# Professional Information

## SCHEDULING STATUS:

**S5**

## PROPRIETARY NAMES AND DOSAGE FORM:

OMNITROPE 5 mg/1,5 mℓ (solution for injection)

OMNITROPE 10 mg/1,5 mℓ (solution for injection)

OMNITROPE 15 mg/1,5 mℓ (solution for injection)

## COMPOSITION:

### Active:

Omnitrope 5 mg/1,5 mℓ: Each mℓ of solution contains 3,3 mg of somatropin (corresponding to 10 IU). One cartridge contains 1,5 mℓ corresponding to 5 mg somatropin (15 IU).

Omnitrope 10 mg/1,5 mℓ: Each mℓ of solution contains 6,7 mg of somatropin (corresponding to 20 IU). One cartridge contains 1,5 mℓ corresponding to 10 mg somatropin (30 IU).

Omnitrope 15 mg/1,5 mℓ: Each mℓ of solution contains 10 mg of somatropin (corresponding to 30 IU). One cartridge contains 1,5 mℓ corresponding to 15 mg somatropin (45 IU).

### Excipients:

Omnitrope 5 mg/1,5 mℓ: Benzyl alcohol, disodium hydrogen phosphate heptahydrate, mannitol, poloxamer 188, sodium dihydrogen phosphate dehydrate, water for injection.
Each mℓ contains 9 mg benzyl alcohol.

Omnitrope 10 mg/1,5 mℓ: Disodium hydrogen phosphate heptahydrate, glycine, phenol, poloxamer 188, sodium dihydrogen phosphate dehydrate, water for injection.

Omnitrope 15 mg/1,5 mℓ: Disodium hydrogen phosphate heptahydrate, phenol, poloxamer 188, sodium dihydrogen phosphate dehydrate, sodium chloride, water for injection.

Omnitrope 5 mg/1,5 mℓ (solution for injection) contains mannitol.

**Contains preservatives:**

Omnitrope 5 mg/1,5 mℓ contains benzyl alcohol 0,9 *% m/v.*

Omnitrope 10 mg/1,5 mℓ contains phenol 0,3 *% m/v.*

Omnitrope 15 mg/1,5 mℓ contains phenol 0,3 *% m/v.*

**PHARMACOLOGICAL CLASSIFICATION:**

A 21.10 Tropic hormones

**PHARMACOLOGICAL ACTION:**

**Pharmacodynamic properties:**

Somatropin is a recombinant human growth hormone (rhGH) produced by *Escherichia coli* by recombinant DNA technology. It has the same structure and activity as the natural human growth hormone.

**Pharmacokinetic properties:**

***Absorption:***

The bioavailability of subcutaneously administered somatropin is approximately 80 %.

A subcutaneous dose of somatropin in healthy adults resulted in the following plasma $C_{max}$ and $t_{max}$ median values:

- 5 mg of 5 mg/1,5 mℓ: 72 ± 28 µg/ℓ and 4,0 ± 2,0 hours,
- 5 mg of 10 mg/1,5 mℓ: 74 ± 22 µg/ℓ and 4,0 ± 2,0 hours,
- 5 mg of 15 mg/1,5 mℓ: 52 ± 19 µg/ℓ and 4,0 ± 2,0 hours, respectively.

The terminal half-life of somatropin after subcutaneous administration was 3 hours.

***Special populations:***

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

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

**INDICATIONS:**

- Short stature due to decreased or failed secretion of pituitary growth hormone. Growth hormone deficiency should be verified before the preparation is administered. This requires a thorough investigation of the pituitary function, including proper provocation tests.
- Short stature in gonadal dysgenesis (Turner's Syndrome).
- Growth disturbance in prepubertal children with chronic renal insufficiency.

**CONTRAINDICATIONS:**

- Hypersensitivity to somatropin or to any of the excipients of OMNITROPE.
- OMNITROPE must not be used when there is any evidence of activity of a tumour. Intracranial tumours must be inactive and anti-tumour therapy must be completed prior to starting growth hormone therapy. Treatment should be discontinued if there is evidence of tumour growth.
- OMNITROPE must not be used for growth promotion in children with closed epiphyses.
- Patients with acute critical illness suffering complications following open-heart surgery, abdominal surgery, multiple accidental trauma, acute respiratory failure or similar conditions must not be treated with somatropin. Regarding patients undergoing substitution therapy, see section on "WARNINGS AND SPECIAL PRECAUTIONS" for use.

**WARNINGS AND SPECIAL PRECAUTIONS:**

**Lipid metabolism:**

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

**Carbohydrate metabolism:**

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

**Water and mineral metabolism:**

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

**Bone metabolism:**

Somatropin stimulates the turnover of skeletal bone. Long-term administration of somatropin to growth hormone deficient patients with osteopoenia 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.

**Insulin sensitivity:**

OMNITROPE may induce a state of insulin resistance. For patients with diabetes mellitus, the insulin dose may require adjustment after OMNITROPE therapy is instituted. Patients with diabetes, glucose intolerance, or additional risk factors for diabetes should be monitored closely during OMNITROPE therapy.

**Thyroid function:**

Growth hormone increases the peripheral conversion of T4 to T3, which may result in a reduction in serum T4 and an increase in serum T3 concentrations. Whereas the peripheral thyroid hormone levels have remained within the reference ranges for healthy subjects, hypothyroidism theoretically may develop in subjects with subclinical hypothyroidism. Consequently monitoring of thyroid function should therefore be conducted in all patients. In patients with hypopituitarism on standard replacement therapy, the potential effect of growth hormone treatment on thyroid function must be closely monitored.

**Malignancy:**

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

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

Leukaemia has been reported in a small number of growth hormone deficiency patients, some of whom have been treated with somatropin. However, there is no evidence that leukaemia incidence is increased in growth hormone recipients without predisposition factors.

**Acquired immune deficiency syndrome (AIDS):**

The safety of use of somatropin in patients affected by HIV has not been established.

**Antibodies:**

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

**Acute critical illness**

The effects of somatropin on recovery were studied in two placebo controlled trials involving 522 critically ill adult patients suffering complications following open heart surgery, abdominal surgery, multiple accidental trauma or acute respiratory failure. Mortality was higher in patients treated with 5,3 or 8 mg somatropin daily compared to patients receiving placebo, 42 % vs. 19 %. Based on this information, these types of patients should not be treated with somatropin. As there is no information available on the safety of growth hormone substitution therapy in acutely critically ill patients, the benefits of continued treatment in this situation should be weighed against the potential risks involved.

In all patients developing other or similar acute critical illness, the possible benefit of treatment with somatropin must be weighed against the potential risk involved.

The maximum recommended daily dose should not be exceeded.

**Pancreatitis in children:**

Children treated with somatropin have an increased risk of developing pancreatitis compared to adults treated with somatropin. Although rare, pancreatitis should be considered in somatropin-treated children who develop abdominal pain.

OMNITROPE 5 mg/1,5 mℓ: Because of the presence of benzyl alcohol the medicinal 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.

**INTERACTIONS:**

Data from an interaction study performed in growth hormone deficient adults suggests that somatropin administration may increase the clearance of compounds known to be metabolised by cytochrome P450 isoenzymes. The clearance of compounds metabolised by cytochrome P450 3A4 (e.g. sex steroids, corticosteroids, anticonvulsants and ciclosporin) may be especially increased resulting in lower plasma levels of these compounds. The clinical significance of this is unknown.

Also see section on “WARNINGS AND SPECIAL PRECAUTIONS” for statements regarding diabetes mellitus and thyroid disorder and section on “DOSAGE AND DIRECTION FOR USE” for statement on oral oestrogen replacement therapy.

**PREGNANCY AND LACTATION:**

**Pregnancy:**

OMNITROPE is not recommended during pregnancy and in women of childbearing potential not using contraception.

**Lactation:**

There have been no clinical studies conducted with somatropin containing products in breastfeeding women. It is not known if somatropin is excreted into breast milk, but absorption of intact protein from the gastrointestinal tract of the infant is extremely unlikely. Therefore, caution should be exercised when OMNITROPE is administered to breastfeeding women.

**Fertility:**

Fertility studies with OMNITROPE have not been performed.

**Effects on ability to drive and use machines:**

OMNITROPE has no or negligible influence on the ability to drive and use machines.

**DOSAGE AND DIRECTIONS FOR USE:**

**Dosage:**

***Short stature due to decreased or failed secretion of pituitary growth hormone:***

The dosage is according to individual requirements. Generally a dose of 0,5 – 0,7 IU/kg body weight per week or approximately 14 – 20 IU/$m^2$ body surface area per week is recommended.

***Turner's Syndrome:***

Generally a dose of 1,0 IU/kg body weight per week is recommended, or 28 IU/$m^2$ body surface area per week.

***Chronic renal insufficiency:***

A dose of 30 IU/$m^2$ body surface area per week (approximately 1 IU/kg body weight per week) is recommended. Higher doses can be needed if growth velocity is too low. A dose correction can be needed after 6 months of treatment.

The weekly dose should be divided into six to seven subcutaneous injections. The injection site should be varied to prevent lipoatrophy.

***Directions for use:***

OMNITROPE 5 mg/1,5 mℓ solution for injection is a sterile, ready-to-use solution for subcutaneous injection filled in a glass cartridge. This presentation is intended for multiple use. It should only be administered with SurePal 5, an injection device specifically developed for use with OMNITROPE 5 mg/1,5 mℓ solution for injection.

OMNITROPE 10 mg/1,5 mℓ solution for injection is a sterile, ready-to-use solution for subcutaneous injection filled in a glass cartridge. This presentation is intended for multiple use. It should only be administered with SurePal 10, an injection device specifically developed for use with OMNITROPE 10 mg/1,5 mℓ solution for injection.

OMNITROPE 15 mg/1,5 mℓ solution for injection is a sterile, ready-to-use solution for subcutaneous injection filled in a glass cartridge. This presentation is intended for multiple use. It should only be administered with SurePal 15, an injection device specifically developed for use with OMNITROPE 15 mg/1,5 mℓ solution for injection.

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

Administration needs to be carried out using sterile, disposable pen needles. Patients and caregivers have to receive appropriate training and instruction on the proper use of the OMNITROPE cartridges and the pen from the physician or other suitable qualified health professionals.

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

1. Hands should be washed.
2. If the solution is cloudy or contains particulate matter, it should not be used. The content must be clear and colourless.
3. Disinfect the rubber membrane of the cartridge with a cleansing swab.
4. Insert the cartridge into SurePal following the instructions for use provided with the pen.
5. Clean the site of injection with an alcohol swab.
6. Administer the appropriate dose by subcutaneous injection using a sterile pen needle. Remove the pen needle and dispose of it in accordance with local requirements.

Any unused product or waste material should be disposed of in accordance with local requirements.

**SIDE EFFECTS:**

Patients with growth hormone deficiency are characterised by extracellular volume deficit. When treatment with OMNITROPE is started, this deficit is rapidly corrected.

OMNITROPE has given rise to the formation of antibodies in approximately 1 % of the patients. The binding capacity of these antibodies has been low and no clinical changes have been associated with their formation.

The following undesirable effects have been observed and reported during treatment with OMNITROPE:

**Neoplasms benign, malignant and unspecified (including cysts and polyps):**

***Less frequent:*** Leukaemia*.

**Immune system disorders:**

***Frequent:*** Formation of antibodies.

**Endocrine disorders:**

***Less frequent:*** Diabetes mellitus type II.

**Nervous system disorders:**

***Less frequent:*** In children: paraesthesia, benign intracranial hypertension.

**Gastrointestinal disorders:**

***Less frequent:*** In children: pancreatitis.

**Skin and subcutaneous tissue disorders:**

***Frequent:*** In children: Transient local skin reactions.

**Musculoskeletal and connective tissue disorders:**

***Less frequent:*** In children: Stiffness in the extremities, arthralgia, myalgia.

**General disorders and administration site conditions:**

***Less frequent:*** In children: Peripheral oedema.

**Description of selected adverse reactions:**

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

*Very rare cases of leukaemia have been reported in growth hormone deficient children treated with OMNITROPE, but the incidence appears to be similar to that in children without growth hormone deficiency.

**KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:**

Acute overdose could lead initially to hypoglycaemia and subsequently to hyperglycaemia. Long-term overdose could result in signs and symptoms consistent with the known effects of human growth hormone excess. Treatment is symptomatic and supportive.

**IDENTIFICATION:**

Omnitrope 5 mg/1,5 mℓ: The solution is clear and colourless. Solution for injection in a cartridge for SurePal 5.

Omnitrope 10 mg/1,5 mℓ: The solution is clear and colourless. Solution for injection in a cartridge for SurePal 10.

Omnitrope 15 mg/1,5 mℓ: The solution is clear and colourless. Solution for injection in a cartridge for SurePal 15.

Omnitrope solution for injection is practically free from visible particulate matter.

**PRESENTATION:**

Omnitrope 5 mg/1,5 mℓ: 1,5 mℓ of solution in a cartridge (colourless type I glass) with a grey plunger on one side (siliconised bromobutyl), a grey disc (bromobutyl) and a gold cap (aluminium) on the other side. The glass cartridge is irreversibly integrated in a transparent container and assembled to a plastic mechanism with a threaded rod at one extremity.

Omnitrope 10 mg/1,5 mℓ: 1,5 mℓ of solution in a cartridge (colourless type I glass) with a grey plunger on one side (siliconised bromobutyl), a grey disc (bromobutyl) and a silver cap (aluminium) on the other side. The glass cartridge is irreversibly integrated in a transparent container and assembled to a plastic mechanism with a threaded rod at one extremity.

Omnitrope 15 mg/1,5 mℓ: 1,5 mℓ of solution in a cartridge (colourless type I glass) with a grey plunger and a blue ring on one side (siliconised bromobutyl), a grey disc (bromobutyl) and a silver cap (aluminium) on the other side. The glass cartridge is irreversibly integrated in a transparent container and assembled to a plastic mechanism with a threaded rod at one extremity.

Pack sizes of 1, 5's and 10's. Not all pack sizes may be marketed.
Omnitrope is packed into an outer cardboard carton.

**STORAGE INSTRUCTIONS:**

**Unopened cartridge:**

Store and transport refrigerated (2 °C – 8 °C). Do not freeze. Store in the original package in order to protect from light.

**Shelf life after first use:**

After first use, the cartridge should remain in the pen and has to be kept in a refrigerator (2 °C – 8 °C) for a maximum of 28 days. Store and transport refrigerated (2 °C – 8 °C). Do not freeze. Store in the original pen in order to protect from light.

**KEEP OUT OF REACH OF CHILDREN.**

**REGISTRATION NUMBER(S):**

Omnitrope 5 mg/1,5 mℓ: 49/21.10/0735.732

Omnitrope 10 mg/1,5 mℓ: 49/21.10/0736.733

Omnitrope 15 mg/1,5 mℓ: 49/21.10/0737.734

**NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE(S) OF REGISTRATION:**

Sandoz SA (Pty) Ltd.[1]

72 Steel Road

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**DATE OF PUBLICATION OF THE PROFESSIONAL INFORMATION:**

**Date of registration:** 17 March 2020

**Date of most recent approval of professional information:** 17 March 2020

[1]Company Reg. No.: 1990/001979/07