydrate and water for injection. Phosphoric acid and/or sodium hydroxide may have been used to adjust pH

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

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.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

General

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

The site of SC injection of Omnitrope should be rotated daily between the thigh, buttocks and abdomen in order to avoid lipoatrophy.

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.

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

Acute Critical Illness

Increased mortality in patients with acute critical illness due to complications following open heart surgery, abdominal surgery or multiple accidental trauma, or those with acute respiratory failure has been reported after treatment with pharmacologic amounts of somatropin (see 2 CONTRAINDICATIONS). The safety of continuing somatropin 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 somatropin in patients having acute critical illnesses should be weighed against the potential risk.

The effects of somatropin on recovery were studied in two placebo controlled trials involving 522 critically ill adult patients suffering complications following open heart surgery, abdominal surgery,

multiple accidental trauma or acute respiratory failure. Mortality was higher in patients treated with daily doses of 5.3 or 8 mg somatropin compared to patients receiving placebo, 42% vs. 19%. Based on this information, these types of patients should not be treated with somatropin.

Carcinogenesis and Mutagenesis

Carcinogenesis studies have not been conducted with rhGH. rhGH is not expected to be carcinogenic in human as the rhGH molecule is identical to the native hormone and the treatment is substitution therapy. No potential mutagenicity of rhGH was revealed in a battery of tests including the Ames test, a test designed to demonstrate chromosome damaging potential, induction of gene mutations in mammalian cells (L5178Y) *in vitro* and in intact bone marrow cells (rats).

Leukemia has been reported in a small number of growth hormone deficient patients, treated with growth hormone, including growth hormone of pituitary origin as well as of recombinant DNA origin (somatrem and somatropin). Based on the current evidence, experts cannot conclude that growth hormone therapy is responsible for these occurrences.

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

Neoplasms

Patients with pre-existing tumours or with GHD secondary to an intracranial lesion should be examined frequently for progression or recurrence of the underlying disease process.

In pediatric patients, clinical literature has revealed no relationship between somatropin replacement therapy and central nervous system (CNS) tumour recurrence or new extracranial tumours. However, in childhood cancer survivors, an increased risk of a second neoplasm has been reported in patients treated with somatropin after their first neoplasm. Intracranial tumours, in particular meningiomas were the most common of these second neoplasms especially in patients treated with radiation to the head. In adults, it is unknown whether there is any relationship between somatropin replacement therapy and CNS tumour recurrence. Patients should be monitored carefully for any malignant transformation of skin lesions.

Closed Epiphyses

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

Treatment of pediatric growth disorders with growth hormones should be discontinued when the patient has reached satisfactory adult height, or when the epiphyses are closed.

Congenital Disorders

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 8 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 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism).

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

Dependence/ Liability

Somatropin is not considered to be a drug that has potential to produce drug dependency. Somatropin does not have stimulant, depressant or hallucinogenic effects on the central nervous system that could be expected to lead to psychological or physical dependency.

Potential for Misuse: 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

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 standard hormonal replacement therapy should be monitored closely when Omnitrope therapy 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.

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 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests).

Fluid Retention

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

Immune

Local allergic reactions:

Patients receiving somatropin treatment may experience redness, swelling, pain, inflammation, or itching at the site of injection (see 8 ADVERSE REACTIONS).

Most of these minor reactions usually resolve in a few days to a few weeks. Such reactions may occur if the injection is given incorrectly (irritants in the skin cleansing agent or poor injection technique), or if the patient is allergic to somatropin or any non-medicinal ingredient (see 2 CONTRAINDICATIONS).

Rarely, subcutaneous administration of somatropin can result in lipoatrophy or lipohypertrophy. Regular rotation of the injection site may help reduce or prevent these reactions.

Patients should be advised to consult their doctor if they notice any of the conditions described above.

On rare occasion, injection site reactions may require discontinuation of somatropin therapy.

Systemic allergic reactions:

As with any protein, local or systemic allergic reactions may occur. Parents/patients should be informed that such reactions are possible and that prompt medical attention should be sought if allergic reactions occur.

These reactions may be characterized by a generalized rash (with pruritus), shortness of breath, wheezing, angioneurotic edema and drop in blood pressure (see 8 ADVERSE REACTIONS).

Severe cases of generalized allergy including anaphylactic reaction may be life-threatening (see 2 CONTRAINDICATIONS).

If any serious hypersensitivity or allergic reactions occurs, somatropin therapy should be discontinued immediately and appropriate therapy initiated.

Serious systemic hypersensitivity reactions including anaphylactic reactions and angioedema have been reported with post-marketing use of somatropin products. Patients and caregivers should be informed that such reactions are possible and that prompt medical attention should be sought if an allergic reaction occurs (see 2 CONTRAINDICATIONS).

Antibody production:

A small percentage of patients treated with somatropin may develop antibodies during treatment that could potentially reduce treatment response (see 8 ADVERSE REACTIONS).

Patients who have demonstrated an allergic reaction to other somatropin products may demonstrate an allergic reaction to Omnitrope.

Intracranial Hypertension

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 weeks of initiation of growth hormone therapy. In all reported cases, IH-associated signs and symptoms resolved after termination of therapy or a reduction of growth hormone dose. Fundoscopic examination of patients is recommended at the initiation, and periodically during the course of, growth hormone therapy. If papilledema is observed by fundoscopy during somatropin treatment, treatment should be stopped. If somatropin-induced IH is diagnosed, treatment with somatropin can be restarted at a lower dose after IH associated signs and symptoms have resolved. Patients with Turner syndrome may be at increased risk for the development of IH.

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 8 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.

Musculoskeletal

Musculoskeletal discomfort (pain, swelling and/or stiffness) may occur during treatment with somatropin (see 8 ADVERSE REACTIONS). These symptoms may resolve spontaneously, with analgesic therapy, or after reducing the dosage (see 4 DOSAGE AND ADMINISTRATION).

Swelling of the hands and feet may occur during treatment with somatropin and may lead to carpal tunnel syndrome, which may be improved by decreasing the dosage of somatropin.

Somatropin has not been shown to increase the incidence of scoliosis. However, progression of pre-existing scoliosis can occur in pediatric patients who experience rapid growth. Therefore, because somatropin increases growth rate, patients with a history of scoliosis who are treated with somatropin 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).

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.

Renal/Hepatic/Biliary/Pancreatic Impairments

Somatropin doses may need to be adjusted in patients with renal and/or hepatic and/or biliary and/or pancreatic impairments.

Reproductive Health: Female and Male Potential

No adequate and well-controlled clinical studies with Omnitrope in reproduction function have been performed (see 7.1 Special Populations, 7.1.1 Pregnant Women).

Animal reproductive studies in rats and rabbits treated during the period of organogenesis have not given evidence of any harmful effects on the fetus. There are however, no adequate and well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

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.

Information for Patients

Patients and/or their caregivers should be informed about potential advantages and disadvantages of Omnitrope therapy including the possible side effects. It should be noted that although serious adverse events may be rare, their occurrence needs to be outweighed by the benefits.

If home use is determined to be desirable by the physician, patients should also be offered instruction for use of injection devices, storage, travelling and other pertinent information. (see PATIENT MEDICATION INFORMATION, INSTRUCTIONS FOR USE).

7.1 Special Populations

7.1.1 Pregnant Women

Reproduction studies have not been conducted with Omnitrope. There are no adequate and well controlled studies of somatropin treatment in pregnant women. Therefore, the safety of somatropin has not been established in this subpopulation. It is also not known whether Omnitrope can cause fetal harm when administered to a pregnant woman. Omnitrope should be given to a pregnant woman only if the benefits clearly outweigh the risks and only under medical supervision.

Female patients should be advised to inform their doctor if they are, or become pregnant, or are contemplating pregnancy.

7.1.2 Breast-feeding

There is no experimental data available that suggests whether peptide hormones, such as growth hormone, pass over into the breast milk but absorption in the gastrointestinal tract of the infant of intact protein is extremely unlikely.

7.1.3 Pediatrics

Pediatric Patients: (see 1 INDICATIONS).

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 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 7 WARNINGS AND PRECAUTIONS, 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.

7.1.4 Geriatrics

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. A lower starting dose and smaller dose increments should be considered for older patients.

7.1.5 Others

Adult Patients: Patients with ephiphyseal closure who were treated with somatropin therapy in childhood should be re-evaluated according to the criteria provided in 1 INDICATIONS 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 8 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.

Obese Patients: Obese individuals are more likely to manifest adverse effects when treated with a weight-based regimen (see 4 DOSAGE AND ADMINISTRATION).

8 ADVERSE REACTIONS

The adverse drug reaction profiles reported in clinical studies that compared Omnitrope to the reference biologic drug were comparable. The description of adverse reactions in this section is based on clinical experience with the reference biologic drug.

8.1 Adverse Reaction Overview

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, face 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. Severe hypersensitivity has been reported in post-marketing use of somatropin products.

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 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism).

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to

the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Adults

Clinical Trials in adults with GHD

In clinical trials with the reference product somatropin 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 somatropin 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 4 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 4: 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.

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

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 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 somatropin 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 somatropin 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 somatropin, 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 5: 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

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 (%)
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				
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 6: 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

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 (%)
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 7: 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)
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)

Body system / Preferred Term	0.033 mg/kg/day N=37	0.067 mg/kg/day N=25	Total N=62
	n (%)	n (%)	n (%)
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)
Allergic reaction	3(8.1)	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 (%)
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.

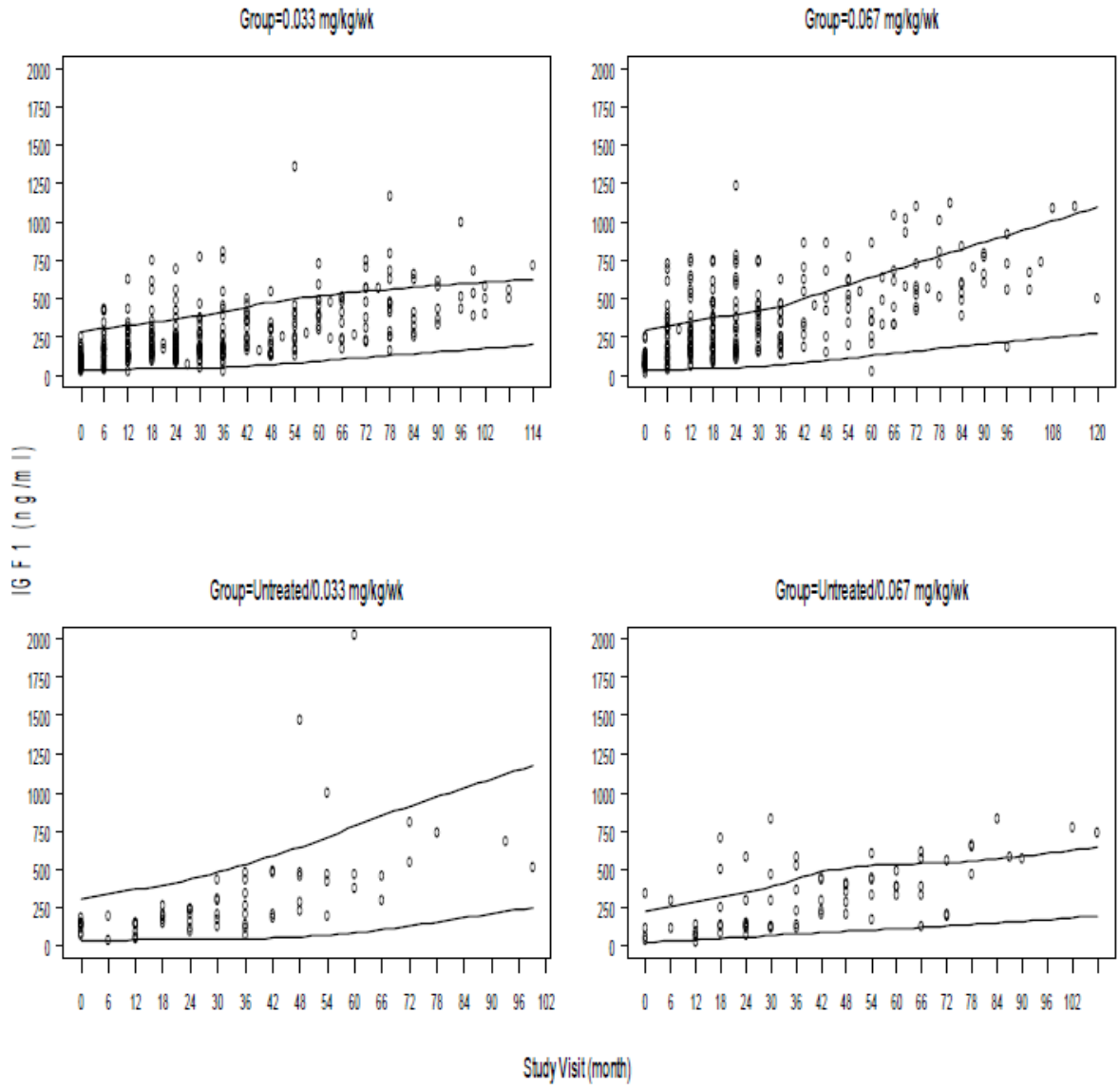
IGF-1 levels

Table 8 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 8: 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 somatropin 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 9: 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 10: 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

WHO dictionary term	Somatropin N=17	Somatropin + oxandrolone N=17
Sinusitis	2 (11.8%)	1 (5.9%)
Influenza	1 (5.9%)	4 (23.5%)
Pneumonia	0	1 (5.9%)
Bronchitis	0	2 (11.8 %)
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 somatropin 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 11: Incidence of treatment-emergent adverse events that occurred in at least 1 patient

Body system / Preferred Term	Prepubertal			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)

Body system / Preferred Term	Prepubertal			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 (%)
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)
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)

Body system / Preferred Term	Prepubertal			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 (%)
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)

Body system / Preferred Term	Prepubertal			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 (%)
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							
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)

Body system / Preferred Term	Prepubertal			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 (%)
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							
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)

Body system / Preferred Term	Prepubertal			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 (%)
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 12: Treatment-related adverse events based on probable, possible, not assessable, and unknown definition and reported in ≥ 2% of somatropin treated subjects

Adverse Event	Somatropin [a] 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

Adverse Event	Somatropin [a] 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	%
Pharyngolaryngeal pain	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 that lead to treatment termination are listed below:

Dissociative identity disorder, pituitary cyst, mood swings and irritability.

Table 13: 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
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

Body system / Preferred Term	Somatropin 0.047 mg/kg/day N = 18		Control group N = 19	
	n	%	n	%
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
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

Body system / Preferred Term	Somatropin 0.047 mg/kg/day N = 18		Control group N = 19	
	n	%	n	%
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).

8.3 Less Common Clinical Trial Adverse Reactions

8.3.1 Less Common Clinical Trial Adverse Reactions – Pediatrics

Less common clinical trial adverse reactions in adults and pediatric patients have been described by indication in section 8.2 above.

8.4 Post-Market Adverse Reactions

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 8.2 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 2 CONTRAINDICATIONS AND 7 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 7 WARNINGS AND PRECAUTIONS), rash (children and adults), pruritus (children and adults) and urticaria (children and adults).

Serious systemic hypersensitivity reactions including anaphylactic reactions and angioedema have been reported with post- marketing use of somatropin products (see 2 CONTRAINDICATIONS and 7 WARNINGS AND PRECAUTIONS – Immune).

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.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

No studies on the interactions with other drugs have been performed since recombinant somatropin has the same amino acid sequence as pituitary-derived growth hormone]

9.4 Drug-Drug Interactions

Cytochrome P450 (CYP450)-Metabolized Drugs

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.

β-Hydroxysteroid Dehydrogenase Type 1

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. GH and somatropin inhibit 11βHSD-1. Consequently, individuals with untreated GH deficiency have relative increases in 11βHSD-1 and serum cortisol. Introduction of somatropin treatment may result in inhibition of 11βHSD-1 and reduced serum cortisol concentrations. As a consequence, previously undiagnosed central (secondary) hypoadrenalism may be unmasked and glucocorticoid replacement may be required in patients treated with somatropin. In addition, patients treated with glucocorticoid replacement for previously diagnosed hypoadrenalism may require an increase in their maintenance or stress doses following initiation of somatropin treatment; this may be especially true for patients treated with cortisone acetate and prednisone since conversion of these drugs to their biologically active metabolites is dependent on the activity of 11βHSD-1.

Concomitant Glucocorticoids

Concomitant glucocorticoid treatment may inhibit the growth-promoting effect of human growth hormone.
GHD children with coexisting ACTH deficiency should have their glucocorticoid replacement dose carefully adjusted to avoid an inhibitory effect on growth. Therefore, patients treated with glucocorticoids should have their growth monitored carefully to assess the potential impact of glucocorticoid treatment on growth. (see 7 WARNINGS AND PRECAUTIONS – Endocrine and Metabolism and 9 DRUG INTERACTIONS - β-Hydroxysteroid Dehydrogenase Type 1)

Patients with ACTH deficiency should be carefully monitored to avoid adrenal insufficiency.

Insulin and/or Oral/Injectable Hypoglycemic Agents

In patients with diabetes mellitus requiring drug therapy, the dose of insulin and/or oral/injectable agent may require adjustment when somatropin therapy is initiated (see 7 WARNINGS AND PRECAUTIONS).

Table 14 - 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.
β-Hydroxysteroid Dehydrogenase Type 1 (11βHSD-1)	Somatropin treatment may inhibit 11βHSD-1 and reduce serum cortisol and untreated GH deficiency may increase 11βHSD-1 and serum cortisol	Glucocorticoid replacement may be required in patients treated with somatropin with careful monitoring of the growth to assess the potential impact of glucocorticoid treatment on growth.
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

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Somatropin is a polypeptide hormone of recombinant DNA origin. The amino acid sequence of the

product is identical to that of human growth hormone of pituitary origin. Somatropin stimulates linear growth in children with growth hormone deficiency.

In vitro, preclinical and clinical tests have demonstrated that somatropin is therapeutically equivalent to pituitary growth hormone and achieves similar pharmacokinetic profiles in normal adults

10.2 Pharmacodynamics

Treatment of growth hormone deficient (GHD) children with Genotropin produces increased growth rate and IGF – I (Insulin like Growth Factor- I) concentrations that are similar to those seen after therapy with pituitary growth hormone

Treatment of GH deficient adults with Genotropin increases serum IGF-I to normal levels, improves body composition and Quality of Life.

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 GHD. The measurable increase in body length after administration of somatropin or pituitary growth hormone 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 GHD children, but tend to increase during treatment with somatropin. 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. Treatment with somatropin results in a similar decrease in serum urea nitrogen. In adults with GHD, treatment with somatropin increases protein synthesis and increases overall lean body mass.

Carbohydrate Metabolism

Children 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

Somatropin induces retention of sodium, potassium, and phosphorus. Retention of sodium, potassium, and phosphorus is induced by pituitary growth hormone in children. In treated adults, osteocalcin and procollagen levels are significantly increased. Serum concentrations of inorganic phosphate are increased in patients with growth hormone deficiency after therapy with somatropin or pituitary growth hormone. Serum calcium is not significantly altered by either somatropin or pituitary growth hormone. Growth hormone could increase calciuria.

Quality of Life

Quality of Life as measured by the Nottingham Health Profile showed significant improvements in "energy" and "sleep" in the GH-treated group in comparison with the placebo group. The total wellbeing score, produced by the Psychological General Well-Being Scale, was significantly better for the GH-group than for the placebo group. For "anxiety", "depression" and "positive well-being" a trend towards improvement was found in the GH treated group but the effect was not statistically significant.

10.3 Pharmacokinetics

Absorption

The pharmacokinetic profile after an intramuscular injection (IM) is similar to SC injection. No significant differences have been noted in T_{max}, C_{max} or area under the curve between these two routes of administration.

Approximately 80% of somatropin is absorbed following subcutaneous (SC) injection. Maximum serum concentrations are achieved 3 - 4 hours following SC injection.

11 STORAGE, STABILITY AND DISPOSAL

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.

12 SPECIAL HANDLING INSTRUCTIONS

No special handling instructions were identified.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

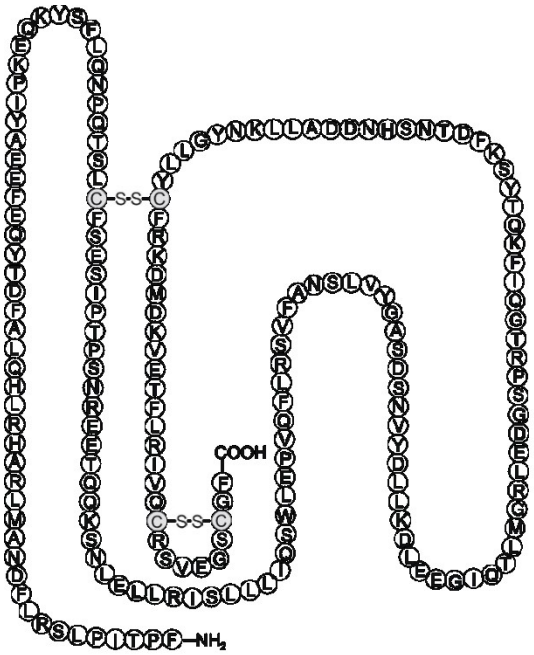
Proper name: Somatropin

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.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Pediatric Growth Hormone Deficiency (GHD)

Five Phase III studies were performed in a total of 190 pediatric patients who had growth failure due to an inadequate secretion of endogenous growth hormone (See Table 15).

Table 15: Summary of Patient Demographics for Clinical Trials in Pediatric Patients with Growth Failure due to Growth Hormone Deficiency (GHD)

Study Number	Length of Study	Study Design	Dosage, Route of Administration	Study Subjects (N)	Sex, Mean Age (Range)
EP2K-99-PhIII	6 months	Phase III, randomized, open-label, 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-label, 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-label, 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-label, 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-label, multicentre study to demonstrate the efficacy and safety of Omnitrope	Omnitrope powder for solution for injection; 5.8 mg/vial	51	30M, 21F 7.6 yrs (2-14 yrs)

Study Number	Length of Study	Study Design	Dosage, Route of Administration	Study Subjects (N)	Sex, Mean Age (Range)
		lyophilizate 5.8 mg in the treatment of growth-deficient children due to GHD.	0.03 mg/kg SC, once daily		

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.

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.

Table 16: Key primary endpoints in Phase III Studies EP2K-99-PhIII/EP2K-00-PhIIIFo (mean ± SD) - direct comparison between Omnitrope and the reference product Genotropin®

	Omnitrope lyophilizate N=44 Mean (SD)	**Genotropin®** N=45 Mean (SD)	**Difference in Mean Change** (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)	
Mean Change from pre-treatment to Month 9	6.9 (3.2)	6.8 (3.3)	-0.2 (-1.0;1.3) †
Height velocity SDS			
Pre-treatment	-2.3 (1.2)	-2.3 (0.9)	
Month 9	5.9 (3.4)	5.0 (2.9)	
Mean Change from pre-treatment to Month 9	8.2 (4.0)	7.4 (3.2)	-0.8 (-2.2;0.6) †
Height SDS			
Pre-treatment	-3.0 (0.7)	-3.1 (0.9)	
Month 9	-2.3 (0.7)	-2.5 (0.7)	
Mean Change from pre-treatment to Month 9	0.8 (0.5)	0.7 (0.5)	-0.13 (-0.31;0.04) †

† The equivalence margin for demonstrating biosimilarity of HVSDS was 2.8, HV was 2.4, and HSDS was 0.35.

Table 17: Key primary endpoitns in Phase III Study EP2K-00-PhIII[AQ] Part A (mean ± SD) comparison between two different formulations of Omnitrope

	Omnitrope lyophilizate N=42 Mean (SD)	**Omnitrope liquid** N=44 Mean (SD)	**Difference in Mean Change** (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)	
Mean Change from Month 9 to Month 15	-1.4 (1.5)	-1.4 (1.3)	0.0 (-0.5;0.5) ‡
Height velocity SDS			
Month 9	5.9 (3.4)	5.0 (2.9)	
Month 15	4.4 (3.0)	3.6 (2.2)	
Mean 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)	
Mean Change from Month 9 to Month 15	0.3 (0.2)	0.3 (0.2)	0.0 (-0.11;0.11) ‡

‡ The equivalence margin for demonstrating biosimilarity of HVSDS was 1.25, HV was 1.05, and HSDS was 0.22.

14.2 Comparative Bioavailability Studies

Six clinical pharmacology studies, EP2K-99-PhISUSA, EP2K-99-PhIUSA, EP2K 00 PhI[AQ], EP00-104, EP00-105 and EP00-107 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.

Study EP2K-99-PhIUSA

Study design: A double-blind, randomized, two-way cross-over, comparative study to compare the pharmacokinetics, pharmacodynamics and safety of EP2000 with that of Genotropin®.

Study objectives:

- To compare the pharmacokinetics of EP2000, a new preparation of r-hGH (test formulation), to

that of Genotropin® (reference formulation), as assessed by a specific immunoassay.
- To compare the pharmacodynamics of EP2000 with Genotropin® in terms of IGF-1 serum profile, IGFBP-3 serum profile, and NEFA serum profile.
- To compare the safety of the test formulation (EP2000) to that of the reference formulation (Genotropin®)

Table 18: Study EP2K-99-PhIUSA

Study	Length of study	Dosage, Route of administration, duration	Study subjects	Range Age	Sex
EP2K-00PhI USA	ten study visits, separated by a washout period of 1 week, and a follow-up visit	EP2000 (recombinant human GH), 5 mg, SC bolus injection Duration:2weeks	25 subjects*	Healthy male and female subjects, aged 18-45 years	12 males, 13 females

* 24 subjects (PP: per protocol) were included in PK/PD analysis (12 males and 12 females)

Comparative Pharmacokinetic data between Omnitrope and reference product are provided in Table 19.

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}

Study EP2K-00-PhI[AQ]

Study design: A double-blind, randomised, two-way cross-over study to establish the bioequivalence of EP2000 AQ liquid formulation and EP2000 lyophilised powder formulation and to compare the pharmacodynamics and safety of the two preparations.

Study objectives:

Primary objective was to establish the bioequivalence of the liquid formulation of EP2000 AQ, a new preparation of r-hGH (test formulation) and the lyophilised powder formulation of EP2000 (reference formulation), as assessed by a specific chemiluminescence assay.

Secondary objectives were to compare the pharmacodynamics of the liquid formulation of EP2000AQ with the lyophilised powder formulation of EP2000 in terms of IGF-1, IGFBP-3 and NEFA serum profiles and the safety of the test formulation liquid formulation of EP2000 AQ to that of the reference formulation (lyophilised powder formulation of EP2000) together with 25-hour infusion of 1 mg octreotide (Sandostatin) to block all endogenous GH-secretions.

Table 20: Study EP2K-00-PhI[AQ]

Study	Length of study	Dosage, Route of administration, duration	Study subjects	Range Age	Sex
EP2K-99-Ph1 [AQ]	two treatment periods, separated by a wash-out period of at least one week. In total, each subject visited the study centre on 10 separate occasions	EP 2000 lyophilised powder formulation, reconstituted in water for injection (recombinant human GH), 5 mg, administered as SC bolus injection	24 subjects	Healthy male and female subjects, aged between 22-50 years	12 males, 12 females

Comparative Pharmacokinetic data between Omnitrope and reference product are provided in Table 21.

Table 21: 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)
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}

Study EP00-104

Study design: A randomized, double-blind, 3-way crossover study to compare the pharmacokinetics and pharmacodynamics, safety, and local tolerance of 5 mg Omnitrope Powder for Solution for Injection, Omnitrope Solution for Injection and Genotropin^{R} after a single subcutaneous dose in healthy subjects

Study objectives:

Primary objective: To compare the pharmacokinetic parameters AUC_{last} and C_{max} of Omnitrope Powder for Solution for Injection, Omnitrope Solution for Injection and Genotropin after a single subcutaneous dose of 5 mg.

Secondary objectives:

- To compare the PD of Omnitrope Powder for Solution for Injection, Omnitrope Solution for Injection and Genotropin after a single subcutaneous dose of 5 mg.
- To evaluate the safety and local tolerance of Omnitrope Powder for Solution for Injection, Omnitrope Solution for Injection and Genotropin after a single subcutaneous dose of 5 mg.
- To compare the pharmacokinetic parameters $t_{1/2}$, t_{max} and CL/F of Omnitrope Powder for Solution for Injection and Omnitrope Solution for Injection and Genotropin after a single subcutaneous dose of 5 mg.

Table 22: Study EP00-104

Study	Length of study	Dosage, Route of admin and duration	Study subjects	Range age Mean age	Sex
EP00-104	The study consisted of 3 treatment periods of 7 days. A follow-up visit was conducted 14 days after administration of IMP in the last treatment period. The total duration of the study from the start of the first treatment period to the follow-up visit was 28 days (4 weeks).	Omnitrope 5 mg/ml Powder for Solution for Injection, Omnitrope 3.3 mg/ml Solution for Injection Genotropin® 5 mg/ml Powder for Solution for Injection after a single subcutaneous dose of 5 mg	Randomized: 36 subjects*	Range: 20-44 years Mean 27.4 Years	30 subject's Male 6 subjects Female

*35 subjects (PP-per protoco) were included in PK/PD analysis (29 males and 6 females)

Comparative Pharmacokinetic data between Omnitrope and reference product are provided in Table

23.

Table 23: 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 [%] Omnitrope 5mg/mL p.s.f.i and Omnitrope 5mg/1.5mL sol for inj	AUC_T: 103.58 [98.86 ; 108.52] AUC_I: 103.90 [99.23 ; 108.78] C_{max}: 102.15 [94.28 ; 110.68]		
Ratio of LS Means and 90% CI [%] Omnitrope 5mg/mL p.s.f.i and Genotropin 5mg/mL p.s.f.i	AUC_T: 94.20 [89.90 ; 98.69] AUC_I: 94.67 [90.42 ; 99.12] C_{max}: 91.57 [84.51 ; 99.22]		
Ratio of LS Means and 90% CI [%] Omnitrope 5mg/1.5mL sol for inj and Genotropin 5mg/mL p.s.f.i	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}

Study EP00-105

Study design: A randomized, double-blind, 3-way crossover study to compare the pharmacokinetics and pharmacodynamics, safety, and local tolerance of Omnitrope 5 mg Powder for Solution for Injection, Omnitrope 6.7 mg/ml Solution for Injection and GenotropinR 5 mg/ml after a single subcutaneous dose of 5 mg in healthy subjects

Study objectives:

Primary objective:

To compare the pharmacokinetic parameters AUC_{last} and C_{max} of Omnitrope 5 mg/ml Powder for Solution for Injection, Omnitrope 6.7 mg/ml Solution for Injection and Genotropin 5 mg/ml after a single subcutaneous dose of 5 mg.

Secondary objectives:

- To compare the pharmacodynamic parameters IGF-1, IGFBP-3 and NEFA of Omnitrope 5 mg/ml Powder for Solution for Injection, Omnitrope 6.7 mg/ml Solution for Injection and Genotropin 5 mg/ml after a single subcutaneous dose of 5 mg.
- To evaluate the safety and local tolerance of Omnitrope 5 mg/ml Powder for Solution for Injection, Omnitrope 6.7 mg/ml Solution for Injection and Genotropin 5 mg/ml after a single subcutaneous dose of 5 mg.
- To compare the pharmacokinetic parameters t1/2, tmax and CL/F of Omnitrope 5 mg/ml Powder for Solution for Injection and 6.7 mg/ml Omnitrope Solution for Injection and Genotropin 5 mg/ml after a single subcutaneous dose of 5 mg.

Table 24: Study EP00-105

Study	Length of study	Dosage, Route of admin and duration	Study subjects	Range age Mean age	Sex
EP00-105	The study consisted of 3 treatment periods of 7 days. A follow-up visit was conducted 14 days after administration of IMP in the last treatment period. The total duration of the study from the start of the first treatment period to the follow-up visit was 35 days (5 weeks).	Omnitrope 5 mg/ml Powder for Solution for Injection, Omnitrope 6.7 mg/ml Solution for Injection and Genotropin® 5 mg/ml after a single subcutaneous dose of 5 mg	Randomized: 36 subjects*	Range: 18-45 years Mean: 27.1 years	Male:30 subject Female: 6 subjects

*32 subjects (PP-per protocol) were included in PK/PD analysis (26 males and 6 females)

Comparative Pharmacokinetic data between Omnitrope and reference product are provided in Table 25.

Table 25: 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 [%] Omnitrope 5mg/mL p.s.f.i and Omnitrope 10mg/1.5mL sol for inj	AUC_T: 98.70 [95.54 ; 101.96] AUC_I: 98.81 [95.64 ; 102.09] C_{max}: 95.28 [90.59 ; 100.22]		
Ratio of LS Means and 90% CI [%] Omnitrope 5mg/mL p.s.f.i and Genotropin 5mg/mL p.s.f.i	AUCT: 102.27 [99.03 ; 105.62] AUC_I: 102.28 [99.03 ; 105.64] C_{max}: 95.89 [91.22 ; 100.81]		
Ratio of LS Means and 90% CI [%] Omnitrope 10mg/1.5mL sol for inj and Genotropin 5mg/mL p.s.f.i	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}

Study EP00-107

Study design: A randomized, double-blind, 3-way crossover study to compare the pharmacokinetics and pharmacodynamics, safety and local tolerance of Omnitrope 5 mg/ml Powder for Solution for Injection, Omnitrope 10 mg/ml Solution for Injection and Genotropin® 5 mg/ml after a single subcutaneous dose of 5 mg in healthy subjects.

Study objectives

Primary objective:

To compare the pharmacokinetic (PK) parameters area under the concentration-time curve from time zero to the time of the last quantifiable concentration (AUC_{last}) and maximum observed concentration (C_{max}) of Omnitrope 5 mg/ml Powder for Solution for Injection, Omnitrope 10 mg/ml Solution for Injection, and Genotropin 5 mg/ml after a single s.c. dose of 5 mg

Secondary objectives:

- To compare the remaining PK parameters area under the concentration-time curve from time zero to infinity (AUC_{inf}), elimination half-time associated with the terminal slope (λz) of a semilogarithmic concentration-time curve ($t_{1/2}$), time to C_{max} (t_{max}), and clearance per bioavailable fraction (CL/F) of Omnitrope 5 mg/ml Powder for Solution for Injection, Omnitrope 10 mg/ml Solution for Injection, and Genotropin 5 mg/ml after a single s.c. dose of 5 mg
- To compare the PD parameters insulin-like growth factor-1 (IGF-1), insulin-like growth factor binding protein-3 (IGFBP-3), and non-esterified fatty acids (NEFA) of Omnitrope 5 mg/ml Powder for Solution for Injection, Omnitrope 10 mg/ml Solution for Injection, and Genotropin 5 mg/ml after a single s.c. dose of 5 mg
- To evaluate the safety and local tolerance of Omnitrope 5 mg/ml Powder for Solution for Injection, Omnitrope 10 mg/ml Solution for Injection, and Genotropin 5 mg/ml after a single s.c. dose of 5 mg

Table 26: Study EP00-107

Study	**Length of study**	**Dosage, Route of admin and duration**	**Study subjects**	**Range age Mean age**	**Sex**
EP00-107	The study consisted of 3 treatment periods of 7 days each plus a follow-up visit 14 days after the last administration of the investigational medicinal product (IMP)	Omnitrope 5 mg/ml Powder for Solution for Injection, Omnitrope 10 mg/ml Solution for Injection and Genotropin® 5 mg/ml after a single subcutaneous dose of 5 mg	Randomized: 36 subjects*	Range: 19-42 years Mean: 26 years	25 subject's Male 11 subjects Female

* 33 subjects (PP- per protocol) were included in PK/PD analysis (male:23 and female:10)

Comparative Pharmacokinetic data between Omnitrope and reference product are provided in Table 27.

Table 27: 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]	4.03 [2.02; 6.03]	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 [%] Omnitrope 15mg/1,5mL sol for inj and Omnitrope 5 mg/ml p.s.f.i		AUC_T: 1.06 [1.03 ; 1.10] AUC_I: 1.070 C_{max}: 1.03 [0.96 ; 1.10]	
Ratio of LS Means and 90% CI [%] Omnitrope 5mg/ml p.s.f.i and Genotropin 5 mg/mL p.s.f.i		AUC_T: 1.04 [1.01 ; 1.07] AUC_I: 1.05 C_{max}: 1.02 [0.95 ; 1.09]	
Ratio of LS Means and 90% CI Omnitrope 15/1.5mL sol for inj and Genotropin 5 mg/mL p.s.f.i.		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}

14.3 Immunogenicity

No comparative immunogenicity data is available between Omnitrope and the reference biologic product Genotropin®.

14.4 Clinical Trials - Reference Biologic Drug

Efficacy and Safety Studies

Children

Patient response to Genotropin 5.3 mg/mL and 1.3 mg/mL has been monitored through the Kabi International Growth Study (KIGS). 46 patients received the 5.3 mg/mL formulation and 342 received the 1.3 mg/mL formulation at a dose of (0.17 - 0.23 IU/kg/wk) for at least one year for growth hormone insufficiency. After 12 months the group treated with Genotropin 1.3 mg/mL showed an increase in mean height from 123.5±19.2 cm to 131.9±18.8 cm, and the group treated with Genotropin 5.3 mg/mL showed an increase in mean height from 125.0 ±20.2 cm to 139.1±17.1 cm. Therefore, although the two formulations have not been shown to be equally bioavailable, they are both efficacious when used in a clinical setting.

SGA

Pediatric Patients Born Small for Gestational Age (SGA) Who Fail to Manifest Catch-up Growth by Age 2: The safety and efficacy of Genotropin in the treatment of children born small for gestational age (SGA) were evaluated in 4 pivotal, randomized, open-label, controlled multicenter, multinational clinical trials that each evaluated 3 parallel groups (2 somatropin-treated groups and one untreated control group). Studies were conducted at study sites in France, the northern European countries of Sweden, Finland, Denmark, and Norway, Germany, and Belgium. All studies used height velocity SDS (HV SDS) as the primary endpoint. Since it is a measure of change in height over a set time period (usually a year), HV SDS is the most appropriate measure for comparisons among treatment groups during periods of rapid growth, such as catch-up growth. HV SDS was measured over two 12- month periods, from baseline to month 12 and from month 12 to month 24. The measurement of height with a Harpenden stadiometer, or comparable wall-mounted device, was used in the studies and is widely employed as an objective measure to assess growth response. Further, to minimize bias, the effects of the drug were assessed relative to an untreated control group, using appropriate statistical methods that incorporated correction for multiple comparisons.

Patients (age range of 2 to 8 years) were observed for 12 months before being randomized to receive either Genotropin (two doses per study, most often 0.24 and 0.48 mg/kg/week) as a daily SC injection or no treatment for the first 24 months of the studies. After 24 months in the studies, all patients received Genotropin.

Patients who received any dose of Genotropin showed significant increases in growth during the first 24 months of study, compared with patients who received no treatment GH treatment accelerated the growth of SGA children in a dose dependent manner. At entry to the study, the mean growth rate SD score (SDS) was -1.1±1.1 for untreated controls (n = 72), -1.2±1.4 for the 0.033 mg/kg/day group (n =

104), and -1.2±1.1 for the 0.067 mg/kg/day group (n = 117). After the start of the study, the growth rate SDS in the respective groups were: -0.8±1.2 (n = 76), 2.5±1.8 (n = 105), and 4.4±2.1 (n = 117) during the first year; and -0.7±1.0 (n = 59), 0.9±1.8 (n = 105), and 2.1±2.0 (n = 117) during the second year (see table 28).

Children receiving 0.48 mg/kg/week demonstrated a significant improvement in height SDS (secondary endpoint) compared with children treated with 0.24 mg/kg/week. Height SDS at entry was -3.1±0.9 for the untreated control (n = 40), -3.2±0.8 for the 0.033 mg/kg/day group (n = 76), and -3.4±1.0 for the 0.067 mg/kg/day group (n = 93). The corresponding values after 24 months of treatment were -2.9±0.9 (n = 40), -2.0±0.8 (n = 76), and -1.7±1.0 (n = 93). Thus, treatment with somatropin improved the height of short-stature children born SGA by 1.2 SDS at 0.033 mg/kg/day and by 1.7 SDS at 0.067 mg/kg/day (Table 29). Both of these doses resulted in a slower but constant increase in growth between months 24 to 72

TABLE 28: Efficacy of Genotropin in Children Born Small for Gestational Age

	(Mean ± SD)		
	Genotropin (0.24 mg/kg/week)	**Genotropin (0.48 mg/kg/week)**	**Untreated Control**
Mean growth rate SD Score (SDS) Baseline SDS	-1.2±1.4 (n = 104)	-1.2±1.1 (n = 117)	-1.1±1.1 (n = 72)
Growth rate SDS at 12 months	2.5*±1.8 (n = 105)	4.4*±2.1 (n = 117)	-0.8±1.2 (n = 76)
Growth rate SDS at 24 months	0.9*±1.8 (n = 105)	2.1*±2.0 (n = 117)	-0.7±1.0 (n = 59)

*p = 0.0001 vs Untreated Control group

TABLE 29: Efficacy of Genotropin in Children Born Small for Gestational Age

	(Mean ± SD)		
	Genotropin (0.24 mg/kg/week) n=76	**Genotropin (0.48 mg/kg/week) n=93**	**Untreated Control n=40**
Height Standard Deviation Score (SDS) Baseline SDS	-3.2 ± 0.8	-3.4 ± 1.0	-3.1 ± 0.9
SDS at 24 months	-2.0 ± 0.8	-1.7 ± 1.0	-2.9 ± 0.9
Change in SDS from baseline to month 24	1.2* ± 0.5	1.7*† ± 0.6	0.1 ± 0.3

*p = 0.0001 vs Untreated Control group
† p = 0.0001 vs group treated with Genotropin 0.24 mg/kg/week

A supplementary analysis of the change in height SDS from baseline to month 24 was performed that included height SDS at baseline, age at baseline, and sex as covariates. The analysis indicates that the effect of somatropin on the change in height SDS is greater at a younger age but that the effect is prominent up to 8 years of age at the start of treatment.

Patients enrolled in the four randomized, multicenter studies of the safety and efficacy of Genotropin therapy in patients with short stature born small for gestational age (SGA) were followed as controls or treated patients for 2 and 6 years, respectively. Forty nine of the total cohort of 188 patients were followed for 2 years as untreated controls, 62 received continuous Genotropin treatment for 6 years and 77 received discontinuous Genotropin treatment for 6 years. Of the 62 patients who received continuous therapy, 35 received a daily Genotropin dose of 33 mcg/kg body weigh/day and 27 received a daily Genotropin dose of 67 mcg/kg body weigh/day. The 77 patients who were treated with discontinuous therapy received Genotropin treatment for 2 to 3 years followed by a withdrawal phase of 1 to 2 yr, and then by either no or 1 or more episodes of further Genotropin treatment at a dose of 33 mcg/kg body weigh/day, averaged over 6 years.

At the start of the studies, the average age of the 188 patients was 5.2 yr (range, 2–8 yr) and the mean height SDS was - 3.4. After 2 yr, the untreated control group experienced an increase in height, of 0.1 ± 0.1 SD over baseline (not shown in table 30). Continuous Genotropin treatment at a dose of 33 mcg/kg/day and 67 mcg/kg/day for 2 years resulted in an increase in height over baseline of 1.2 SD and 1.7 SD respectively, and an increase in height over baseline of 2.1 SD and 2.6 SD, in the 0.033 mg/kg/day and 0.067 mg/kg/day groups at 6 years, respectively. After 2 years there were no untreated control patients available for comparison. The height SDS at 72 months in all groups is greater than - 2, in the normal range.

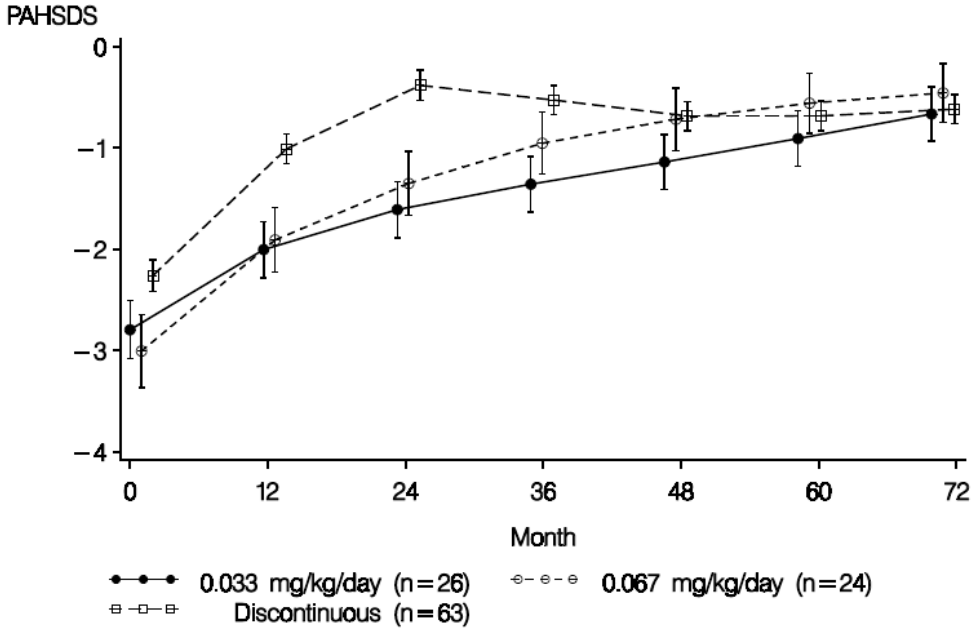
TABLE 30: Effect of No Treatment, Some Treatment, or Continuous Treatment on Height SDS During Month 24 to Month 72 - PP 0-72 Population

Mean Height SDS	Treatment Group			
	Disc/Not Re-trt N=15	Disc/Some Re-trt N=50	Continuous 0.033 mg/kg/day N=27	Continuous 0.067 mg/kg/day N=25
Change from baseline to month 24	2.4	1.7	1.2	1.7
Change from baseline to month 72	1.6	1.6	2.1	2.6
Change from month 24 to month 72	-0.8	-0.1	0.9	0.9
Height SDS at month 72	-1.7	-1.6	-1.4	-1.3

Abbreviations: Disc/Not Re-trt= patients in the discontinuous group who were not treated during month 24 to month 72; Disc/some trt=patients in the discontinuous group who received some treatment during month 24 to month 72

Mean PAH SDS during the baseline to month 72 period is displayed graphically in Figure 2. As expected, the mean PAH SDS curves over the 72-month treatment period show a pattern similar to the non-adjusted mean height SDS curves. The PAH SDS curves for all treatment groups approached 0 SD, thus indicating a normalization of childhood stature when adjusted for genetic potential.

FIGURE 2. Effect of Somatropin Treatment on Mean (±SEM) PAH SDS PP 0-72 Population



Note: 13 patients excluded (1 in the 0.033 mg/kg/day group, 1 in the 0.067 mg/kg/day group and 11 in the discontinuous group) due to missing observations.

Turner Syndrome

Two randomized, open-label, clinical trials were conducted that evaluated the efficacy and safety of Genotropin in Turner syndrome patients with short stature. Turner syndrome patients were treated with Genotropin alone or Genotropin plus adjunctive hormonal therapy (ethinylestradiol or oxandrolone). A total of 38 patients were treated with Genotropin alone in the two studies. In Study 055, 22 patients were treated for 12 months, and in Study 092, 16 patients were treated for 12 months. Patients received Genotropin at a dose between 0.13 to 0.33 mg/kg/week.

SDS for height velocity and height are expressed using either the Tanner (Study 055) or Sempé (Study 092) standards for age-matched normal children as well as the Ranke standard (both studies) for age-matched, untreated Turner syndrome patients.

Both studies demonstrated statistically significant increases from baseline in all of the linear growth variables (i.e., mean height velocity, height velocity SDS, and height SDS) after treatment with Genotropin (see Table 31). The linear growth response was greater in Study 055 wherein patients were treated with a larger dose of Genotropin.

TABLE 31: Growth Parameters (Mean ± SD) after 12 Months of Treatment with Genotropin In Pediatric Patients with Turner Syndrome in Two Open Label Studies

	Genotropin 0.33 mg/kg/week Study 055, n=22	Genotropin 0.13–0.23 mg/kg/week Study 092, n=16
Height Velocity (cm/yr)		
Baseline	4.1 ± 1.5	3.9 ± 1.0
Month 12	7.8 ± 1.6	6.1 ± 0.9
Change from baseline (95% CI)	3.7 (3.0, 4.3)	2.2 (1.5, 2.9)
Height Velocity SDS (Tanner^/Sempé# Standards)	(n=20)	
Baseline	-2.3 ± 1.4	-1.6 ± 0.6
Month 12	2.2 ± 2.3	0.7 ± 1.3
Change from baseline (95% CI)	4.6 (3.5, 5.6)	2.2 (1.4, 3.0)
Height Velocity SDS (Ranke Standard)		
Baseline	-0.1 ± 1.2	-0.4 ± 0.6
Month 12	4.2 ± 1.2	2.3 ± 1.2
Change from baseline (95% CI)	4.3 (3.5, 5.0)	2.7 (1.8, 3.5)
Height SDS (Tanner^/Sempé# Standards)		
Baseline	-3.1 ± 1.0	-3.2 ± 1.0
Month 12	-2.7 ± 1.1	-2.9 ± 1.0
Change from baseline (95% CI)	0.4 (0.3, 0.6)	0.3 (0.1, 0.4)
Height SDS (Ranke Standard)		
Baseline	-0.2 ± 0.8	-0.3 ± 0.8
Month 12	0.6 ± 0.9	0.1 ± 0.8
Change from baseline (95% CI)	0.8 (0.7, 0.9)	0.5 (0.4, 0.5)

SDS = Standard Deviation Score
Ranke standard based on age-matched, untreated Turner syndrome patients
Tanner^/Sempé# standards based on age-matched normal children
$p < 0.05$, for all changes from baseline

Idiopathic Short Stature

The long-term efficacy and safety of Genotropin in patients with idiopathic short stature (ISS) were evaluated in one randomized, open-label, clinical trial that enrolled 105 prepubertal children with ISS and in one small supportive open-label trial that included 37 randomized prepubertal children with ISS. In the pivotal trial, patients were enrolled on the basis of short stature, stimulated GH secretion > 10 ng/mL. A total of 177 patients were intitially enrolled, but criteria for idiopathic short stature were retrospectively applied and therefore patients with SGA and those that were pubertal were removed

from the ISS pre-pubertal analysis. All patients were observed for height progression for 12 months and were subsequently randomized to Genotropin or observation only and followed to final height. Two Genotropin doses were evaluated in this trial: 0.23 mg/kg/week (0.033 mg/kg/day) and 0.47 mg/kg/week (0.067 mg/kg/day). Baseline patient characteristics for the ISS patients who remained prepubertal at randomization (n= 105) were: mean (± SD): chronological age 11.4 (1.3) years, height SDS -2.4 (0.4), height velocity SDS -1.1 (0.8), and height velocity 4.4 (0.9) cm/yr, IGF-1 SDS -0.8 (1.4). Patients were treated for a median duration of 5.7 years. Results for final height SDS are displayed by treatment arm in Table 32. Genotropin therapy improved final height in ISS children relative to untreated controls. The observed mean gain in final height was 9.8 cm for females and 5.0 cm for males for both doses combined compared to untreated control subjects. A height gain of 1 SDS was observed in 10 % of untreated subjects, 50% of subjects receiving 0.23 mg/kg/week and 69% of subjects receiving 0.47 mg/kg/week.

TABLE 32: Final Height SDS Results for Pre-Pubertal Patients with ISS*

	Untreated (n=30)	GEN 0.033 mg/kg/day (0.23 mg/kg/week) (n=33)	GEN 0.067 mg/kg/day (0.47 mg/kg/week) (n=42)	GEN 0.033 mg/kg/day (0.23 mg/kg/week) vs. Untreated (95% CI) **	GEN 0.067 mg/kg/day (0.47 mg/kg/week) vs. Untreated (95% CI)**	GEN 0.033 mg/kg/day (0.23 mg/kg/week) vs. GEN 0.067 mg/kg/day (0.47 mg/kg/week)**
Final height SDS minus baseline SDS	0.41 (0.58)	0.95 (0.75)	1.36 (0.64)	+0.53 (0.20, 0.87) p=0.0022	+0.94 (0.63,1.26) p<0.0001	-0.41(-0.72,-0.10) p=0.0105
Final height SDS minus baseline predicted final height SDS	0.23 (0.66)	0.73 (0.63)	1.05 (0.83)	+0.60 (0.09, 1,11) p=0.0217	+0.90 (0.42,1.39) p=0.0004	-0.30(-0.69,0.09) p= 0.1272

*Mean (SD) are observed values.

**Least square means based on ANCOVA (final height SDS and final height SDS minus baseline predicted height SDS were adjusted for baseline height SDS)

Supportive Study CTN 89-050 was a randomized, open-label, multicenter study that evaluated the efficacy and safety of Genotropin treatment in prepubertal children diagnosed with ISS. Thirty seven children who fulfilled the study entry criteria were randomly assigned to receive Genotropin at a dosage of 0.047 mg/kg body weight per day (n=18) or to serve as untreated controls (n=19). The primary efficacy variable, the change in height SDS for bone age (HSDS-BA) after 36 months, was evaluated in the ITT population, which included 18 subjects in each group who were randomized and had at least one post-baseline efficacy measurement. All subjects were prepubertal at study start and remain so throughout the study. After 36 months, the mean HSDS-BA increased by 0.34 ± 1.60 from baseline in the treated group (n = 18) and decreased -0.46 ± 1.58 SD in the untreated control group (n =17), but the difference in the mean change (0.8 SD) did not reach statistical significance (p = 0.192).

Height SDS, however, increased significantly compared to untreated controls at both Months 12 and 36 (p<0.001), as did growth velocity SDS for bone age and growth velocity SDS (each p< 0.001) at both

time points. Mean changes from baseline in height (cm) and growth velocity (cm/year) were both significantly greater in the Genotropin group compared to the untreated control group (each $p<0.001$). The number of subjects who achieved an increase of at least 1.0 SDS in height SDS was significantly greater in the Genotropin group at Month 36 than in the untreated control group ($p<0.001$). Improvements in growth variables involving chronologic age were better predictors of response to therapy than variables that were adjusted for bone age.

Adults

Adult Growth Hormone Deficiency (GHD)

Genotropin lyophilized powder was compared with placebo in six randomized clinical trials involving a total of 172 adult GHD patients. These trials included a 6-month double-blind treatment period, during which 85 patients received Genotropin and 87 patients received placebo, followed by an open-label treatment period in which participating patients received Genotropin for up to a total of 24 months. Genotropin was administered as a daily SC injection at a dose of 0.04 mg/kg/week for the first month of treatment and 0.08 mg/kg/week for subsequent months.

Beneficial changes in body composition were observed at the end of the 6-month treatment period for the patients receiving Genotropin as compared with the placebo patients. Lean body mass, total body water, and lean/fat ratio increased while total body fat mass and waist circumference decreased. These effects on body composition were maintained when treatment was continued beyond 6 months. Bone mineral density declined after 6 months of treatment but returned to baseline values after 12 months of treatment.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

16.1 Comparative Non-Clinical Pharmacology and Toxicology

16.1.1 Comparative Non-Clinical Pharmacodynamics

The pharmacodynamic response to Omnitrope (somatropin for injection) and reference product Genotropin was compared in both *in vitro* and *in vivo* studies.

***In vitro* Studies**

The biological activity of Omnitrope was confirmed to be similar to that of Genotropin in an *in vitro* cell proliferation bioassay that is sensitive to the effects of human growth hormone.

***In vivo* studies**

Rat Weight Gain Bioassay

The *in vivo* pharmacodynamics of Omnitrope were compared with those of Genotropin in the rat weight gain bioassay performed in the hypophysectomized rat model. Male hypophysectomized rats were administered 0 (vehicle) or 5 mcg/animal/day of Omnitrope or Genotropin by subcutaneous injection for 10 consecutive days. Both Omnitrope and Genotropin induced body weight gain in this model and the effects were comparable between the two products.

Rat Tibial Width Assay

The *in vivo* pharmacodynamics of Omnitrope were compared with those of Genotropin in the rat tibial width assay performed in immature hypophysectomized rats. Animals were administered 0 (vehicle), 0.02, or 0.16 IU/animal/day of Omnitrope or Genotropin by subcutaneous injection for 10 consecutive days. Both Omnitrope and Genotropin induced an increase in the thickness of the proximal epiphysis of the tibia in this model and the effects were comparable between the two products.

16.1.2 Comparative Toxicology

Comparative *in vivo* animal toxicology studies evaluating the similarity of the toxicity profile of Omnitrope with that of the reference biologic drug, Genotropin, were not conducted.

16.2 Non-Clinical Toxicology – Reference Biologic Drug

General Toxicology:

Acute Toxicity

A single subcutaneous dose of 300 mg/kg of somatropin (more than 8000 times the intended human dose) was given to Sprague Dawley rats with no lethality during the 48 hour observation period.

Short Term Toxicity

The general toxicity of somatropin in Sprague Dawley rats has been studied after repeated intramuscular administration of 0.34 (0.125 mg), 1.7 (0.625 mg) and 8.14 (3.125 mg) IU/kg/day. A positive control group received pituitary human growth hormone (pit hGH) at 3.125 mg/ day, and a negative control group received glycine phosphate solution.

No deaths occurred and no drug related clinical signs were observed. A dose related increase in body weight gain, as compared to the controls, was recorded in females receiving 0.625 or 3.125 mg/kg/day recombinant somatropin. Females given pit hGH (3.125 mg/kg/day) also showed increased weight gain. The body weight gain of male rats was similar in all groups, including control. The food consumption of drug treated animals was comparable to that of the controls, except for an increase in food intake in females given 3.125 mg/kg/day of either recombinant somatropin or pit hGH.

Organ weight analysis showed statistically significant increased absolute and relative group mean weights of the adrenals in males, but not in females, receiving 0.625 or 3.125 mg/kg/day of somatropin, as well as in males given pit hGH. A marginal increase in the absolute group mean weights of the ovaries was recorded in females receiving 3.125 mg/kg/day of recombinant somatropin or pit hGH.

In total, intramuscular treatment with somatropin for one month was well tolerated in all treatment groups. A growth promoting effect (increase in body weight gain) was demonstrated in female rats at the two highest dose levels, but in none of the male groups, with an associated increase in food consumption. A small uterine nodule, compatible with a decidual cell reaction, was observed in one rat from the high dose somatropin group. A hormonal influence was also evidenced by a dose related mammary gland hyperplasia in females at the two highest dose levels of somatropin as well as in females from the pit hGH group.

Chronic Toxicity

The general toxicity of somatropin has been evaluated in cynomolgus monkeys following daily subcutaneous injections of 0.13, 0.65 or 3.23 mg/kg for 52 weeks. Administration at dose levels up to 3.23 mg/kg did not produce any clinical toxic effects. Drug-related changes associated with a dose level of 3.23 mg/kg were a decrease of serum progesterone levels at the estimated luteal phase and a tendency to reduce serum prolactin levels for males and females. In addition, there was an indication of increased immunoreactivite insulin levels in serum from male animals. Prolonged menstrual cycles, and/or absence of cyclicity was seen in some high dose females.

Microscopic examination showed a dose-related adipocyte hypertrophy in the abdominal fat in treated males and females alveolar dilatation/hyperplasia of the mammary gland. The alveolar dilitation was found in three females from each of the treatment groups. Mammary gland hyperplasia was seen only in high dose animals (one male and one female). The microscopic findings showed regression during the recovery period.

Reproductive Studies:

Studies for effects on embro-fetal development carried out with somatropin at doses of 1, 3 and 10 IU/kg/day administered SC in the rat and 0.25, 1 and 4 IU/kg/day administered IM in the rabbit, resulted in effects on maternal body weight gains (increased in rats and decreased in rabbits) but were not teratogenic. In rats receiving SC doses during gametogenesis and up to seven days of pregnancy, 10 IU/kg/day produced anestrus or extended estrus cycles and fewer and less motile sperm in males. When given to pregnant female rats (days one to seven of gestation) at 10 IU/kg/day a very slight increase in fetal deaths were observed. At 3 IU/kg/day rats showed slightly extended estrus cycles, whereas at 1 IU/kg/day no effects were noted.

In perinatal and postnatal studies in rats, somatropin doses of 1, 3 and 10 IU/kg/day produced growth-promoting effects in the dams but not in the fetuses. Young rats at the highest doses showed increased weight gain during suckling but the effect was not apparent by 10 weeks of age. No adverse effects were observed on gestation, morphogenesis, parturition, lactation, postnatal development or reproductive capacity of the offspring due to somatropin.

Mutagenicity Studies:

No potential mutagenicity of somatropin was revealed in a battery of mutagenicity tests including bacterial tests to demonstrate induction of gene mutations (Ames test in *Salmonella* and *E. coli*), a test to demonstrate the chromosome damaging potential in human cells cultured *in vitro* (human lymphocytes), a test to demonstrate the induction of gene mutations in mammalian cells grown *in vitro* (mouse lymphoma L5178Y cells) and a test to demonstrate the induction of chromosomal damage *in vivo* (bone marrow cells in rats).

Immunotoxicity:

In the three month monkey study the immunological investigation comprised assays for antibodies both to growth hormone and to periplasmic *E. coli* peptides in selected animals at completion of the treatment period. No antibodies could be detected either to growth hormone or to periplasmic *E. coli* peptides. Furthermore, no changes suggestive of an immunological response or changes in the immune system were seen.

17 SUPPORTING PRODUCT MONOGRAPHS

1. GENOTROPIN®GoQuick™ Lyophilized Powder for reconstitution: 5 mg, 5.3 mg, 12 mg pre-filled pen, GoQuick; GENOTROPIN®MiniQuickTM Lyophilized Powder for reconstitution: 0.2 mg, 0.4 mg, 0.6 mg, 0.8 mg, 1.0 mg, 1.2 mg, 1.4 mg, 1.6 mg, 1.8 mg, and 2.0 mg prefilled syringe, MiniQuick, submission control 229726, Product Monograph, Pfizer Canada ULC. June 22, 2020.

PATIENT MEDICATION INFORMATION (LYOPHILIZED POWDER)

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrOMNITROPE®

AWM nee trope

(Somatropin for Injection)

Lyophilized powder: 5.8 mg/vial

Read this carefully before you start taking **Omnitrope** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Omnitrope**.

Omnitrope *is a biosimilar biologic drug (biosimilar) to the reference biologic drug Genotropin®. A biosimilar is authorized based on its similarity to a reference biologic drug that was already authorized for sale.*

Serious Warnings and Precautions

- **A doctor trained in hormone and growth disorders must examine the patient to decide if it is safe to use Omnitrope.**
- **After the Omnitrope powder has been dissolved it must be water-clear and free of particles.**

What is Omnitrope 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.

How does Omnitrope work?

Omnitrope is a recombinant human growth hormone (also called somatropin). It has the same structure as natural human growth hormone which is needed for bones and muscles to grow. It also

helps your fat and muscle tissues to develop in the right amounts. Recombinant means it is made using bacteria instead of being taken out of human or animal tissue.

What are the ingredients in Omnitrope?

Medicinal ingredient: Somatropin (recombinant human growth hormone)

Non-medicinal ingredients:

Omnitrope Lyophilized Powder: Glycine, disodium hydrogen phosphate, sodium dihydrogen phosphate.

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

Omnitrope comes in the following dosage forms:

Omnitrope (somatropin for injection) is supplied as follows: Lyophilized powder: 5.8 mg/vial.

Do not use Omnitrope if:

- 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 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.
- You have uncontrolled diabetes or active psychosis.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Omnitrope. Talk about any health conditions or problems you may have.

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.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Omnitrope:

You should tell your doctor if you are using:
- medicines to treat diabetes,
- thyroid hormones,
- synthetic adrenal hormones (corticosteroids),
- sex hormones (for example oral estrogens),
- cyclosporine (a medicine that weakens the immune system after transplantation),
- medicines to control epilepsy (anticonvulsants).

Your doctor may need to adjust the dose of these medicines or the dose of Omnitrope.

How to take Omnitrope:

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.

Overdose:

If you think you, or a person you are caring for, have taken too much Omnitrope, contact a healthcare professional, 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:

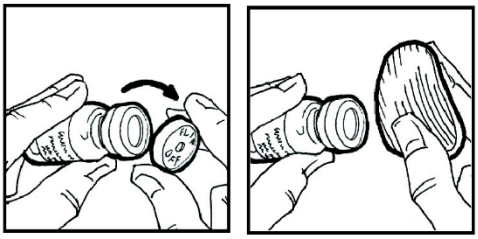
- a vial with 5.8 mg Omnitrope powder for solution for injection.
- a cartridge with diluent (Bacteriostatic Water for Injection containing benzyl alcohol as

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

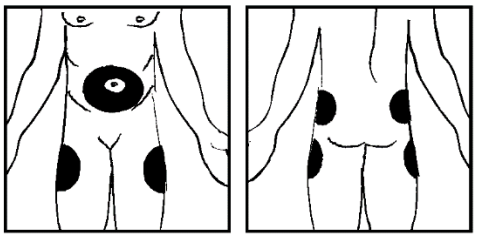
- Remove the protective cap from the vial. With one alcohol swab, disinfect both the rubber membrane of the vial with powder and the cartridge containing diluent.



- 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.

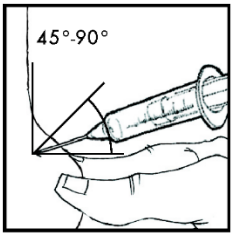
Injecting Omnitrope 5.8 mg/vial

- 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.

What are possible side effects from using Omnitrope?

These are not all the possible side effects you may have when taking Omnitrope. If you experience any side effects not listed here, tell your healthcare professional.

Like all medicines, Omnitrope can cause side effects, although not everybody gets them.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	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.		✓	

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
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.

Since Somatropin has been on the market, serious strong reactions have occurred in patients including very bad allergic reactions that can cause difficulty breathing and swelling of the face and lips. Patients and caregivers should get medical attention immediately if an allergic reaction occurs.

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- 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.

If you want more information about Omnitrope:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.sandoz.ca, or by calling 1-800-361-3062.

This leaflet was prepared by Sandoz Canada Inc.

Last Revised: November 1, 2022

PATIENT MEDICATION INFORMATION (SOLUTION FOR INJECTION)

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

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

Read this carefully before you start taking **Omnitrope** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Omnitrope**.

Omnitrope *is a biosimilar biologic drug (biosimilar) to the reference biologic drug Genotropin®. A biosimilar is authorized based on its similarity to a reference biologic drug that was already authorized for sale.*

Serious Warnings and Precautions

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What is Omnitrope 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.

How does Omnitrope work?

Omnitrope is a recombinant human growth hormone (also called somatropin). It has the same structure as natural human growth hormone which is needed for bones and muscles to grow. It also helps your fat and muscle tissues to develop in the right amounts. Recombinant means it is made using

bacteria instead of being taken out of human or animal tissue.

What are the ingredients in Omnitrope?

Medicinal ingredient: Somatropin (recombinant human growth hormone)

Non-medicinal ingredients:

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, sodium chloride, poloxamer 188, phenol, water for injection.

Omnitrope comes in the following dosage forms:

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.

Do not use Omnitrope if:

- 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 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.
- You have uncontrolled diabetes or active psychosis.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Omnitrope. Talk about any health conditions or problems you may have.

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.

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.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Omnitrope:

You should tell your doctor if you are using:
- medicines to treat diabetes,
- thyroid hormones,
- synthetic adrenal hormones (corticosteroids),
- sex hormones (for example oral estrogens),
- cyclosporine (a medicine that weakens the immune system after transplantation),
- medicines to control epilepsy (anticonvulsants).

Your doctor may need to adjust the dose of these medicines or the dose of Omnitrope.

How to take Omnitrope:

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:

If you think you, or a person you are caring for, have taken too much Omnitrope, contact a healthcare professional, 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

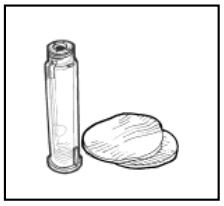
The following instructions explain how to inject Omnitrope 5.0 mg/1.5 mL yourself. Please read the instructions carefully and follow them step by step. Your doctor or other suitably qualified healthcare professionals will show you how to inject Omnitrope. Do not attempt to inject unless you are sure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

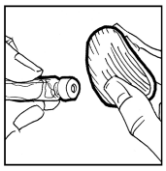
- a cartridge with Omnitrope 5.0 mg/1.5 mL solution for injection.
- the Omnitrope® Surepal 5, an injection device specifically developed for use with Omnitrope 5.0 mg/1.5 mL solution for injection (not supplied in the pack; see Instructions for Use provided with the Omnitrope® Surepal 5).
- a pen needle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



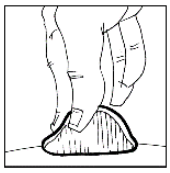
Wash your hands before you continue with the next steps.

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

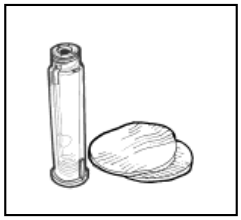
professionals will show you how to inject Omnitrope. Do not attempt to inject unless you are sure you understand the procedure and requirements for injection.

- 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:

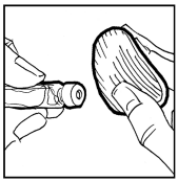
- a cartridge with Omnitrope 10.0 mg/1.5 mL solution for injection.
- the Omnitrope® Surepal 10, an injection device specifically developed for use with Omnitrope 10.0 mg/1.5 mL solution for injection (not supplied in the pack; see Instructions for Use provided with the Omnitrope® Surepal 10).
- a pen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



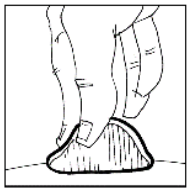
Wash your hands before you continue with the next steps.

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

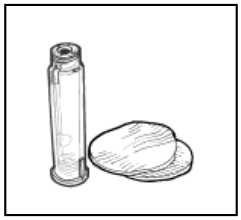
The following instructions explain how to inject Omnitrope 15.0 mg/1.5 mL yourself. Please read the instructions carefully and follow them step by step. Your doctor or other suitably qualified healthcare professionals will show you how to inject Omnitrope. Do not attempt to inject unless you are sure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

What are possible side effects from using Omnitrope?

These are not all the possible side effects you may have when taking Omnitrope. If you experience any side effects not listed here, tell your healthcare professional.

Like all medicines, Omnitrope can cause side effects, although not everybody gets them.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	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			

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
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.

Since Somatropin has been on the market, serious strong reactions have occurred in patients including very bad allergic reactions that can cause difficulty breathing and swelling of the face and lips. Patients and caregivers should get medical attention immediately if an allergic reaction occurs.

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- 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.

If you want more information about Omnitrope:

- Talk to your healthcare professional

- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.sandoz.ca, or by calling 1-800-361-3062.

This leaflet was prepared by Sandoz Canada Inc.

Last Revised: November 1, 2022