HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use OMNITROPE® safely and effectively. See full prescribing information for OMNITROPE®.

OMNITROPE® (somatropin [rDNA origin] injection), for SUBCUTANEOUS use.

Initial U.S. Approval: 1987

---------- RECENT MAJOR CHANGES ----------

Warnings and Precautions,
Neoplasm 8/2014

---------- INDICATIONS AND USAGE ----------

OMNITROPE® is a recombinant human growth hormone indicated for:

- ***Pediatric:*** Treatment of children with growth failure due to growth hormone deficiency (GHD), Prader-Willi Syndrome, Small for Gestational Age, Turner syndrome, and Idiopathic Short Stature (1.1)
- ***Adult:*** Treatment of adults with either adult onset or childhood onset GHD (1.2)

---------- DOSAGE AND ADMINISTRATION ----------

OMNITROPE® should be administered subcutaneously (2).

- *Pediatric GHD:* 0.16 to 0.24 mg/kg/week, divided into 6 to 7 daily injections, (2.1)
- *Prader-Willi Syndrome:* 0.24 mg/kg/week, divided into 6 to 7 daily injections, (2.1)
- *Small for Gestational Age:* Up to 0.48 mg/kg/week, divided into 6 to 7 daily injections, (2.1)
- *Turner Syndrome:* 0.33 mg/kg/week, divided into 6 to 7 daily injections (2.1)
- *Idiopathic Short Stature:* Up to 0.47 mg/kg/week, divided into 6 to 7 daily injections (2.1)
- *Adult GHD:* not more than 0.04 mg/kg/week (divided into daily injections) to be increased as tolerated to not more than 0.08 mg/kg/week); to be increased gradually every 1 to 2 months (2.2)
- OMNITROPE® Cartridges 5 mg/1.5 mL and 10 mg/1.5 mL must be used with the corresponding OMNITROPE® Pen 5 and Pen 10 delivery system, respectively (2.3)
- Injection sites should always be rotated to avoid lipoatrophy (2.3)

---------- DOSAGE FORMS AND STRENGTHS ----------

- OMNITROPE® Cartridge 5 mg/1.5 mL is a prefilled sterile solution in a glass cartridge ready to be administered with the Omnitrope® Pen 5.(3).
- OMNITROPE® Cartridge 10 mg/1.5 mL is a prefilled sterile solution in a glass cartridge ready to be administered with the Omnitrope® Pen 10.(3).
- OMNITROPE® for injection 5.8 mg/vial is supplied with two vials, one containing somatropin as a powder and the other vial containing diluent (3).

---------- CONTRAINDICATIONS ----------

- Acute Critical Illness (4.1, 5.1)
- Children with Prader-Willi Syndrome who are severely obese or have severe respiratory impairment - reports of sudden death (4.2, 5.2)
- Active Malignancy (4.3, 5.3)
- Active Proliferative or Severe Non-Proliferative Diabetic Retinopathy (4.4)
- Children with closed epiphyses (4.5)
- Known hypersensitivity to somatropin or excipients (4.6)

---------- WARNINGS AND PRECAUTIONS ----------

- Acute Critical Illness: Potential benefit of treatment continuation should be weighed against the potential risk (5.1)
- Prader-Willi Syndrome in children: Evaluate for signs of upper airway obstruction and sleep apnea before initiation of treatment. Discontinue treatment if these signs occur (5.2).
- Neoplasm: Monitor patients with preexisting tumors for progression or recurrence. Increased risk of a second neoplasm in childhood cancer survivors treated with somatropin - in particular meningiomas in patients treated with radiation to the head for their first neoplasm (5.3).
- Impaired Glucose Tolerance and Diabetes Mellitus: May be unmasked. Periodically monitor glucose levels in all patients. Doses of concurrent antihyperglycemic drugs in diabetics may require adjustment (5.4).
- Intracranial Hypertension: Exclude preexisting papilledema. May develop and is usually reversible after discontinuation or dose reduction (5.5).
- Fluid Retention (i.e., edema, arthralgia, carpal tunnel syndrome - especially in adults): May occur frequently. Reduce dose as necessary (5.6).
- Hypopituitarism: Closely monitor other hormone replacement therapies (5.7)
- Hypothyroidism: May first become evident or worsen (5.8)
- Slipped Capital Femoral Epiphysis: May develop. Evaluate children with the onset of a limp or hip/knee pain (5.9)
- Progression of Preexisting Scoliosis: May develop (5.10)
- Pancreatitis: Consider pancreatitis in patients with persistent severe abdominal pain (5.15)

---------- ADVERSE REACTIONS ----------

Other common somatropin-related adverse reactions include injection site reactions/rashes and lipoatrophy (6.1) and headaches (6.3).

To report SUSPECTED ADVERSE REACTIONS, contact Sandoz Inc. at 1-800-525-8747 or FDA at 1-800-FDA-1088 or **www.fda.gov/medwatch**

---------- DRUG INTERACTIONS ----------

- 11β-Hydroxysteroid Dehydrogenase Type 1: May require the initiation of glucocorticoid replacement therapy. Patients treated with glucocorticoid replacement for previously diagnosed hypoadrenalism may require an increase in their maintenance doses (7.1, 7.2).
- Pharmacologic Glucocorticoid Therapy and Supraphysiologic Glucocorticoid Treatment: Should be carefully adjusted (7.2)
- Cytochrome P450-Metabolized Drugs: Monitor carefully if used with somatropin (7.3)
- Oral Estrogen: Larger doses of somatropin may be required in women (7.4)
- Insulin and/or Oral Hypoglycemic Agents: May require adjustment (7.5)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 8/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Pediatric Patients

Omnitrope® (somatropin [rDNA origin] injection) is indicated for the treatment of children with growth failure due to inadequate secretion of endogenous growth hormone (GH).

Omnitrope® [somatropin (rDNA origin) injection] is indicated for the treatment of pediatric patients who have growth failure due to Prader-Willi Syndrome (PWS). The diagnosis of PWS should be confirmed by appropriate genetic testing *[see Contraindications (4.2) and Warnings And Precautions (5.2)]*.

Omnitrope® [somatropin (rDNA origin) injection] is indicated for the treatment of growth failure in children born small for gestational age (SGA) who fail to manifest catch-up growth by age 2 years.

Omnitrope® [somatropin (rDNA origin) injection] is indicated for the treatment of growth failure associated with Turner syndrome.

Omnitrope® (somatropin [rDNA origin] injection) is indicated for the treatment of idiopathic short stature (ISS), also called non-growth hormone-deficient short stature, defined by height standard deviation score (SDS) ≤ -2.25, and associated with growth rates unlikely to permit attainment of adult height in the normal range, in pediatric patients whose epiphyses are not closed and for whom diagnostic evaluation excludes other causes associated with short stature that should be observed or treated by other means.

1.2 Adult Patients

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

- Adult Onset (AO): Patients who have GHD, either alone or associated with multiple hormone deficiencies (hypopituitarism), as a result of pituitary disease, hypothalamic disease, surgery, radiation therapy, or trauma; or
- Childhood Onset (CO): Patients who were GH deficient during childhood as a result of congenital, genetic, acquired, or idiopathic causes.

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

2 DOSAGE AND ADMINISTRATION

The weekly dose should be divided over 6 or 7 days of **subcutaneous** injections.

Therapy with Omnitrope® should be supervised by a physician who is experienced in the diagnosis and management of pediatric patients with short stature associated with GHD, Prader-Willi Syndrome (PWS), Turner syndrome (TS), those who were born small for gestational age (SGA), Idiopathic Short Stature (ISS) and adult patients with either childhood onset or adult onset GHD.

2.1 Dosing of Pediatric Patients

General Pediatric Dosing Information

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

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

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

Pediatric Growth Hormone Deficiency (GHD)

Generally, a dosage of 0.16 to 0.24 mg/kg body weight /week is recommended. The weekly dose should be divided over 6 or 7 days of subcutaneous injections.

Prader-Willi Syndrome (PWS)

Generally, a dosage of 0.24 mg/kg body weight/week is recommended. The weekly dose should be divided over 6 or 7 days of subcutaneous injections.

Small for Gestational Age (SGA)

Generally, a dosage of up to 0.48 mg/kg body weight/week is recommended. The weekly dose should be divided over 6 or 7 days of subcutaneous injections.

Turner Syndrome (TS)

Generally, a dose of 0.33 mg/kg body weight/week is recommended. The weekly dose should be divided over 6 or 7 days of subcutaneous injections.

Idiopathic Short Stature (ISS)

Generally, a dose up to 0.47 mg/kg of body weight/week is recommended. The weekly dose should be divided over 6 or 7 days of subcutaneous injections.

2.2 Dosing of Adult Patients

Adult Growth Hormone Deficiency (GHD)

Based on the weight-based dosing utilized in clinical studies with another somatropin product, the recommended dosage at the start of therapy is not more than 0.04 mg/kg/week given as a daily subcutaneous injection. The dose may be increased at 4- to 8-week intervals according to individual patient requirements to not more than 0.08 mg/kg/week. Clinical response, side effects, and determination of age- and gender-adjusted serum IGF-I levels may be used as guidance in dose titration.

Alternatively, taking into account recent literature, a starting dose of approximately 0.2 mg/day (range, 0.15-0.30 mg/day) may be used without consideration of body weight. This dose can be increased gradually every 1-2 months by increments of approximately 0.1 to 0.2 mg/day, according to individual patient requirements based on the clinical response and serum IGF-I concentrations. During therapy, the dose should be decreased if required by the occurrence of adverse events and/or serum IGF-I levels above the age- and gender-specific normal range. Maintenance dosages vary considerably from person to person.

A lower starting dose and smaller dose increments should be considered for older patients, who are more prone to the adverse effects of somatropin than younger individuals. In addition, obese individuals are more likely to manifest adverse effects when treated with a weight-based regimen. In order to reach the defined treatment goal, estrogen-replete women may need higher doses than men. Oral estrogen administration may increase the dose requirements in women.

2.3 Preparation and Administration

Omnitrope® Cartridge 5 mg/1.5 mL and Cartridge 10 mg/1.5 mL

Each cartridge of Omnitrope® must be inserted into its corresponding Omnitrope® Pen 5 or Omnitrope® Pen 10 delivery system. Instructions for delivering the dosage are provided in the Omnitrope® INSTRUCTIONS FOR USE booklet enclosed with the Omnitrope® drug and the Omnitrope® Pens.

Omnitrope® for injection 5.8 mg/vial

Instructions for delivering the dosage are provided in the INSTRUCTIONS FOR USE leaflets enclosed with the Omnitrope® drug.

Once the diluent is added to the lyophilized powder, swirl gently; **do not shake.** Shaking may cause denaturation of the active ingredient.

Parenteral drug products should always be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Omnitrope® MUST NOT BE INJECTED if the solution is cloudy or contains particulate matter. Use it only if it is clear and colorless. Omnitrope must be refrigerated at 2° to 8°C (36° to 46°F).

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

The dosage of Omnitrope® must be adjusted for the individual patient. The dose should be given daily by **subcutaneous** injections (administered preferably in the evening). Omnitrope® may be given in the thigh, buttocks, or abdomen.

Injection sites should always be rotated to avoid lipoatrophy.

3 DOSAGE FORMS AND STRENGTHS

Omnitrope® Cartridges and vials (for injection) are available:

- 5 mg/1.5 mL Cartridge is a prefilled sterile somatropin solution containing benzyl alcohol in a glass cartridge ready to be administered with the Omnitrope® Pen 5.
- 10 mg/1.5 mL Cartridge is a prefilled sterile somatropin solution in a glass cartridge ready to be administered with the Omnitrope® Pen 10.
- 5.8 mg/vial is supplied with two vials, one containing somatropin as a powder and the other vial containing diluent (Bacteriostatic Water for Injection containing benzyl alcohol as a preservative).

4 CONTRAINDICATIONS

4.1 Acute Critical Illness

Treatment with pharmacologic amounts of somatropin is contraindicated in patients with acute critical illness due to complications following open heart surgery, abdominal surgery or multiple accidental trauma, or those with acute respiratory failure. Two placebo-controlled clinical trials in non-growth hormone deficient adult patients (n=522) with these conditions in intensive care units revealed a significant increase in mortality (41.9% vs. 19.3%) among somatropin-treated patients (doses 5.3-8 mg/day) compared to those receiving placebo *[see Warnings And Precautions (5.1)]*.

4.2 Prader-Willi Syndrome in Children

Somatropin is contraindicated in patients with Prader-Willi Syndrome who are severely obese, have a history of upper airway obstruction or sleep apnea, or have severe respiratory impairment. There have been reports of sudden death when somatropin was used in such patients *[see Warnings And Precautions (5.2)]*.

4.3 Active Malignancy

In general, somatropin is contraindicated in the presence of active malignancy. Any preexisting malignancy should be inactive and its treatment complete prior to instituting therapy with somatropin. Somatropin should be discontinued if there is evidence of recurrent activity. Since GHD may be an early sign of the presence of a pituitary tumor (or, rarely, other brain tumors), the presence of such tumors should be ruled out prior to initiation of treatment. Somatropin should not be used in patients with any evidence of progression or recurrence of an underlying intracranial tumor.

4.4 Diabetic Retinopathy

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

4.5 Closed Epiphyses

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

4.6 Hypersensitivity

Omnitrope® is contraindicated in patients with a known hypersensitivity to somatropin or any of its excipients. Localized reactions are the most common hypersensitivity reactions.

5 WARNINGS AND PRECAUTIONS

5.1 Acute Critical Illness

Increased mortality in patients with acute critical illness due to complications following open heart surgery, abdominal surgery or multiple accidental trauma, or those with acute respiratory failure has been reported after treatment with pharmacologic amounts of somatropin *[see Contraindications (4.1)]*. The safety of continuing somatropin treatment in patients receiving replacement doses for approved indications who concurrently develop these illnesses has not been established. Therefore, the potential benefit of treatment continuation with somatropin in patients experiencing acute critical illnesses should be weighed against the potential risk.

5.2 Prader-Willi Syndrome in Children

There have been reports of fatalities after initiating therapy with somatropin in pediatric patients with Prader-Willi Syndrome who had one or more of the following risk factors: severe obesity, history of upper airway obstruction or sleep apnea, or unidentified respiratory infection. Male patients with one or more of these factors may be at greater risk than females. Patients with Prader-Willi Syndrome should be evaluated for signs of upper airway obstruction (including onset of or increased snoring) and sleep apnea before initiation of treatment with somatropin. If, during treatment with somatropin, patients show signs of upper airway obstruction (including onset of or increased snoring) and/or new onset sleep apnea, treatment should be interrupted. All patients with Prader-Willi Syndrome treated with somatropin should also have effective weight control and be monitored for signs of respiratory infection, which should be diagnosed as early as possible and treated aggressively *[see Contraindications (4.2)]*.

5.3 Neoplasms

In childhood cancer survivors who were treated with radiation to the brain/head for their first neoplasm and who developed subsequent GHD and were treated with somatropin, an increased risk of a second neoplasm has been reported. Intracranial tumors, in particular meningiomas, were the most common of these second neoplasms. In adults, it is unknown whether there is any relationship between somatropin replacement therapy and CNS tumor recurrence *[see Contraindications (4.3)]*. Monitor all patients with a history of GHD secondary to an intracranial neoplasm routinely while on somatropin therapy for progression or recurrence of the tumor.

Because children with certain rare genetic causes of short stature have an increased risk of developing malignancies, practitioners should thoroughly consider the risks and benefits of starting somatropin in these patients. If treatment with somatropin is initiated, these patients should be carefully monitored for development of neoplasms.

Monitor patients on somatropin therapy carefully for increased growth, or potential malignant changes, of preexisting nevi.

5.4 Impaired Glucose Tolerance and Diabetes Mellitus

Treatment with somatropin may decrease insulin sensitivity, particularly at higher doses in susceptible patients. As a result, previously undiagnosed impaired glucose tolerance and overt diabetes mellitus may be unmasked, and new onset type 2 diabetes mellitus has been reported in patients taking somatropin. Therefore, glucose levels should be monitored periodically in all patients treated with somatropin, especially in those with risk factors for diabetes mellitus, such as obesity, Turner Syndrome, or a family history of diabetes mellitus. Patients with preexisting type 1 or type 2 diabetes mellitus or impaired glucose tolerance should be monitored closely during somatropin therapy. The doses of

antihyperglycemic drugs (i.e., insulin or oral agents) may require adjustment when somatropin therapy is instituted in these patients. *[See Drug Interactions (7.5)]*

5.5 Intracranial Hypertension (IH)

Intracranial hypertension (IH) with papilledema, visual changes, headache, nausea, and/or vomiting has been reported in a small number of patients treated with somatropin products. Symptoms usually occurred within the first eight (8) weeks after the initiation of somatropin therapy. In all reported cases, IH-associated signs and symptoms rapidly resolved after cessation of therapy or a reduction of the somatropin dose.

Funduscopic examination should be performed routinely before initiating treatment with somatropin to exclude preexisting papilledema, and periodically during the course of somatropin therapy. If papilledema is observed by funduscopy during somatropin treatment, treatment should be stopped. If somatropin-induced IH is diagnosed, treatment with somatropin can be restarted at a lower dose after IH-associated signs and symptoms have resolved. Patients with Turner syndrome and Prader-Willi Syndrome may be at increased risk for the development of IH.

5.6 Fluid Retention

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

5.7 Hypopituitarism

Patients with hypopituitarism (multiple pituitary hormone deficiencies) should have their other hormonal replacement treatments closely monitored during somatropin treatment.

5.8 Hypothyroidism

Undiagnosed/untreated hypothyroidism may prevent an optimal response to somatropin, in particular, the growth response in children. Patients with Turner syndrome have an inherently increased risk of developing autoimmune thyroid disease and primary hypothyroidism and should have their thyroid function checked prior to initiation of somatropin therapy. In patients with GHD, central (secondary) hypothyroidism may first become evident or worsen during somatropin treatment. Therefore, patients treated with somatropin should have periodic thyroid function tests and thyroid hormone replacement therapy should be initiated or appropriately adjusted when indicated.

5.9 Slipped Capital Femoral Epiphysis in Pediatric Patients

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

5.10 Progression of Preexisting Scoliosis in Pediatric Patients

Progression of scoliosis can occur in patients who experience rapid growth. Because somatropin increases growth rate, patients with a history of scoliosis who are treated with somatropin should be monitored for progression of scoliosis. However, somatropin has not been shown to increase the occurrence of scoliosis. Skeletal abnormalities including scoliosis are commonly seen in untreated Turner syndrome patients. Scoliosis is also commonly seen in untreated patients with Prader-Willi Syndrome. Physicians should be alert to these abnormalities, which may manifest during somatropin therapy.

5.11 Confirmation of Childhood Onset Adult GHD

Patients with epiphyseal closure who were treated with somatropin replacement therapy in childhood should be reevaluated according to the criteria in *Indications And Usage (1.2)* before continuation of somatropin therapy at the reduced dose level recommended for GH deficient adults.

5.12 Otitis Media and Cardiovascular Disorders in Turner Syndrome

Patients with Turner syndrome should be evaluated carefully for otitis media and other ear disorders since these patients have an increased risk of ear and hearing disorders. Somatropin treatment may increase the occurrence of otitis media in patients with Turner syndrome. In addition, patients with Turner syndrome should be monitored closely for cardiovascular disorders (e.g., stroke, aortic aneurysm/dissection, hypertension) as these patients are also at risk for these conditions.

5.13 Local and Systemic Reactions

When somatropin is administered subcutaneously at the same site over a long period of time, tissue atrophy may result. This can be avoided by rotating the injection site *[see Dosage And Administration (2.3)]*.

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

5.14 Laboratory Tests

Serum levels of inorganic phosphorus, alkaline phosphatase, parathyroid hormone (PTH) and IGF-I may increase after somatropin therapy.

5.15 Pancreatitis

Cases of pancreatitis have been reported rarely in children and adults receiving somatropin treatment, with some evidence supporting a greater risk in children compared with adults. Published literature indicates that girls who have Turner syndrome may be at greater risk than other somatropin-treated children. Pancreatitis should be considered in any somatropin treated patient, especially a child, who develops persistent severe abdominal pain.

5.16 Benzyl Alcohol

Benzyl alcohol, a component of Omnitrope® Cartridge 5 mg/1.5 mL and the diluent for Omnitrope® for injection 5.8 mg/vial, has been associated with serious adverse events and death, particularly in pediatric patients. The “gasping syndrome,” (characterized by central nervous system depression, metabolic acidosis, gasping respirations, and high levels of benzyl alcohol and its metabolites found in the blood and urine) has been associated with benzyl alcohol dosages >99 mg/kg/day in neonates and low-birth weight neonates. Additional symptoms may include gradual neurological deterioration, seizures, intracranial hemorrhage, hematologic abnormalities, skin breakdown, hepatic and renal failure, hypotension, bradycardia, and cardiovascular collapse. Practitioners administering this and other medications containing benzyl alcohol should consider the combined daily metabolic load of benzyl alcohol from all sources.

6 ADVERSE REACTIONS

6.1 Most Serious and/or Most Frequently Observed Adverse Reactions

This list presents the most serious[b] and/or most frequently observed[a] adverse reactions during treatment with somatropin:

- [b]Sudden death in pediatric patients with Prader-Willi Syndrome with risk factors including severe obesity, history of upper airway obstruction or sleep apnea and unidentified respiratory infection *[see Contraindications (4.2) and Warnings and Precautions (5.2)]*.
- [b]Intracranial tumors, in particular meningiomas, in teenagers/young adults treated with radiation to the head as children for a first neoplasm and somatropin *[see Contraindications (4.3) and Warnings and Precautions (5.3)]*
- [a,b]Glucose intolerance including impaired glucose tolerance/impaired fasting glucose as well as overt diabetes mellitus *[Warnings and Precautions (5.4)]*
- [b]Intracranial hypertension *[see Warnings and Precautions (5.5)]*

- [b]Significant diabetic-retinopathy *[see Contraindications (4.4)]*
- [b]Slipped capital femoral epiphysis in pediatric patients *[see Warnings and Precautions (5.9)]*
- [b]Progression of preexisting scoliosis in pediatric patients *[see Warnings and Precautions (5.10)]*
- [b]Pancreatitis *[see Warnings and Precautions (5.15)]*
- [a]Fluid retention manifested by edema, arthralgia, myalgia, nerve compression syndromes including carpal tunnel syndrome/paraesthesias *[see Warnings and Precautions (5.6)]*
- [a]Unmasking of latent central hypothyroidism *[see Warnings and Precautions (5.8)]*
- [a]Injection site reactions/rashes and lipoatrophy (as well as rare generalized hypersensitivity reactions) *[see Warnings and Precautions (5.12)]*

6.2 Clinical Trials Experience

Because clinical trials are conducted under varying conditions, adverse reaction rates observed during the clinical trials performed with one somatropin formulation cannot always be directly compared to the rates observed during the clinical trials performed with a second somatropin formulation, and may not reflect the adverse reaction rates observed in practice.

Clinical Trials in Pediatric GHD Patients

The following events were observed during clinical studies with Omnitrope® Cartridge conducted in children with GHD:

Table 1. Incidence of Adverse Reactions Reported in ≥ 5% Pediatric Patients with GHD During Treatment with Omnitrope® Cartridge (N=86)

Adverse Event	n (%)
Elevated HbA1c	12 (14%)
Eosinophilia	10 (12%)
Hematoma	8 (9%)

N=number of patients receiving treatment
n=number of patients who reported the event during study period
%=percentage of patients who reported the event during study period

The following events were observed during clinical studies with Omnitrope® for injection conducted in children with GHD:

Table 2. Incidence of Adverse Reactions Reported in ≥ 5% Pediatric Patients with GHD During Treatment with Omnitrope® for Injection (N=44)

Adverse Event	n (%)
Hypothyroidism	7 (16%)
Eosinophilia	5 (11%)
Elevated HbA1c	4 (9%)
Hematoma	4 (9%)
Headache	3 (7%)
Hypertriglyceridemia	2 (5%)
Leg Pain	2 (5%)

N=number of patients receiving treatment
n=number of patients who reported the event during study period
%= percentage of patients who reported the event during study period

Clinical Trials in PWS

In two clinical studies in pediatric patients with Prader-Willi Syndrome carried out with another somatropin product, the following drug-related events were reported: edema, aggressiveness, arthralgia, benign intracranial hypertension, hair loss, headache, and myalgia.

Clinical Trials in Children with SGA

In clinical studies of 273 pediatric patients born small for gestational age treated with another somatropin product, the following clinically significant events were reported: mild transient hyperglycemia, one patient with benign intracranial hypertension, two patients with central precocious puberty, two patients with jaw prominence, and several patients with aggravation of preexisting scoliosis, injection site reactions, and self-limited progression of pigmented nevi.

Clinical Trials in Children with Idiopathic Short Stature

In two open-label clinical studies conducted with another somatropin product in pediatric patients with ISS, the most commonly encountered adverse events were upper respiratory tract infections, influenza, tonsillitis, nasopharyngitis, gastroenteritis, headaches, increased appetite, pyrexia, fracture, altered mood, and arthralgia. In one of the two studies during treatment with this other somatropin product, the mean IGF-1 standard deviation (SD) scores were maintained in the normal range. IGF-1 SD scores above +2 SD were observed as follows: 1 subject (3%), 10 subjects (30%) and 16 subjects (38%) in the untreated control, 0.23 and the 0.47 mg/kg/week groups respectively, had at least one measurement; while 0 subjects (0%), 2 subjects (7%) and 6 subjects (14%) had two or more consecutive IGF-1 measurements above +2 SD.

Clinical Trials in Children with Turner Syndrome

In two clinical studies with another somatropin product in pediatric patients with Turner syndrome, the most frequently reported adverse events were respiratory illnesses (influenza, tonsillitis, otitis, sinusitis), joint pain, and urinary tract infection. The only treatment-related adverse event that occurred in more than 1 patient was joint pain.

Clinical Trials in Adults with GHD

In clinical trials with another somatropin product in 1,145 GHD adults, the majority of the adverse events consisted of mild to moderate symptoms of fluid retention, including peripheral swelling, arthralgia, pain and stiffness of the extremities, peripheral edema, myalgia, paresthesia, and hypoesthesia. These events were reported early during therapy, and tended to be transient and/or responsive to dosage reduction.

Table 3 displays the adverse events reported by 5% or more of adult GHD patients in clinical trials after various durations of treatment with another somatropin product. Also presented are the corresponding incidence rates of these adverse events in placebo patients during the 6-month double-blind portion of the clinical trials.

Table 3. Adverse Events Reported by ≥ 5% of 1,145 Adult GHD Patients During Clinical Trials of Another Somatropin Product and Placebo, Grouped by Duration of Treatment

	Double Blind Phase		Open Label Phase Another Somatropin Product		
Adverse Event	**Placebo 0–6 mo. (n = 572) % Patients**	**Another Somatropin Product 0–6 mo. (n = 573) % Patients**	**6–12 mo. (n = 504) % Patients**	**12–18 mo. (n = 63) % Patients**	**18–24 mo. (n = 60) % Patients**
Swelling, peripheral	5.1	17.5[1]	5.6	0	1.7
Arthralgia	4.2	17.3[1]	6.9	6.3	3.3
Upper respiratory infection	14.5	15.5	13.1	15.9	13.3
Pain, extremities	5.9	14.7[1]	6.7	1.6	3.3
Edema, peripheral	2.6	10.8[1]	3.0	0	0
Paresthesia	1.9	9.6[1]	2.2	3.2	0
Headache	7.7	9.9	6.2	0	0
Stiffness of extremities	1.6	7.9[1]	2.4	1.6	0
Fatigue	3.8	5.8	4.6	6.3	1.7
Myalgia	1.6	4.9[1]	2.0	4.8	6.7
Back pain	4.4	2.8	3.4	4.8	5.0

n=number of patients receiving treatment during the indicated period
%=percentage of patients who reported the event during the indicated period
1. Increased significantly when compared to placebo, $P \leq .025$: Fisher's Exact Test (one-sided)

Post-Trial Extension Studies in Adults

In expanded post-trial extension studies, diabetes mellitus developed in 12 of 3,031 patients (0.4%) during treatment with another somatropin product. All 12 patients had predisposing factors, e.g., elevated glycated hemoglobin levels and/or marked obesity, prior to receiving this other somatropin product. Of the 3,031 patients receiving this other somatropin product, 61 (2%) developed symptoms of carpal tunnel syndrome, which lessened after dosage reduction or treatment interruption (52) or surgery (9). Other adverse events that have been reported include generalized edema and hypoesthesia.

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

6.3 Post-Marketing Experience

Because these adverse events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. The adverse events reported during post-marketing surveillance do not differ from those listed/discussed above in Sections 6.1 and 6.2 in children and adults.

Leukemia has been reported in a small number of GH deficient children treated with somatropin, somatrem (methionylated rhGH) and GH of pituitary origin. It is uncertain whether these cases of leukemia are related to GH therapy, the pathology of GHD itself, or other associated treatments such as radiation therapy. On the basis of current evidence, experts have not been able to conclude that GH therapy per se was responsible for these cases of leukemia. The risk for children with GHD, if any, remains to be established *[see Contraindications (4.3) and Warnings And Precautions (5.3)]*.

The following additional adverse reactions have been observed during the use of somatropin: headaches (children and adults), gynecomastia (children), and pancreatitis (children and adults *[see Warnings and Precautions (5.15)]*.

New-onset type 2 diabetes mellitus has been reported.

7 DRUG INTERACTIONS

7.1 11β-Hydroxysteroid Dehydrogenase Type 1 (11βHSD-1)

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

7.2 Pharmacologic Glucocorticoid Therapy and Supraphysiologic Glucocorticoid Treatment

Pharmacologic glucocorticoid therapy and supraphysiologic glucocorticoid treatment may attenuate the growth promoting effects of somatropin in children. Therefore, glucocorticoid replacement dosing should be carefully adjusted in children receiving concomitant somatropin and glucocorticoid treatments to avoid both hypoadrenalism and an inhibitory effect on growth.

7.3 Cytochrome P450-Metabolized Drugs

Limited published data indicate that somatropin treatment increases cytochrome P450 (CYP450)-mediated antipyrine clearance in man. These data suggest that somatropin administration may alter the clearance of compounds known to be metabolized by CYP450 liver enzymes (e.g., corticosteroids, sex steroids, anticonvulsants, cyclosporine). Careful monitoring is advisable when somatropin is administered in combination with other drugs known to be metabolized by CYP450 liver enzymes. However, formal drug interaction studies have not been conducted.

7.4 Oral Estrogen

In adult women on oral estrogen replacement, a larger dose of somatropin may be required to achieve the defined treatment goal *[see Dosage And Administration (2.2)]*.

7.5 Insulin and/or Oral Hypoglycemic Agents

In patients with diabetes mellitus requiring drug therapy, the dose of insulin and/or oral agent may require adjustment when somatropin therapy is initiated *[see Warnings And Precautions (5.4)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

Animal reproduction studies have not been conducted with Omnitrope®. It is not known whether Omnitrope® can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity.

Reproduction studies carried out with another somatropin product at doses of 0.3, 1, and 3.3 mg/kg/day administered subcutaneously in the rat and 0.08, 0.3, and 1.3 mg/kg/day administered intramuscularly in the rabbit (highest doses approximately 24 times and 19 times the recommended human therapeutic levels, respectively, based on body surface area) resulted in decreased maternal body weight gains but were not teratogenic. In rats receiving subcutaneous doses during gametogenesis and up to 7 days of pregnancy, 3.3 mg/kg/day (approximately 24 times human dose) produced anestrus or extended estrus cycles in females and fewer and less motile sperm in males. When given to pregnant female rats (days 1 to 7 of gestation) at 3.3 mg/kg/day a very slight increase in fetal deaths was observed. At 1 mg/kg/day (approximately seven times human dose) rats showed slightly extended estrus cycles, whereas at 0.3 mg/kg/day no effects were noted.

In perinatal and postnatal studies in rats, doses of 0.3, 1, and 3.3 mg/kg/day of this other somatropin product produced growth-promoting effects in the dams but not in the fetuses. Young rats at the highest dose showed increased weight gain during suckling but the effect was not apparent by 10 weeks of age. No adverse effects were observed on gestation, morphogenesis, parturition, lactation, postnatal development, or reproductive capacity of the offspring due to this other somatropin product. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

8.3 Nursing Mothers

It is not known whether Omnitrope® is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Omnitrope® is administered to a nursing woman.

8.5 Geriatric Use

The safety and effectiveness of Omnitrope® in patients aged 65 and over have not been evaluated in clinical studies. Elderly patients may be more sensitive to the action of somatropin, and therefore may be more prone to develop adverse reactions. A lower starting dose and smaller dose increments should be considered for older patients *[see Dosage And Administration (2.2)]*.

10 OVERDOSAGE

Short-Term

Short-term overdosage could lead initially to hypoglycemia and subsequently to hyperglycemia. Furthermore, overdose with somatropin is likely to cause fluid retention.

Long-Term

Long-term overdosage could result in signs and symptoms of gigantism and/or acromegaly consistent with the known effects of excess growth hormone *[see Dosage And Administration (2)]*.

11 DESCRIPTION

Omnitrope® (somatropin-[rDNA] origin) is a polypeptide hormone of recombinant DNA origin. It has 191 amino acid residues and a molecular weight of 22,125 daltons. The amino acid sequence of the product is identical to that of human growth hormone of pituitary origin (somatropin). Omnitrope® is synthesized in a strain of. Escherichia coli that has been modified by the addition of the gene for human growth hormone. Omnitrope® Cartridge is a clear, colorless, sterile solution for subcutaneous injection. Omnitrope® for Injection is a lyophilized powder that is reconstituted for subcutaneous injection.

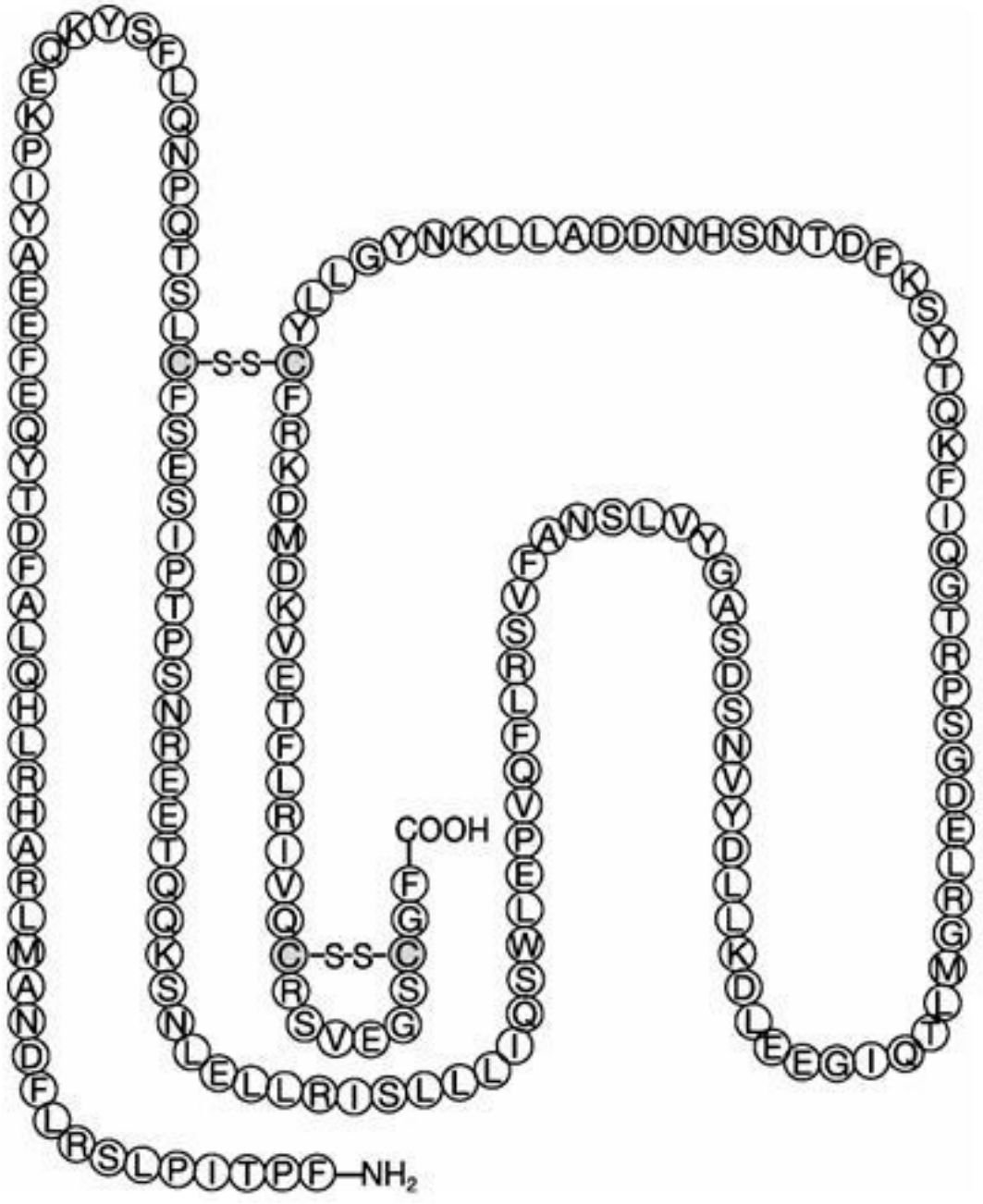


Figure 1. Schematic amino acid sequence of human growth hormone including the disulfide bonds

Each **Omnitrope® Cartridge or vial** contains the following (see **Table 4**):

Table 4. Contents of Omnitrope® Cartridges and Vial

Product	**Cartridge 5 mg/ 1.5 mL**	**Cartridge 10 mg/ 1.5 mL**	**For Injection 5.8 mg/ vial**
Component			
Somatropin	5 mg	10 mg	5.8 mg
Disodium hydrogen phosphate heptahydrate	1.3 mg	1.70 mg	2.09 mg
Sodium dihydrogen phosphate dihydrate	1.6 mg	1.35 mg	0.56 mg
Poloxamer 188	3.0 mg	3.0 mg	-
Mannitol	52.5 mg	-	-
Glycine	-	27.75 mg	27.6 mg
Benzyl alcohol	13.5 mg	-	-
Phenol	-	4.50 mg	-
Water for Injection	to make 1.5 mL	to make 1.5 mL	-
Diluent (vials only)			**Bacteriostatic Water for Injection**
Water for injection			to make 1.14 mL
Benzyl alcohol			17 mg

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Somatropin (as well as endogenous GH) binds to a dimeric GH receptor in the cell membrane of target cells resulting in intracellular signal transduction and a host of pharmacodynamic effects. Some of these pharmacodynamic effects are primarily mediated by IGF-1 produced in the liver and also locally (e.g., skeletal growth, protein synthesis), while others are primarily a consequence of the direct effects of somatropin (e.g., lipolysis) *[see Pharmacodynamics (12.2)]*.

12.2 Pharmacodynamics

Tissue Growth

The primary and most intensively studied action of somatropin is the stimulation of linear growth. This effect is demonstrated in children with GHD and children who have PWS, were born SGA, have TS or have ISS.

Skeletal Growth

The measurable increase in bone length after administration of somatropin results from its effect on the cartilaginous growth areas of long bones. Studies *in vitro* have shown that the incorporation of sulfate into proteoglycans is not due to a direct effect of somatropin, but rather is mediated by the somatomedins or insulin-like growth factors (IGFs). The

somatomedins, among them IGF-1, are polypeptide hormones which are synthesized in the liver, kidney, and various other tissues. IGF-1 levels are low in the serum of hypopituitary dwarfs and hypophysectomized humans or animals, and increase after treatment with somatropin.

Cell Growth

It has been shown that the total number of skeletal muscle cells is markedly decreased in children with short stature lacking endogenous GH compared with normal children, and that treatment with somatropin results in an increase in both the number and size of muscle cells.

Organ Growth

Somatropin influences the size of internal organs, and it also increases red cell mass.

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 and blood urea nitrogen following the initiation of somatropin therapy.

Carbohydrate Metabolism

Hypopituitary children sometimes experience fasting hypoglycemia that may be improved by treatment with somatropin. In healthy subjects, large doses of somatropin may impair glucose tolerance. Although the precise mechanism of the diabetogenic effect of somatropin is not known, it is attributed to blocking the action of insulin rather than blocking insulin secretion. Insulin levels in serum actually increase as somatropin levels increase. Administration of human growth hormone to normal adults and patients with growth hormone deficiency results in increases in mean serum fasting and postprandial insulin levels, although mean values remain in the normal range. In addition, mean fasting and postprandial glucose and hemoglobin A_{1C} levels remain in the normal range.

Lipid Metabolism

Somatropin stimulates intracellular lipolysis, and administration of somatropin leads to an increase in plasma free fatty acids and triglycerides. Untreated GHD is associated with increased body fat stores, including increased abdominal visceral and subcutaneous adipose tissue. Treatment of growth hormone deficient patients with somatropin results in a general reduction of fat stores, and decreased serum levels of low density lipoprotein (LDL) cholesterol.

Mineral Metabolism

Administration of somatropin results in an increase in total body potassium and phosphorus and to a lesser extent sodium. This retention is thought to be the result of cell growth. Serum levels of phosphate increase in children with GHD after somatropin therapy due to metabolic activity associated with bone growth. Serum calcium levels are not altered. Although calcium excretion in the urine is increased, there is a simultaneous increase in calcium absorption from the intestine. Negative calcium balance, however, may occasionally occur during somatropin treatment.

Connective Tissue Metabolism

Somatropin stimulates the synthesis of chondroitin sulfate and collagen, and increases the urinary excretion of hydroxyproline.

12.3 Pharmacokinetics

There are no pharmacokinetic studies using Omnitrope® Cartridges in patients with growth hormone deficiency.

Absorption

Following a subcutaneous injection of single dose of 5 mg Omnitrope® 5 mg/1.5 mL Cartridge or 5 mg Omnitrope® 10 mg/1.5 mL Cartridge in healthy male and female adults, the peak concentration (C_{max}) was 72-74 mcg/L. The time to reach C_{max} (t_{max}) for Omnitrope was 4.0 hours.

The aqueous formulations of 5 mg/1.5 mL Omnitrope® cartridge and 10 mg/mL Omnitrope® cartridge are bioequivalent to the lyophilized 5.8 mg/vial Omnitrope® formulation.

Metabolism

Somatropin is metabolized in both the liver and kidneys by proteolytic degradation. In renal cells, at least a portion of the breakdown products are returned to the systemic circulation.

Excretion

The mean terminal half-life of somatropin after subcutaneous administration of Omnitrope® Cartridge in healthy adults is 2.5-2.8 hours. The mean clearance of subcutaneously administered Omnitrope® Cartridge in healthy adults was about 0.14 L/hr·kg.

Specific Populations

Pediatric: No pharmacokinetic studies of Omnitrope® have been conducted in pediatric patients.

Gender: The effect of gender on pharmacokinetics of Omnitrope® has not been evaluated in pediatric patients.

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

Renal or hepatic impairment: No pharmacokinetic studies have been conducted with Omnitrope® in patients with renal or hepatic impairment.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity, mutagenicity, and fertility studies have not been conducted with Omnitrope® *See Use In Specific Populations (8.1)* for effect on fertility.

14 CLINICAL STUDIES

14.1 Pediatric Growth Hormone Deficiency (GHD)

The efficacy and safety of Omnitrope® were compared with another somatropin product approved for growth hormone deficiency (GHD) in pediatric patients. In sequential clinical trials involving a total of 89 GHD children, 44 patients received Omnitrope® for Injection (lyophilized powder) 5.8 mg/vial and 45 patients received the comparator somatropin product for 9 months. After 9 months of treatment patients who had received the comparator somatropin product were switched to Omnitrope® Cartridge (liquid) 5 mg/1.5 mL. After 15 months of treatment, all patients were switched to Omnitrope® Cartridge to collect long-term efficacy and safety data.

In both groups, somatropin was administered as a daily subcutaneous injection at a dose of 0.03 mg/kg. Similar effects on growth were observed between Omnitrope® for Injection and the comparator somatropin product during the initial 9 months of treatment.

The efficacy results after 9 months of treatment (Omnitrope® for Injection vs. the comparator somatropin product) and after 15 months (Omnitrope® Cartridge) are summarized in Table 5.

Table 5. Baseline Growth Characteristics and Effect of Omnitrope® after 9 and 15 Months of Treatment

Treatment Duration	**Treatment Group**	**Treatment Group**
0 - 9 months	**Omnitrope® for Injection** (n=44)	**Another Somatropin Product** (n=45)
9 - 15 months	**Omnitrope® for Injection** (n=42)	**Omnitrope® Cartridge** (n=44)
Treatment Parameter	**Mean (SD)**	**Mean (SD)**
Height velocity (cm/yr)		
Pre-treatment	3.8 (1.2)	4.0 (0.8)
Month 9	10.7 (2.6)	10.7 (2.9)
Month 15	8.5 (1.8)	8.6 (2.0)
Height velocity SDS		
Pre-treatment	-2.4 (1.3)	-2.3 (1.1)
Month 9	6.1 (3.7)	5.4 (3.2)
Month 15	3.4 (2.6)	3.2 (2.9)
Height SDS		
Pre-treatment	-3.0 (0.7)	-3.1 (0.9)
Month 9	-2.3 (0.7)	-2.5 (0.7)
Month 15	-2.0 (0.7)	-2.2 (0.7)
IGF-1[1]		
Pre-treatment	159 (92)	158 (43)
Month 9	291 (174)	302 (183)
Month 15	300 (225)	323 (189)
IGFBP-3[1]		
Pre-treatment	3.5 (1.3)	3.5 (1.0)
Month 9	4.6 (3.0)	4.0 (1.5)
Month 15	4.6 (1.3)	4.9 (1.4)

1. Calculated only for patients with measurements above the level of detection

14.2 Adult Growth Hormone Deficiency (GHD)

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

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

14.3 Prader-Willi Syndrome (PWS)

The safety and efficacy of another somatropin product in the treatment of pediatric patients with Prader-Willi Syndrome (PWS) were evaluated in two randomized, open-label, controlled clinical trials. Patients received either this other somatropin product or no treatment for the first year of the studies, while all patients received this other somatropin product during the second year. This other somatropin product was administered as a daily SC injection, and the dose was calculated for each patient every 3 months. In Study 1, the treatment group received this other somatropin product at a dose of 0.24 mg/kg/week during the entire study. During the second year, the control group received this other somatropin product at a dose of 0.48 mg/kg/week. In Study 2, the treatment group received this other somatropin product at a dose of 0.36 mg/kg/week during the entire study. During the second year, the control group received this other somatropin product at a dose of 0.36 mg/kg/week.

Patients who received this other somatropin product showed significant increases in linear growth during the first year of study, compared with patients who received no treatment (see **Table 6**). Linear growth continued to increase in the second year, when both groups received treatment with this other somatropin product.

Table 6. Efficacy of Another Somatropin Product in Pediatric Patients with Prader-Willi Syndrome (Mean ± SD)

	Study 1		*Study 2*	
	Another Somatropin Product (0.24 mg/kg/week) (n=15)	**Untreated Control (n=12)**	**Another Somatropin Product (0.36 mg/kg/week) (n=7)**	**Untreated Control (n=9)**
Linear growth (cm) Baseline height	112.7 ± 14.9	109.5 ± 12.0	120.3 ± 17.5	120.5 ± 11.2
Growth from months 0 to 12	11.6[1] ± 2.3	5.0 ± 1.2	10.7[1] ± 2.3	4.3 ± 1.5
Baseline SDS	-1.6 ± 1.3	-1.8 ± 1.5	-2.6 ± 1.7	-2.1 ± 1.4
SDS at 12 months	-0.5[2] ± 1.3	-1.9 ± 1.4	-1.4[2] ± 1.5	-2.2 ± 1.4

1. $p \leq 0.001$
2. $p \leq 0.002$ (when comparing SDS change at 12 months)

Changes in body composition were also observed in the patients receiving this other somatropin product (see **Table 7**). These changes included a decrease in the amount of fat mass, and increases in the amount of lean body mass and the ratio of lean-to-fat tissue, while changes in body weight were similar to those seen in patients who received no treatment. Treatment with this other somatropin product did not accelerate bone age, compared with patients who received no treatment.

Table 7. Effect of Another Somatropin Product on Body Composition in Pediatric Patients with Prader-Willi Syndrome (Mean ± SD)

	Another Somatropin Product (n=14)	Untreated Control (n=10)
Fat mass (kg)		
Baseline	12.3 ± 6.8	9.4 ± 4.9
Change from months 0 to 12	-0.9[1] ± 2.2	2.3 ± 2.4
Lean body mass (kg)		
Baseline	15.6 ± 5.7	14.3 ± 4.0
Change from months 0 to 12	4.7[1] ± 1.9	0.7 ± 2.4
Lean body mass/Fat mass		
Baseline	1.4 ± 0.4	1.8 ± 0.8
Change from months 0 to 12	1.0[1] ± 1.4	-0.1 ± 0.6
Body weight (kg)[2]		
Baseline	27.2 ± 12.0	23.2 ± 7.0
Change from months 0 to 12	3.7[3] ± 2.0	3.5 ± 1.9

1. $p < 0.005$
2. n=15 for the group receiving another somatropin product; n=12 for the Control group
3. n.s.

14.4 Pediatric Patients Born Small for Gestational Age (SGA) Who Fail to Manifest Catch-up Growth by Age 2

The safety and efficacy of another somatropin product in the treatment of children born small for gestational age (SGA) were evaluated in 4 randomized, open-label, controlled clinical trials. Patients (age range of 2 to 8 years) were observed for 12 months before being randomized to receive either this other somatropin product (two doses per study, most often 0.24 and 0.48 mg/kg/week) as a daily SC injection or no treatment for the first 24 months of the studies. After 24 months in the studies, all patients received this other somatropin product.

Patients who received any dose of this other somatropin product showed significant increases in growth during the first 24 months of study, compared with patients who received no treatment (see **Table 8**). Children receiving 0.48 mg/kg/week demonstrated a significant improvement in height standard deviation score (SDS) compared with children treated with 0.24 mg/kg/week. Both of these doses resulted in a slower but constant increase in growth between months 24 to 72 (data not shown).

Table 8. Efficacy of Another Somatropin Product in Children Born Small for Gestational Age (Mean ± SD)

	Another Somatropin Product (0.24 mg/kg/week) (n=76)	Another Somatropin Product (0.48 mg/kg/week) (n=93)	Untreated Control (n=40)
Height Standard Deviation Score (SDS)			
Baseline SDS	-3.2 ± 0.8	-3.4 ± 1.0	-3.1 ± 0.9
SDS at 24 months	-2.0 ± 0.8	-1.7 ± 1.0	-2.9 ± 0.9
Change in SDS from baseline to month 24	1.2[1] ± 0.5	1.7[1,2] ± 0.6	0.1 ± 0.3

1. $p = 0.0001$ vs Untreated Control group
2. $p = 0.0001$ vs group treated with another somatropin product 0.24 mg/kg/week

14.5 Idiopathic Short Stature (ISS)

The long-term efficacy and safety of another somatropin product in patients with idiopathic short stature (ISS) were evaluated in one randomized, open-label, clinical trial that enrolled 177 children. Patients were enrolled on the basis of short stature, stimulated GH secretion > 10 ng/mL, and prepubertal status (criteria for idiopathic short stature were retrospectively applied and included 126 patients). All patients were observed for height progression for 12 months and were subsequently randomized to this other somatropin product or observation only and followed to final height. Two somatropin doses were evaluated in this trial: 0.23 mg/kg/week (0.033 mg/kg/day) and 0.47mg/kg/week (0.067 mg/kg/day). Baseline patient characteristics for the ISS patients who remained prepubertal at randomization (n= 105) were: mean (± SD): chronological age 11.4 (1.3) years, height SDS -2.4 (0.4), height velocity SDS -1.1 (0.8), and height velocity 4.4 (0.9) cm/yr, IGF-1 SDS -0.8 (1.4). Patients were treated for a median duration of 5.7 years. Results for final height SDS are displayed by treatment arm in Table 9. Therapy with this other somatropin product improved final height in ISS children relative to untreated controls. The observed mean gain in final height was 9.8 cm for females and 5.0 cm for males for both doses combined compared to untreated control subjects. A height gain of 1 SDS was observed in 10 % of untreated subjects, 50% of subjects receiving 0.23 mg/kg/week and 69% of subjects receiving 0.47 mg/kg/week.

Table 9. Final height SDS results for pre-pubertal patients with ISS[1]

	Untreated (n=30)	**Another Somatropin Product 0.033 mg/kg/day (n=30)**	**Another Somatropin Product 0.067 mg/kg/day (n=42)**	**Another Somatropin Product 0.033 vs. Untreated (95% CI)**	**Another Somatropin Product 0.067 vs. Untreated (95% CI)**
Baseline height SDS Final height SDS minus Baseline	0.41 (0.58)	0.95 (0.75)	1.36 (0.64)	+0.53 (0.20, 0.87) p=0.0022	+0.94 (0.63, 1.26) p<0.0001
Baseline predicted ht Final height SDS minus baseline predicted final height SDS	0.23 (0.66)	0.73 (0.63)	1.05 (0.83)	+0.60 (0.09, 1.11) p=0.0217	+0.90 (0.42, 1.39) p=0.0004

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

1. Mean (SD) are observed values.

14.6 Turner Syndrome

Two randomized, open-label, clinical trials were conducted that evaluated the efficacy and safety of another somatropin product in Turner syndrome patients with short stature. Turner syndrome patients were treated with this other somatropin product alone or this other somatropin product plus adjunctive hormonal therapy (ethinylestradiol or oxandrolone). A total of 38 patients were treated with this other somatropin product alone in the two studies. In Study 1, 22 patients were treated for 12 months, and in Study 2, 16 patients were treated for 12 months. Patients received this other somatropin product at a dose between 0.13 to 0.33 mg/kg/week.

SDS for height velocity and height are expressed using either the Tanner (Study 1) or Sempé (Study 2) standards for age-matched normal children as well as the Ranke standard (both studies) for age-matched, untreated Turner syndrome patients. As seen in Table 10, height velocity SDS and height SDS values were smaller at baseline and after treatment

with this other somatropin product when the normative standards were utilized as opposed to the Turner syndrome standard.

Both studies demonstrated statistically significant increases from baseline in all of the linear growth variables (i.e., mean height velocity, height velocity SDS, and height SDS) after treatment with this other somatropin product (see **Table 10**). The linear growth response was greater in Study 1 wherein patients were treated with a larger dose of this other somatropin product.

Table 10. Growth Parameters (mean ± SD) after 12 Months of Treatment with Another Somatropin Product in Pediatric Patients with Turner Syndrome in Two Open Label Studies

	Another somatropin product 0.33 mg/kg/week Study 1* n=22	**Another somatropin product 0.13-0.23 mg/kg/week Study 2† n=16**
Height Velocity (cm/yr)		
Baseline	4.1 ± 1.5	3.9 ± 1.0
Month 12	7.8 ± 1.6	6.1 ± 0.9
Change from baseline (95% CI)	3.7 (3.0, 4.3)	2.2 (1.5, 2.9)
Height Velocity SDS (Tanner*/Sempé† Standards) (n=20)		
Baseline	-2.3 ± 1.4	-1.6 ± 0.6
Month 12	2.2 ± 2.3	0.7 ± 1.3
Change from baseline (95% CI)	4.6 (3.5, 5.6)	2.2 (1.4, 3.0)
Height Velocity SDS (Ranke Standard)		
Baseline	-0.1 ± 1.2	-0.4 ± 0.6
Month 12	4.2 ± 1.2	2.3 ± 1.2
Change from baseline (95% CI)	4.3 (3.5, 5.0)	2.7 (1.8, 3.5)
Height SDS (Tanner*/Sempé† Standards)		
Baseline	-3.1 ± 1.0	-3.2 ± 1.0
Month 12	-2.7 ± 1.1	-2.9 ± 1.0
Change from baseline (95% CI)	0.4 (0.3, 0.6)	0.3 (0.1, 0.4)
Height SDS (Ranke Standard)		
Baseline	-0.2 ± 0.8	-0.3 ± 0.8
Month 12	0.6 ± 0.9	0.1 ± 0.8
Change from baseline (95% CI)	0.8 (0.7, 0.9)	0.5 (0.4, 0.5)

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

16 HOW SUPPLIED/STORAGE AND HANDLING

Storage

Store Omnitrope® refrigerated at 2° to 8°C (36° to 46°F).

Do not freeze.

Omnitrope® is light sensitive and should be stored in the carton.

16.1 OMNITROPE® Cartridge 5 mg/1.5 mL

Omnitrope® Cartridge (somatropin-[rDNA origin]) 5 mg/1.5 mL is supplied in the following package sizes:

- One cartridge (NDC 0781-3001-07)
- Five cartridges (NDC 0781-3001-26)

For use only with the Omnitrope® Pen 5 delivery system, which is sold separately After the first use the cartridge should remain in the pen and has to be kept in a refrigerator at 2° to 8°C (36° to 46°F) for a maximum of 28 days (see **Table 11**).

16.2 OMNITROPE® Cartridge 10 mg/1.5 mL

Omnitrope® Cartridge (somatropin-[rDNA origin]) 10 mg/1.5 mL is supplied in the following package sizes:

- One cartridge (NDC 0781-3004-07)
- Five cartridges (NDC 0781-3004-26)

For use only with the Omnitrope® Pen 10 delivery system, which is sold separately. After the first use the cartridge should remain in the pen and has to be kept in a refrigerator at 2° to 8°C (36° to 46°F) for a maximum of 28 days (see **Table 11**).

16.3 OMNITROPE® (somatropin [rDNA origin]) for injection 5.8 mg/vial

After reconstitution, the concentration is 5 mg/mL.

- Carton contains 8 vials of Omnitrope® 5.8 mg and 8 vials of diluent (Bacteriostatic Water for injection containing 1.5% benzyl alcohol as a preservative.)

NDC 0781-4004-36

Omnitrope® 5.8 mg is supplied with a diluent containing benzyl alcohol as a preservative. After reconstitution, the contents of the vial must be used within 3 weeks. After the first injection, the vial should be stored in the carton in a refrigerator at 2° to 8°C (36° to 46°F) (see **Table 11**).

Table 11. Storage Options

Omnitrope® Product Formulation	**Storage Requirement**	
	Before Use	**In-use (after 1st injection)**
5 mg/1.5 mL Cartridge	2-8ºC/ 36-46ºF Until exp date	2-8 ºC/36-46 ºF 4 weeks
10 mg/1.5 mL Cartridge		2-8 ºC/36-46 ºF 4 weeks
5.8 mg/vial		2-8 ºC/36-46 ºF 3 weeks

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Instructions For Use: Omnitrope Pen 5 Instructions For Use, Omnitrope Pen 10 Instructions For Use, Instructions For Omnitrope 5.8 mg/Vial).

Patients being treated with Omnitrope® (and/or their parents) should be informed about the potential risks and benefits associated with somatropin treatment *[in particular, see Adverse Reactions (6.1) for a listing of the most serious and/or most frequently observed adverse reactions associated with somatropin treatment in children and adults]*. This

information is intended to better educate patients (and caregivers); it is not a disclosure of all possible adverse or intended effects.

Patients and caregivers who will administer Omnitrope® should receive appropriate training and instruction on the proper use of Omnitrope® from the physician or other suitably qualified health care professional. A puncture-resistant container for the disposal of used syringes and needles should be strongly recommended. Patients and/or parents should be thoroughly instructed in the importance of proper disposal, and cautioned against any reuse of needles and syringes. Counsel patients and parents that they should never share an Omnitrope Pen with another person, even if the needle is changed. Sharing of the pen between patients may pose a risk of transmission of infection.

If patients are prescribed Omnitrope® Cartridge 5 mg/1.5 mL or 10 mg/1.5 mL (to be inserted into Omnitrope Pen 5 or Pen 10 delivery systems), physicians should instruct patients to read the corresponding *Instructions For Use* provided with the Omnitrope® Pens delivery systems and the Omnitrope® Cartridges.

If patients are prescribed Omnitrope® for injection, physicians should instruct patients to read the *Instructions For Use* leaflets provided with the Omnitrope® for injection 5.8 mg/vial.

Omnitrope® is a trademark of Novartis.

Manufactured in Austria by Sandoz GmbH

Distributed by Sandoz Inc., Princeton, NJ 08540

OMNITROPE® PEN 5 INSTRUCTIONS FOR USE

For use with Omnitrope® (Somatropin [rDNA origin] Injection) 5 mg/1.5 mL cartridges

TABLE OF CONTENTS

READ FIRST: Important Safety Information

1. Read the following instructions before using the Omnitrope® Pen 5. Ask your healthcare professional if there is something you do not understand.

2. The Omnitrope® Pen 5 is a pen injector. It is for use with Omnitrope® cartridges 5 mg/1.5 mL and BD® pen needles (29G x 12.7 mm or 31G x 8 mm or 31G x 5 mm).

3. People with very poor vision should not use the Omnitrope® Pen 5 unless someone with good eyesight is able to help.

DOS AND DON'TS

DOs

1. Always keep Omnitrope® cartridges refrigerated.

2. Cartridges should be handled with care at all times.

3. After taking a cartridge out of the refrigerator, allow it to reach room temperature (about 30 minutes) before injecting the medicine.

4. When starting a new cartridge, always ready (prime) the pen.

5. When making an injection, insert the pen needle into the skin in the way that your healthcare professional teaches you. After pen needle insertion, push the injection button in as far as it will go and continue to press firmly for at least five seconds, before you remove the pen needle from the skin. If medicine continues to drip from the pen needle after injection, hold the pen needle in the skin longer the next time you inject.

6. This device **must not be shared with other patients** even if the needle is changed. Sharing of the pen between patients may pose a risk of transmission of infection. However, if you are giving an injection to another person, be careful when removing the pen needle. Accidental pen needle sticks can transmit infections.

7. **For safety and injection comfort, use a new, sterile pen needle with each injection.**

DON'Ts

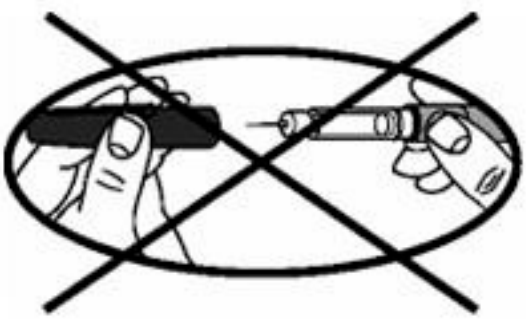
1. Do not share the Omnitrope® Pen5 even if the needle is changed. It is made for only one person to use.

2. The pen needle unit is sterile. To avoid contaminating the pen needle after opening, **do not place it on a surface or touch exposed parts.**

3. Never dial your dose or attempt to correct a dialing error with the pen needle in your skin. This may result in a wrong dose.

4. **Never store or carry your Omnitrope® Pen 5 with a pen needle attached.**

Never recap pen with pen needle on.



Storing or carrying your Omnitrope® Pen 5 with a pen needle attached may lead to needle pricks and leaves an open passage for:

- Air to enter the cartridge
- Medicine to leak out

Both of these conditions can affect the dose of the injection.

5. Do not use your Omnitrope® Pen 5 if the cap or other parts are missing.

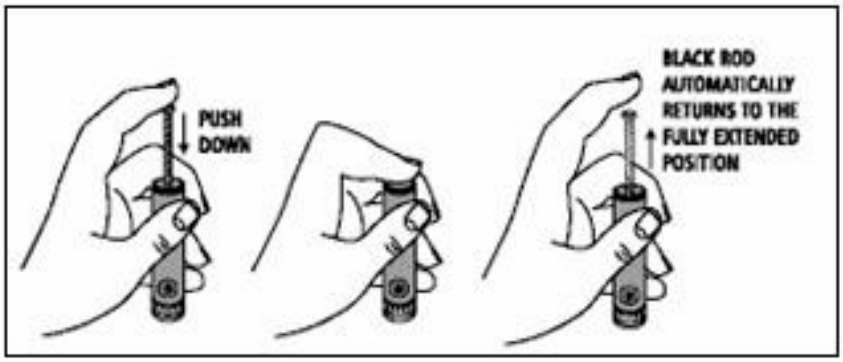
PEN PARTS

AUTO-POSITIONING FEATURE

The Omnitrope® Pen 5 has a black rod with an auto-positioning feature. This auto-positioning feature makes priming easier (fewer steps), especially when a new cartridge is used.

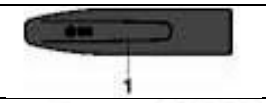
How it works

(Pictures are included only to demonstrate the auto-positioning feature. These steps are not necessary to operate pen).



Notice that the black rod moves into the pen easily and returns to the fully extended position automatically. This automatic extension of the black rod positions it correctly against the cartridge plunger.

PEN PARTS

	**PEN CAP** 1. Clip
	**CARTRIDGE HOLDER**
	**PEN BODY** 2. Black rod 3. Dose window with arrow indicator 4. White dose knob 5. Red injection button
	**PEN NEEDLE UNIT** 6. Outer pen needle shield 7. Inner pen needle shield 8. Pen needle 9. Hub 10. Paper tab

Note – Pen Needle Unit is supplied assembled and sterile. Do not disassemble at this point.

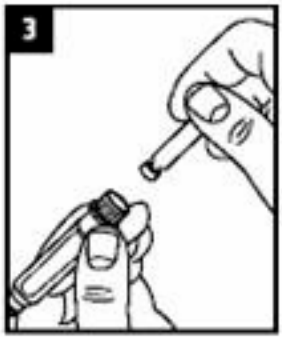
	**CARTRIDGE** 11. Rubber septum 12. Metal Cap 13. Cartridge plunger

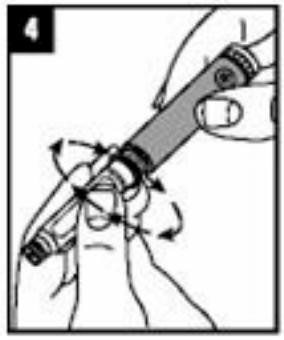
HOW TO USE YOUR OMNITROPE® PEN 5

LOADING THE CARTRIDGE INTO THE PEN

1. Remove the pen cap by pulling it off the pen.

2. Unscrew the cartridge holder from the pen body



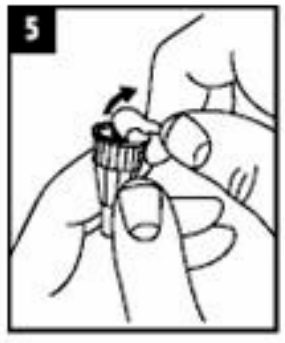


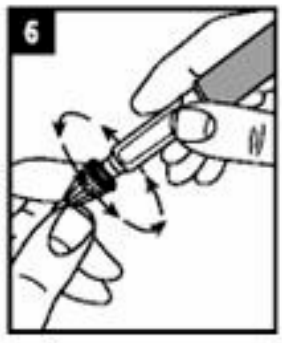
3. Insert the cartridge, metal cap first, into the cartridge holder

4. Lower the pen body onto the cartridge holder so that the black rod presses against the cartridge plunger. Screw the cartridge holder onto the pen body until no gap remains. One of the blue arrows must line-up with the yellow line mark on the pen body.

Note – Do not overtighten.

ATTACHING THE PEN NEEDLE





5. Remove the paper tab from the back of a new pen needle.

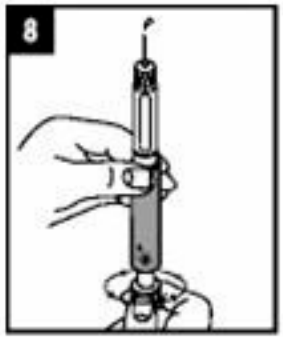
6a. Holding the cartridge holder, push the pen needle unit onto the pen. Then screw the threaded hub of the pen needle onto the cartridge holder as shown.

6b. With a gentle pull, remove the outer pen needle shield. Save the outer shield. You will use it to remove the pen needle from the pen after your injection is finished.

6c. Do not remove the inner pen needle shield at this time.

6d. Check that the cartridge holder is attached to the pen body, with the blue arrow lined-up with the yellow mark on the pen body before each injection.

PRIMING



Important – Before using a new cartridge, you must prime the Omnitrope® Pen 5.

For a New Cartridge Only

7. Hold the pen with the needle pointing upwards. Gently tap the cartridge holder with your finger to help air bubbles rise to the top of the cartridge. Set the dose to 0.05 mg (one click) by turning the dose knob.

8. Remove the inner pen needle shield. With the pen needle pointing up, firmly turn the dose knob back to the “0” position and hold for at least 5 seconds. At least 2 drops of medicine must flow out of the pen needle for the pen to be properly primed.

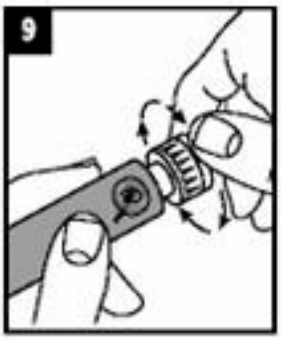
If at least 2 drops do not flow out, set the dose to 0.05 mg and repeat the steps until at least 2 drops of medicine appear at the tip of the pen needle.

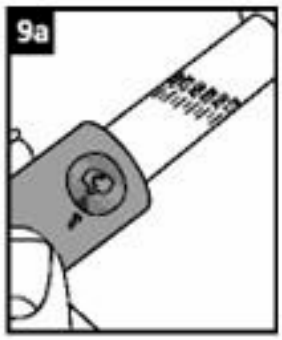
When medicine appears, the Omnitrope® Pen 5 is properly primed for injection and ready to use.

For a previously used Cartridge

No priming is needed. Remove the inner pen needle shield and continue with dose dialing.

DOSE DIALING





9. To set your dose, turn the dose knob until you see the number of mg for your dose in the middle of the dose window lined-up with the arrow. You will hear a click for each dose increment you dial. However, do not rely on counting these clicks to measure the right dose.

Important – Dose Correction

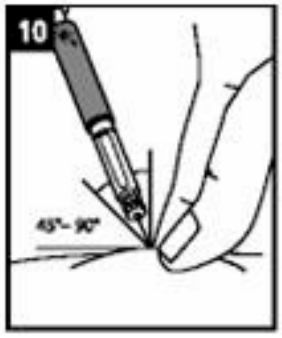
If you turn the dose knob past your dose, **do not dial backwards.**

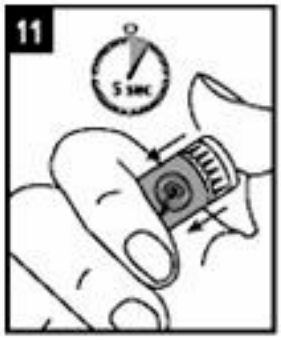
Hold the pen body and turn the dose knob until it is fully extended as shown in picture 9a. You will see a bent arrow ( ) in the dose dialing window. The injection button can now be fully pressed, resetting the dial to "0" without giving medicine. The right dose can now be redialed as described in step 9.

Note – Check that the cartridge holder is still attached to the pen body, with the blue arrow lined-up with the yellow mark on the pen body.

MAKING THE INJECTION

10. Insert the pen needle into the skin as instructed by your healthcare professional.





11. After inserting the pen needle, push the injection button in as far in as it will go and press firmly. A clicking sound will be heard while your dose is injecting. Continue to press firmly for at least 5 seconds, before you remove the pen needle from the skin.

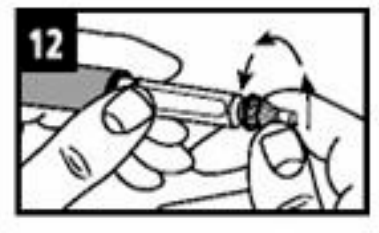
If medicine continues to drip from the pen needle after injection, hold the pen needle in your skin for a longer time the next time you inject.

If you cannot push the Injection button in as far in as it goes and the dose window does not read "0", the cartridge is empty and the full dose of medicine has not been injected. The dose indicator window will show the amount of medicine still needed. Remove the pen needle from the skin and note the number. Reset the dose knob to "0" by holding the pen and turning the dose knob until it is fully extended as shown in picture 9a. The dose injection button can now be fully pressed

to “0”. Remove the pen needle from the pen (see **step 12** below) and remove the empty cartridge by unscrewing the cartridge holder. Insert a new cartridge and prime the pen as described in steps 7 and 8. Set the dose, which you noted, and inject. This completes your dose.

Important – Before replacing a cartridge, be sure that the pen needle unit is **NOT** attached to the Omnitrope® Pen 5.

REMOVING THE PEN NEEDLE



12. Carefully replace the outer pen needle shield. Hold the pen by the cartridge holder and unscrew the pen needle from the cartridge holder. Recap the pen.

13. Store your Omnitrope® Pen 5 with attached Omnitrope cartridge in its pouch or refrigerator storage box. Store in a refrigerator between 36 and 46°F (2 and 8°C).

14. Dispose of used pen needles in a special container called a “sharps” container. Your healthcare professional can give you a sharps container or tell you how to make one. Do not dispose of used pen needles in the trash.

TROUBLESHOOTING

PROBLEM	POSSIBLE CAUSE	HOW TO FIX
Dial unit does not turn easily.	Dust or dirt	Turn the dial beyond the highest setting on the scale. Wipe all exposed surfaces with a clean, damp cloth. Please also refer to the chapter “Care and Storage”.
You have dialed a higher dose than needed.		Correct dose as described in step 9, “Dose correction”.
The injection button cannot be pushed or stops during injection. (Dose knob does not return to “0”).	Cartridge is empty and full dose has not been dispensed.	Remove the pen needle as per step 12 and replace the empty cartridge with a new cartridge. Refer to step 11, “If the injection button stops”.
	Clogged pen needle.	Remove the pen needle as per step 12 and replace it with a new needle as described in step 5.
No clicking is heard during the injection (Dose knob moves freely).	Pen is in dose correction mode.	Remove pen needle from skin. Press injection button all the way in so the dial returns to zero and repeat from step 9 to make the injection.
Medicine continues to drip from the pen needle after injection.	Pen needle was removed from the skin too early.	Hold the pen needle in your skin longer next time you inject.
	Cartridge holder is not properly attached to the pen body.	Line-up blue arrow on cartridge holder with yellow mark on pen body.

CARE AND STORAGE

Once your Omnitrope® Pen 5 contains a somatropin cartridge, it has to be stored in the refrigerator between 36 and 46°F (2 and 8°C). Do not remove the cartridge between injections.

Protect your Omnitrope® Pen 5 and cartridge from light by storing in its pouch or refrigerator storage box.

The Omnitrope cartridge must be discarded 28 days after the first injection. The Omnitrope® Pen 5 can be reloaded with a new cartridge and be used multiple times.

Your Omnitrope® Pen 5 must be properly cared for.

- Only a clean, damp cloth should be used for routine cleaning. Never wash the pen in water or with strong surgical disinfectants.
- Avoid exposure to dust, moisture and temperature extremes. Do not expose to heat or freeze.

If your Omnitrope® Pen 5 is damaged or you cannot get it to work, contact the pharmacy that provided you the Omnitrope® Pen 5 or, if OmniSource provided you with your Omnitrope® Pen 5, call 1-877-456-6794. For other questions or additional information please call OmniSource at 1-877-456-6794. Do not attempt to repair the pen yourself.

GUARANTEE

Your Omnitrope® Pen 5 is covered by a 2 year guarantee. Contact your Omnitrope® Pen 5 provider after you have used the pen for 2 years to have it replaced by a new one.

If your Omnitrope® Pen 5 is defective in materials or workmanship within the period of the guarantee, the provider of your Omnitrope® Pen 5 will replace your pen and/or rectify the fault at its own cost. If OmniSource provided your Omnitrope® Pen 5, call 1-877-456-6794. Otherwise call the pharmacy that provided the Omnitrope® Pen 5.

In case of complaints, please contact your Omnitrope® Pen 5 provider to report a complaint.

This guarantee is invalid if your Omnitrope® Pen 5 has not been used in accordance with the manufacturer`s instruction leaflet or if the defect has been caused by neglect, misuse or accident.

ACCURACY – Omnitrope® Pen 5 complies with the accuracy requirements of the International Standard EN ISO11608-1/2000 Pen Injectors for medical use – Requirements and test methods.

IMPORTANT PERSONAL NOTES

Date I first used the Omnitrope® Pen 5: (dd/mm/yy)

Pen log no:

Additional Comments:

Omnitrope® is a trademark of Novartis.

BD and BD Logo are trademarks of Becton, Dickinson and Company.

OP5.ifU.06.1

Manufactured by

BD Medical-Pharmaceutical Systems

Franklin Lakes, NJ 07417

Packaged by

Sandoz GmbH, Kundl, Austria

Distributed by

Sandoz Inc., Princeton, NJ 08540

OMNITROPE® PEN 10 INSTRUCTIONS FOR USE

For use with Omnitrope® (Somatropin [rDNA origin] Injection) 10 mg/1.5 mL cartridges

TABLE OF CONTENTS

READ FIRST: Important Safety Information

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2. The Omnitrope® Pen 10 is a pen injector. It is for use with Omnitrope® cartridges 10 mg/1.5 mL and BD® pen needles (29G x 12.7 mm or 31G x 8 mm or 31G x 5 mm).

3. People with very poor vision should not use the Omnitrope® Pen 10 unless someone with good eyesight is able to help.

DOS AND DON'TS

DOs

1. Always keep Omnitrope® cartridges refrigerated.

2. Cartridges should be handled with care at all times.

3. After taking a cartridge out of the refrigerator, allow it to reach room temperature (about 30 minutes) before injecting the medicine.

4. When starting a new cartridge, always ready (prime) the pen.

5. When making an injection, insert the pen needle into the skin in the way that your healthcare professional teaches you. After pen needle insertion, push the injection button in as far as it will go and continue to press firmly for at least five seconds, before you remove the pen needle from the skin. If medicine continues to drip from the pen needle after injection, hold the pen needle in the skin longer the next time you inject.

6. This device **must not be shared with other patients** even if the needle is changed. Sharing of the pen between patients may pose a risk of transmission of infection. However, if you are giving an injection to another person, be careful when removing the pen needle. Accidental pen needle sticks can transmit infections.

7. **For safety and injection comfort, use a new, sterile pen needle with each injection.**

DON'Ts

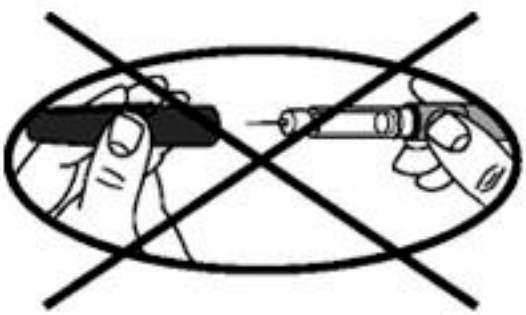
1. Do not share the Omnitrope® Pen 10 even if the needle is changed. It is made for only one person to use.

2. The pen needle unit is sterile. To avoid contaminating the pen needle after opening, **do not place it on a surface or touch exposed parts.**

3. Never dial your dose or attempt to correct a dialing error with the pen needle in your skin. This may result in a wrong dose.

4. **Never store or carry your Omnitrope® Pen 10 with a pen needle attached.**

Never recap pen with pen needle on.



Storing or carrying your Omnitrope® Pen 10 with a pen needle attached may lead to needle pricks and leaves an open passage for:

- Air to enter the cartridge
- Medicine to leak out

Both of these conditions can affect the dose of the injection.

5. Do not use your Omnitrope® Pen 10 if the cap or other parts are missing.

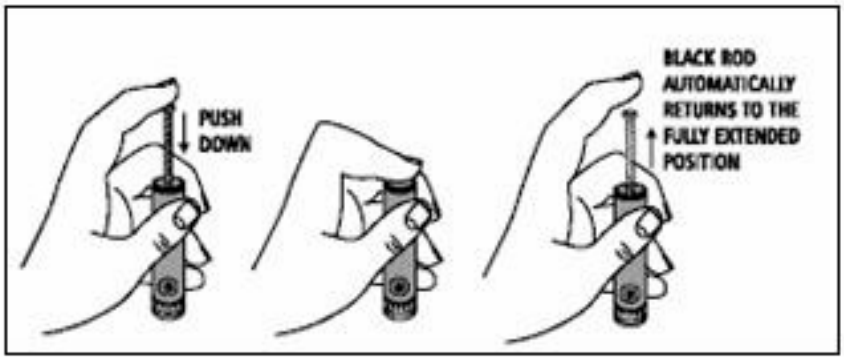
PEN PARTS

AUTO-POSITIONING FEATURE

The Omnitrope® Pen 10 has a black rod with an auto-positioning feature. This auto-positioning feature makes priming easier (fewer steps), especially when a new cartridge is used.

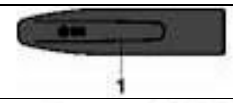
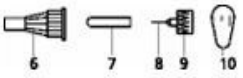
How it works

(Pictures are included only to demonstrate the auto-positioning feature. These steps are not necessary to operate pen).

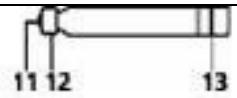


Notice that the black rod moves into the pen easily and returns to the fully extended position automatically. This automatic extension of the black rod positions it correctly against the cartridge plunger.

PEN PARTS

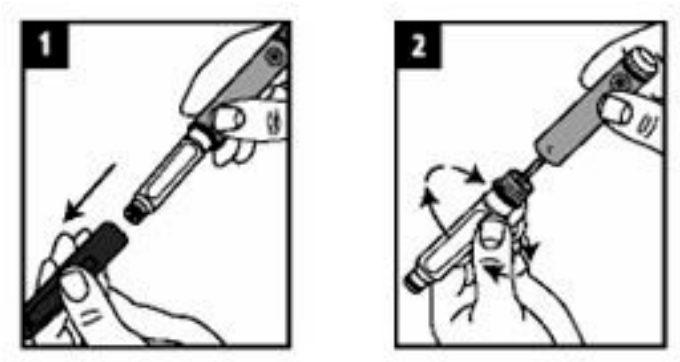
	**PEN CAP** 1. Clip
	**CARTRIDGE HOLDER**
	**PEN BODY** 2. Black rod 3. Dose window with arrow indicator 4. White dose knob 5. Red injection button
	**PEN NEEDLE UNIT** 6. Outer pen needle shield 7. Inner pen needle shield 8. Pen needle 9. Hub 10. Paper tab

Note – Pen Needle Unit is supplied assembled and sterile. Do not disassemble at this point.

	**CARTRIDGE** 11. Rubber septum 12. Metal Cap 13. Cartridge plunger

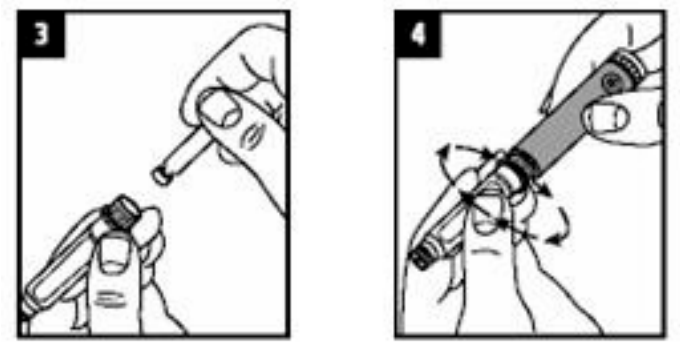
HOW TO USE YOUR OMNITROPE® PEN 10

LOADING THE CARTRIDGE INTO THE PEN



1. Remove the pen cap by pulling it off the pen.

2. Unscrew the cartridge holder from the pen body

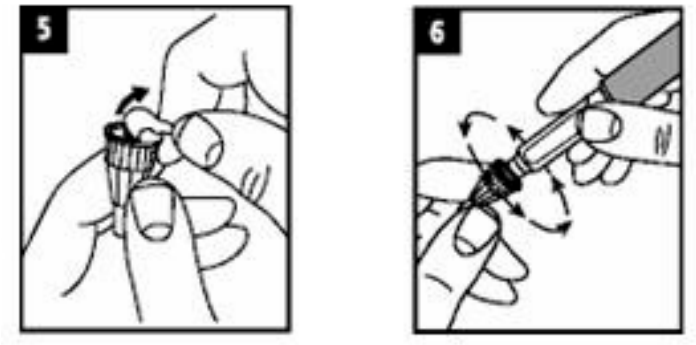


3. Insert the cartridge, metal cap first, into the cartridge holder

4. Lower the pen body onto the cartridge holder so that the black rod presses against the cartridge plunger. Screw the cartridge holder onto the pen body until no gap remains. One of the blue arrows must line-up with the white line mark on the pen body.

Note – Do not overtighten.

ATTACHING THE PEN NEEDLE



5. Remove the paper tab from the back of a new pen needle.

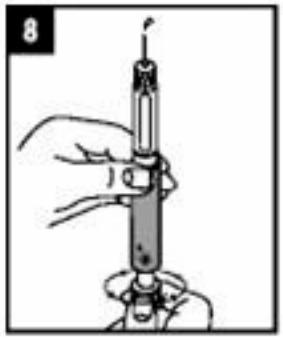
6a. Holding the cartridge holder, push the pen needle unit onto the pen. Then screw the threaded hub of the pen needle onto the cartridge holder as shown.

6b. With a gentle pull, remove the outer pen needle shield. Save the outer shield. You will use it to remove the pen needle from the pen after your injection is finished.

6c. Do not remove the inner pen needle shield at this time.

6d. Check that the cartridge holder is attached to the pen body, with the blue arrow lined-up with the white mark on the pen body before each injection.

PRIMING



Important – Before using a new cartridge, you must prime the Omnitrope® Pen 10.

For a New Cartridge Only

7. Hold the pen with the needle pointing upwards. Gently tap the cartridge holder with your finger to help air bubbles rise to the top of the cartridge. Set the dose to 0.1 mg (one click) by turning the dose knob.

8. Remove the inner pen needle shield. With the pen needle pointing up, firmly turn the dose knob back to the “0” position and hold for at least 5 seconds. At least 2 drops of medicine must flow out of the pen needle for the pen to be properly primed.

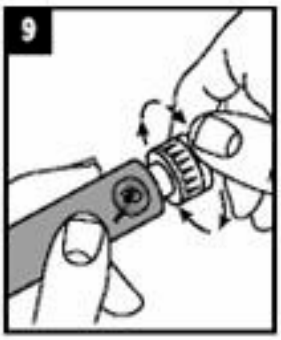
If at least 2 drops do not flow out, set the dose to 0.1 mg and repeat the steps until at least 2 drops of medicine appear at the tip of the pen needle.

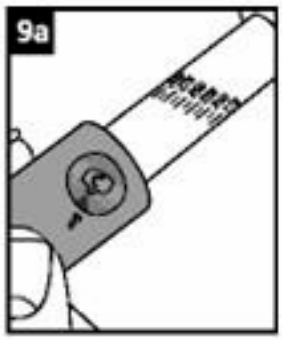
When medicine appears, the Omnitrope® Pen 10 is properly primed for injection and ready to use.

For a previously used Cartridge

No priming is needed. Remove the inner pen needle shield and continue with dose dialing.

DOSE DIALING





9. To set your dose, turn the dose knob until you see the number of mg for your dose in the middle of the dose window lined-up with the arrow. You will hear a click for each dose increment you dial. However, do not rely on counting these clicks to measure the right dose.

Important – Dose Correction

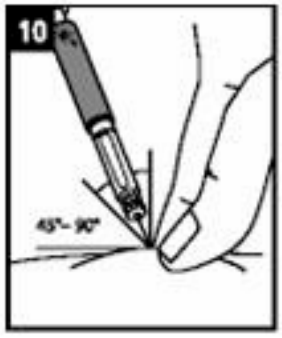
If you turn the dose knob past your dose, **do not dial backwards.**

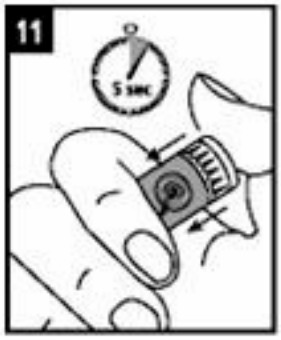
Hold the pen body and turn the dose knob until it is fully extended as shown in picture 9a. You will see a bent arrow ( ) in the dose dialing window. The injection button can now be fully pressed, resetting the dial to "0" without giving medicine. The right dose can now be redialed as described in step 9.

Note – Check that the cartridge holder is still attached to the pen body, with the blue arrow lined-up with the white mark on the pen body.

MAKING THE INJECTION

10. Insert the pen needle into the skin as instructed by your healthcare professional.





11. After inserting the pen needle, push the injection button in as far in as it will go and press firmly. A clicking sound will be heard while your dose is injecting. Continue to press firmly for at least 5 seconds, before you remove the pen needle from the skin.

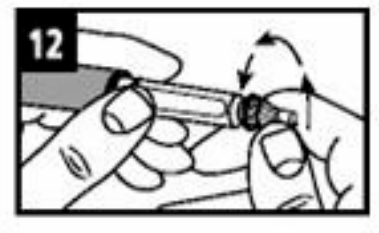
If medicine continues to drip from the pen needle after injection, hold the pen needle in your skin for a longer time the next time you inject.

If you cannot push the Injection button in as far in as it goes and the dose window does not read "0", the cartridge is empty and the full dose of medicine has not been injected. The dose indicator window will show the amount of medicine still needed. Remove the pen needle from the skin and note the number. Reset the dose knob to "0" by holding the pen and turning the dose knob until it is fully extended as shown in picture 9a. The dose injection button can now be fully pressed

to “0”. Remove the pen needle from the pen (see **step 12** below) and remove the empty cartridge by unscrewing the cartridge holder. Insert a new cartridge and prime the pen as described in steps 7 and 8. Set the dose, which you noted, and inject. This completes your dose.

Important – Before replacing a cartridge, be sure that the pen needle unit is **NOT** attached to the Omnitrope® Pen 10.

REMOVING THE PEN NEEDLE



12. Carefully replace the outer pen needle shield. Hold the pen by the cartridge holder and unscrew the pen needle from the cartridge holder. Recap the pen.

13. Store your Omnitrope® Pen 10 with attached Omnitrope cartridge in its pouch or refrigerator storage box. Store in a refrigerator between 36 and 46°F (2 and 8°C).

14. Dispose of used pen needles in a special container called a “sharps” container. Your healthcare professional can give you a sharps container or tell you how to make one. Do not dispose of used pen needles in the trash.

TROUBLESHOOTING

PROBLEM	POSSIBLE CAUSE	HOW TO FIX
Dial unit does not turn easily.	Dust or dirt	Turn the dial beyond the highest setting on the scale. Wipe all exposed surfaces with a clean, damp cloth. Please also refer to the chapter “Care and Storage”.
You have dialed a higher dose than needed.		Correct dose as described in step 9, “Dose correction”.
The injection button cannot be pushed or stops during injection. (Dose knob does not return to “0”).	Cartridge is empty and full dose has not been dispensed.	Remove the pen needle as per step 12 and replace the empty cartridge with a new cartridge. Refer to step 11, “If the injection button stops”.
	Clogged pen needle.	Remove the pen needle as per step 12 and replace it with a new needle as described in step 5.
No clicking is heard during the injection (Dose knob moves freely).	Pen is in dose correction mode.	Remove pen needle from skin. Press injection button all the way in so the dial returns to zero and repeat from step 9 to make the injection.
Medicine continues to drip from the pen needle after injection.	Pen needle was removed from the skin too early.	Hold the pen needle in your skin longer next time you inject.
	Cartridge holder is not properly attached to the pen body.	Line-up blue arrow on cartridge holder with white mark on pen body.

CARE AND STORAGE

Once your Omnitrope® Pen 10 contains a somatropin cartridge, it has to be stored in the refrigerator between 36 and 46°F (2 and 8°C). Do not remove the cartridge between injections.

Protect your Omnitrope® Pen 10 and cartridge from light by storing in its pouch or refrigerator storage box.

The Omnitrope cartridge must be discarded 28 days after the first injection. The Omnitrope® Pen 10 can be reloaded with a new cartridge and be used multiple times.

Your Omnitrope® Pen 10 must be properly cared for.

- Only a clean, damp cloth should be used for routine cleaning. Never wash the pen in water or with strong surgical disinfectants.
- Avoid exposure to dust, moisture and temperature extremes. Do not expose to heat or freeze.

If your Omnitrope® Pen 10 is damaged or you cannot get it to work, contact the pharmacy that provided you the Omnitrope® Pen 10 or, if OmniSource provided you with your Omnitrope® Pen 10, call 1-877-456-6794. For other questions or additional information please call OmniSource at 1-877-456-6794. Do not attempt to repair the pen yourself.

GUARANTEE

Your Omnitrope® Pen 10 is covered by a 2 year guarantee. Contact your Omnitrope® Pen 10 provider after you have used the pen for 2 years to have it replaced by a new one.

If your Omnitrope® Pen 10 is defective in materials or workmanship within the period of the guarantee, the provider of your Omnitrope® Pen 10 will replace your pen and/or rectify the fault at its own cost. If OmniSource provided your Omnitrope® Pen 10, call 1-877-456-6794. Otherwise call the pharmacy that provided the Omnitrope® Pen 10.

In case of complaints, please contact your Omnitrope® Pen 10 provider to report a complaint.

This guarantee is invalid if your Omnitrope® Pen 10 has not been used in accordance with the manufacturer`s instruction leaflet or if the defect has been caused by neglect, misuse or accident.

ACCURACY – Omnitrope® Pen 10 complies with the accuracy requirements of the International Standard EN ISO11608-1/2000 Pen Injectors for medical use – Requirements and test methods.

IMPORTANT PERSONAL NOTES

Date I first used the Omnitrope® Pen 10: (dd/mm/yy)

Pen log no:

Additional Comments:

OP10.ifU.07.1

Manufactured by

BD Medical-Pharmaceutical Systems

Franklin Lakes, NJ 07417

Packaged by

Sandoz GmbH, Kundl, Austria

Distributed by

Sandoz Inc., Princeton, NJ 08540

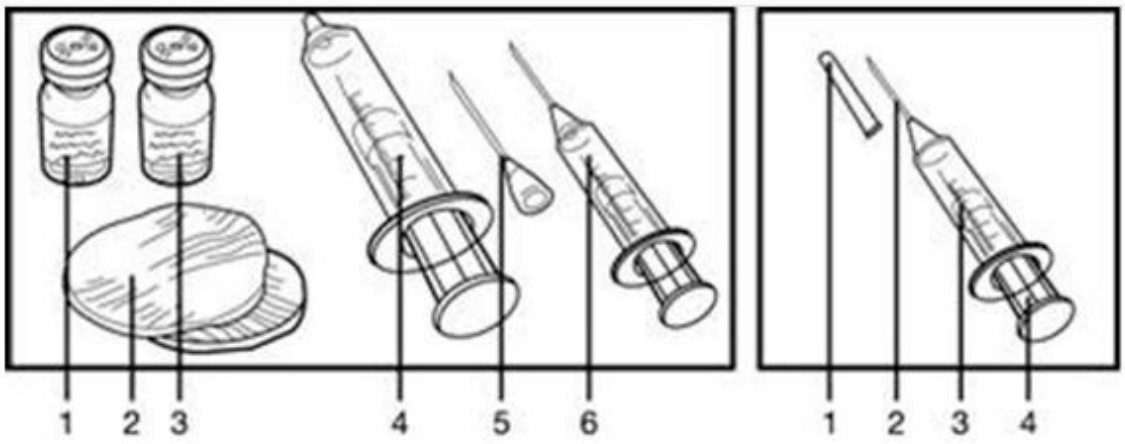
INSTRUCTIONS FOR OMNITROPE® 5.8 MG/VIAL

The following instructions explain how to inject OMNITROPE® 5.8 mg. Do not inject OMNITROPE® yourself until your healthcare provider has taught you and you understand the instructions. Ask your healthcare provider or pharmacist if you have any questions about injecting OMNITROPE®.

- OMNITROPE® 5.8 mg is for multiple uses.
- The concentration of OMNITROPE® after mixing is 5 mg/mL.
- After mixing, OMNITROPE® 5.8 mg contains a preservative and should not be used in newborns.

Preparation

Collect necessary items before you begin:



1. vial with lyophilized powder
2. alcohol swabs
3. vial with diluent for OMNITROPE™
4. sterile, disposable syringe (e. g. a 3 mL syringe)
5. needle for withdrawing the diluent from the vial
6. sterile, disposable syringe of appropriate size (e.g. a 1 mL syringe) and needle for subcutaneous injection

1. needle cap
2. needle
3. barrel with dosing scale
4. plunger

- a vial with OMNITROPE® 5.8 mg
- a vial with diluent (mixing liquid - Bacteriostatic Water for Injection containing benzyl alcohol as preservative) for OMNITROPE® 5.8 mg
- a sterile, disposable 3 mL syringe and needle for withdrawing the diluent from the vial (not supplied in the pack)
- sterile disposable 1 mL syringes and needles for under the skin (subcutaneous) injection (not supplied in the pack)
- 2 alcohol swabs (not supplied in the pack)

Wash your hands before you start with the next steps.

Mixing OMNITROPE® 5.8 mg

- Remove the protective caps from the two vials. With one alcohol swab, clean both the rubber top of the vial that contains the powder and the rubber top of the vial that contains diluent.

- Use next the sterile diluent vial, the disposal 3 mL syringe and a needle.

- Attach the needle to the syringe (if not attached already). Pull back the syringe plunger and fill the syringe with air. Push the needle fitted to the syringe through the rubber top of the diluent vial, push all the air from the syringe into the vial, turn the vial upside down, and withdraw all the diluent from the vial into the syringe. Remove the syringe and needle.

- Next take the syringe with the diluent in it and push the needle through the rubber stopper of the vial that contains the white powder. Inject the diluent slowly. Aim the stream of liquid against the glass wall in order to avoid foam. Remove the syringe and needle and dispose of them.

- Gently swirl the vial until the content is completely dissolved. **Do not shake.**

- If the medicine is cloudy or contains particles, it should not be used. The medicine must be clear and colorless after mixing.
- **After mixing the medicine, the medicine in the vial must be used within 3 weeks. Store the vial in a refrigerator at 2° to 8°C (36° to 46°F) after mixing and using it each time.**

Measuring the Dose of OMNITROPE® 5.8 mg to Be Injected

- Next use the sterile, disposable 1 mL (or similar) syringe and needle for subcutaneous injection. Push the needle through the rubber top of the vial that contains the medicine that you have just mixed.
- Turn the vial and the syringe upside down.

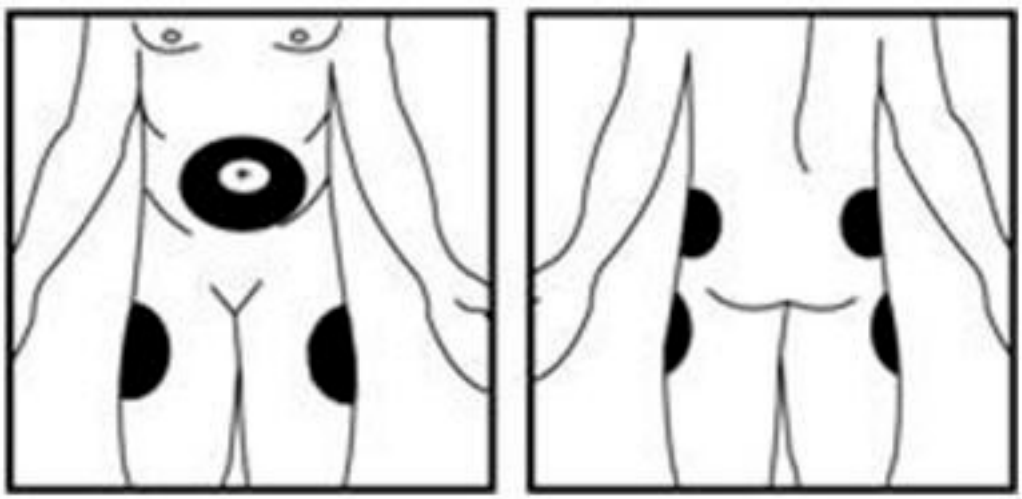
- Be sure the tip of the syringe is in the OMNITROPE® mixed medicine.
- Pull back on the plunger slowly and withdraw the dose prescribed by your doctor into the syringe.
- Hold the syringe with the needle in the vial pointing up and remove the syringe from the vial.
- Check for air bubbles in the syringe. If you see any bubbles, pull the plunger slightly back; tap the syringe gently, with the needle pointing upwards, until the bubble disappears. Push the plunger slowly back up to the correct dose. If

there is not enough medicine in the syringe after removing the air bubbles, draw more medicine into the syringe from the mixed medicine vial and repeat checking for bubbles.

- Look at the mixed medicine in the syringe before using. Do not use if discolored or particles are present. You are now ready to inject the dose.

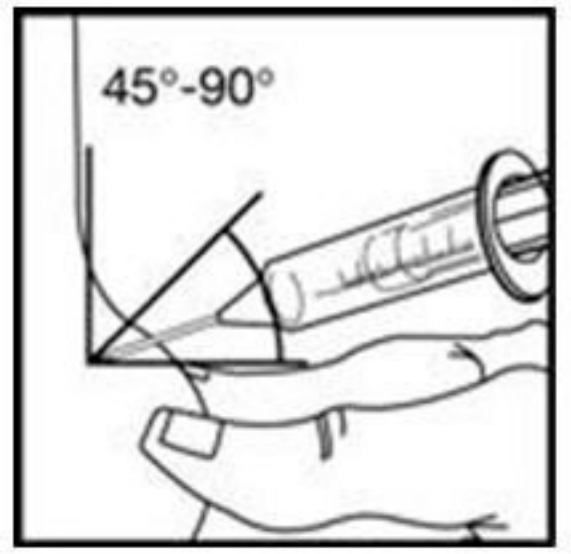
Injecting OMNITROPE® 5.8 mg

- Choose the site of injection on your body. The best sites for injection are tissues with a layer of fat between skin and muscle such as the upper leg (thigh), buttocks, or stomach area (abdomen) as in the picture shown below. **Do not inject near your belly button (navel) or waistline.**



- Make sure you rotate the injection sites on your body. Inject at least 1/2 inch from the last injection. Change the places on your body where you inject, as you have been taught.
- Before you make an injection, clean your skin well with an alcohol swab. Wait for the area to air dry.

- With one hand, pinch a fold of loose skin at the injection site. With your other hand, hold the syringe as you would a pencil. Insert the needle into the pinched skin straight in or at a slight angle (an angle of 45° to 90°). After the needle is in, remove the hand used to pinch the skin and use it to hold the syringe barrel. Pull back the plunger very slightly with one hand. If blood comes into the syringe, the needle has entered a blood vessel. Do not inject into this site; withdraw the needle and repeat the procedure at a different site. If no blood comes into the syringe, inject the solution by pushing the plunger all the way down gently.



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

After Injecting OMNITROPE® 5.8 mg

- Discard the injection materials.
- Dispose the syringes safely in a closed container. You can ask your healthcare provider or pharmacist for a “sharps” container. A sharps container is a special container to put used needles and syringes in. You can return a full sharps container to your pharmacist or healthcare provider for disposal.
- The vial of mixed medicine must be stored in the refrigerator in its carton at 2° to 8°C (36° to 46°F) and used within 3 weeks.
- The solution should be clear after removal from the refrigerator. If the solution is cloudy or contains particles, **discard the vial. Do not inject the medicine from this vial.** Start over with a new vial of OMNITROPE® 5.8 mg. Call your pharmacist if you need a replacement.
- Before each use disinfect the rubber top of the reconstituted vial with an alcohol swab. You **must** use a new disposable 1 mL syringe and needle for each injection.

Manufactured in Austria by Sandoz GmbH

Distributed by Sandoz Inc., Princeton, NJ 08540

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