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) injection, for subcutaneous use

OMNITROPE® (somatropin) for injection, for subcutaneous use

Initial U.S. Approval: 1987

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

Warnings and Precautions, Slipped Capital Femoral Epiphysis in Pediatric Patients (5.10) …….. 07/2025

---------- 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 ----------

- Injection: 5 mg/1.5 mL or 10 mg/1.5 mL solution in a single-patient-use prefilled cartridge (3)
- For injection: 5.8 mg lyophilized powder in a single-patient-use vial (3)

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

- Acute Critical Illness (4)
- Children with Prader-Willi Syndrome who are severely obese or have severe respiratory impairment - reports of sudden death (4)
- Active Malignancy (4)
- Hypersensitivity to somatropin or its excipients (4)
- Active Proliferative or Severe Non-Proliferative Diabetic Retinopathy (4)
- Children with closed epiphyses (4)

---------- 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)
- Hypersensitivity: Serious hypersensitivity reactions may occur. In the event of an allergic reaction, seek prompt medical attention (5.6)
- Fluid Retention (i.e., edema, arthralgia, carpal tunnel syndrome - especially in adults): May occur frequently. Reduce dose as necessary (5.7)
- Hypoadrenalism: Monitor patients for reduced serum cortisol levels and/or need for glucocorticoid dose increases in those with known hypoadrenalism (5.8)
- Hypothyroidism: May first become evident or worsen (5.9)
- Slipped Capital Femoral Epiphysis: May develop. Evaluate children with the onset of a limp or hip/knee pain (5.10)
- Progression of Preexisting Scoliosis: May develop (5.11)
- 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 (6.2).

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: 07/2025

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Pediatric Patients

OMNITROPE is indicated for the treatment of children with growth failure due to inadequate secretion of endogenous growth hormone (GH).

OMNITROPE 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) and Warnings and Precautions (5.2)]*.

OMNITROPE 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 is indicated for the treatment of growth failure associated with Turner Syndrome.

OMNITROPE 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 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)

Weight-Based Dosing

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-1 levels may be used as guidance in dose titration.

Non-Weight Dosing
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-1 concentrations. During therapy, the dose should be decreased if required by the occurrence of adverse events and/or serum IGF-1 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

Injection: 5 mg/1.5 mL or 10 mg/1.5 mL clear, colorless solution in a single-patient-use prefilled cartridge.

For Injection: 5.8 mg white to off-white lyophilized powder in a single-patient-use vial.

4 CONTRAINDICATIONS

OMNITROPE is contraindicated in patients with:

- **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 *[see Warnings and Precautions (5.1)]*.

- **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)]*.

- **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 *[see Warnings and Precautions (5.3)]*.

- **Hypersensitivity**

OMNITROPE is contraindicated in patients with a known hypersensitivity to somatropin or any of its excipients. Systemic hypersensitivity reactions have been reported with postmarketing use of somatropins *[see Warnings and Precautions (5.6)]*.

- **Diabetic Retinopathy**

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

- **Closed Epiphyses**

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

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)]*. 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 (42% vs. 19%) among somatropin-treated patients (doses 5.3-8 mg/day) compared to those receiving placebo. 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)]*.

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)]*. 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 *[see Contraindications (4)]*.

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 somatropins. 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 fundoscopy during somatropin treatment, treatment should be stopped. If somatropin-induced IH is diagnosed, treatment with somatropin can be restarted at a lower dose after IH-associated signs and symptoms have resolved. Patients with Turner Syndrome and Prader-Willi Syndrome may be at increased risk for the development of IH.

5.6 Hypersensitivity

Serious systemic hypersensitivity reactions including anaphylactic reactions and angioedema have been reported with postmarketing use of somatropins. Patients and caregivers should be informed that such reactions are possible and that prompt medical attention should be sought if an allergic reaction occurs *[see Contraindications (4)]*.

5.7 Fluid Retention

Fluid retention during somatropin replacement therapy in adults may frequently occur. Clinical manifestations of fluid retention (e.g. edema, arthralgia, myalgia, nerve compression syndromes including carpal tunnel syndrome/paresthesias) are usually transient and dose dependent.

5.8 Hypoadrenalism

Patients receiving somatropin therapy who have or are at risk for pituitary hormone deficiency(s) may be at risk for reduced serum cortisol levels and/or unmasking of central (secondary) hypoadrenalism. 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 *[see Drug Interactions (7.1)]*.

5.9 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.

5.10 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. Slipped capital femoral epiphysis may lead to osteonecrosis. Cases of slipped capital femoral epiphysis with or without osteonecrosis have been reported in pediatric patients with short stature receiving somatropin. Any pediatric patient with the onset of a limp or complaints of hip or knee pain during OMNITROPE therapy should be evaluated for slipped capital femoral epiphysis and osteonecrosis and managed accordingly.

5.11 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.

5.12 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 Lipoatrophy

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)]*.

5.14 Laboratory Tests

Serum levels of inorganic phosphorus, alkaline phosphatase, parathyroid hormone (PTH) and IGF-1 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

The following important adverse reactions are also described elsewhere in labeling:

- Increased mortality in patients with acute critical illness *[see Warnings and Precautions (5.1)]*
- Fatalities in children with Prader-Willi Syndrome *[see Warnings and Precautions (5.2)]*
- Neoplasms *[see Warnings and Precautions (5.3)]*
- Glucose intolerance and diabetes mellitus *[see Warnings and Precautions (5.4)]*
- Intracranial hypertension *[see Warnings and Precautions (5.5)]*
- Severe hypersensitivity *[see Warnings and Precautions (5.6)]*
- Fluid retention *[see Warnings and Precautions (5.7)]*
- Hypoadrenalism *[see Warnings and Precautions (5.8)]*
- Hypothyroidism *[see Warnings and Precautions (5.9)]*
- Slipped capital femoral epiphysis in pediatric patients *[see Warnings and Precautions (5.10)]*
- Progression of preexisting scoliosis in pediatric patients *[see Warnings and Precautions (5.11)]*
- Otitis media and cardiovascular disorders in patients with Turner Syndrome *[see Warnings and Precautions (5.12)]*
- Lipoatrophy *[see Warnings and Precautions (5.13)]*
- Pancreatitis *[see Warnings and Precautions (5.15)]*
- Benzyl Alcohol *[see Warnings and Precautions (5.16)]*

6.1 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.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of somatropin or OMNITROPE. 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 postmarketing surveillance do not differ from those listed/discussed above in Sections 6.1 and 6.2 in children and adults.

Serious systemic hypersensitivity reactions including anaphylactic reactions and angioedema have been reported with postmarketing use of somatropins *[see Warnings and Precautions (5.6)]*.

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) 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), osteonecrosis (children), and pancreatitis (children and adults) *[see Warnings and Precautions (5.16)]*.

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 *[see Warnings and Precautions (5.8)]*.

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

Risk Summary

OMNITROPE contains the preservative benzyl alcohol. Because benzyl alcohol is rapidly metabolized by a pregnant woman, benzyl alcohol exposure in the fetus is unlikely. However, adverse reactions have occurred in premature neonates

and low birth weight infants who received intravenously administered benzyl alcohol-containing drugs *[see Warnings and Precautions (5.16)]*.

Limited available data with somatropin use in pregnant women are insufficient to determine a drug-associated risk of adverse developmental outcomes. In animal studies (rats and rabbits), there was no evidence of embryo-fetal or neonatal harm following somatropin administration during organogenesis at doses approximately 24 times and 19 times the recommended human therapeutic levels, respectively, based on body surface area *(*see *Data)*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

Animal reproduction studies with somatropin during the period of organogenesis at doses of 0.3, 1, and 3.3 mg/kg/day administered subcutaneously in pregnant rats and 0.08, 0.3, and 1.3 mg/kg/day administered intramuscularly in pregnant rabbits were not teratogenic (highest doses approximately 24 times and 19 times the recommended human therapeutic levels, respectively, based on body surface area).

In perinatal and postnatal studies in rats, doses of 0.3, 1, and 3.3 mg/kg/day somatropin 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 somatropin.

8.2 Lactation

Risk Summary

There is no information regarding the presence of somatropin in human milk. Limited published data indicate that exogenous somatropin does not increase normal breastmilk concentrations of growth hormone. No adverse effects related to somatropin in the breastfed infant have been reported. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for OMNITROPE and any potential adverse effects on the breastfed infant from OMNITROPE or from the underlying maternal condition.

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

Somatropin is a human growth hormone (GH) produced by recombinant DNA technology using Escherichia coli. The protein is comprised of 191 amino acid residues and a molecular weight of approximately 22,125 daltons. The amino acid sequence is identical to that of human GH of pituitary origin.

OMNITROPE (somatropin) injection is a clear, colorless, sterile solution for subcutaneous injection supplied in a cartridge for use with OMNITROPE Pen delivery system. Sodium hydroxide and/or phosphoric acid may be added during manufacture to adjust pH.

OMNITROPE (somatropin) for injection is a white to off-white lyophilized powder supplied in a vial for subcutaneous injection after reconstitution. Sodium hydroxide and/or hydrochloric acid may be added during manufacture to adjust pH. Vials are co-packaged with accompanying 1.14 mL vials of a diluent containing Bacteriostatic Water for Injection with 1.5% benzyl alcohol as a preservative. After reconstitution, the concentration is 5 mg/mL.

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
Dibasic sodium phosphate	0.609 mg	0.71 mg	0.996 mg
Monobasic sodium phosphate	1.28 mg	1.2 mg	0.52 mg
Poloxamer	3 mg	3 mg	-
Mannitol	52.5 mg	-	-
Glycine	-	27.75 mg	27.6 mg
Benzyl alcohol	13.5 mg	-	-
Phenol	-	4.5 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.

12.6 Immunogenicity

The observed incidence of anti-drug antibodies is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies in the studies described below with the incidence of anti-drug antibodies in other studies, including those of OMNITROPE or other somatropins.

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.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity, mutagenicity, and fertility studies have not been conducted with OMNITROPE.

In rats receiving subcutaneous somatropin 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.

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 lyophilized powder was compared with placebo in six randomized clinical trials involving a total of 172 adult GHD patients. These trials included a 6-month double-blind treatment period, during which 85 patients received this other somatropin and 87 patients received placebo, followed by an open-label treatment period in which participating patients received this other somatropin 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

16.1 How Supplied

OMNITROPE (somatropin) injection is a clear, colorless, sterile solution for subcutaneous injection supplied in a cartridge for use with OMNITROPE Pen delivery system.

OMNITROPE (somatropin) for injection is a white to off-white lyophilized powder supplied in a vial for subcutaneous injection after reconstitution with co-packaged diluent.

Carton Contents	**Strength**	**NDC**
1 single-patient-use cartridge	5 mg/1.5 mL[a]	NDC 0781-3001-07

5 single-patient-use cartridges	5 mg/1.5 mL[a]	NDC 0781-3001-26
1 single-patient-use cartridge	10 mg/1.5 mL[b]	NDC 0781-3004-07
5 single-patient-use cartridges	10 mg/1.5 mL[b]	NDC 0781-3004-26
8 single-patient-use vials 8 single-dose vials of diluent (Bacteriostatic Water for Injection containing 1.5% benzyl alcohol as a preservative)	5.8 mg per vial	NDC 0781-4004-36

[a] For use only with the OMNITROPE Pen 5 delivery system, which is sold separately.
[b] For use only with the OMNITROPE Pen 10 delivery system, which is sold separately.

16.2 Storage and Handling

Before use, store OMNITROPE vials and cartridges refrigerated at 2° to 8°C (36° to 46°F) in the original carton to protect from light. Do not freeze.

After first use, the OMNITROPE cartridge should remain in the pen and kept the original carton in a refrigerator at 2° to 8°C (36° to 46°F) for a maximum of 28 days (see **Table 11**). Discard unused portions in the cartridge after 28 days.

After reconstitution of the lyophilized powder, the contents of the OMNITROPE vial must be used within 21 days. After the first injection, store the vial in the original carton in a refrigerator at 2° to 8°C (36° to 46°F) (see **Table 11**). Discard unused portions after 21 days.

Table 11. Storage Options

OMNITROPE Product Formulation	**Storage Requirement**	
	Before Use	**In-use (after 1st injection)**
5 mg/1.5 mL cartridge	Refrigerate at 2° to 8°C (36° to 46°F) Until exp date	Refrigerate at 2° to 8°C (36° to 46°F) **up to 28 days**
10 mg/1.5 mL cartridge		Refrigerate at 2° to 8°C (36° to 46°F) **up to 28 days**
5.8 mg per vial	Refrigerate at 2° to 8°C (36° to 46°F) Until exp date	Refrigerate at 2° to 8°C (36° to 46°F) **up to 21 days**

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. 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.

Manufactured by:

Sandoz Inc., Princeton, NJ 08540

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