NEW ZEALAND DATA SHEET
OMNITROPE® (SOMATROPIN (R-HGH))

1. PRODUCT NAME

OMNITROPE®

Somatropin (r-hGH) 5 mg/1.5 mL, 10 mg/1.5 mL and 15 mg/1.5 mL solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Omnitrope is a biosimilar medicinal product. The prescribing physician should be involved in any decision regarding interchangeability with other products. Additional information is available on the following website (http://www.medsafe.govt.nz/profs/RIss/Biosimilars.asp). Data comparing Omnitrope to Genotropin can be found in Section 5.3 Preclinical safety data of this datasheet.

Omnitrope 5 mg/1.5 mL Solution for Injection contains 3.33 mg/mL somatropin (rbe).

Omnitrope 10 mg/1.5 mL Solution for Injection contains 6.67 mg/mL somatropin (rbe).

Omnitrope 15 mg/1.5 mL Solution for Injection contains 10 mg/mL somatropin (rbe).

For full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Omnitrope Solution for Injection is a clear, colourless solution.

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS

Children

Growth disturbance due to insufficient secretion of growth hormone and growth disturbance associated with Turner syndrome or chronic renal insufficiency. Prader-Willi syndrome, for improvement of growth and body composition.

Adults

Replacement therapy in adults with pronounced growth hormone deficiency as diagnosed in two different dynamic tests for growth hormone deficiency. Patients must also fulfill the following criteria.

Childhood onset: Patients, who were diagnosed as growth hormone deficient during childhood, must be retested and their growth hormone deficiency confirmed before replacement therapy with OMNITROPE is started.

Adult onset: Patients must have growth hormone deficiency as a result of hypothalamic or pituitary disease and at least one other hormone deficiency diagnosed (except for prolactin) and adequate replacement therapy instituted, before replacement therapy using growth hormone may begin.

Prader-Willi syndrome, for improvement of body composition.

4.2. DOSE AND METHOD OF ADMINISTRATION

The dosage and administration schedule should be individualized.

The maximum recommended daily dose should not be exceeded.

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

Growth disturbance due to insufficient secretion of growth hormone in children

Generally, a dose of 0.025 to 0.035 mg/kg body weight per day or 0.7 to 1.0 mg/m^2 body surface area per day is recommended. Even higher doses have been used.

Prader-Willi syndrome, for improvement of growth and body composition in children:
Generally a dose of 0.035 mg/kg body weight per day or 1.0 mg/m^2 body surface area per day is recommended.

Growth disturbance due to Turner syndrome

A dose of 0.045 to 0.05 mg/kg body weight per day or 1.4 mg/m^2 body surface area per day is recommended.

Growth disturbance in chronic renal insufficiency

A dose of 1.4 mg/m^2 body surface area per day (approximately 0.045 - 0.05 mg/kg body weight per day) is recommended. Higher doses can be needed if growth velocity is too low. A dose correction can be needed after six months of treatment.

Dosage recommendations in children:

Indication	mg/kg body weight dose per day	**mg/m^2** body surface area dose per day
Growth hormone deficiency	0.025 - 0.035	0.7 - 1.0
Prader-Willi syndrome	0.035	1.0
Turner syndrome	0.045 - 0.05	1.4
Chronic renal insufficiency	0.045 - 0.05	1.4

Adult patients with growth hormone deficiency or Prader-Willi syndrome:

The recommended starting dose is 0.15 to 0.30 mg per day. The final dose should be individually titrated as needed with respect to age and gender. The daily maintenance dose seldom exceeds 1.3 mg per day. Women may require higher doses than men. As normal physiological growth hormone production decreases with age, dose requirements may be reduced. Clinical response, side effects, and determination of IGF-1 in serum may be used as guidance for dose titration.

Duration of treatment

There is no specific time limit for the duration of treatment with somatropin. Treatment is to be discontinued when the patient has reached a satisfactory final height, when the epiphyses are closed or when the patient no longer responds to growth hormone therapy. Response to somatropin therapy in paediatric patients tends to decrease with time. However, failure to increase growth velocity, particularly during the first year of treatment, suggests the need for

close assessment of compliance and other causes of growth failure such as hypothyroidism, under-nutrition and advanced bone age.

4.3. CONTRAINDICATIONS

Treatment with OMNITROPE is contraindicated:

- In patients with evidence of malignancies. Intracranial lesions have to be inactive.
- Anti-tumour therapy has to be completed prior to treatment. Treatment with OMNITROPE should be discontinued if there is any evidence of recurrent tumour activity.
- For growth promotion in paediatric patients with closed epiphyses.
- In patients with acute critical illness due to complications following open heart surgery, abdominal surgery, multiple accident trauma or to patients having acute respiratory failure or similar conditions (Regarding patients undergoing substitution therapy, see Section 4.4 Special warnings and precautions for use).
- In patients with known hypersensitivity to somatropin or to any of the excipients
- In patients with Prader-Willi syndrome who are severely obese or have severe respiratory impairment (see Section 4.4 Special warnings and precautions for use).

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Diagnosis and therapy with OMNITROPE should be initiated and monitored by physicians who are appropriately qualified and experienced in the diagnosis and management of patients with growth hormone deficiency. The maximum recommended daily dose should not be exceeded. (see Section 4.2 Dose and method of administration).

Prader-Willi Syndrome

There have been reports of fatalities associated with the use of growth hormone in paediatric patients with Prader-Willi syndrome who had one or more of the following risk factors: severe obesity, history of respiratory impairment or sleep apnoea, or unidentified respiratory infection. Another possible risk factor may be male gender. Patients with Prader-Willi syndrome should be evaluated for upper airway obstruction before initiation of treatment with somatropin. If during treatment with somatropin patients show signs of upper airway obstruction (including onset of or increased snoring), treatment should be interrupted. All patients with Prader-Willi syndrome should be evaluated for sleep apnoea and monitored if sleep apnoea is suspected. These patients should also have effective weight control and be monitored for signs of respiratory infections, which should be diagnosed as early as possible and treated aggressively (see Section 4.3 Contraindications).

Progression of scoliosis can occur in patients who experience rapid growth. Because growth hormone increases growth rate, physicians should be alert to the abnormality, which may manifest during growth hormone therapy. Scoliosis is commonly seen in patients with Prader-Willi syndrome.

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

Somatropin may reduce insulin resistance and therefore patients should be observed for evidence of glucose intolerance. In rare cases, therapy with somatropin may produce sufficient glucose intolerance to meet diagnostic criteria for Type 2 diabetes mellitus. The risk of developing diabetes during treatment with somatropin is greatest in those patients with other risk factors for Type 2 diabetes mellitus, such as obesity, family history of diabetes, treatment with steroids, or prior impaired glucose tolerance. In patients with pre-existing diabetes mellitus, the dose of anti-diabetic therapy might require adjustment when somatropin is instituted.

During treatment with somatropin an enhanced T4 to T3 conversion has been found which may result in a reduction in serum T4 and an increase in serum T3 concentrations. In general, the peripheral thyroid hormone levels have remained within the reference ranges for healthy subjects. The effects of somatropin on thyroid hormone levels may be of clinical relevance in patients with central subclinical hypothyroidism in whom hypothyroidism theoretically may develop. Conversely, in patients receiving replacement therapy with thyroxin mild hyperthyroidism may occur. It is therefore particularly advisable to test thyroid function after starting treatment with somatropin and after dose adjustments.

Introduction of somatropin treatment may result in inhibition of 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD-1) and reduced serum cortisol concentrations. In patients treated with somatropin, previously undiagnosed central (secondary) hypoadrenalism may be unmasked and glucocorticoid replacement may be required. In addition, patients treated with glucocorticoid replacement therapy for previously diagnosed hypoadrenalism may require an increase in their maintenance or stress doses, following initiation of somatropin treatment (see Section 4.5 Interactions with other medicines and other forms of interactions).

If a woman taking somatropin begins oral oestrogen therapy, the dose of somatropin may need to be increased to maintain the serum insulin-like growth factor-I (IGF-I) levels within the normal age-appropriate range. Conversely, if a woman on somatropin discontinues oral oestrogen therapy, the dose of somatropin may need to be reduced to avoid excess of growth hormone and/or side effects (see Section 4.5 Interactions with other medicines and other forms of interactions).

In patients with endocrine disorders, including growth hormone deficiency, slipped epiphyses of the hip may occur more frequently than in the general population. Children limping during treatment with somatropin should be examined clinically.

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

In case of severe or recurrent headache, visual problems, nausea and/or vomiting, a funduscopy for papilloedema is recommended. If papilloedema is confirmed, a diagnosis of benign intracranial hypertension should be considered and, if appropriate, the growth hormone treatment should be discontinued. At present there is insufficient evidence to guide clinical decision making in patients with resolved intracranial hypertension. If growth hormone treatment is restarted, careful monitoring for symptoms of intracranial hypertension is necessary.

In chronic renal insufficiency, renal function should be below 50 percent of normal before institution of therapy. To verify growth disturbance, growth should be followed for a year preceding institution of therapy. During this period, conservative treatment for renal insufficiency (which includes control of acidosis, hyperparathyroidism and nutritional status) should have been established and should be maintained during treatment.

The treatment should be discontinued at renal transplantation.

To date, no data on final height in patients with chronic renal insufficiency treated with OMNITROPE are available.

The effects of somatropin on recovery were studied in two placebo controlled trials involving 522 critically ill adult patients suffering complications following open heart surgery, abdominal surgery, multiple accidental trauma or acute respiratory failure. Mortality was higher in patients treated with 5.3 or 8 mg somatropin daily compared to patients receiving placebo, 42% vs. 19%.

Based on this information, these types of patients should not be treated with somatropin. As there is no information available on the safety of growth hormone substitution therapy in acutely critically ill patients, the benefits of continued treatment in this situation should be weighed against the potential risks involved (see Section 4.3 Contraindications). In all patients developing other or similar acute critical illness, the possible benefit of treatment with somatropin must be weighed against the potential risk involved.

Other Precautions

Experience in patients above 60 years is limited

Experience with prolonged treatment in adults is limited.

Because of the presence of benzyl alcohol in the 5 mg/1.5 mL solution for injection, the product must not be given to premature babies or neonates. It may cause toxic reactions and anaphylactoid reactions in infants and children up to 3 years old.

4.5. INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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

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

Data from an interaction study performed in growth hormone deficient adults suggests that somatropin administration may increase the clearance of compounds known to be metabolized by cytochrome P450 isoenzymes. The clearance of compounds metabolized by cytochrome P 450 3A4 (e.g. sex steroids, corticosteroids, anticonvulsants and ciclosporin) may be especially increased resulting in lower plasma levels of these compounds. The clinical significance of this is unknown. Also, see Section 4.4 Special warnings and precautions for use**,** for statements regarding diabetes mellitus and thyroid disorder.

In women on oral oestrogen replacement, a higher dose of growth hormone may be required to achieve the treatment goal (see Section 4.4 Special warnings and precautions for use).

See also statements under Section 4.4 Special warnings and precautions for use regarding diabetes mellitus and thyroid disorder.

4.6. FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Use in pregnancy

Category B2.

No clinical experience of use in pregnant women is available. Animal reproduction studies have not shown evidence of harmful effects on the foetus. Treatment with OMNITROPE should be interrupted if pregnancy occurs.

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

Use in lactation

It is not known if somatropin is excreted into breast milk, but absorption of intact protein from the gastrointestinal tract of the infant is extremely unlikely.

Caution should be exercised when somatropin is administered to breastfeeding women.

4.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Somatropin does not influence the ability to drive and use machines.

4.8. UNDESIRABLE EFFECTS

The following undesirable effects have been observed and reported during treatment with OMNITROPE with the following frequencies: Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000).

System Organ Class

Neoplasms benign, malignant and unspecified (including cysts and polyps):
Very rare: children leukemia*

Metabolism and Nutrition Disorders:
Frequently not known: type 2 diabetes mellitus

Nervous system disorders:
Common: In adults: paraesthesia
Uncommon: In adults: carpal tunnel syndrome. In children: paraesthesia
Rare: Children: Benign intracranial hypertension
Frequently not known: adults: benign intracranial hypertension

Musculoskeletal and connective tissue disorders:
Very common: Adults: arthralgia
Common: In adults: stiffness in the extremities, myalgia
Children: arthralgia
Rare: children: myalgia
Very rare: Children: musculoskeletal stiffness

General disorders and administration site conditions:
Very Common: In adults: peripheral oedema

Common: In children: injection-site reactions
Uncommon: In children: peripheral oedema
Frequently not known: Adults: injection-site reactions
Adults and children: face oedema

Investigations:
Frequently not known: serum cortisol decreased.

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 somatropin therapy.

Immune system disorders:
Common: formation of antibodies.

The binding capacity of these antibodies has been low and no clinical changes have been associated with their formation.

Skin and subcutaneous tissue disorders:
Common: In children: transient local skin reactions

Patients with growth hormone deficiency are characterised by extracellular volume deficit. When treatment with somatropin is started this deficit is rapidly corrected. In adult patients adverse effects related to fluid retention, such as peripheral oedema, musculoskeletal stiffness, arthralgia, myalgia and paraesthesia are common (> 1/100 and < 1/10). In general these adverse effects are mild to moderate, arise within the first months of treatment and subside spontaneously or with dose-reduction.

The incidence of these adverse effects is related to the administered dose, the age of patients, and possibly inversely related to the age of patients at the onset of growth hormone deficiency. In children such adverse effects are uncommon (≥ 1/1000 and < 1/100).

*Very rare cases of leukemia (< 1/10,000) have been reported in growth hormone deficient children treated with somatropin, but the incidence appears to be similar to that in children without growth hormone Deficiency.

Post-marketing experience

In the post-marketing experience, rare cases of sudden death have been reported in patients affected by Prader-Willi syndrome treated with somatropin, although no causal relationship has been demonstrated.

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.

Rash, pruritis and urticaria have been reported in both adult patients (frequency not known) and paediatric patients (frequency uncommon).

Reporting suspected adverse effects

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

4.9. OVERDOSE

Acute overdosage could lead initially to hypoglycaemia and subsequently to hyperglycaemia.

Long-term overdosage could result in signs and symptoms consistent with the known effects of human growth hormone excess.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES

Mechanism of action

Somatropin is a potent metabolic hormone of importance for the metabolism of lipids, carbohydrates and proteins. In children with inadequate endogenous growth hormone and in children with Prader-Willi syndrome, somatropin stimulates linear growth and increases growth rate. In adults, as well as in children, somatropin maintains a normal body composition by increasing nitrogen retention and stimulation of skeletal muscle growth, and by mobilization of body fat. Visceral adipose tissue is particularly responsive to somatropin. In addition to enhanced lipolysis, somatropin decreases the uptake of triglycerides into body fat stores. Serum concentrations of IGF-1 (Insulin-like Growth Factor-I), and IGFBP3 (Insulin-like Growth Factor Binding Protein 3) are increased by somatropin. In addition, the following actions have been demonstrated:

Lipid metabolism: Somatropin induces hepatic LDL cholesterol receptors, and affects the profile of serum lipids and lipoproteins. In general, administration of somatropin to growth hormone deficient patients results in reductions in serum LDL and apolipoprotein B. A reduction in serum total cholesterol may also be observed.

Carbohydrate metabolism: Somatropin increases insulin but fasting blood glucose is commonly unchanged. Children with hypopituitarism may experience fasting hypoglycemia. This condition is reversed by somatropin.

Water and mineral metabolism: Growth hormone deficiency is associated with decreased plasma and extracellular volumes. Both are rapidly increased after treatment with somatropin. Somatropin induces the retention of sodium, potassium and phosphorus.

Bone metabolism: Somatropin stimulates the turnover of skeletal bone. Long-term administration of somatropin to growth hormone deficient patients with osteopenia results in an increase in bone mineral content and density at weight-bearing sites.

Physical capacity: Muscle strength and physical exercise capacity are improved after long-term treatment with somatropin. Somatropin also increases cardiac output, but the mechanism has yet to be clarified. A decrease in peripheral vascular resistance may contribute to this effect

OMNITROPE improves energy, vitality, memory functions and subjective well-being.

Clinical trials

Comparative Pharmacokinetic and Pharmacodynamics Studies

During the clinical development of the lyophilized powder and the liquid formulations of Omnitrope, six clinical pharmacology studies, EP2K-99-PhISUSA, EP2K-99-PhIUSA

EP2K-00-PhI[AQ], EP00-104, EP00-105 and EP00-107, were performed in healthy volunteers after a single subcutaneous dose of 5 mg. Five of these Phase I studies were comparative bioavailability studies.

Pharmacokinetics

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

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

Pharmacodynamics

The results for the pharmacodynamic parameters IGF-1, IGFBP-3, and NEFA determined during the 5 comparative Phase I studies have been summarized.

The pharmacodynamic responses in terms of IGF-1, IGFBP-3, and NEFA were highly comparable after single doses of 5 mg of the different strengths and formulations of Omnitrope (Omnitrope lyophilized powder 5.8 mg/vial, solution for injection 5 mg/1.5 mL, solution for injection 10 mg/1. 5mL and solution for injection 15 mg/1.5 mL) and of Genotropin® 5.8 mg (5 mg/mL) administered via the same route in adult healthy volunteers.

Clinical Efficacy and Safety Studies

Pediatric Growth Hormone Deficiency (GHD)

Five Phase III studies were performed in a total of 190 pediatric patients who have growth failure due to an inadequate secretion of endogenous growth hormone (see Table 1).

Table 1. Study demographics and trial design for Phase III trials

Study Number	Length of Study	Trial Design	Dosage, Route of Administration and Duration	Study Subjects (N)	Gender, Mean Age (Range)
EP2K-99-PhIII	6 months	Phase III, randomized, open, multicentre, controlled, parallel two-group study of Omnitrope lyophilizate and Genotropin® in GHD children with growth failure	S: Omnitrope powder for solution for injection; 5.8 mg/vial C: Genotropin® 5mg/mL powder 0.03 mg/kg SC, once daily	89	S: 28M, 16F 7.8 yrs (3-13 yrs) C: 21M/24F 7.4 yrs (2-14 yrs)
EP2K-00-PhIIIFo	3 months				
EP2K-00-PhIII[AQ] **Part A**	6 months (from months 9 to 15 of overall GH therapy)	Phase III, open, multicentre, comparative, parallel two-group study of Omnitrope lyophilizate and Omnitrope liquid.	S1: Omnitrope powder for solution for injection; 5.8 mg/vial S2: Omnitrope 5 mg/1.5 mL	86	S1: 27M, 15F 8.8 yrs (4-14 yrs) S2: 20M, 24F

Study Number	Length of Study	Trial Design	Dosage, Route of Administration and Duration	Study Subjects (N)	Gender, Mean Age (Range)
			solution for injection 0.03 mg/kg SC, once daily		8.1 yrs (3-14 yrs)
Part B	69 months, (from months 16 - 84 of overall GH therapy)	Phase III, open, multicentre, non-comparative follow-up study of Omnitrope liquid.	Omnitrope 5 mg/1.5 mL solution for injection 0.03 mg/kg SC, once daily		47M, 39F 9.4 yrs (4-15 yrs)
EP2K-00-PhIIIb-E	60 months,	Phase III, open, multicentre study to demonstrate the efficacy and safety of Omnitrope liquid 5.0 mg/1.5 mL in the treatment of growth-deficient children due to GHD.	Omnitrope 5 mg/1.5 mL solution for injection 0.03 mg/kg SC, once daily	50	44M, 26F 8.7 yrs (4-12 yrs)
EP2K-02-PhIII-Lyo	48 months, (up to 54 months)	Phase III, open, multicentre study to demonstrate the efficacy and safety of Omnitrope lyophilizate 5.8 mg in the treatment of growth-deficient children due to GHD.	Omnitrope powder for solution for injection; 5.8 mg/vial 0.03 mg/kg SC, once daily	51	30M, 21F 7.6 yrs (2-14 yrs)

C: Comparator

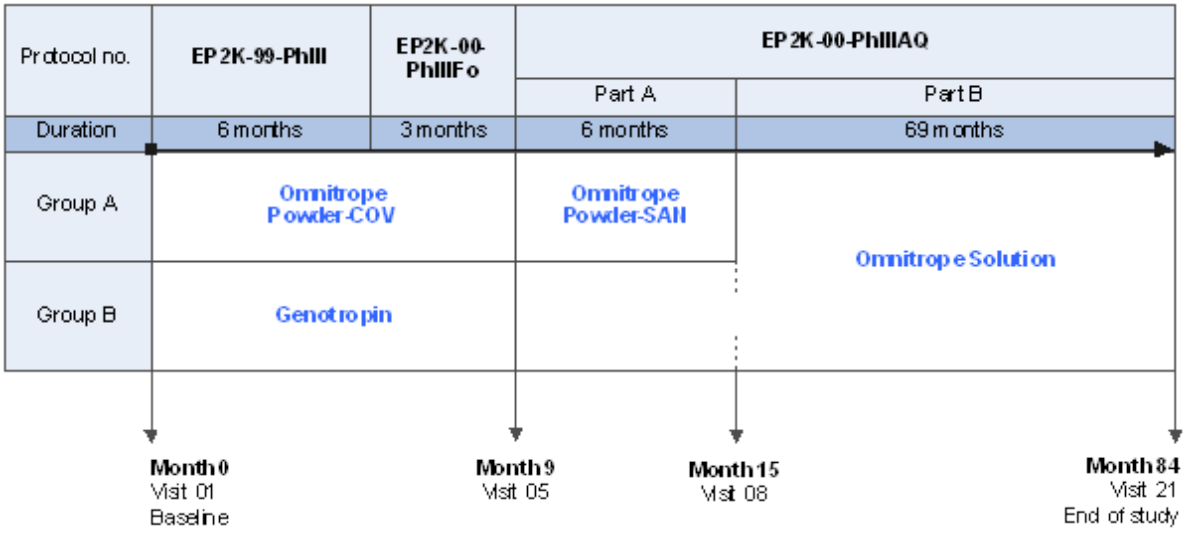
S: Omnitrope lyophilize powder with active ingredient from Covance Biotechnology, USA (not available on the market).

S1: Omnitrope lyophilize powder with active ingredient from Sandoz, Austria.

S2: Omnitrope solution for injection with active ingredient from Sandoz, Austria.

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

Figure 1. Design of the three consecutive Phase III studies EP2K-99-PhIII/ EP2K-00-PhIIIFo/ EP2K-00-PhIIIAQ



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

The efficacy results of treatment with Omnitrope lyophilized powder, Omnitrope Solution and the Genotropin® are summarized in Table 2, Table 3 and Table 4.

Table 2. Key primary endpoints in Phase III Studies EP2K-99-PhIII/EP2K-00-PhIIIFo (mean ± SD)

	Omnitrope lyophilizate N=44 Mean (SD)	**Genotropin®** N=45 Mean (SD)	**Treatment effect** Mean (95% CI)
Height Velocity (cm/yr)			
Pre-treatment	3.8 (1.2)	3.9 (0.8)	
Month 9	10.7 (2.6)	10.7 (2.9)	
Change from pre-treatment to Month 9	6.9 (3.1)	6.8 (3.2)	-0.1 (-1.5;1.3)
Height velocity SDS			
Pre-treatment	-2.3 (1.3)	-2.3 (0.9)	
Month 9	5.9 (3.4)	5.0 (2.9)	
Change from pre-treatment to Month 9	8.2 (4.0)	7.4 (3.2)	-0.9 (-2.4;0.7)
Height SDS			
Pre-treatment	-3.0 (0.7)	-3.1 (0.9)	
Month 9	-2.3 (0.7)	-2.5 (0.7)	
Change from pre-treatment to Month 9	0.8 (0.4)	0.7 (0.5)	-0.1 (-0.3;0.1)
IGF-1			
Pre-treatment	158.6 (92.0)	157.7 (43.0)	
Month 9	291.1 (174.0)	301.9 (182.9)	
IGFBP-3			
Pre-treatment	3.5 (1.3)	3.5 (1.0)	

	Omnitrope lyophilizate N=44 Mean (SD)	**Genotropin®** N=45 Mean (SD)	**Treatment effect** Mean (95% CI)
Month 9	4.6 (3.0)	4.0 (1.5)	

Table 3. Key primary endpoints in Phase III Study EP2K-00-PhIIIAQ Part A (mean ± SD)

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

Table 4. Key primary endpoints in Phase III Study EP2K-00-PhIIIAQ Part B (mean ± SD)

		Omnitrope liquid N=86 Mean (SD)	
Height velocity (cm/yr)	N		
Month 15	86	9.32.	(1.95)
Month 24	80	7.69	(1.58))..
Month 36	75	7.06	(2.04).
Month 48	69	6.58	(1.60).
Month 60	65	6.07	(2.08)
Month 72	59	5.69	(2.33)
Month 84	49	5.53	(2.34)
Height velocity SDS			
Month 15	86	4.01	2.64
Month 24	79	2.17	2.18
Month 36	75	1.82	2.50

		Omnitrope liquid N=86 Mean (SD)	
Month 48	66	1.58	1.94
Month 60	59	0.87	1.91
Month 72	53	0.26	1.92
Month 84	47	–0.02	2.68
Height SDS			
Month 15	85	–2.10	0.73
Month 24	80	–1.86	0.80
Month 36	75	–1.59	0.89
Month 48	69	–1.31	0.89
Month 60	64	–1.16	0.97
Month 72	58	–0.97	0.87
Month 84	49	–0.91	0.97
IGF-1			
Month 15	86	296.1	209.9
Month 24	80	330.8	168.6
Month 36	75	443.1	230.3
Month 48	69	467.7	218.2
Month 60	65	403.4	167.1
Month 72	59	447.3	154.9
Month 84	49	395.1	132.7
IGFBP-3			
Month 15	86	6.66	1.89
Month 24	80	8.52	2.27
Month 36	75	6.54	1.76
Month 48	69	6.35	1.23
Month 60	65	5.76	0.95
Month 72	59	6.09	1.11
Month 84	49	5.72	1.43

Height velocity SDS: peak centered

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

Omnitrope has a clinical efficacy and safety profile in the treatment of GHD children which is comparable to Genotropin®.

The lyophilized powder and liquid formulations of Omnitrope have comparable clinical efficacy and safety profiles in the treatment of children with GHD.

Omnitrope given to GHD children up to 84 months, was shown to be efficacious.

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

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

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

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

Table 5. Baseline growth characteristics and effect of OMNITROPE™ in Phase III studies (mean ± SD)

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

	EP2K-02-PhIII-Lyo Omnitrope powder for solution for injection; 5.8 mg/vial N=51 Mean (SD)	**EP2K-00-PhIIIb-E Omnitrope 5.0 mg/1.5 mL solution for injection** N=50 Mean (SD)
Month 24	389 (860.1)	3713.8 (866.7)
Month 30	3518.7 (787.7)	3986.6 (823.6)
Month 48	4009.1 (961.8)	3793.0 (793.4)
Month 60		3711.3 (69.9)

Adult Growth Hormone Deficiency (GHD)

There are no clinical trials conducted with Omnitrope in adult GHD patients. The use of Omnitrope in adult GHD patients is supported in consideration of the similar product quality characteristics of Omnitrope and Genotropin® and the similar pathophysiology of adult GHD to GHD in children. In addition, comparative non-clinical, human pharmacokinetic/ pharmacodynamic and clinical efficacy and safety studies in children (see the above) have been conducted to demonstrate comparable clinical profiles between Omnitrope and the reference product.

5.2. PHARMACOKINETIC PROPERTIES

Absorption

The bioavailability of subcutaneously administered somatropin is approximately 80% in both healthy subjects and growth hormone deficient patients. A subcutaneous dose of 5 mg of Omnitrope powder and solvent for solution for injection in healthy adults results in plasma C_{max} values of 71 ± 24 µg/L (mean ± SD) and median t_{max} value of 4 hours (range 2-8 hours), respectively.

Elimination

The mean terminal half-life of somatropin after intravenous administration in growth hormone deficient adults is about 0.4 hours. However, after subcutaneous administration of Omnitrope powder and solvent for solution for injection, a half-life of 3 hours is achieved. The observed difference is likely due to slow absorption from the injection site following subcutaneous administration.

Sub-populations

The absolute bioavailability of somatropin seems to be similar in males and females following s.c. administration.

Information about the pharmacokinetics of somatropin in geriatric and paediatric populations, in different races and in patients with renal, hepatic or cardiac insufficiency is either lacking or incomplete.

5.3. PRECLINICAL SAFETY DATA

In studies regarding general toxicity, local tolerance and reproduction toxicity no clinically relevant effects have been observed.

In vitro and in vivo genotoxicity studies on gene mutations and induction of chromosome aberrations have been negative.

An increased chromosome fragility has been observed in one in-vitro study on lymphocytes taken from patients after long term treatment with somatropin and following the addition of the radiomimetic drug bleomycin. The clinical significance of this finding is unclear.

In another study, no increase in chromosomal abnormalities was found in the lymphocytes of patients who had received long term somatropin therapy.

Comparability of Omnitrope® with Genotropin®

A comprehensive study was performed to investigate the similarity of Omnitrope 5 mg/mL with its reference product Genotropin EU at the physicochemical and biological activity levels with regard to purity, identity and quantity of the active ingredient. A further study was conducted to show the identity of the reference product Genotropin EU and the reference product Genotropin New Zealand (NZ).

The combined data from an array of state-of-the-art methods for physicochemical characterization confirmed the identity of the active ingredient Somatropin of Omnitrope and Genotropin:

Mass spectra of the intact protein revealed the correspondence of the mass of the intact protein and the theoretical mass. Peptide mapping with mass detection confirmed the primary amino acid sequence and the correct formation of disulfide bridges.

Further the identity was confirmed by use of spectroscopic methods, providing information regarding the secondary and tertiary structure of the active ingredient.

Finally, separation methods probed molecular attributes, namely charge, hydrophobicity and molecular size.

With comparable results obtained from all the applied identity methods all Omnitrope and all Genotropin batches investigated are shown to be identical with regards to the main component Somatropin.

All samples displayed comparable biological activity in an *in-vitro* cell proliferation assay.

The purity of the samples was evaluated and compared using an array of state of the artmethods for physicochemical characterization. These included orthogonal separation methods probing hydrophobicity, charge and size, and the applied methods were capable of resolving product variants based on these principles. A similar purity profile of the products near release and subsequent comparable impurity profiles found at later time points demonstrates that the active ingredient Somatropin undergoes degradation along the same pathway in each formulation.

Chromatographic analysis showed similar overall purity with highly comparable amounts of product related impurities Detected variants exhibit full biological activity and established safety. The amounts of monomeric Somatropin and the amounts of size variants (dimers, trimers andoligomers of Somatropin) are highly comparable for all tested batches of Omnitrope Genotropin.

The combined results from the physicochemical and biological characterization of Omnitrope, Genotropin 5 mg/mL (EU) and Genotropin 5.3 mg/mL (NZ and EU) demonstrate the identity of the activesubstances, indistinguishable biological activity, a high level of congruence of the purity and comparable impurity profiles of the three drug products.

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS

5 mg/1.5 mL

Dibasic sodium phosphate, monobasic dihydrate sodium phosphate, poloxamer, mannitol, benzyl alcohol as preservative, phosphoric acid, sodium hydroxide, water for injections.

10 mg/1.5 mL

Monobasic dihydrate sodium phosphate, dibasic sodium phosphate, poloxamer, phenol as preservative, glycine, phosphoric acid, sodium hydroxide, water for injections.

15 mg/1.5 mL

Monobasic dihydrate sodium phosphate, dibasic sodium phosphate, poloxamer, phenol as preservative, sodium chloride, phosphoric acid, sodium hydroxide, water for injections.

6.2. INCOMPATIBILITIES

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

6.3. SHELF LIFE

5 mg/1.5 mL – 24 months from date of manufacture

10 mg/1.5 mL – 18 months from date of manufacture

15 mg/1.5 mL – 18 months from date of manufacture

6.4. SPECIAL PRECAUTIONS FOR STORAGE

Store at 2°C to 8°C (in a refrigerator). Do not freeze. Store in the original package in order to protect from light. In-use shelf-life is 28 days refrigerated from first injection for all strengths.

6.5. NATURE AND CONTENTS OF CONTAINER

Colourless glass cartridges containing clear and colourless solution.

Each pack contains 1, 5 or 10 cartridges.

Not all pack sizes are marketed.

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL

No special requirements for disposal.

Omnitrope 5 mg/1.5 mL Solution for Injection

Omnitrope 5 mg/1.5 mL is a ready-to-use solution which is filled in glass cartridges. The glass cartridge is irreversibly integrated in a transparent container and assembled to a plastic mechanism with a threaded rod at one extremity. This presentation is intended for multiple use with a pen device. SurePal 5 pen needs to be used to administer Omnitrope 5 mg/1.5 mL. After the first injection, the contents of the cartridge must be used within 28 days and the cartridge should remain in the pen and has to be kept at 2°C to 8°C (in a refrigerator). For microbiological reasons, any remaining solution should be discarded after 28 days.

SUREPAL 5 IS INTENDED FOR USE BY A SINGLE PATIENT ONLY.

Omnitrope 10 mg/1.5 mL Solution for Injection

Omnitrope 10 mg/1.5 mL is a ready-to-use solution which is filled in glass cartridges. The glass cartridge is irreversibly integrated in a transparent container and assembled to a plastic mechanism with a threaded rod at one extremity. This presentation is intended for multiple use with a pen device. SurePal 10 pen needs to be used to administer Omnitrope 10 mg/1.5 mL. After the first injection, the contents of the cartridge must be used within 28 days and the cartridge should remain in the pen and has to be kept at 2°C to 8°C (in a refrigerator). For microbiological reasons, any remaining solution should be discarded after 28 days.

SUREPAL 10 IS INTENDED FOR USE BY A SINGLE PATIENT ONLY.

Omnitrope 15 mg/1.5 mL Solution for Injection

Omnitrope 15 mg/1.5 mL is a ready-to-use solution which is filled in glass cartridges. The glass cartridge is irreversibly integrated in a transparent container and assembled to a plastic mechanism with a threaded rod at one extremity. This presentation is intended for multiple use with a pen device. SurePal 15 needs to be used to administer Omnitrope 15 mg/1.5 mL. After the first injection, the contents of the cartridge must be used within 28 days and the cartridge should remain in the pen and has to be kept at 2°C to 8°C (in a refrigerator). For microbiological reasons, any remaining solution should be discarded after 28 days.

SUREPAL 15 IS INTENDED FOR USE BY A SINGLE PATIENT ONLY.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

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9. DATE OF FIRST APPROVAL

19/12/2013

10. DATE OF REVISION OF THE TEXT

19/05/2020

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	Minor editorial changes throughout document.
4.8	Added injection-site reactions and face oedema under “General disorders and administration site conditions”. Added post-marketing ADRs of rash, pruritis and urticaria.