OMNITROPE®

NAME OF THE MEDICINE

Active
Somatropin (rbe) (recombinant human growth hormone, r-hGH)

DESCRIPTION

Omnitrope® is produced using recombinant DNA technology. The active substance somatropin (biosynthetic human growth hormone, rDNA-derived human growth hormone [r-hGH]) is produced in cell culture by *Escherichia coli* cells bearing the gene for human growth hormone.

Omnitrope Solution for Injection is a clear, colourless solution. Omnitrope Powder for Injection* is a white to off-white powder.

Omnitrope 5mg/1.5mL Solution for Injection contains 3.33mg/mL somatropin and the following excipients: dibasic sodium phosphate heptahydrate, monobasic sodium phosphate, poloxamer, mannitol, phosphoric acid, sodium hydroxide and water for injections. Contains benzyl alcohol as preservative.

Omnitrope 5mg/1.5mL Solution for Injection for SurePal 5 contains 3.33mg/mL somatropin and the following excipients: dibasic sodium phosphate heptahydrate, monobasic sodium phosphate, poloxamer, mannitol, phosphoric acid, sodium hydroxide and water for injections. Contains benzyl alcohol as preservative.

Omnitrope 10mg/1.5mL Solution for Injection contains 6.67mg/mL somatropin (rbe) and the following excipients: monobasic sodium phosphate, dibasic sodium phosphate heptahydrate, poloxamer, phenol, glycine, phosphoric acid, sodium hydroxide and water for injections.

Omnitrope 10mg/1.5mL Solution for Injection for SurePal 10 contains 6.67mg/mL somatropin (rbe) and the following excipients: monobasic sodium phosphate, dibasic sodium phosphate heptahydrate, poloxamer, phenol, glycine, phosphoric acid, sodium hydroxide and water for injections.

Omnitrope 15mg/1.5mL Solution for Injection for SurePal 15 contains 10mg/mL somatropin (rbe) and the following excipients: monobasic sodium phosphate, dibasic sodium phosphate heptahydrate, poloxamer, phenol, sodium chloride, phosphoric acid, sodium hydroxide and water for injections.

PHARMACOLOGY

Pharmacodynamics

Human growth hormone (somatropin) is a 191 amino-acid polypeptide hormone (molecular weight 22 kilodaltons) normally synthesised and secreted by the somatotrophic cells of the anterior lobe of the pituitary gland. The secretion of growth hormone is controlled by two

hypothalamic hormones: growth hormone releasing factor (GRF) and growth hormone inhibiting hormone (somatostatin), and is tightly regulated by an integrated system of neural, metabolic and hormonal factors. Growth hormone is present throughout life and its secretion is both age- and sex-dependent.

Growth hormone binds to specific receptors that have recently been described and identified on hepatocytes, fibroblasts and lymphoid cells. Its known physiological roles are probably due to both direct actions of growth hormone and indirect actions that are mediated by the somatomedins (also called insulin-like growth factors, IGFs).

The somatomedins are themselves peptide hormones whose secretion is stimulated predominantly by the action of growth hormone and include IGF-1 (somatomedin C) and IGF-2. The major site of somatomedin production is the liver but they may also be synthesised at peripheral sites.

Growth hormone has effects not only on growth but also on body composition and metabolism. The following actions have been demonstrated for somatropin:

Skeletal Growth - Somatropin and its mediator IGF-1 stimulate skeletal growth in children with inadequate endogenous secretion of growth hormone. The measurable increase in body length after administration of somatropin results from an effect on the epiphysial plates of long bones. Concentrations of IGF-1 tend to increase during treatment with somatropin.

Cell Growth - It has been shown that there are fewer skeletal muscle cells in short-statured children who lack endogenous growth hormone when compared to normal children, and that treatment with somatropin results in an increase in both the number and size of muscle cells.

Protein Metabolism – Linear growth is facilitated in part by increased cellular protein synthesis. This synthesis and growth are reflected by nitrogen retention which can be quantitated by observing the decline in urinary nitrogen excretion following the initiation of somatropin therapy.

Carbohydrate Metabolism - Growth hormone is a well-known modulator of carbohydrate metabolism. Children with hypopituitarism sometimes experience hypoglycaemia that is improved by somatropin. Large doses of somatropin may impair glucose tolerance.

Lipid Metabolism - Somatropin administration has resulted in lipid mobilisation, reduction in body fat stores, and increased plasma free fatty acids in patients with growth hormone deficiency.

Mineral Metabolism - Retention of sodium, potassium and phosphorus is induced by somatropin. Serum concentrations of inorganic phosphate are increased in patients with growth hormone deficiency after therapy with somatropin due to metabolic activity associated with bone growth and increased tubular reabsorption in the kidney. Serum calcium is not significantly altered by somatropin.

Connective Tissue Metabolism - Somatropin stimulates the synthesis of chondroitin sulphate and collagen as well as the urinary excretion of hydroxyproline.

Pharmacokinetics

Maximum somatropin concentrations are reached approximately 4 hours after administration. The elimination half-life is approximately 3 hours. Somatropin serum concentrations return to baseline within 24 hours.

Bioequivalence

Bioequivalence between Omnitrope Powder for Injection and Genotropin® Powder for Injection was demonstrated in a double-blind, randomised, two-way cross-over study in 24 healthy volunteers (12 males, 12 females) receiving a single dose of 5mg somatropin subcutaneously. The pharmacokinetic parameters are summarised in the following table.

	Omnitrope Powder for Injection	**Genotropin Powder for Injection**
C_{max} (μg/L)	49 ± 19	48 ± 20
t_{max} (h)	4.1 ± 1.6	4.9 ± 1.8
AUC_{inf} (h·μg/L)	394 ± 102	395 ± 108
$t_{1/2}$ (h)	2.7 ± 0.6	2.9 ± 0.6

Area under the plasma concentration curve (AUC) and maximum observed plasma concentration (C_{max}) were used to test for bioequivalence between Omnitrope Powder for Injection and Genotropin Powder for Injection. The standard criterion for bioequivalence was met in that the 90% confidence interval (CI) for the ratio between Omnitrope Powder for Injection and Genotropin Powder for Injection was between 0.80 and 1.25. The AUC ratio for Omnitrope Powder for Injection to Genotropin Powder for Injection was 1.00, 90% CI [0.96; 1.04] and the C_{max} ratio was 1.03, 90% CI [0.94; 1.12].

Bioequivalence between Omnitrope Powder for Injection and Omnitrope 5mg/1.5mL Solution for Injection was demonstrated in a double-blind, randomised, two-way cross-over study in 24 healthy volunteers (12 males, 12 females) receiving a single dose of 5mg somatropin subcutaneously. The pharmacokinetic parameters are summarised in the following table.

	Omnitrope Powder for Injection	**Omnitrope 5mg/1.5mL Solution for Injection**
C_{max} (μg/L)	53 ± 12	53 ± 10
t_{max} (h)	3.92 ± 1.79	3.54 ± 1.28
AUC_{inf} (h·μg/L)	435 ± 40	433 ± 45
$t_{1/2}$ (h)	2.4 ± 0.6	2.4 ± 0.7

Area under the plasma concentration curve (AUC) and maximum observed plasma concentration (C_{max}) were used to test for bioequivalence between Omnitrope Powder for Injection and Omnitrope 5mg/1.5mL Solution for Injection. The standard criterion for

bioequivalence was met in that the 90% confidence interval (CI) for the ratio between Omnitrope Powder for Injection and Omnitrope 5mg/1.5mL Solution for Injection was between 0.80 and 1.25. The AUC ratio for Omnitrope Powder for Injection to Omnitrope 5mg/1.5mL Solution for Injection was 1.00, 90% CI [0.96; 1.03] and the C_{max} ratio was 1.01, 90% CI [0.97; 1.06].

In a double-blind, randomised, 3-way crossover study in 36 healthy volunteers receiving a single dose of 5mg somatropin subcutaneously, the bioequivalence between Omnitrope Powder for Injection, Omnitrope 10mg/1.5mL Solution for Injection and Genotropin 5 mg Powder for Injection was demonstrated. The pharmacokinetic parameters are summarised in the following table.

	Genotropin Powder for Injection	**Omnitrope Powder for Injection**	**Omnitrope 10mg/1.5mL Solution for Injection**
C_{max} (μg/L)	73 ± 20	69 ± 16	74 ± 22
t_{max} (h)	4.0* (2.0 – 6.0)	4.0* (2.0 – 6.0)	4.0* (2.0 – 6.0)
AUC_{inf} (h·μg/L)	540 ± 110	555 ± 96	561 ± 114
$t_{1/2}$ (h)	2.5 ± 0.7	2.9 ± 0.5	2.5 ± 0.7

* median value (min-max)

Area under the plasma concentration curve (AUC) and maximum observed plasma concentration (C_{max}) were used to test for bioequivalence between Genotropin, Omnitrope Powder for Injection and Omnitrope 10mg/1.5mL Solution for Injection. The standard criterion for bioequivalence was met in that the 90% confidence interval (CI) for the ratio between these products was between 0.80 and 1.25. The ratios of the means of AUC_{last} and C_{max} between these products are presented in the following table.

	AUC_{last} [90% CI]	**C_{max} [90% CI]**
Omnitrope Powder for Injection vs. Genotropin	1.031 [0.997; 1.065]	0.968 [0.920; 1.019]
Omnitrope 10mg/1.5mL Solution for injection vs. Genotropin	1.038 [1.004; 1.073]	1.008 [0.958; 1.061]
Omnitrope Powder for Injection vs. Omnitrope 10mg/1.5mL Solution for injection	0.993 [0.961; 1.026]	0.960 [0.912; 1.011]

In a randomised, double-blind, 3 way crossover study in 33 subjects receiving a single dose of 5mg somatropin subcutaneously the bioequivalence of Omnitrope 15mg/1.5mL Solution for Injection, Omnitrope Powder for Injection and the reference product Genotropin (sourced in EU) was shown. The results of the study demonstrated that Omnitrope 15mg/1.5mL sfi, Omnitrope Powder for Injection and Genotropin are bioequivalent, based on the primary pharmacokinetic variables AUC_{last} and C_{max}.

The pharmacokinetic parameters are summarised below:

	Omnitrope 5mg/mL Powder for Injection Mean (SD)	Omnitrope 15mg/1.5mL s.f.i Mean (SD)	Genotropin 5mg/mL Mean (SD)
AUC_{last} (h*ug/l)	419.162(112.34)	391.508 (100.47)	403.857 (115.79)
C_{max} (ug/l)	55.22 (21.49)	52.89(19.09)	53.63 (20.33)

The ratios of AUC_{last} and C_{max} were 106.4% and 102.9% for Omnitrope Powder for Injection compared to Omnitrope 15mg/1.5mL sfi with associated 90% CIs of 103.0% to 110.0% and 96.3% to 110.1% respectively.

For the comparison of Omnitrope Powder for Injection to Genotropin 5 mg/ml, the ratios of AUC_{last} and C_{max} were 103.9% and 101.8%, respectively. The associated 90% CIs were 100.5% to 107.4% for AUC_{last} and 95.2% to 108.9% for C_{max}.

For the comparison of Omnitrope 10 mg/ml Solution for Injection to Genotropin 5 mg/ml, the ratios of AUC_{last} and C_{max} were 97.6% and 98.9%, respectively. The associated 90% CIs were 94.5% to 100.9% for AUC_{last} and 92.5% to 105.8% for C_{max}.

The upper and lower boundaries of the 90% confidence intervals were well within the bioequivalence limits of 80%-125% for all comparisons.

CLINICAL TRIALS

The efficacy and safety of Omnitrope were compared with Genotropin in a randomised controlled open study involving a total of 89 prepubertal children (49 boys, 40 girls) with growth hormone deficiency. Inclusion criteria were height of <-2 standard deviation score (SDS) for chronological age, spontaneous growth velocity <-1 SDS assessed over an interval of at least 6 months before enrolment, and documented results of two standard pharmacological provocation tests with growth hormone peak <10µg/L.

Forty-four children with a mean age of 7.8 years (3.0-13.0 years) received Omnitrope Powder for Injection and 45 children with a mean age of 7.6 years (2.0-14.0 years) received Genotropin Powder for Injection. Both Omnitrope and Genotropin were administered subcutaneously at a daily dose of 0.03mg/kg for 9 months.

The following results of the primary efficacy endpoints, obtained in the intention-to-treat population, demonstrated a comparable efficacy profile between Omnitrope and Genotropin.

- Mean body height at the start of treatment was 113.3cm ± 13.33 and 109.3cm ± 15.68 in the Omnitrope and Genotropin groups respectively. After 9 months of treatment, mean body height was 121.9cm ± 13.06 and 117.7cm ± 14.71, showing an increase of 8.6cm and 8.4cm respectively.
- Mean height velocity (HV) at the start of treatment was 3.8cm/year ± 1.23 and 4.0cm/year ± 0.83 in the Omnitrope and Genotropin groups respectively. After 9 months of treatment, mean HV was 10.7cm/year ± 2.57 and 10.7cm/year ± 2.90, showing an increase of 6.9cm/year and 6.7cm/year respectively.

- The mean height standard deviation score (HSDS) at the start of treatment was -3.0 ± 0.72 SDS and -3.1 ± 0.89 SDS in the Omnitrope and Genotropin groups. After 9 months of treatment, mean HSDS had increased to -2.3 ± 0.68 SDS and -2.5 ± 0.73 SDS respectively.
- The mean height velocity standard deviation score (HVSDS) at the start of treatment was -2.4 ± 1.30 in the Omnitrope and -2.3 ± 1.12 in the Genotropin group. Over the 9 months of treatment, patients grew at an average rate of 6.1 ± 3.67 and 5.4 ± 3.16 respectively above the mean growth rate for the normal population.

Mean levels of the two pharmacodynamic markers IGF-1 and IGFBP3 were also comparable between the two treatment groups.

The study was extended to compare the efficacy and safety of Omnitrope Powder for Injection with Omnitrope Solution for Injection. Children were eligible for the study if they had completed 9 months of treatment in the previous study. Forty-two children who had received Omnitrope Powder for Injection continued with the same treatment, whereas 44 children who had previously received Genotropin Powder for Injection were switched to Omnitrope Solution for Injection. Both treatments were administered subcutaneously at a daily dose of 0.03mg/kg for 6 months.

- After a total of 15 months of treatment, i.e., 15 months with Omnitrope Powder for Injection or 9 months with Genotropin Powder for Injection plus 6 months with Omnitrope Solution for Injection, body height had increased significantly by an average of 12.7cm in both groups, to a mean body height of 126.1cm ± 12.95 and 122.0cm ± 14.68, respectively.
- Average HV after 15 months of treatment was 8.5cm/year ± 1.80 in the Omnitrope Powder for Injection group and 8.6cm/year ± 2.04 in the Omnitrope Solution for Injection group.
- Mean HSDS after 15 months of treatment had increased to -2.0 ± 0.72 SDS in the Omnitrope Powder for Injection group and to -2.2 ± 0.73 SDS in the Omnitrope Solution for Injection group.
- The mean HVSDS after 15 months of treatment was 3.4 ± 2.55 SDS in the Omnitrope Powder for Injection group and 3.2 ± 2.89 SDS in the Omnitrope Solution for Injection group.

To obtain long-term efficacy and safety data on Omnitrope Solution for Injection, the study was further extended. Children were eligible for the study if they had completed 15 months of treatment in the previous studies. Forty-two children who had previously received Omnitrope Powder for Injection were switched to Omnitrope Solution for Injection, whereas 44 children who had received Omnitrope Solution for Injection continued with the same treatment. Both treatments were administered subcutaneously at a daily dose of 0.03mg/kg for 15 months.

After a total of 30 months i.e., 15 months with Omnitrope Powder for Injection plus 15 months with Omnitrope Solution for Injection or 9 months with Genotropin Powder for Injection plus 21 months with Omnitrope Solution for Injection, 78 patients had completed treatment. Body height had increased by an average of 21.3cm, to a mean body height of 132.6cm ± 14.01. Average HV after 30 months of treatment was 7.4cm/year ± 1.60. Mean HSDS had increased to -1.7 ± 0.87 SDS. The mean HVSDS after 30 months of treatment was 2.5 ± 3.25 SDS.

The results obtained in these studies are consistent with other somatropin preparations in the treatment of children with growth hormone deficiency.

INDICATIONS

Omnitrope is intended for the long term treatment of children (above three years of age) with:
- growth disturbance due to insufficient secretion of pituitary growth hormone.
- growth disturbance associated with gonadal dysgenesis (Turner syndrome).
- growth disturbance associated with chronic renal insufficiency.

CONTRAINDICATIONS

Treatment with Omnitrope is contraindicated:
- in patients with evidence of malignancies. Intracranial lesions have to be inactive and 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 known hypersensitivity to somatropin or to any of the excipients.
- in patients with acute critical illness due to complications following open heart surgery or abdominal surgery, multiple accident trauma or to patients having acute respiratory failure (see PRECAUTIONS).
- in new-borns, Omnitrope 5mg/1.5mL Solution for Injection/Omnitrope 5mg/1.5mL Solution for Injection for SurePal 5 and Omnitrope 5mg/mL Powder for Injection * (after reconstitution with the solvent) should not be used because of the presence of the preservative, benzyl alcohol.

*not marketed

PRECAUTIONS

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 Dosage and Administration).

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. (**Omnitrope is not indicated for use in patients with Prader-Willi syndrome)**

Metabolism

Somatropin may induce a state of insulin resistance and in some patients hyperglycaemia. Therefore patients should be observed for evidence of glucose intolerance during Omnitrope treatment. In rare cases the diagnostic criteria for diabetes mellitus type II may be fulfilled as a result of the somatropin therapy, but risk factors such as obesity, family history, steroid treatment or pre-existing impaired glucose tolerance have been present in most cases where

this occurred. Omnitrope should be used with caution in patients with diabetes mellitus or a family history of diabetes mellitus. In patients with already manifested diabetes mellitus, the anti-diabetic therapy might require adjustment when somatropin is instituted.

Endocrine system
Hypothyroidism may develop during therapy with somatropin, and inadequate treatment of hypothyroidism may prevent optimal response to treatment with Omnitrope. Therefore, thyroid hormone levels must be checked periodically during Omnitrope therapy and patients should be treated with thyroid hormone, when indicated.

During treatment with somatropin, an enhanced T4 to T3 conversion has been found, which may result in a reduction in serum T4 concentrations 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 advisable to test thyroid function after starting treatment with somatropin and after dose adjustment.

Large doses of glucocorticoids may inhibit the growth promoting effect of growth hormone. Patients with co-existing corticotropin deficiencies should have their glucocorticoid replacement doses carefully adjusted.

Somatropin has been reported to reduce serum cortisol levels. Changes to serum levels of unbound serum cortisol have not been reported. The clinical relevance of these findings seems limited. Nevertheless, corticosteroid replacement therapy should be optimised before initiation of Omnitrope therapy.

To achieve a satisfactory stimulation of growth, some girls with Turner syndrome may require a higher dose during the first year of treatment.

Patients with pan hypopituitarism are at risk of adrenal insufficiency after treatment with growth hormone is commenced, particularly if this has not previously been recognised or the patients are on inadequate replacement. Standard replacement therapy should be closely monitored in patients with (pan) hypopituitarism.

Patients with chronic renal disease may develop hyperparathyroidism which should be treated appropriately before initiation of somatropin therapy.

Nervous system
In cases of severe or recurrent headache, visual problems, nausea and/or vomiting, a fundoscopy for papilloedema is recommended as some rare cases of benign intracranial hypertension have been reported during somatropin treatment. If papilloedema is confirmed, a diagnosis of benign intracranial hypertension has to be considered, and if appropriate, Omnitrope treatment should be interrupted. At present, insufficient experience exists on how to restart treatment in patients after normalisation of intracranial pressure. If restarting treatment is considered appropriate, the patient has to be carefully monitored for the absence of symptoms of increased intracranial pressure.

Musculoskeletal system
Progression of scoliosis can occur in patients who experience rapid growth. Physicians should be alert to this abnormality which may become apparent during growth hormone therapy due to the rapid increase in growth rate. Signs of scoliosis should be monitored during treatment.

Patients with endocrine disorders, including growth hormone deficiency, hypopituitarism and renal osteodystrophy, may have an increased incidence of slipped capital femoral epiphyses. Any child who develops a limp or complains of hip or knee pain during Omnitrope treatment should be evaluated as this may indicate development of slipped capital femoral epiphysis (see ADVERSE EFFECTS – Post-marketing Experience).

Urinary system
In chronic renal insufficiency, the renal function should have decreased below 50% of normal before initiation of therapy. Growth should have been followed for a year preceding initiation of therapy with Omnitrope in order to verify the growth disturbance. Conservative treatment for the renal insufficiency should have been established and should be maintained during treatment. Treatment should be discontinued after renal transplantation.

Growth hormone treatment may represent an increased risk for acute rejection in patients with renal allograft and a history of two or more rejection episodes.

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

Newly diagnosed and recurrent cases of leukaemia have been reported in growth hormone deficient children treated with somatropin. These children had other risk factors for leukaemia. A causal association with somatropin has not been identified.

Critically ill patients
Two placebo controlled clinical trials of patients in intensive care units have demonstrated an increased mortality among patients suffering from acute critical illness due to complications following open heart surgery, abdominal surgery, multiple accidental trauma or acute respiratory failure who were treated with somatropin in high doses (5.3mg to 8mg/day). These types of patients should not be treated with somatropin (see CONTRAINDICATIONS). Because there is no information available on the safety of growth hormone therapy in acutely critically ill patients, the benefits of continued treatment in this situation should be weighed against the potential risks involved. In all patients developing other or similar acute critical illness, the possible benefits of treatment with somatropin must be weighed against the potential risk involved.

Effects on fertility
No specific study has been conducted in animals to examine the effect of Omnitrope on fertility. However, somatropin is known to have adverse effects on reproduction. Inhibition of reproduction was reported in male and female rats at somatropin doses of 1mg/kg/day or more, with reduced copulation and conception rates, lengthened or absent oestrus cycles and, at 3.3mg/kg/day, a lack of responsiveness of females to males and slight reductions in sperm motility and survival. Rat reproduction was unaffected by 0.3mg/kg/day somatropin, which

resulted in a systemic exposure (based on body surface area) of approximately 2 times that anticipated in adult patients at the maximal clinical dose of 0.01mg/kg/day.

Use in pregnancy (Category B2)
No specific study has been conducted in animals to examine the reproductive toxicity of Omnitrope. However somatropin was not teratogenic and did not affect foetal growth at subcutaneous maternal doses up to 3.3mg/kg/day in rats or 1.3mg/kg/day in rabbits, which resulted in systemic exposures based on body surface area of approximately 40 times the anticipated maximum clinical exposure.
There is no experience with somatropin during pregnancy, nor has the need for such use been established. Treatment with Omnitrope should be interrupted if pregnancy occurs.

Use in lactation
It is not known whether somatropin is excreted in breast milk, but the possibility cannot be excluded. However, absorption of intact protein from the gastrointestinal tract of the infant is extremely unlikely. As a general precaution, treatment with Omnitrope should be interrupted during breastfeeding.

Carcinogenicity
Somatropin raises the serum levels of IGF-1. Associations between elevated serum IGF-1 concentrations and risks of certain cancers have been reported in epidemiological studies. Causality has not been demonstrated. The clinical significance of these associations, especially for subjects treated with somatropin who do not have growth hormone deficiency and who are treated for prolonged periods, is not known. Serum IGF-1 levels can be affected by factors other than growth hormone status including nutrition.

Genotoxicity
No specific study has been conducted to examine the genotoxic potential of Omnitrope. However, there was no evidence for somatropin genotoxicity in assays for gene mutation in bacteria and mouse lymphoma cells or chromosomal damage in human lymphocytes and rat bone marrow cells.

INTERACTIONS WITH OTHER MEDICINES

Concomitant glucocorticoid therapy may inhibit growth and thereby oppose the growth promoting effect of Omnitrope. If glucocorticoid replacement therapy is required, the glucocorticoid dose and compliance have to be monitored carefully to avoid either adrenal insufficiency or inhibition of the growth promoting effects of Omnitrope.

Data from an interaction study conducted in growth hormone deficient adults, suggest that somatropin administration may increase the clearance of compounds known to be metabolised by cytochrome P450 3A4 (e.g. sex steroids, corticosteroids, anticonvulsants and cyclosporin). The clinical significance of this is unknown.

See also statements under PRECAUTIONS regarding diabetes mellitus, thyroid disorder and corticotropin deficiencies.

Insulin dosage may need to be adjusted when Omnitrope is administered to patients with diabetes mellitus.

ADVERSE EFFECTS

In general, mild to moderate uncommon (0.1% to 1%) adverse effects, such as peripheral oedema, stiffness in the extremities, arthralgia, myalgia and paraesthesia are observed within the first months of treatment, but they usually subside either spontaneously or with dose reduction.

Somatropin has been reported to reduce serum cortisol levels, possibly by affecting carrier proteins or by increasing hepatic clearance. The clinical relevance of these findings may be limited. Nevertheless, corticosteroid replacement therapy should be optimised before initiation of therapy.

The following events have been reported in patients treated with somatropin preparations:

Body system	**Nature of adverse effects**	**Frequency**
General and local reactions	Transient local injection site reactions, such as pain, numbness, redness and swelling	Common (1%-10%)
	Oedema	Uncommon (0.1%-1%)
Immune system	As with all protein pharmaceuticals, a small percentage of patients may develop anti-hGH antibodies, without growth-inhibiting effects.	Common (1%-10%)
Musculoskeletal system and connective tissue	Arthralgia, myalgia, stiffness of the extremities and paraesthesia	Uncommon (0.1%-1%)
Endocrine system	Diabetes mellitus	Rare (0.01%-0.1%)
Nervous system	Benign intracranial hypertension	Rare (0.01%-0.1%)
Neoplasms	Leukaemia. The relationship, if any, between leukaemia and growth hormone therapy is uncertain	Very rare (below 0.01%)

Some cases of leukaemia 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 (see PRECAUTIONS).

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. **Omnitrope is not indicated for use in patients with Prader-Willi syndrome** (see PRECAUTIONS).

Slipped capital femoral epiphysis and Legg-Calve-Perthes disease have been reported in children treated with growth hormone.

DOSAGE AND ADMINISTRATION

Therapy with somatropin should be initiated and monitored by physicians who are experienced in the diagnosis and management of patients with growth hormone deficiency.

The dose is based on body weight and must always be adjusted individually in accordance with the response to therapy.

Daily administration by subcutaneous injection in the evening is recommended. The injection sites have to be rotated to minimise the risk of local lipoatrophy.

Patients and caregivers have to receive appropriate training and instruction on the proper use of the Omnitrope vials, the cartridges with solvent, the transfer set, and the pen, from their physician or other suitably qualified health professionals.

Growth disturbance due to insufficient secretion of growth hormone in children
Generally, a dose of 0.025 to 0.035mg/kg body weight per day or 0.7 to 1.0mg/m^2 body surface area per day is recommended. If the response to therapy is not satisfactory in the following years, the dose can be increased, as higher doses have been used.

Growth disturbance in girls due to Turner syndrome
A dose of 0.045 to 0.05mg/kg body weight per day or 1.4mg/m^2 body surface area per day is recommended. If the response to therapy is not satisfactory in the following years, the dose can be increased.

Growth disturbance in chronic renal insufficiency
A dose of 0.045 to 0.05mg/kg body weight per day or 1.4mg/m^2 body surface area per day is recommended. A dosage adjustment may be necessary after 6 months. If the response to therapy is not satisfactory, the dose can be increased.

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.

Reconstitution and stability of solution

As with all parenteral drug products, the solution should be clear after reconstitution and storage. If the solution is cloudy, the contents MUST NOT be injected.

Omnitrope 5mg/1.5mL Solution for Injection

Omnitrope 5mg/1.5mL is a ready-to-use solution which is filled in glass cartridges. This presentation is intended for multiple use with a pen device. The Omnitrope Pen needs to be used to administer Omnitrope 5mg/1.5mL. After the first injection, the contents of the cartridge must be used within 21 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 21 days.

THE OMNITROPE PEN 5 IS INTENDED FOR USE BY A SINGLE PATIENT ONLY.

Omnitrope 5mg/1.5mL Solution for Injection for SurePal 5

Omnitrope 5mg/1.5mL is a ready-to-use solution which is filled in glass cartridges. This presentation is intended for multiple use with a pen device (SurePal). SurePal 5 needs to be used to administer Omnitrope 5mg/1.5mL. The cartridges for SurePal 5 are irreversibly integrated in a transparent container called cartridge holder which serves as an adaptor for SurePal 5. After the first injection, the contents of the cartridge must be used within 21 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 21 days.

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

Omnitrope 10 mg/1.5 mL Solution for Injection

Omnitrope 10mg/1.5mL is a ready-to-use solution which is filled in glass cartridges. This presentation is intended for multiple use with a pen device. The Omnitrope Pen 10 needs to be used to administer Omnitrope 10mg/1.5mL. 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.

THE OMNITROPE PEN 10 IS INTENDED FOR USE BY A SINGLE PATIENT ONLY.

Omnitrope 10 mg/1.5 mL Solution for Injection for SurePal 10

Omnitrope 10mg/1.5mL is a ready-to-use solution which is filled in glass cartridges. This presentation is intended for multiple use with a pen device (SurePal). SurePal 10 needs to be used to administer Omnitrope 10mg/1.5mL. The cartridges for SurePal 10 are irreversibly integrated in a transparent container called cartridge holder which serves as an adaptor for SurePal 10. 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 15mg/1.5mL Solution for Injection for SurePal 15

Omnitrope 15mg/1.5mL is a ready-to-use solution which is filled in glass cartridges. This presentation is intended for multiple use with a pen device (-Sure Pal). SurePal15 needs to be used to administer Omnitrope 15mg/1.5mL. The cartridges for SurePal 15 are irreversibly

integrated in a transparent container called cartridge holder which serves as an adaptor for SurePal 15. 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.

*Omnitrope 1.33mg/mL Powder for Injection**
Omnitrope 1.33mg/mL is supplied in a vial containing the active substance as a powder and the solvent filled in a vial for single use. Each vial must be reconstituted with the accompanying water for injection.

The reconstituted solution is clear and colourless. As the reconstituted solution contains no preservative, use once only and discard any residue. If storage is necessary, the reconstituted solution should be stored at 2°C to 8°C for not more than 24 hours.

THE PRODUCT IS FOR SINGLE USE IN ONE PATIENT ONLY.

*Omnitrope 5mg/mL Powder for Injection**
Omnitrope 5mg/mL is supplied in a vial containing the active substance as a powder and a cartridge containing the solvent. It should be reconstituted with a transfer set as recommended in the information provided with the transfer set. Reconstitute the Omnitrope vial only with the accompanying solvent for parenteral use. Use the complete contents of the cartridge. This presentation is intended for multiple use with a pen device. The Omnitrope Pen L needs to be used to administer Omnitrope 5mg/mL.

After reconstitution, the content of the cartridge is stable for at least 21 days when stored at 2°C to 8°C. The reconstituted solution is clear and colourless. For microbiological reasons, any remaining solution should be discarded after 21 days.

After reconstitution and first injection, the cartridge should remain in the pen and has to be kept at 2°C to 8°C (in a refrigerator).

THE PEN IS INTENDED FOR USE BY A SINGLE PATIENT ONLY.

*product is not marketed.

OVERDOSAGE

Contact the Poisons Information Centre on 13 11 26 for advice on management of overdose.

An acute overdose may lead initially to hypoglycaemia and subsequently to hyperglycaemia.

Long term overdosing could result in signs and symptoms similar to gigantism or acromegaly, consistent with the known effects of excess exposure to growth hormone.

PRESENTATION AND STORAGE CONDITIONS

Solution for injection
Colourless glass cartridges containing clear and colourless solution

5mg/1.5mL
Each pack contains 1, 5 or 10 cartridges.

- Each cartridge of Omnitrope contains 3.33mg/mL somatropin (rbe) and the following excipients:
  - dibasic sodium phosphate heptahydrate
  - monobasic sodium phosphate
  - poloxamer
  - mannitol
  - benzyl alcohol as preservative
  - phosphoric acid
  - sodium hydroxide
  - water for injections.

10 mg/1.5 mL
Each pack contains 1, 5 or 10 cartridges.
Each cartridge of Omnitrope contains 6.67mg/mL somatropin (rbe) and the following excipients:

- monobasic sodium phosphate
- dibasic sodium phosphate heptahydrate
- poloxamer
- phenol
- glycine
- phosphoric acid
- sodium hydroxide
- water for injections.

Store at 2°C to 8°C (in a refrigerator). Do not freeze. Store in the original package in order to protect from light.

Not all presentations may be marketed in Australia.

Solution for injection for SurePal
Colourless glass cartridges (irreversibly integrated in a transparent container called cartridge holder) containing clear and colourless solution

5mg/1.5mL for SurePal 5
Each pack contains 1, 5 or 10 cartridges for SurePal 5.

- Each cartridge of Omnitrope contains 3.33mg/mL somatropin (rbe) and the following excipients:
  - dibasic sodium phosphate heptahydrate
  - monobasic sodium phosphate
  - poloxamer
  - mannitol
  - benzyl alcohol as preservative
  - phosphoric acid

- sodium hydroxide
- water for injections.

10 mg/1.5 mL for SurePal 10
Each pack contains 1, 5 or 10 cartridges for SurePal 10.

- Each cartridge of Omnitrope contains 6.67mg/mL somatropin (rbe) and the following excipients:
  - monobasic sodium phosphate
  - dibasic sodium phosphate heptahydrate
  - poloxamer
  - phenol
  - glycine
  - phosphoric acid
  - sodium hydroxide
  - water for injections.

Store at 2°C to 8°C (in a refrigerator). Do not freeze. Store in the original package in order to protect from light.

15mg/1.5mL for SurePal 15
Each pack contains 1, 5 or 10 cartridges for SurePal 15.
Each cartridge of Omnitrope contains 10mg/mL somatrophin (rbe) and the following excipients:

- monobasic sodium phosphate
- dibasic sodium phosphate heptahydrate
- poloxamer
- phenol
- sodium chloride
- phosphoric acid
- sodium hydroxide
- water for injections.

Store at 2°C to 8°C (in a refrigerator). Do not freeze. Store in the original package in order to protect from light.

Not all presentations may be marketed in Australia.

Powder for Injection
Colourless glass vials containing white to off-white lyophilised powder

1.33mg/mL
Each pack contains 1 vial of Omnitrope and 1 vial of solvent.

- Each vial of Omnitrope contains 1.33mg/mL somatropin (rbe) and the following excipients:
  - dibasic sodium phosphate heptahydrate
  - monobasic sodium phosphate
  - glycine
  - sodium hydroxide
  - hydrochloric acid.

- Each vial of solvent contains 1.13mL of water for injection.

5mg/mL
Each pack contains 8 vials of Omnitrope, 8 cartridges of solvent and 8 transfer needles.

- Each vial of Omnitrope contains 5mg/mL somatropin (rbe) and the following excipients:
  - dibasic sodium phosphate heptahydrate
  - monobasic sodium phosphate
  - glycine
  - sodium hydroxide
  - hydrochloric acid.
- Each cartridge of solvent contains 1.14mL of water for injection and 1.5% benzyl alcohol as preservative.

Not all presentations may be marketed in Australia

NAME AND ADDRESS OF THE SPONSOR

Sandoz Pty Ltd
ABN 60 075 449 553
54 Waterloo Road
Macquarie Park, NSW 2113
Australia
Tel: 1800 634 500

POISON SCHEDULE OF THE MEDICINE

Schedule 4 – Prescription Only Medicine

Date of first inclusion in the Australian Register of Therapeutic Goods (ARTG):

Omnitrope 1.33mg p.f.i, Omnitrope 5mg/1.5mL s.f.i, Omnitrope 10mg/1.5mL s.f.i - 11/10/2004
Omnitrope 15mg/1.5mL s.f.i – 16/12/2013
Omnitrope 5mg/1.5mL s.f.i & Omnitrope 10mg/1.5mL s.f.i with pre-assembled cartridge holder – 28/10/2014

Date of most recent amendment: 11 November 2016