CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 021426/S-008

Trade Name: **OMNITROPE**

Generic Name: Somatropin Recombinant

Sponsor: Sandoz Inc.

Approval Date: 04/23/2010

Indications: OMNITROPE ® is a recombinant human growth hormone indicated for:

- Adult: Treatment of adults with either adult onset or childhood onset GHD
- Pediatric: Treatment of children with growth failure due to growth hormone deficiency (GHD), Prader-Willi Syndrome, Small for Gestational Age

CENTER FOR DRUG EVALUATION AND RESEARCH

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021426/S-008

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021426/S-007 & S-008 **SUPPLEMENT APPROVAL**

Sandoz Inc.
Attention: John Pakulski, R.Ph.
Director - Specialty Biologics, Regulatory Affairs
506 Carnegie Center, Suite 400
Princeton, NJ 08540

Dear Mr. Pakulski:

Please refer to your supplemental new drug applications dated November 24, 2008, received June 23, 2009, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Omnitrope (somatropin [rDNA origin] injection), 1.5 mg/vial and 5.8 mg/vial; and 5 mg/1.5 mL and 10 mg/1.5 mL Cartridges.

We acknowledge receipt of your submissions dated June 26 and October 13, 2009, and March 17, and April 23(email), 2010.

These "Prior Approval" supplemental new drug applications provide for addition of the following new indications:
Supplement-007 to treat children with short stature who have Prader-Willi syndrome (PWS)
Supplement-008 to treat children with short stature who were born small for their gestational age (SGA).

We have completed our review of these supplemental applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling (text for the package insert and text for the patient instructions for use) and include any labeling changes proposed in pending "Changes Being Effected" (CBE) supplements. Information on submitting SPL files using eLIST may be found in the guidance for industry titled *SPL Standard for Content of Labeling Technical Qs and As* at

http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA that include labeling, including pending "Changes Being Effected" (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in *MS Word* format that includes the changes approved in these supplemental applications.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indications in pediatric patients unless this requirement is waived, deferred, or inapplicable.

This product is appropriately labeled for use in all relevant pediatric populations. Therefore, no additional pediatric studies are needed at this time.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instructions on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important safety related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration
5600 Fishers Lane, Room 12B05
Rockville, MD 20857

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Enid Galliers, Chief, Project Management Staff, at (301) 796-1211.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Content of Labeling:
Package Insert
Instructions for Use

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21426	SUPPL-8	SANDOZ INC	OMNITROPE(SOMATROPIN[RDNA ORIGIN] FORINJ
NDA-21426	SUPPL-7	SANDOZ INC	OMNITROPE(SOMATROPIN[RDNA ORIGIN] FORINJ

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARY H PARKS
04/23/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021426/S-008

LABELING

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----------
Indications and Usage (1.1)
Prader-Willi Syndrome
Small for Gestational Age
Dosage and Administration (2.1)
Prader-Willi Syndrome
Small for Gestational Age

----------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 (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 - 7 daily injections, (2.1)
- ***Prader-Willi Syndrome:*** 0.24 mg/kg/week, divided into 6 - 7 daily injections, (2.1)
- ***Small for Gestational Age:*** Up to 0.48 mg/kg/week, divided into 6 - 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 - 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 (15 IU) is a prefilled sterile solution in a glass cartridge ready to be administered with the Omnitrope® Pen 5. (3.1).
- OMNITROPE® Cartridge 10 mg/1.5 mL (30 IU) is a prefilled sterile solution in a glass cartridge ready to be administered with the Omnitrope® Pen 10. (3.1).
- OMNITROPE® for injection 1.5 mg/vial is supplied with two vials, one containing somatropin as a powder and the other vial containing the diluent (3.2).
- OMNITROPE® for injection 5.8 mg/vial is supplied with two vials, one containing somatropin as a powder and the other vial containing diluent (3.3).

----------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)
- Active Malignancy (4.3)
- Active Proliferative or Severe Non-Proliferative Diabetic Retinopathy (4.4)
- Children with closed epiphyses (4.5)
- Known hypersensitivity to somatropin or excipients (4.6)
- Formulations containing benzyl alcohol (5 mg/1.5 mL Omnitrope Cartridges and the Bacteriostatic Water for Injection diluent for the 5.8 mg/vial Omnitrope) should not be used in premature babies or neonates (4.7)

----------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).
- Hypo pituitarism: 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)

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

- Inhibition of 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).
- Glucocorticoid Replacement: 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**

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® [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** (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.

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 into 6 or 7 **daily 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), those who were born small for gestational age (SGA), 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, under nutrition, 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 - 0.24 mg/kg body weight/week, divided into 6 - 7 daily doses, is recommended.

Prader-Willi Syndrome (PWS)

Generally, a dosage of 0.24 mg/kg body weight/week, divided into 6 - 7 daily doses, is recommended.

Small for Gestational Age (SGA)

Generally, a dosage of up to 0.48 mg/kg body weight/week, divided into 6 - 7 daily doses, is recommended.

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 0.1-0.2 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 1.5 mg/vial and 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.
- 1.5 mg/vial is supplied with two vials, one containing somatropin as a powder and the other vial containing the diluent (Sterile Water for Injection).
- 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.

4.7 Benzyl Alcohol Sensitivity

Benzyl alcohol, a preservative in Omnitrope Cartridge 5 mg/1.5 mL and in Bacteriostatic Water for Injection, has been associated with toxicity in newborns.

Omnitrope® Cartridge 5 mg/1.5 mL and Omnitrope® for Injection 5.8 mg/vial must not be given to premature babies or neonates.

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

Patients with preexisting tumors or GHD secondary to an intracranial lesion should be monitored routinely for progression or recurrence of the underlying disease process. In pediatric patients, clinical literature has revealed no relationship between somatropin replacement therapy and central nervous system (CNS) tumor recurrence or new extracranial tumors. However, in childhood cancer survivors, an increased risk of a second neoplasm has been reported in patients treated with somatropin after their first neoplasm. Intracranial tumors, in particular meningiomas, in patients treated with radiation to the head for their first neoplasm, 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.

Patients should be monitored carefully for potential malignant transformation of skin lesions, i.e. increased growth of preexisting nevi.

5.4 Glucose Intolerance

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 during somatropin treatment. 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 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 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 an inherently increased risk of developing autoimmune thyroid disease and primary hypothyroidism 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 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. Scoliosis is 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 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.

5.12/13 Laboratory Tests

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

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** (5.5)]
- [b]Intracranial hypertension [see **WARNINGS AND PRECAUTIONS** (5.6)]
- [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)]
- [a]Fluid retention manifested by edema, arthralgia, myalgia, nerve compression syndromes including carpal tunnel syndrome/paraesthesias [see **WARNINGS AND PRECAUTIONS** (5.7)]
- [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.

As with all protein drugs, a small percentage of patients may develop antibodies to the protein. GH antibodies with binding capacities lower than 2 mg/L have not been associated with growth attenuation. In a very small number of patients, when binding capacity was greater than 2 mg/L, interference with the growth response was observed.

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 occurring 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 occurring 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 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

Adverse Event	**Double Blind Phase**		**Open Label Phase** *Another Somatropin Product*		
	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*	5.6	0	1.7
Arthralgia	4.2	17.3*	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*	6.7	1.6	3.3
Edema, peripheral	2.6	10.8*	3.0	0	0
Paresthesia	1.9	9.6*	2.2	3.2	0
Headache	7.7	9.9	6.2	0	0
Stiffness of extremities	1.6	7.9*	2.4	1.6	0
Fatigue	3.8	5.8	4.6	6.3	1.7
Myalgia	1.6	4.9*	2.0	4.8	6.7
Back pain	4.4	2.8	3.4	4.8	5.0

* Increased significantly when compared to placebo, $P \leq .025$: Fisher´s Exact Test (one-sided)

n = number of patients receiving treatment during the indicated period.

% = percentage of patients who reported the event during the indicated period.

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.

6.3 Post-Marketing Surveillance

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).

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.

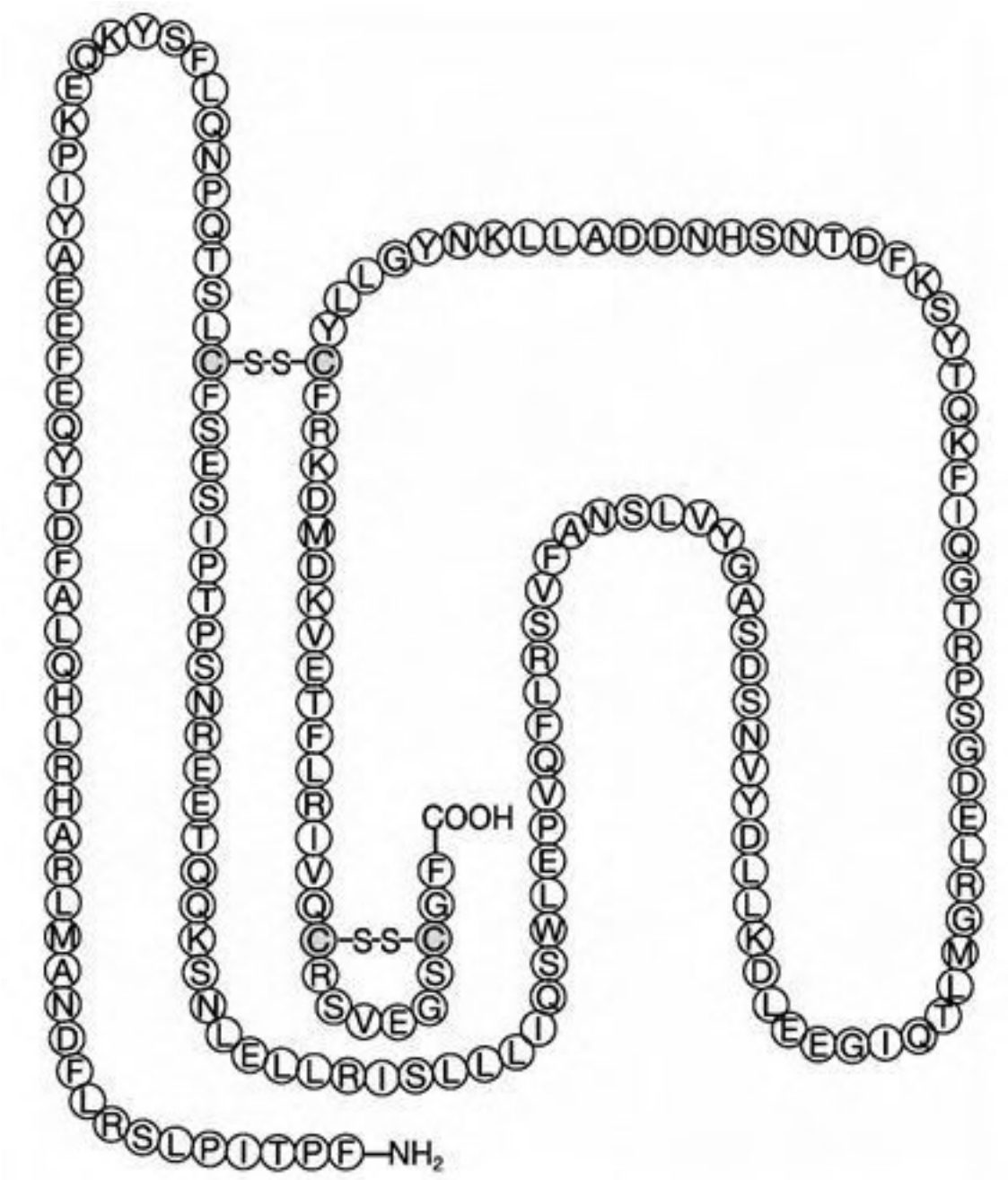

Figure 1. Schematic amino acid sequence of human growth hormone including the disulfide bonds

The bioidentity of the recombinant protein is measured by comparing its growth inducing effect with the growth inducing effect of a reference preparation calibrated in International Units.

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

Table 4

Product	Cartridge 5 mg/ 1.5 mL	Cartridge 10 mg/ 1.5 mL	For Injection 1.5 mg/ vial	For Injection 5.8 mg/ vial
Component				
Somatropin	5 mg	10 mg	1.5 mg	5.8 mg
Disodium hydrogen phosphate heptahydrate	1.3 mg	1.70 mg	0.88 mg	2.09 mg
Sodium dihydrogen phosphate dihydrate	1.6 mg	1.35 mg	0.21 mg	0.56 mg
Poloxamer 188	3.0 mg	3.0 mg	-	-
Mannitol	52.5 mg	-	-	-
Glycine	-	27.75 mg	27.6 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)			**Water for Injection**	**Bacteriostatic Water for Injection**
Water for injection			1.13 mL	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-I 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 **CLINICAL PHARMACOLOGY** (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 or were born SGA.

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-I, are polypeptide hormones which are synthesized in the liver, kidney, and various other

tissues. IGF-I 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 Cmax (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 **PREGNANCY** section 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[a]		
Pre-treatment	159 (92)	158 (43)
Month 9	291 (174)	302 (183)
Month 15	300 (225)	323 (189)
IGFBP-3[a]		
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)

a) 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 5). Linear growth continued to increase in the second year, when both groups received treatment with this other somatropin product.

Table 5

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* ± 2.3	5.0 ± 1.2	10.7* ± 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† ± 1.3	-1.9 ± 1.4	-1.4† ± 1.5	-2.2 ± 1.4

* $p \leq 0.001$

† $p \leq 0.002$ (when comparing SDS change at 12 months)

Changes in body composition were also observed in the patients receiving this other somatropin product (see Table 6). 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 6
Effect of Somatropin Product on Body Composition
in Pediatric Patients with Prader-Willi Syndrome (Mean ± SD)

	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[*] ± 2.2	2.3 ± 2.4
Baseline	15.6 ± 5.7	14.3 ± 4.0
Change from months 0 to 12	4.7[*] ± 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[*] ± 1.4	-0.1 ± 0.6
Body weight (kg)[†] Baseline	27.2 ± 12.0	23.2 ± 7.0
Change from months 0 to 12	3.7[‡] ± 2.0	3.5 ± 1.9

[*] $p < 0.005$

[†] n=15 for the group receiving another somatropin product; n=12 for the Control group

[‡] 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 7). 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 7
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[*] ± 0.5	1.7[*†] ± 0.6	0.1 ± 0.3

[*] p = 0.0001 vs Untreated Control group
[†] p = 0.0001 vs group treated with another somatropin product 0.24 mg/kg/week

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 (15 IU) is supplied in the following package sizes:

- One cartridge (NDC 0781-3001-07)
- Five cartridges (NDC 0781-3001-26)
- Ten cartridges (NDC 0781-3001-44).

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.

16.2 OMNITROPE® Cartridge 10 mg/1.5 mL

Omnitrope® Cartridge (somatropin-[rDNA origin]) 10 mg/1.5 mL (30 IU) is supplied in the following package sizes:

- One cartridge (NDC 0781-3004-07)
- Five cartridges (NDC 0781-3004-26)
- Ten cartridges (NDC 0781-3004-44).

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.

16.3 OMNITROPE® (somatropin [rDNA origin]) for injection 1.5 mg/vial

After reconstitution, the concentration is 1.33 mg/mL (approximately 4 IU/mL).

Carton contains 1 vial of Omnitrope® 1.5 mg and 1 vial of diluent (Sterile Water for Injection).

NDC 0781-4002-32

Omnitrope® 1.5 mg is supplied with a diluent without preservative.

After reconstitution, the vial may be stored under refrigeration for up to 24 hours.

Use once and discard any remaining solution.

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

After reconstitution, the concentration is 5 mg/mL (approximately 15 IU/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)

Table 8. 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
1.5 mg/vial		2-8 ºC/36-46 ºF 24 hours
5.8 mg/vial		2-8 ºC/36-46 ºF 3 weeks

17. PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling.

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. This information is intended to aid in the safe and effective administration of the medication.

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 1.5 mg/vial or 5.8 mg/vial.

Omnitrope® is a trademark of Novartis.

06-2009

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

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

4. 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.

5. This device **must not be shared with other patients.** However, if you are giving an injection to another person, be careful when removing the pen needle. Accidental pen needle sticks can transmit infections.

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

DON’Ts

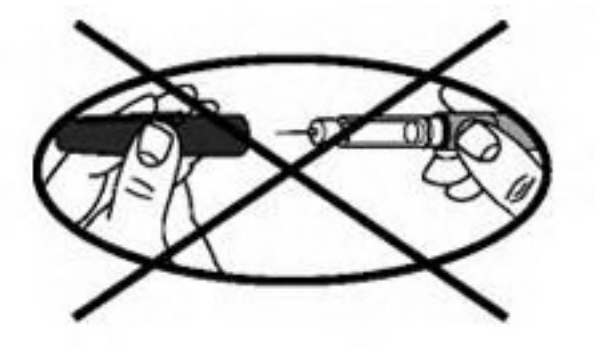
1. Do not share the Omnitrope® Pen 5. It is made for only one person to use.

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.

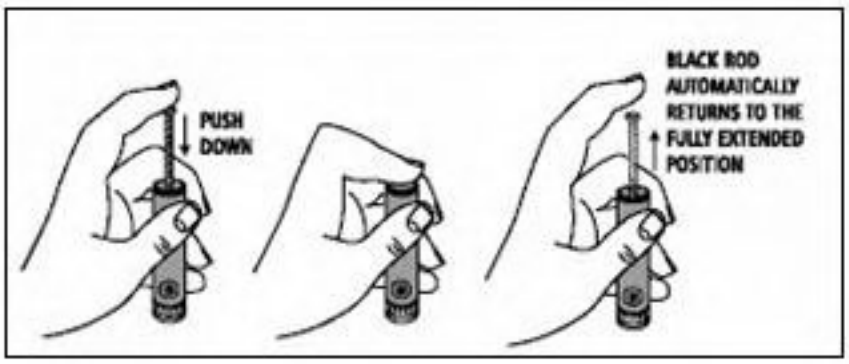
PEN PARTS

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.

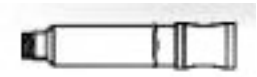
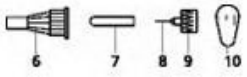
How it works

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

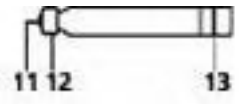


Notice that the black rod moves into the pen easily and returns to the fully extended position automatically. This automatic extension of the black rod positions it correctly against the cartridge plunger.

PEN PARTS

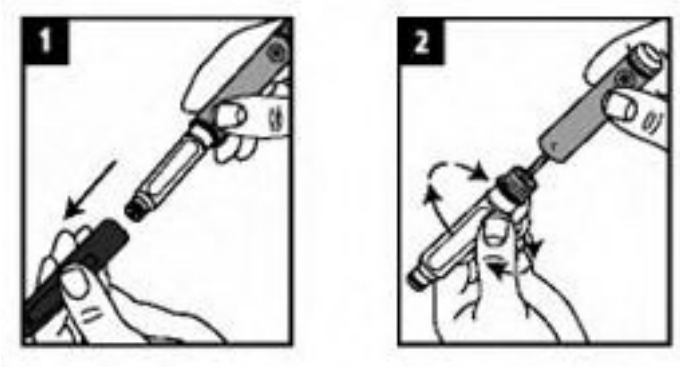
	**PEN CAP** 1. Clip
	**CARTRIDGE HOLDER**
	**PEN BODY** 2. Black rod 3. Dose window with arrow indicator 4. White dose knob 5. Red injection button
	**PEN NEEDLE UNIT** 6. Outer pen needle shield 7. Inner pen needle shield 8. Pen needle 9. Hub 10. Paper tab

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

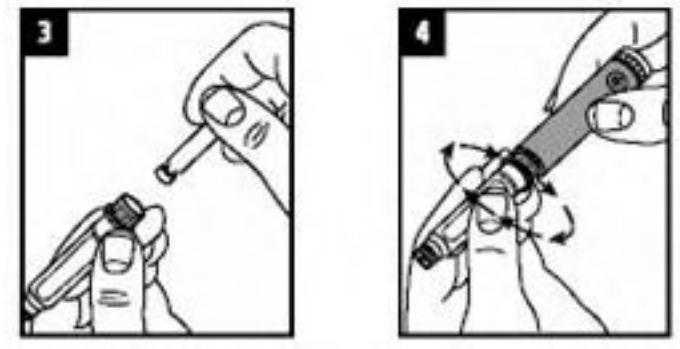
	**CARTRIDGE** 11. Rubber septum 12. Metal Cap 13. Cartridge plunger

HOW TO USE YOUR OMNITROPE® PEN 5

LOADING THE CARTRIDGE INTO THE PEN



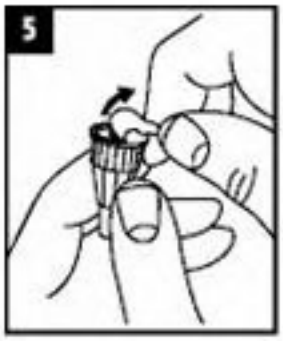
1. Remove the pen cap by pulling it off the pen.
2. Unscrew the cartridge holder from the pen body

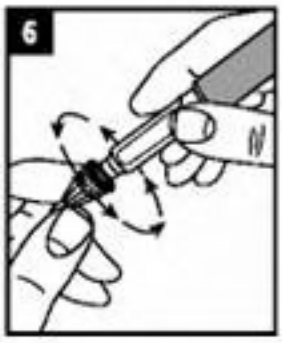


3. Insert the cartridge, metal cap first, into the cartridge holder
4. Lower the pen body onto the cartridge holder so that the black rod presses against the cartridge plunger. Screw the cartridge holder onto the pen body until no gap remains. One of the blue arrows must line-up with the yellow line 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.

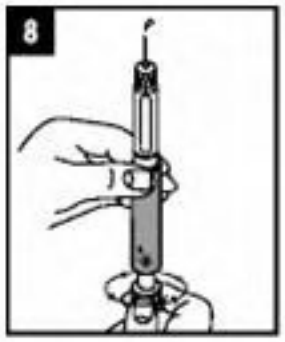
6a. Holding the cartridge holder, push the pen needle unit onto the pen. Then screw the threaded hub of the pen needle onto the cartridge holder as shown.

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.

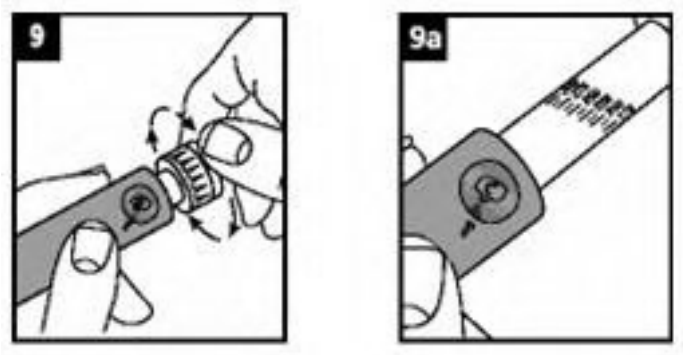
If at least 2 drops do not flow out, set the dose to 0.05 mg and repeat the steps until at least 2 drops of medicine appear at the tip of the pen needle.

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

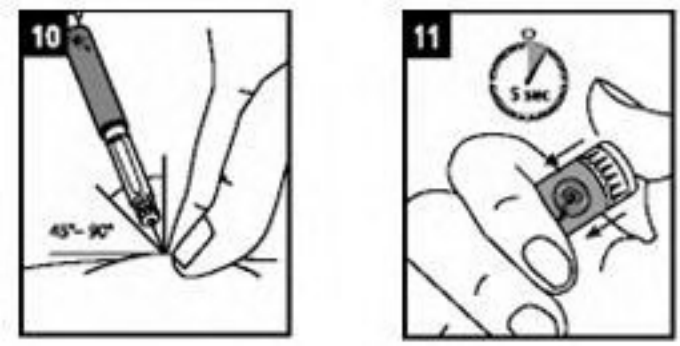
If you turn the dose knob past your dose, **do not dial backwards.**

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.



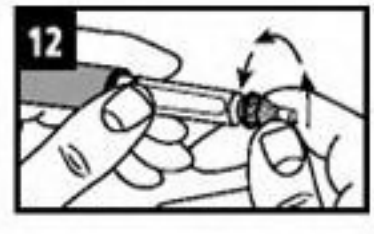
11. After inserting the pen needle, push the injection button in as far in as it will go and press firmly. A clicking sound will be heard while your dose is injecting. Continue to press firmly for at least 5 seconds, before you remove the pen needle from the skin.

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).

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:

SERVICE MATERIALS*

POUCH to store and protect your pen and other components, such as needles

REFRIGERATOR STORAGE BOX to protect the drug from odors and accidental spills

COOLBAG to help maintain Omnitrope® at refrigerator temperature when traveling
*Optional; please check availability with your local Sandoz representative
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

1. Read the following instructions before using the Omnitrope® Pen 10. Ask your healthcare professional if there is something you do not understand.

2. The Omnitrope® Pen 10 is a pen injector. It is for use with Omnitrope® cartridges 10 mg/1.5 mL (30 IU) 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. After taking a cartridge out of the refrigerator, allow it to reach room temperature (about 30 minutes) before injecting the medicine.

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

4. 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.

5. This device **must not be shared with other patients.** However, if you are giving an injection to another person, be careful when removing the pen needle. Accidental pen needle sticks can transmit infections.

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

DON’Ts

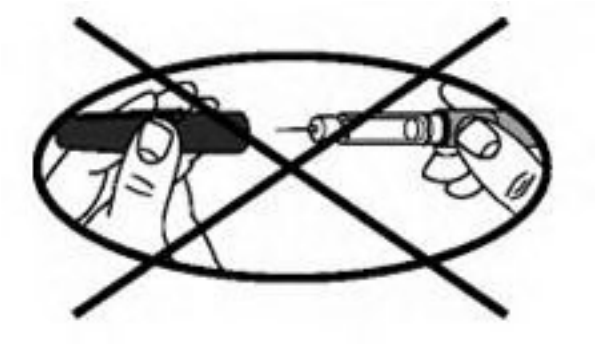
1. Do not share the Omnitrope® Pen 10. It is made for only one person to use.

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.

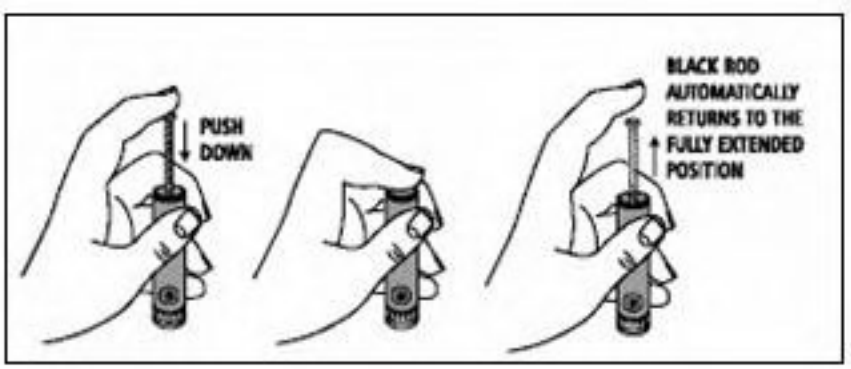
PEN PARTS

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.

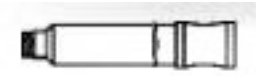
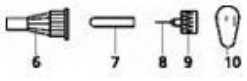
How it works

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

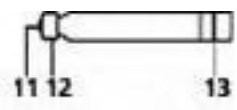


Notice that the black rod moves into the pen easily and returns to the fully extended position automatically. This automatic extension of the black rod positions it correctly against the cartridge plunger.

PEN PARTS

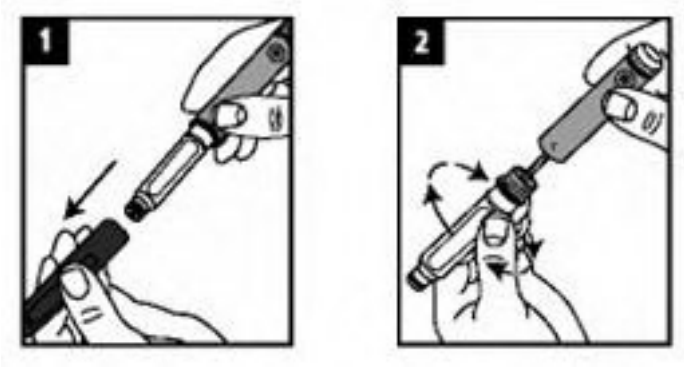
	**PEN CAP** 1. Clip
	**CARTRIDGE HOLDER**
	**PEN BODY** 2. Black rod 3. Dose window with arrow indicator 4. White dose knob 5. Red injection button
	**PEN NEEDLE UNIT** 6. Outer pen needle shield 7. Inner pen needle shield 8. Pen needle 9. Hub 10. Paper tab

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

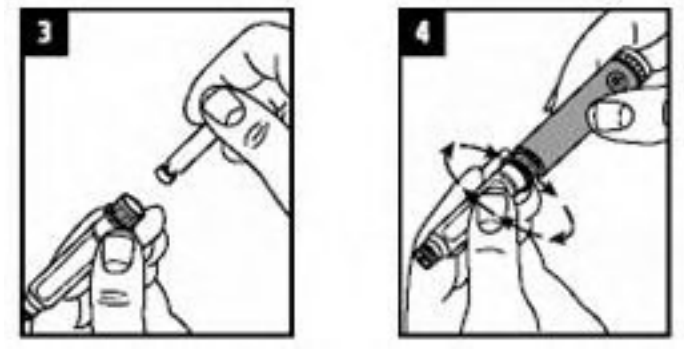
	**CARTRIDGE** 11. Rubber septum 12. Metal Cap 13. Cartridge plunger

HOW TO USE YOUR OMNITROPE® PEN 10

LOADING THE CARTRIDGE INTO THE PEN



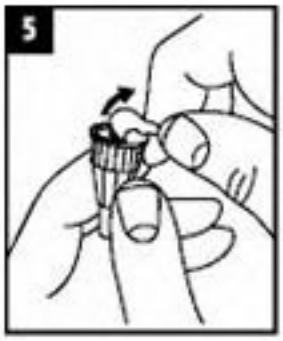
1. Remove the pen cap by pulling it off the pen.
2. Unscrew the cartridge holder from the pen body

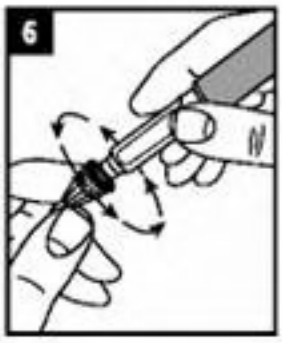


3. Insert the cartridge, metal cap first, into the cartridge holder
4. Lower the pen body onto the cartridge holder so that the black rod presses against the cartridge plunger. Screw the cartridge holder onto the pen body until no gap remains. One of the blue arrows must line-up with the white line mark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

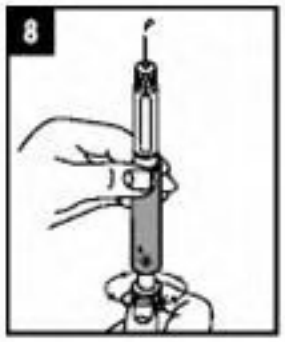
6a. Holding the cartridge holder, push the pen needle unit onto the pen. Then screw the threaded hub of the pen needle onto the cartridge holder as shown.

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.

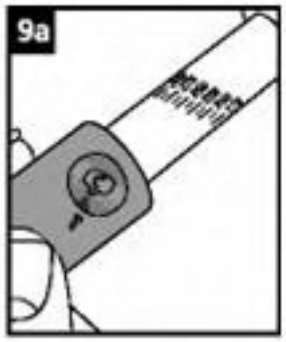
If at least 2 drops do not flow out, set the dose to 0.1 mg and repeat the steps until at least 2 drops of medicine appear at the tip of the pen needle.

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

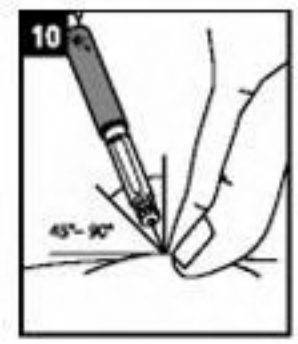
If you turn the dose knob past your dose, **do not dial backwards.**

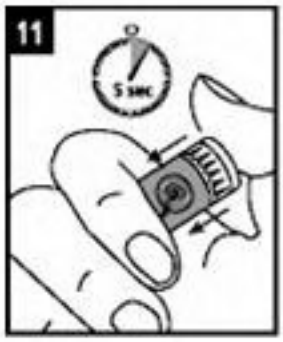
Hold the pen body and turn the dose knob until it is fully extended as shown in picture 9a. You will see a bent arrow () in the dose dialing window. The injection button can now be fully pressed, resetting the dial to "0" without giving medicine. The right dose can now be redialed as described in step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





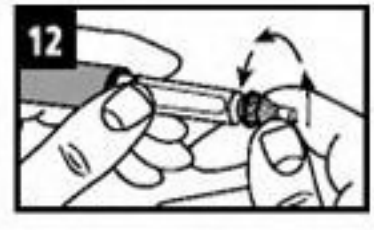
11. After inserting the pen needle, push the injection button in as far in as it will go and press firmly. A clicking sound will be heard while your dose is injecting. Continue to press firmly for at least 5 seconds, before you remove the pen needle from the skin.

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).

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:

SERVICE MATERIALS*

POUCH to store and protect your pen and other components, such as needles

REFRIGERATOR STORAGE BOX to protect the drug from odors and accidental spills

COOLBAG to help maintain Omnitrope® at refrigerator temperature when traveling
*Optional; please check availability with your local Sandoz representative
Omnitrope® is a trademark of Novartis.
BD and BD Logo are trademarks of Becton, Dickinson and Company.

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

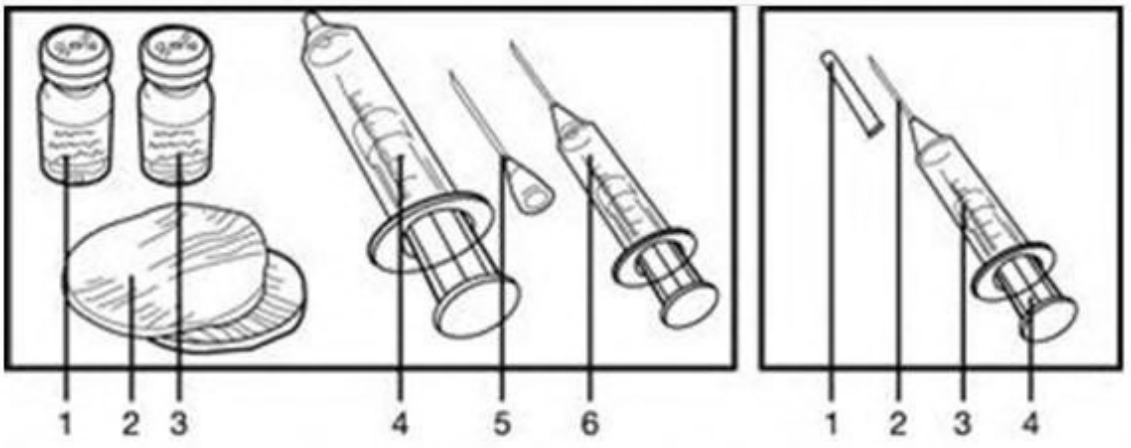
INSTRUCTIONS FOR OMNITROPE® 1.5 MG/VIAL

The following instructions explain how to inject OMNITROPE® 1.5 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® 1.5 mg is for single use.
- The concentration of OMNITROPE® after mixing is 1.3 mg/mL.

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

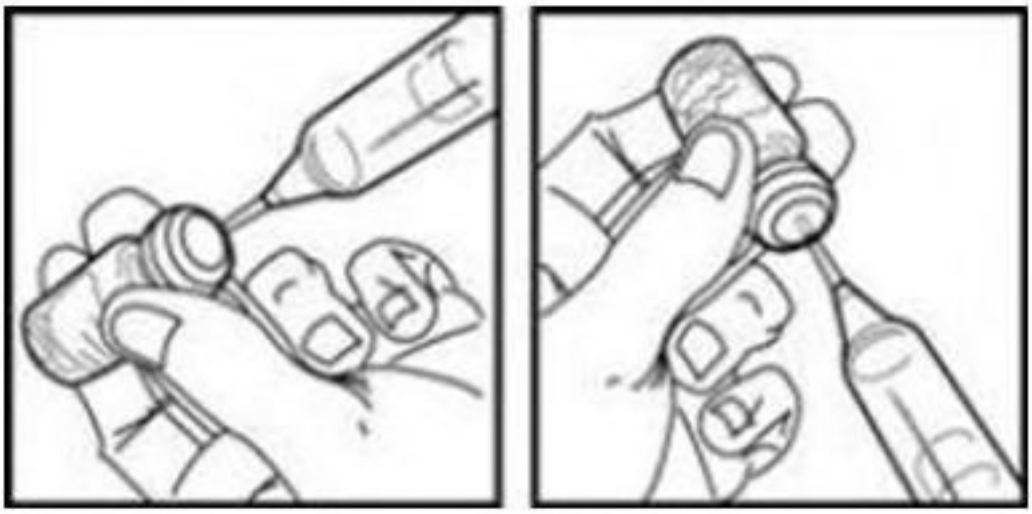
- a vial with OMNITROPE® 1.5 mg
- a vial with diluent (mixing liquid - Sterile Water for Injection) for OMNITROPE® 1.5 mg
- a sterile, disposable 3 mL syringe and needle for withdrawing the diluent from the vial (not supplied in the pack)
- sterile disposable 1 mL syringes and needles for under the skin (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® 1.5 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.

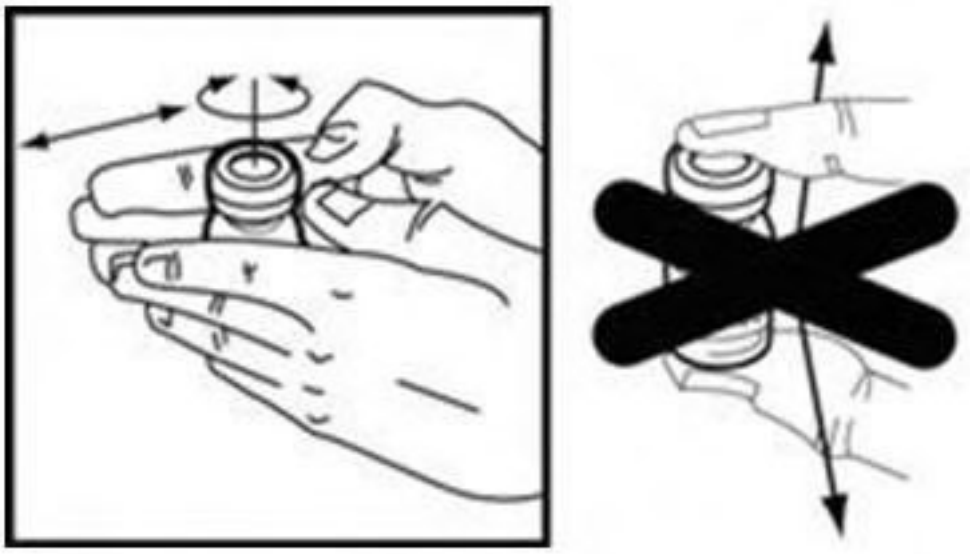
- Use next the sterile diluent vial, the disposal 3 mL syringe and a needle.
- Attach the needle to the syringe (if not attached already). Pull back the syringe plunger and fill the syringe with air. Push the needle fitted to the syringe through the rubber top of the diluent vial, push all the air from 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 use the solution immediately or at a maximum 24 hours after reconstitution.

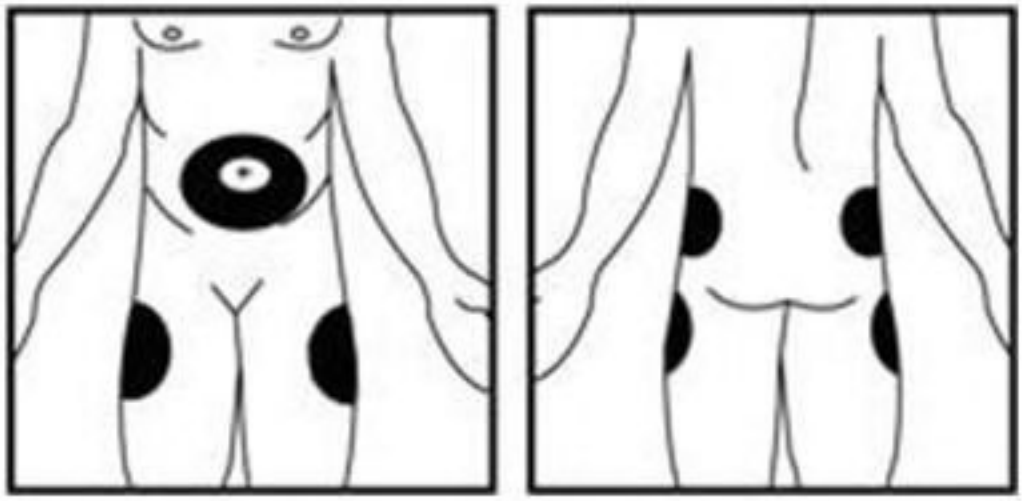
Measuring the Dose of OMNITROPE® 1.5 mg to Be Injected

- 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.

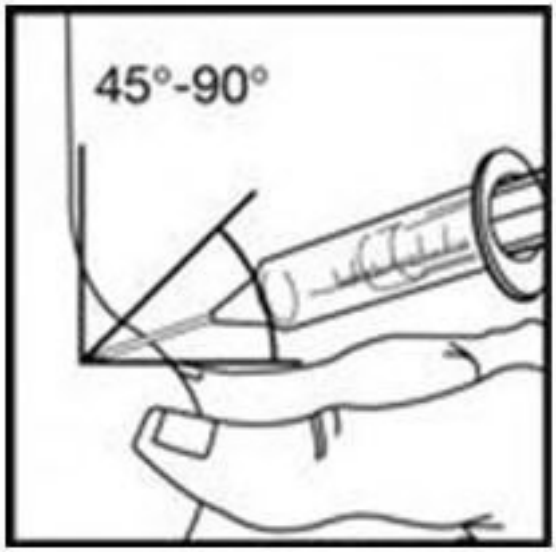
Injecting OMNITROPE® 1.5 mg

- 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® 1.5 mg

- Discard the vials and 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.

03-2009

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Manufactured in Austria by Sandoz GmbH

Distributed by Sandoz Inc., Princeton, NJ 08540

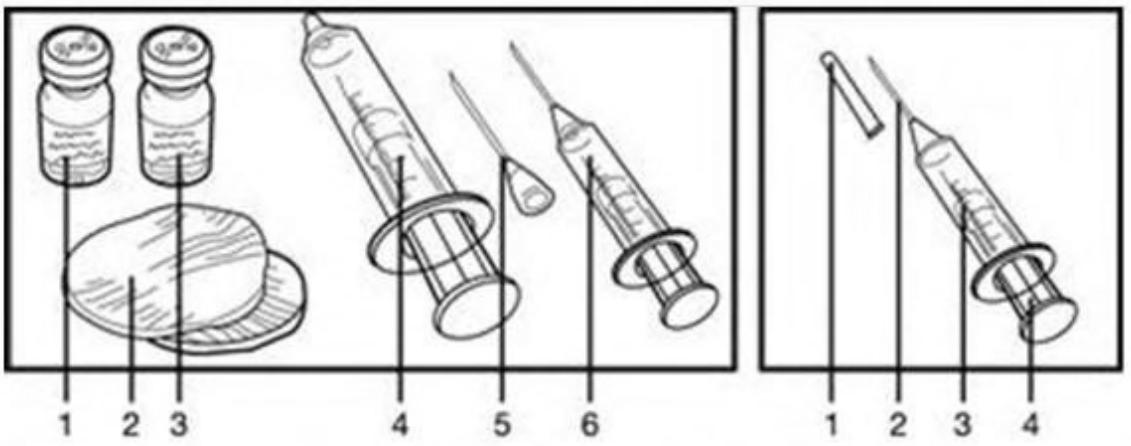
INSTRUCTIONS FOR OMNITROPE® 5.8 MG/VIAL

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

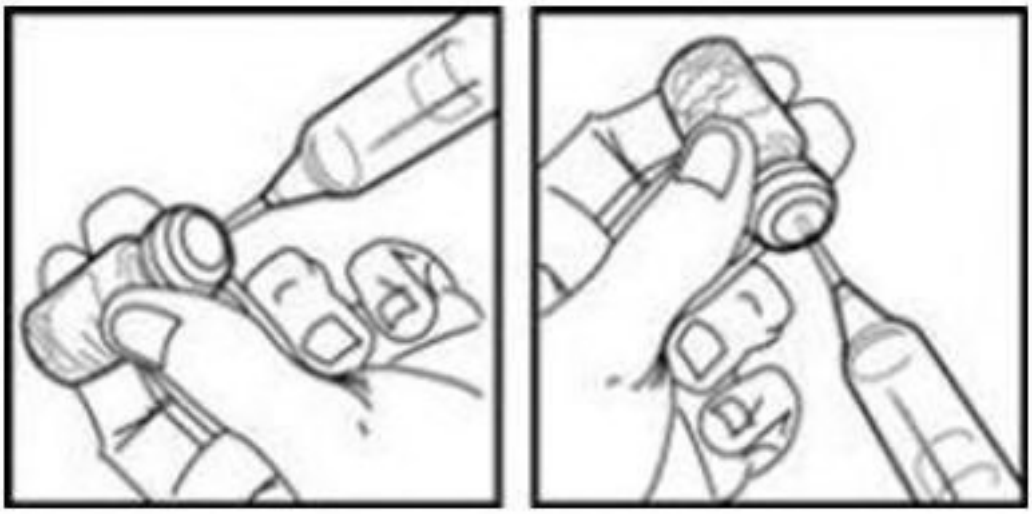
- a vial with OMNITROPE® 5.8 mg
- a vial with diluent (mixing liquid - Bacteriostatic Water for Injection containing benzyl alcohol as preservative) for OMNITROPE® 5.8 mg
- a sterile, disposable 3 mL syringe and needle for withdrawing the diluent from the vial (not supplied in the pack)
- sterile disposable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

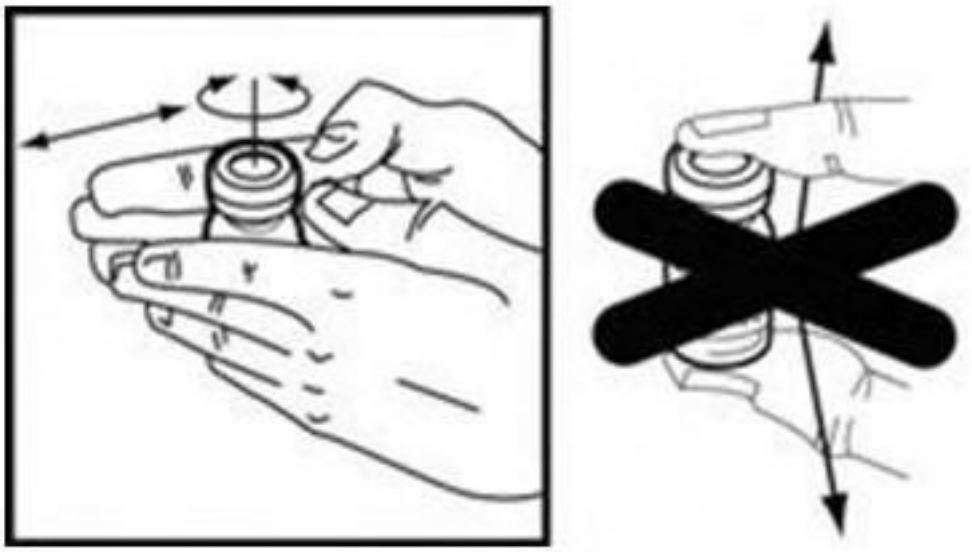
- Remove the protective caps from the two vials. With one alcohol swab, clean both the rubber top of the vial that contains the powder and the rubber top of the vial that contains diluent.

- 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.

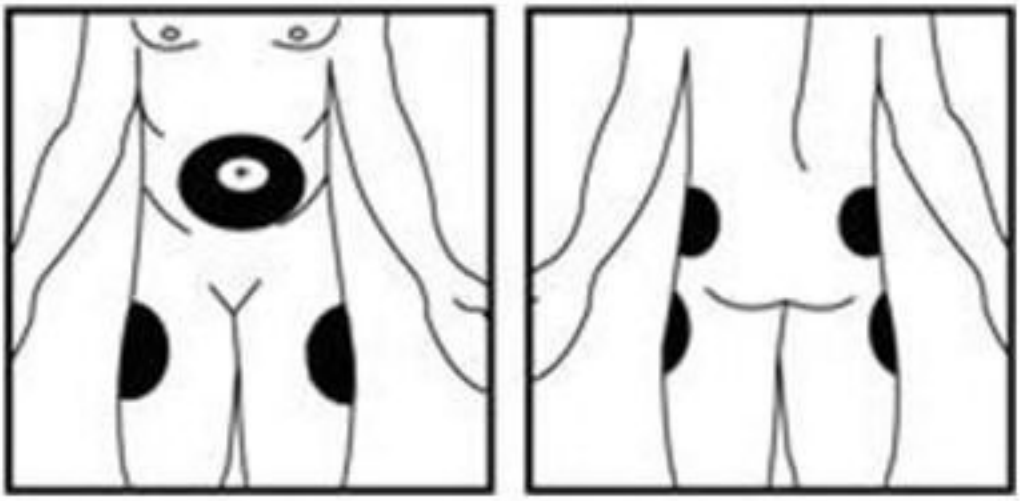
Measuring the Dose of OMNITROPE® 5.8 mg to Be Injected

- 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.

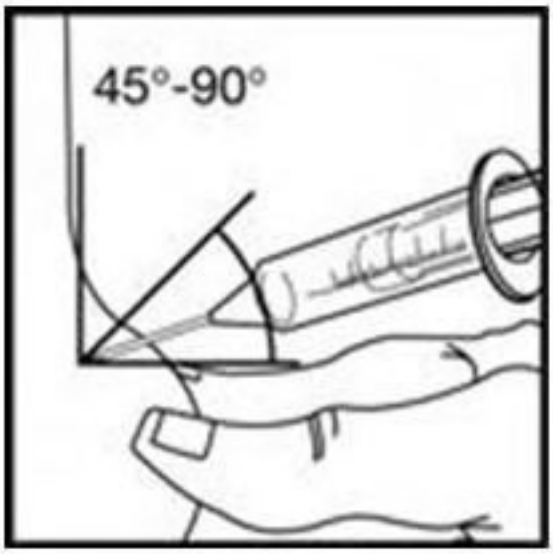
Injecting OMNITROPE® 5.8 mg

- 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.

Omnitrope® is a trademark of Novartis.

06-2009

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Manufactured in Austria by Sandoz GmbH

Distributed by Sandoz Inc., Princeton, NJ 08540

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021426/S-008

MEDICAL REVIEW(S)

Division Director's Memo

NDA	21-426 Supplement 007 and 008
Drug Product	Omnitrope® [somatropin (rDNA origin) injection
Sponsor	Sandoz Inc.
Proposed Indications	Treatment of short stature in children with Prader-Willi Syndrome (S007) Treatment of short stature in children born small for gestational age (SGA) (S008)
Date of Submission	June 26, 2009
PDUFA goal date	April 23, 2010

This memo serves as the Division's decisional memo for NDA 21-426, supplements 007 and 008, submitted to the FDA in accordance with section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (the Act) on June 26, 2009. Each of these supplements proposes a new indication for the use of Omnitrope (somatropin), a recombinant human growth hormone (rhGH). Supplement 007 is for the treatment of short stature in children with Prader-Willi Syndrome (PWS) and Supplement 008 is for the treatment of short stature in children born small for gestational age (SGA).

As a submission pursuant to section 505(b)(2) of the Act, the supplements contain full reports of investigations of safety and effectiveness, where at least some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use. In these particular supplements, the applicant (Sandoz) is relying upon the Agency's finding of safety and effectiveness for Pfizer's Genotropin (NDA 20-280), which was approved for PWS and SGA in 2000 and 2001, respectively, and published literature to support approval. The orphan drug exclusivity granted to Genotropin for both of these indications expired on June 20, 2007, and July 25, 2008, respectively.

As background, Omnitrope was approved for the treatment of pediatric and adult growth hormone (GH) deficiency on May 30, 2006. As Dr. Roman indicated in his review, somatropin (as distinguished from more complex protein products) is a well-characterized and well-understood recombinant DNA-derived protein product that has a long history of clinical use. The original 505(b)(2) application for Omnitrope contained data and information demonstrating that Omnitrope is highly similar to Genotropin physicochemically, pharmacokinetically, pharmacodynamically, biologically, and clinically. This "bridging" data warranted reliance on FDA's finding of safety and effectiveness for Genotropin for pediatric GH deficiency and adult GH deficiency to support the approval of Omnitrope. The 505(b)(2) application also contained independent evidence of the safety and effectiveness of Omnitrope for use in pediatric GH deficiency. Indeed, the original 505(b)(2) application for Omnitrope contained data that would otherwise fulfill the requirements for approval of a stand-alone NDA (a 505(b)(1) application) for a new rhGH for treatment of pediatric GH deficiency through submission of CMC, nonclinical

pharmacology and toxicology, clinical pharmacology, and clinical efficacy and safety data (including immunogenicity data) specific to Omnitrope.

The "bridging" data that supported reliance on the Agency's finding of safety and effectiveness for Genotropin included, among other things, a 15-month, comparative efficacy and safety trial between Omnitrope and Genotropin in pediatric patients with GH deficiency. Sandoz also provided a summary of published Genotropin studies in adults with GH deficiency. The clinical data comparing Omnitrope to Genotropin and other data supporting reliance on the Agency's finding of safety and effectiveness for Genotropin enabled the Agency to grant an indication for adult GH deficiency despite the absence of clinical trial data with Omnitrope in this patient population. The approval of this second indication for treatment of GH deficiency in adults is particularly relevant to Supplements 007 and 008. Sandoz was not required to conduct additional clinical studies with Omnitrope to seek approval for an indication for treatment of short stature in patients with PWS or born small for gestational age (SGA) based on: the clinical data submitted in the original 505(b)(2) application; the demonstration that Omnitrope was highly similar to Genotropin and thus could rely on the Agency's finding of safety and effectiveness for Genotropin in these indications; and the scientific justification for extrapolation of these data to the PWS and SGA indications based on a shared mechanism of action.

The Agency required Sandoz to provide the following:

- a summary of the clinical data obtained with the listed drug relied upon (Genotropin) in support of PWS and SGA indications;
- a scientific justification supporting the appropriateness of reliance on the Agency's finding of safety and/or effectiveness for Genotropin for the PWS and SGA indications to support approval of Omnitrope for these indications; and
- a summary of the relevant clinical trials involving somatropin conducted in the PWS and SGA populations and published to date. (The purpose of this recommendation is to provide context for the data obtained with the listed drug relied upon with respect to safety and effectiveness of somatropin in the non-GH-deficient short stature syndromes of PWS and SGA. This information would be considered supportive to the approval of the application.)

These data and information were submitted by the applicant and reviewed by Dr. Roman in his review dated February 24, 2010. Although Dr. Roman's review references the centrality of the mechanism of GH-GHR coupling for the therapeutic effects demonstrated by all growth hormone products used in clinical investigations and clinical practice to date, it is important to note that this review is limited to evaluation of the mechanism of action of Omnitrope and Genotropin in pediatric and adult GH deficiency and the non-GH-deficiency short stature indications of PWS and SGA, and extrapolation of data demonstrating the highly similar pharmacodynamic and therapeutic effects of Omnitrope and Genotropin in pediatric GH deficiency to these indications.

I concur with Dr. Roman's recommendation that these two supplements can be approved. The acceptance of the applicant's reliance on the Agency's finding of safety and effectiveness of Genotropin in these two specific indications (PWS and SGA) without requiring indication-specific clinical studies with Omnitrope is supported by the following considerations:

1. Recombinant human growth hormone's target/receptor is well-defined.

2. There is strong evidence that there are no additional molecular target/receptors by which rhGH may effect its physiologic activity on the efficacy endpoint of interest for these two indications.

With respect to Points 1 and 2, rhGH has the identical amino acid sequence as that of endogenous human growth hormone. The molecular structure of GH has been well-characterized and much

evidence has been provided that upon binding to the GH receptor, GH exerts many of its physiologic functions through the transcription of genes for a variety of proteins. Most notable of these proteins is insulin-like growth factor or IGF-1. Both GH and IGF-1 stimulate epiphyseal growth plates and the formation of new bone resulting in linear growth until fusion of the growth plates. It is this effect of GH and its mediator, IGF-1, which contributes to the efficacy endpoint of interest for PWS and SGA: linear growth as measured by height velocity and predicted final height.

As summarized above, the original application for Omnitrope has already provided sufficient scientific evidence that this rhGH binds to the GH receptor, has highly similar PK and PD characteristics to Genotropin, and most importantly through its own clinical data, can increase linear growth in GHD pediatric patients as assessed with the same efficacy endpoints of interest in PWS and SGA.

As noted by Dr. Roman, patients with PWS and SGA do not meet the current definition for pediatric GH deficiency. However, GHD and non-GH deficient short stature syndrome share a common clinical feature of growth failure that is responsive to exogenous GH therapy. However, the latter conditions require higher doses (pharmacologic dosing) to exert the desirable effect on linear growth.

3. The interaction between rhGH and its receptor is well-understood with a well-defined and consistent dose-response with respect to the efficacy endpoint of interest for these two indications.

The applicant provided data from several published studies describing the effect of Genotropin on improving linear growth in patients with PWS and SGA. These studies have been summarized in Dr. Roman's review. A consistent effect of Genotropin on improving height velocity was observed across a range of doses with some studies which evaluated more than one dosing regimen supporting a dose-response for the efficacy endpoint of interest.

4. The interaction between rhGH with the known target/receptor and its efficacy/dose-response are not impacted by minor structural differences

This has already been established in the original application for Omnitrope which contained sufficient evidence that, despite differences in manufacturing of this rhGH and Genotropin, both products achieve similar IGF-1 serum concentrations and both increase height velocity. Furthermore, there was no evidence that these minor structural differences resulted in different toxicities, including immunogenicity profile. As PWS and SGA are not growth hormone deficiency states, it is unlikely these patients will have a different immunogenic response to what has already been observed with Omnitrope in clinical trials of pediatric GH deficiency.

It should also be noted that there are currently 9 sponsors of several approved rhGH product lines which have different manufacturing processes using different host cell systems with resulting structural differences across these products. Seven of these products have been approved for a variety of non-GH deficient short stature syndromes and all such development programs have demonstrated an ability to improve height velocity in pediatric patients with growth failure. While it should be emphasized that the FDA is <u>not relying upon</u> the other products for approval of these two supplements, it provides reassuring supportive evidence that minor structural differences in the currently available immediate-release rhGH products have not resulted in lack of efficacy (or novel safety concerns) across several different non-GH deficient short stature syndromes.

5. Disease models or clinical data are available to support the reliance on the mechanism of action of rhGH at the target/receptor for these two different indications.

Much of our knowledge of GH and rhGH function comes from clinical disease states of GH deficiency (pediatric and adult GH deficiency) and GH excess (acromegaly). This has already been addressed in the original 505(b)(2) application for Omnitrope. This knowledge is applicable to the PWS and SGA indications with respect to efficacy (effect on linear growth) and safety (excess dosing results in predictable side effects).

In conclusion, the applicant has provided extensive scientific evidence from its own clinical development program to demonstrate that Omnitrope is highly similar to Genotropin with similar effect on the linear growth in pediatric patients with GHD. In addition, the applicant has provided scientific evidence on the mechanism of action of growth hormone to support the conclusion that a rhGH that has been demonstrated to be highly similar to Genotropin can also, through its binding to the GH receptor, be an effective treatment of short stature in patients with Prader-Willi Syndrome or patients who were born small for gestational age.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21426	SUPPL-8	SANDOZ INC	OMNITROPE(SOMATROPIN[RDNA ORIGIN] FORINJ

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARY H PARKS
04/23/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: February 24, 2010

FROM: Dragos Roman, MD, Division of Metabolism and Endocrinology Products

THROUGH: Mary Parks, MD, Director, Division of Metabolism and Endocrinology Products

TO: File (NDA 21-426)

SUBJECT: Omnitrope Supplement 007 for new indication: treatment of short stature in children with Prader Willi Syndrome.
Omnitrope Supplement 008 for new indication: treatment of short stature in children born small for gestational age.

I. Background

Omnitrope (somatropin) is a recombinant human growth hormone manufactured by Sandoz Inc. The original Omnitrope NDA (21-426) was approved on May 30, 2006 under Section 505(b)(2) of the Food, Drugs, and Cosmetics Act for the indications of pediatric and adult growth hormone (GH) deficiency. This initial Omnitrope approval was for two lyophilized formulations (5.8-mg multiple dose and 1.5-mg single dose). Two liquid Omnitrope formulations were subsequently approved on the basis of demonstrated bioequivalence to lyophilized Omnitrope; approval letters were issued for an Omnitrope cartridge of 5 mg/1.5 ml to be used with a reusable injector pen (Omnitrope Pen 5) on January 16, 2008, and for a cartridge of 10 mg/1.5 mL to be used with a reusable injector pen (Omnitrope Pen 10) on August 25, 2008, respectively. Both liquid Omnitrope formulations were approved, as the original NDA, under Section 505(b)(2) of the Food, Drugs, and Cosmetics (FD&C) Act. The listed drug relied upon for all the above mentioned Omnitrope applications is Pfizer's version of recombinant human GH: Genotropin.

On June 26,2009, Sandoz submitted two new efficacy supplements under Section 505(b)(2) of the FD&C Act for two new indications: treatment of short stature associated with Prader-Willi Syndrome (Supplement 07) and treatment of growth failure in children born small for gestational age (SGA) who do not show catch up growth by 2 years of age (Supplement 08). As in the case of the pediatric and adult GH deficiency indications, these two supplements are relying on the Agency's finding of safety and effectiveness of Pfizer's Genotropin in patients with Prader-Willi Syndrome (PWS) or SGA. In support of the PWS and SGA indications Sandoz has submitted the following:
1) A "mode of action" document that summarizes the current understanding of the molecular structure and mechanism of action of GH, as well as its therapeutic role for the approved indications (pediatric and adult growth hormone deficiency) and for the two indications for which Sandoz is seeking approval (PWS and SGA).
2) A summary of clinical studies conducted with Genotropin in children with PWS and published in peer review journals.
3) A summary of clinical studies conducted with Genotropin in SGA children and published in peer review journals.
4) Updated labels which includes two new indications: PWS and SGA.

Because there is considerable overlap between the content of the PWS and SGA submissions, and given the fact that the basis for regulatory approval is shared by both applications, this review will address jointly Supplements 007 and 008.

II. Reviewer's Comments

Applicant's "mode of action" document provides an extensive and well referenced review of GH physiology and details GH's therapeutic benefit in the treatment of growth hormone deficiency (GHD), PWS and SGA. Of particular relevance is the description of the molecular interaction between the GH molecule and the GH receptor, which is the very scientific foundation that justifies the use of somatropin for the treatment of pediatric and adult GHD in particular, and short stature in general.

Judged in the context of currently approved protein drug products, GH is a relatively simple molecule. It consists of a single-chain, unglycosylated, 191 amino acid polypeptide that contains two intramolecular disulfide bonds. The tertiary structure of the GH molecule has been elucidated and consists of 4 α-helices organized in an anti-parallel configuration. The structure-function relationship of the various domains in the GH molecule has been extensively studied and largely elucidated following a wide range of investigations that included X-ray crystallography, in vitro mutagenesis, mutational analysis of the GH molecule in patients with GHD phenotype, and studies of mutated GH molecule in relevant experimental systems. Many of these studies were conducted in the 1980s and 1990s after the GH molecule underwent molecular cloning. The body of knowledge accumulated following these extensive investigations is now part of the scientific canon that is being propagated via textbooks and standard reviews. It is noteworthy that primary structure analyses and mutagenesis studies did not identify any functional domains in the GH molecule other than those related to its binding to the GH receptor (as expected, the GH molecule has also structural features in common with other secretory proteins which allows it to be appropriately processed intracellularly and subsequently released in circulation). Thus, it can be stated with a high degree of certainty that, once secreted by the pituitary somatotroph, human GH has no other fundamental role than that of binding to the GH receptor (GHR). The wide range of biological effects assigned to date to GH (anabolic, lipolytic, immune modulator, etc.) is achieved via tissue specific subsets of responses that follow the same fundamental mechanism of GH-GHR coupling (GH receptors are ubiquitously expressed albeit at different levels in various tissues)[1].

One needs to acknowledge the fact that the centrality of GH-GHR coupling does not apply only to the functions of the endogenous GH but also to the therapeutic effects demonstrated by all the GH products that have been used in clinical investigations and clinical practice to date. Specifically, all purified pituitary GH products (no longer marketed), somatrems (methionyl-GH), or somatropins (native GH sequence) exert their beneficial therapeutic activities via coupling with the GHR. Both Genotropin and Omnitrope contain somatropin as active pharmaceutical ingredient. Somatropin, which incorporates the entire GH sequence of the 22kd endogenous GH molecule (endogenous GH has also a 20 kd major variant that has not been targeted for therapeutic interventions), was engineered with the specific purpose of reproducing the functions of the human GH. Omnitrope and Genotropin have been shown to generate the same pharmacodynamic and therapeutic effects that are to be expected from any active GH molecule capable of GH receptor activation.

The initial Omnitrope approval was for both the pediatric and adult GHD indications. The approval of the adult indication was based on a scientific and regulatory "bridge" that allowed the Omnitrope application to rely on the previous findings of safety and efficacy demonstrated by Genotropin for the adult GHD indication. This bridge included, among others, a summary of clinical studies conducted with Genotropin in adult GHD patients published in peer reviewed journals, as well as a recognition of the fact that adult and pediatric GHD share several important features in common. First and foremost, because in both

[1] The GH molecule has two binding domains. Once one GH binding domain recognizes the corresponding configuration on the GHR, the second binding domain becomes capable of binding a second GHR molecule, thus inducing GH receptor dimerization. Formation of a 1:2 GH:GHR complex triggers the association and activation of Janus Kinase 2 (JAK 2). JAK 2 is responsible of the subsequent activation of various groups of molecules involved in intracellular signal transduction such as mitogen activated protein (MAP) kinase, insulin receptor substrate (IRS), signal transducers, activators of transcription (STAT), etc. Among the genes that become activated in the wake of the above described sequence of events is IGF-1, the main effector molecule for GH's anabolic activity.

conditions exogenous somatropin treatment aims at mimicking the function of the absent or inadequate endogenous GH secretion, somatropin treatment is in fact replacement therapy. Furthermore, these two indications have another element in common in that some of the adult GHD patients are former pediatric patients who continue to exhibit manifestations of GH deficiency into adulthood.

PWS and SGA are not traditional GHD deficiency states. Although arguments have been proposed that endogenous GH secretion is not entirely normal in these two conditions, none of them meets the currently accepted definition of pediatric GH deficiency: failure to raise GH over 7-10 ng/ml following the administration of two validated GH stimulation tests. Thus, somatropin treatment in PWS and SGA patients is not currently viewed as replacement therapy but rather as pharmacological intervention. Despite the above-highlighted differences between short stature due to GH deficiency and the non-GHD short stature of PWS and SGA, it is important to recognize that the approval of Genotropin for the PWS and SGA indications was based, as for all other short stature indications, on the ability of this particular somatropin to increase height velocity, reduce growth deficit and even normalize linear growth. All these effects that Genotropin has demonstrated in the past are due to its binding and stimulation of the GH receptor and not to an alternative disease- or syndrome-specific mechanism. Thus, it is the opinion of this reviewer that the reliance of Omnitrope on the findings of efficacy and safety of Genotropin does not apply only to the adult GHD indication but also to the non-GHD short stature indications of Prader Willi Syndrome and SGA. As argued above, it is the somatropin-GH receptor interaction that constitutes the scientific underpinning and the true therapeutic common denominator for all pediatric short stature indications, including Prader Willi Syndrome and SGA.

A summary of the results of the Genotropin studies conducted in patients with Prader Willi syndrome and published in peer-reviewed journals can be found in Appendix B. A similar summary for the Genotropin studies conducted in SGA patients is in Appendix C. The recommended changes to the proposed Omnitrope label are attached in Appendix C.

III. Recommendation:
Omnitrope should be approved for the treatment of short stature associated with Prader Willi Syndrome and short stature in children born small for gestational age who do not display catch up growth by 2 years of age.

Appendix A.

Summary of published Genotropin studies in Pradder Willi Syndrome

Lindgren et al 1998, Lindgren and Ritzen 1999 & Lindgren and Lindberg 2008
These three publications describe the same study cohort of PWS patients treated with Genotropin for 1 year (Lindgren 1998), 5 years (Lindgren 1999) and until patients reached near adult height (Lindgren 2008). A group of 29 patients with PWS aged 3-12 years were randomized to either 0.03 mg/kg/day of Genotropin given subcutaneously or to no treatment (observational group). After one year, the treatment group continued Genotropin at the same dose of 0.03 mg/kg/day for 12 additional months, while the control group initiated Genotropin treatment at twice the dose: 0.06 mg/kg/day. Efficacy variables were height SDS, height velocity SDS, lean body mass (kg), body fat (%), BMI SDS, IGF-1 SDS, and change in bone age. The efficacy data following the first year of treatment is presented in applicant's Table 2-2. It indicates that on Genotropin treatment linear growth was accelerated from a baseline height velocity SDS of -1.9 to 6.0, while in the untreated group it barely changed from -1.7 to -1.8. In addition to increases in height and height velocity, Genotropin treatment was associated with an increase in lean body mass, a reduction in % body fat and BMI SDS, and a comparable change in bone age relative to control. Safety assessments for this first year of treatment indicated normal fasting glucose, glucose tolerance test and Hb A1c, and an increase in basal insulin levels (still within the normal range) for the Genotropin group. One patient had a low T4 which was not associated with changes in TSH levels. Bone mineral density did not differ between the groups. Following this 2-year study, patients discontinued Genotropin treatment for 6 months and then restarted GH at a standard dose of 0.03 mg/kg/day and were enrolled in the postmarketing study KIGS.

Table 2-2 Main efficacy results in PWS children (GH and controls) at the start and after 1 year in the study (mean and range or mean plus minus SD)

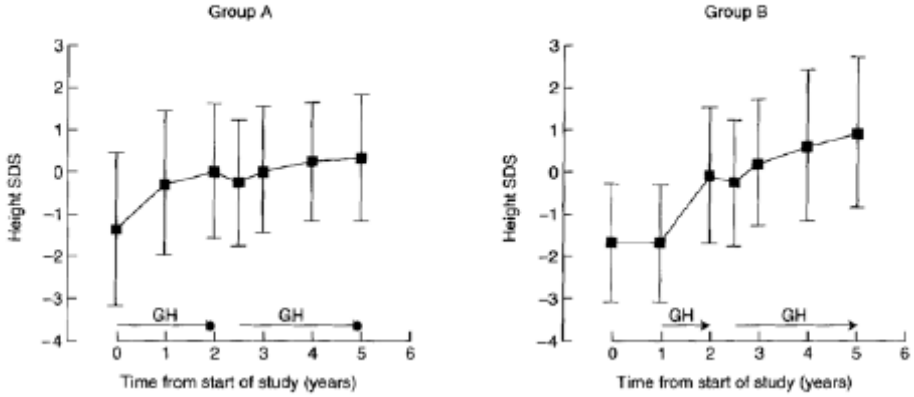
Efficacy parameter		Baseline	1 year
Height SDS	Control group (n=12)	-1.7 (-5.3 to 0.4)	-1.8 (-5.1 to 0.2)
	GH group (n=15)	-1.6 (-4.0 to 0.5)	-0.4 (-2.7 to 1.9)*
Height velocity SDS	Control group (n=12)	-0.1 (-1.7 to 2.7)	-1.4 (-3.2 to 0.3)
	GH group (n=15)	-1.9 (-6.4 to 0.9)	6.0 (1.4 to 11.9)*
BMI SDS	Control group (n=12)	2.1 (-1.3 to 5.1)	2.5 (0.1 to 6.1)
	GH group (n=15)	3.0 (-0.7 to 7.6)	2.0 (-2.4 to 6.7)*
IGF-1 SDS	Control group (n=12)	-1.4 (-2.4 to -0.1)	-1.4 (-2.9 to -0.3)
	GH group (n=15)	-1.6 (-3.0 to 0.6)	1.8 (-0.1 to 4.1)*
Lean Body Mass (kg)	Control group (n=12)	14.1 ± 3.0	15.2 ± 2.9
	GH group (n=15)	14.9 ± 4.1	19.8 ± 5.2**
Body fat (%)	Control group (n=12)	34.8 ± 7.9	38.2 ± 9.1
	GH group (n=15)	40.0 ± 10.5	30.9 ± 11.4**
Change bone age (y)	Control group (n=12)	_____	1.5 (0.4-2.6)
	GH group (n=15)	_____	1.4 (0.0-2.8)

*P<0.05, **P<0.001 compared to baseline
Change bone age= advancement in bone age during the 1-y study period

The study findings were updated after 5-years of treatment (Lindgren and Ritzen 1999). The results for height SDS are presented in Figure 2-1. Time 0 represents the beginning of the original trial. Group A of the graph represents the cohort of patients who were treated with GH in the first year of study and Group B is the cohort that was observed for one year followed by double-dose therapy during the 2nd year. Across both groups there were 22 patients who contributed data at 5 years. For Group A, mean height SDS, which increased from -1.7 to -0.3 during the first year of treatment, continued to grow during the second year, slowed down following the period of transient treatment discontinuation and started to grow again but at a slower rate through the 5th year. For group B, initiation of treatment with a double Genotropin dose resulted in a distinct height SDS augmentation for the following year, followed by a brief dip after treatment discontinuation and a clear increase once treatment was re-initiated at a lower dose in the KIGGS study. From a safety standpoint, higher Genotropin doses were associated with mean fasting insulin levels

above the normal range that normalized once Genotropin treatment was discontinued. Following resumption of treatment, 3 patients in group B developed hyperinsulinemia on the low dose and 2 developed type 2 diabetes (while having concomitant rapid weight gain) that was reversed by discontinuation of GH treatment. Four patients reached final height, all four within the statistical definition of normal height (-2SD to +2SD).

Figure 2-1 Height SDS and BMI SDS during 5 years of interrupted GH treatment in children with PWS (n=22).



The 2008 study update presents near-adult height data for 22 patients from the above-mentioned studies and publications. The mean near-final height data are presented by gender in applicant's Table 2-3 (12 boys and 9 girls). Girls reached a mean height SDS of -0.5 after a mean duration of treatment of 8.2 years, while boys reached a final height SDS of 0.9 following a mean treatment length of 10.2 years. All but one child (a girl) had final height in the normal range. Some improvements in lean body mass were seen but the fat/lean ratio was similar to that observed at baseline, despite showing improvements during the first year of treatment.

Table 2-3 Main efficacy results in PWS children at start of GH treatment and at near adult height (defined as height velocity <2 cm/year)

Efficacy parameter	Baseline		Near adult	
	Boys (n=13)	Girls (n=9)	Boys (n=12)	Girls (n=9)
Age (years)	6.2 (4.9 to 8.9)	8.2 (4.4 to 12.9)	18.1 (16.2 to 21.2)	
Mean duration of treatment (years)	____	____	10.2 (6.9 to 11.5)	8.2 (5.8 to 11.7)
Height SDS	-1.4 (-2.3 to -0.2)	-1.8 (-4.0 to -1.1)	0.9 (-0.2 to 2.2)	-0.5 (-1.2 to 0.1)
BMI SDS	2.3 (0.6 to 3.8)	1.5 (0.9 to 2.1)	1.6 (0.1 to 2.7)	2.2 (0.5 to 2.9)
Bone mineral density (BMD) SDS	-0.3 (-2.0 to 1.6)	-0.8 (-1.5 to 1.9)	0.4 (-2.0 to 2.0)	-0.5 (-1.5 to 1.1)

Median and 10th to 90th percentile

From a safety perspective, two patients developed glucose intolerance and type 2 diabetes with concomitant weight gain (weight reduction resulted in normalization of glucose levels) and one patient developed worsening of scoliosis that required surgical intervention.

Eiholzer and l'Allemand 2000

This study presents data for a total of 23 children with PWS divided in three groups: young underweight children (n=10, mean age =1.05 years); prepubertal overweight children (n=8, mean age=6.8 years); and pubertal overweight children (n=5, mean age=13.3 years). All children were treated with Genotropin at 0.037 mg/kg/day for up to 5.5 years. Standard auxological information is provided that indicates that for the prepubertal groups Genotropin treatment resulted in changes in height and height velocity consistent

with those described in similar studies. Due to the small size of the pubertal group and the advanced bone age, there was marked variability in individual responses to treatment in this cohort.

Myers et al 2007, Carrel et al 2004 & Whitman et al 2004

These 3 publications describe the results of a randomized, two-center, clinical trial conducted in the US in infants and toddlers with PWS. Patients were randomized in a 60:40 ratio to either Genotropin (0.03 mg/kg/day) or no treatment control. After one year in the study, patients in the no-treatment control group were started on a higher dose (0.06 mg/kg/day) of GH. Only results for the 12-month and 2-year time point are summarized. The study enrolled 25 patients with PWS (age range 4-37 months), 15 of which were initially randomized to GH and 10 to no treatment. The main auxological data as well as data on body composition changes are summarized in Table 2-7. Statistically significant changes in mean height SDS, head circumference SDS, % body fat, and lean mass (kg) were noted in the Genotropin group when compared to controls at Month 12 (no control group was available at Month 24 for a similar comparison). For patients who initiated Genotropin treatment at the beginning of the trial, height SDS increased from -1.6 at baseline, to -0.2 at one year and 0.6 at two years. Although a reduction in % body fat was seen after one year of treatment, it returned to baseline values at the end of the second year of treatment. Lean body mass increased for both years (but no control was available for the Month 24 time point). Overall, the study indicates that administration of GH to infants and toddlers normalizes height and improves lean body mass. From a safety standpoint, scoliosis progression was noted in a 3-year-old patient who required spinal rod placement for support.

Anthropometric and Body Composition Data

Table 2-7 **Anthropometric and Body Composition Data in GH-treated and untreated (control) PWS subjects.**

	GH-treated PWS subjects			Untreated PWS subjects	
	Baseline	1 year	2 years	Baseline	1 year
Height SDS	-1.6 ± 1.2	-0.2 ± 1.5*	0.6 ± 1.2	-1.3 ± 1.1	-1.5 ± 0.7
Head circumference SDS	-0.9 ± 0.8	-0.1 ± 0.9**	0.4 ± 1.2	-0.5 ± 0.7	-0.2 ± 0.7
Body fat %	28 ± 7	23 ± 9*	27 ± 10	29 ± 12	33 ± 8
Lean mass [kg]	5.8 ± 1.9	9.8 ± 2.0*	12.4 ± 1.9	6.9 ± 2.0	8.5 ± 1.9
Bone mineral density [g/cm^2]	0.60 ± 0.08	0.67 ± 0.05	0.73 ± 0.04	0.64 ± 0.09	0.69 ± 0.06

*P<0.005

**P<0.01 compared with 12-month changes in the PWS control group

Eiholzer et al 2004 and Eiholzer et al 2008

The first publication describes a 30 month study conducted in 17 patients with PWS <2years of age comparing a Genotropin regimen of 0.025 mg/kg/day to Coenzyme Q10 (ubiquinone), a component of the mitochondrial respiratory chain which is found to be present at reduced levels in PWS patients. Efficacy endpoints were height SDS, lean mass, % fat mass, and weight. Comparative data were available only for the first year of the trial. Main efficacy data are summarized in applicant's Table 2-10. While height SDS rose from a baseline of -2.7 over the next 24-30 months to -0.77 and -0.85, respectively, no height benefit was seen with Coenzyme Q10. Similar effects were seen with lean body mass SDS (increased with Genotropin, no change with Coenzyme Q). Despite GH treatment (and its known lipolytic effect), PWS patients continued to accumulate fat mass and gain weight. As the previous study, this clinical trial provides evidence that early intervention with GH therapy results in normalization and maintenance of a normal height SDS and lean body SDS.

Table 2-10 **Height (SDS), Weight for height (SDS) and Lean mass for age (SDS) in young children with PWS, treated with GH (n=11) or with coenzyme Q10 (n=6)**

	Group	Baseline	12 months	24 months	30 months
Height (SDS)	GH	-2.7 ± 1.8	-1.13 ± 1.4*	-0.77 ± 1.2*	-0.85 ± 1.2
	Q10	-1.87 ± 0.8	-1.73 ± 0.9	-	-
Weight for height (SDS)	GH	-1.14 ± 1.0	0.02 ± 1.4	1.47 ± 2.7*	2.05 ± 2.6
	Q10	-0.64 ± 1.1	-0.22 ± 1.2	-	-
Lean mass for age (SDS)	GH	-2.99 ± 0.9	-1.76 ± 1.2*	-1.53 ± 1.2*	-1.39 ± 1.1
	Q10	-2.20 ± 0.7	-2.12 ± 0.7	-	-

Values are mean ± SD

*$P<0.05$, $P<0.01$ vs baseline, within groups

Similar results are presented by Eihotzer et al. in a 2008 retrospective analysis of 26 newborns and toddlers with PWS who were treated with either Genotropin or Coenzyme Q10.

Haqq et al 2003

This randomized, double-blind, placebo-controlled, cross-over study was conducted in 12 PWS patients (mean age of 9 years) who received sequentially either 0.043 mg/kg/day of Genotropin or placebo. The study sought to evaluate linear growth, body composition, and pulmonary function. GH treatment resulted in an improvement of approximately 30% of peak flow rate (PFR) and forced expiratory flow rate (FEF25–75) relative to placebo. IGF-1 and IGFBP-3 levels increased significantly in the GH group. Following 6 months of GH treatment lean body mass increased significantly by 7.6%, fat mass and percentage body fat significantly decreased by 10.3% and 8.1%, respectively, and height velocity increased.

Festen et al 2008b

This 12 month, randomized, multicenter study evaluated the effects of Genotropin (0.03 mg/kg/day) in 29 PWS infants and toddlers randomized to either GH or to a no treatment observational group. Auxological and body composition data are summarized in applicant's Table 2-19. After 12 month of GH treatment, height SDS increased from -2.6 into the normal range (-1.6) while remained low in the control group. The changes in body composition (body fat, lean body mass) were not significant in either group. As expected IGF-1 and IGFBP-3 increased and normalized in the GH group only. A positive effect of GH on psychomotor development was also observed (Bayley Scales of Infant Development II: mental and motor).

Table 2-19 **Anthropometric and body composition parameters at baseline and after 12 months of GH treatment**

	GH group		Control group	
	0 (n=15)	12 months (n=15)	0 (n=14)	12 months (n=14)
Height SDS	-2.6 (-3.3 to -1.8)	-1.6** (-2.1 to -0.8)	-2.3 (-3.3 to -1.1)	-2.3 (-3.9 to -1.5)
BMI SDS	-0.3 (-1.1 to 1.3)	0.3 (-0.9 to 1.8)	-0.9 (-1.8 to -0.8)	-0.4* (-0.8 to 1.3)
Head circumference SDS	-1.0 (-1.7 to -0.3)	-0.2**° (-1.2 to 0.6)	-1.1 (-1.8 to -0.9)	-1.1° (-1.6 to -0.6)
Body fat (%)	26.2 (22.2 – 28.9)	22.5 (11.3 – 33.2)	25.8 (23.1 – 27.7)	22.8 (19.5 – 32.9)
LBM (%)	72.1 (69.8 – 75.7)	74.8 (63.7 – 82.3)	73.3 (70.9 – 75.2)	73.6 (61.6 – 75.9)
IGF-1 SDS	-2.1 (-2.7 to -1.7)	1.7**°° (0.1 to 2.5)	-2.0 (-2.6 to -0.3)	-2.6°° (-4.1 to -0.4)
IGFBP-3 SDS	-2.8 (-3.5 to -2.4)	0.4°° (-0.3 to 1.1)	-1.8 (-3.4 to -0.9)	-3.1° (-4.0 to -2.2)

*P<0.05, **P<0.005: 12 vs 0 months

°P<0.05, °°P<0.001; GH group vs control group

Festen et al 2008a

This was a 2-year, randomized, multicenter trial in which 91 PWS prepubertal patients (42 infants/toddlers [6-months – 3 years] and 49 older children [3-14 years]), received either Genotropin 0.03 mg/kg/day or no treatment; given the two different age cohorts and the treatment/ no treatment allocation, the study had 4

arms. The efficacy data for the infant/toddler group are presented in applicant's Table 2-21. Consistent with observations made in similar studies, there were larger elevations in IGF-1 concentration in the Genotropin group, along with mean height SDS normalization (-1 at 12 months, -0.4 at 24 months) and height gain in excess of that observed in the no treatment group.

Table 2-21 Main efficacy results in PWS infants (aged 6 months – 3 years at baseline)

Efficacy parameter		Baseline	1 year (control: untreated)	2 years (control: 1 year GH)
N	Control group	22	15	12
	GH group	20	16	12
Height SDS	Control group	-2.1 (-3.2 to -1.0)	-1.8 (-3.5 to -1.4)§§	-1.2 (-2.3 to 0.1)** §
	GH group	-2.3 (-2.8 to -0.7)	-1.0 (-1.9 to 0.1)**** §§	-0.4 (-1.1 to 0.0)*** §
BMI SDS	Control group	-0.8 (-1.7 to 1.6)	0.1 (-0.7 to 2.6)**	0.9 (0.5 to 1.9)*
	GH group	0.5 (-0.9 to 1.9)	0.3 (-0.1 to 1.6)	0.8 (0.1 to 2.8)*
Head circumference SDS	Control group	-1.1 (-1.8 to -0.5)	-0.8 (-1.6 to -0.3)* §§	0.0 (-0.6 to 0.6)**
	GH group	-0.8 (-1.6 to -0.3)	0.0 (-0.9 to 0.7)*** §§	0.4 (-0.5 to 1.1)***
IGF-1 SDS	Control group	-1.6 (-2.6 to -0.4)	-2.1 (-3.1 to -0.5)	2.4 (2.2 to 3.0)
	GH group	-1.9 (-2.8 to -1.3)	2.5 (1.6 to 3.0)***	3.2 (1.9 to 4.3)***
IGFBP-3 SDS	Control group	-1.5 (-2.6 to -0.7)	-2.4 (-3.5 to -1.2)	0.7 (0.5 to 1.1)
	GH group	-2.6 (-3.3 to -2.0)	0.5 (0.0 to 1.2)**	1.5 (0.4 to 2.3)*

Median (interquartile range) values are given

*P<0.05, **P<0.01, ***P<0.005, ****P<0.001 compared to baseline

§P<0.05, §§P<0.001 change GH group *vs.* control group

The data for older children are summarized in Table 2-22. Gains relative to the no treatment control group were seen in the GH-treated group for IGF-1 SDS, height SDS, and lean body mass for age SDS. Reductions in % trunk fat were seen in association to GH but not in absence of treatment. There were no significant safety issues reported.

Table 2-22 Main efficacy results in prepubertal PWS children (aged 3-14 years at baseline)

Efficacy parameter		Baseline	2 years
N	Control group	22	20
	GH group	25	20
Height SDS	Control group	-2.5 (-3.3 to -1.9)	-2.6 (-3.4 to -2.3) §§§
	GH group	-2.0 (-3.1 to -1.7)	-0.6 (-1.1 to -0.1)*** §§§
BMI SDS	Control group	1.3 (1.1 to 1.6)	1.3 (1.1 to 1.6) §§
	GH group	1.2 (0.1 to 2.2)	0.6 (-0.4 to 1.6)** §§
IGF-1 SDS	Control group	-1.9 (-2.6 to -1.2)	-1.8 (-2.6 to -1.0) §§§
	GH group	-1.7 (-2.3 to -1.2)	2.4 (2.1 to 2.8)*** §§§
IFBBP-3 SDS	Control group	-2.2 (-3.1 to -1.4)	-1.7 (-2.3 to -1.2) §§§
	GH group	-1.9 (-2.8 to -1.2)	0.6 (0.3 to 1.1)*** §§§
Fat percentage SDS	Control group	2.3 (1.9 to 2.6)	2.4 (2.1 to 2.7) §§§
	GH group	2.1 (1.7 to 2.7)	1.9 (0.7 to 2.3)** §§§
LBM_{age} SDS	Control group	-1.9 (-3.4 to -1.2)	-2.5 (-3.8 to -1.4)** §§§
	GH group	-1.7 (-3.0 to -1.0)	-0.1 (-1.3 to 0.6) §§§
LBM_{height} SDS	Control group	-1.4 (-2.9 to 0.9)	-2.3 (-2.7 to -1.3)** §
	GH group	-1.7 (-3.8 to -0.6)	-1.9 (-2.4 to -1.4) §
Trunk fat (%)	Control group	36.0 (29.2 to 41.2)	37.9 (35.0 to 45.7)* §§§
	GH group	36.0 (24.8 to 46.2)	33.3 (17.3 to 40.9)** §§§

Median (interquartile range) values are given

*P<0.05, **P<0.005, ***P<0.001 compared to baseline

§P<0.05, §§P<0.005, §§§P<0.001 change GH group *vs.* control group

Festen et al 2006

This is a report of polysomnographic changes after 6 months of treatment in 35 patients from the Festen et al. study summarized above. The baseline subtracted data are presented in applicant's Table 2-24. None of the findings was statistically significant. Of interest is that one patient evaluated in this study died during an episode of upper tract respiratory infection after 13 months of GH treatment; this patient is reported to

have had had near-normal sleep-related breathing during polysomnography before and after 6 months of treatment.

Table 2-24 Clinical and respiratory parameters at baseline and after 6 month of GH therapy (n=35)

	Baseline	After 6 months of GH	*P* value
Age	6.0 (2.3-8.6)	6.8 (301-9.9)	
BMI SDS	0.8 (-0.1 to 1.5)	0.8 (-0.1 to 1.2)	0.19
AHI	4.8 (2.6-7.9)	4.0 (2.7-6.2)	0.36
Central Apnea Index	2.9 (1.5-5.2)	2.2 (0.8-4.1)	0.15
Obstructive apnea index	0.0 (0.0-0.3)	0.0 (0.0-0.2)	0.73
Hypopnea index	0.7 (0-1.9)	1.0 (0.7-2.0)	0.26
Longest apnea duration (sec)	15.0 (13.0-28.0)	17.0 (14.0-23.3)	0.92

Median (interquartile range) values are given

Festen et al 2007b

This 2-year multicenter study included 20 treatment-naïve prepubertal children with PWS who were randomized to either Genotropin 0.015 mg/kg/day for 4 weeks followed by 0.03 mg/kg/day, or to no treatment and observation. Several pharmacodynamic and metabolic measures of GH action were evaluated (IGF-1, IGFBP-3, adiponectin levels, HOMA index, lean body mass, % fat, triglycerides) in addition to height SDS. After 2 years, height SDS increased and normalized in the GH group (-2.2 to -0.6), while it decreased slightly in the control group from -2.2 to -3. Similar trends were seen for lean body mass SDS (increased from -2.2 to -1.2 in the GH group and decreased in the control group from -2.3 to -2.8), IGF-1, and IGFBP-3. Percent fat SDS increased in the control group and remained unchanged in the Genotropin group. Triglycerides decreased minimally in the GH group and worsened in the controls. HOMA index increased in both groups but more so in the control group where it doubled. Finally, adiponectin levels (which are inversely related to triglyceride levels) increased significantly in the GH group relative to controls.

Table 2-26 Main clinical results of Festen et al 2007b

		Baseline	After 2 years of GH
Age	Control group	5.8	
	GH group	6.2	
Height SDS	Control group	-2.8 (-3.4 to -2.0)	-3.0 (-3.5 to -1.8)
	GH group	-2.2 (-3.1 to -1.8)	-0.6 (-0.9 to -0.3)*
BMI SDS	Control group	1.1 (0.6 to 1.5)	1.2 (0.- to 1.5)
	GH group	0.8 (0.1 to 1.2)	0.4 (-0.3 to 1.1)
Adiponectin (mg/liter)	Control group	17.1 (13.1 - 23.1)	15.8 (12.5 – 19.2)
	GH group	15.9 (13.3 - 23.9)	24.6 (15.4 – 28.2)**
Percent fat SDS	Control group	1.8 (1.5 - 2.4)	2.1 (1.9 - 2.4)**
	GH group	1.7 (1.6 - 2.0)	1.7 (0.9 – 1.9)
LBM (SDS)	Control group	-2.3 (-2.8 to -1.8)	-2.8 (-3.3 to -1.9)**
	GH group	-2.2 (-2.7 to -2.0)	-1.2 (-1.7 to -1.1)**
HOMA index	Control group	0.7 (0.6-0.9)	1.4 (0.8-3.0)**
	GH group	0.8 (0.5-13)	1.0 (0.7-1.5)
Triglycerides (mmol/liter)	Control group	0.7 (0.6-1.0)	1.0 (0.6-1.0)
	GH group	0.9 (0.7-1.7)	0.7 (0.6-0.8)
IGF-1 SDS	Control group	-1.7 (-2.9 to -1.0)	-2.0 (-2.7 to 1.0)
	GH group	-1.7 (-2.2 to -1.2)	2.3 (2.1 to 2.9)**
IGFBP-3 SDS	Control group	-2.5 (-3.2 to -1.5)	-1.8 (-2.7 to -1.5)
	GH group	-2.0 (-3.0 to -1.3)	0.6 (0.47 to 1.1)**

Median (interquartile range) values are given

* *P*<0.05, compared with baseline

** *P*<0.05, compared with baseline corrected for multiple testing

de Lind van Wijngaarden et al 2009

This multicenter, randomized Dutch study enrolled 91 PWS children in several arms: an "infant" group (n=38, 6-months of age to 3.5 years; treated for 1 year), a prepubertal group (n=44, age range 3.5 years to 12 years; treated for 2 years), and a pubertal group (n=9, age range 12-16 years). Patients were randomized to either no treatment with observation, or to Genotropin 0.015 mg/kg/day for 4 weeks followed by 0.03 mg/kg/day; pubertal children received Genotropin doses of 0.03 mg/kg/day or 0.045 mg/kg/day. The study objective was to evaluate the effect of GH on the onset and progression of scoliosis (onset of scoliosis was defined as a COBB angle >10 degrees and progression of scoliosis as a change in the COBB angle). After one year of treatment there were no statistical differences between treatment groups in the "infant" group (p=0.71 for onset and 0.48 for progression of scoliosis, respectively). Similar results were observed for the prepubertal and pubertal group.

l'Allemand et al 2003

This prospective, longitudinal study was conducted in 17 PWS children with the objective of evaluating glucose metabolism over a 3-year period of GH treatment consisting in 0.037 mg/kg /day of Genotropin administered subcutaneously. The study results are summarized in Table 2-35. Mean fasting glucose levels did not change over time. HbA1c increased minimally at 1 year but remained in the normal range. Median insulin levels almost doubled at 1-year but returned to baseline levels after 3 years.

Table 2-35 Parameters of body composition and metabolism

	Baseline (n=17)	After 1 year GH (n=17)	After 3 years GH (n=14)	Reference range
BMI SDS	2.5 ± 0.8	1.5 ± 0.9*	1.0 ± 0.4	-2 to 2 SD
Fat mass SDS	1.18 ± 0.45	0.08 ± 0.46*	0.24 ± 0.23	-2 to 2 SD
Lean mass SDS	-1.4 ± 0.2	-0.85 ± 0.3*	-1.1 ± 0.4	-2 to 2 SD
Relative fat %	39.5 ± 3.4	30.3 ± 2.6**	28.3 ± 2.0*	16 - 30
Triglycerides [mmol/l]	0.88 ± 0.05	0.91 ± 0.09	0.74 ± 0.06	0.35-1.55
HbA_{1c} %	4.66 ± 0.1	5.10 ± 0.1**	4.95 ± 0.2	3.8 - 6.0
Fasting glucose [mmol/l]	4.1 ± 0.10	4.3 ± 0.1	4.1 ± 0.2	3.8 - 6.4
Fasting insulin[a] [pmol/l]	28.1 (14-251)	54.1** (16-212)	24.6 (9-63)	<7-122

Mean ± SEM values are given, unless otherwise stated

*p < 0.05, **p < 0.01 : significant change versus baseline data. n.s. = not significant.

[a] Given as median and range.

Schmidt, Bechtold, and Schwarz 2000

Ten children with PWS and GH deficiency aged 7-16 years were treated for 1 year (n=10) and up to 5 years (n=2) with Genotropin at a dose of 0.02 mg/kg/day. Data for the first 2 years of treatment are presented in Table 2-38. Statistically significant changes in height SDS and height velocity SDS relative to baseline were observed.

Table 2-38 Response to GH treatment in PWS patients (1 and 2 years therapy)

	Baseline	1 year n=10	2 years n=9
Height SDS	-3.47 ± 1.34	-2.78* ± 1.21	-2.27° ± 1.02
Height velocity SDS	-1.74 ± 1.93	2.65** ± 1.74	1.78** ± 2.08
BMI	22.6 ± 5.44	22.93 ± 5.15	22.71 ± 5.01

* $P<0.01$, ** $P<0.005$ compared to baseline

° $P<0.01$ compared to 1-year HSDS

Craig et al 2006

This study reports on the efficacy and safety of Genotropin in the treatment of children with PWS enrolled in the post-marketing surveillance study KIGS. Data following one year of treatment are presented for 328 children, out of which 274 were prepubertal (median age 6 years; range 1.4 to 10.2 years) and 54 were prepubertal (median age: 12.7 years, range 9.8 to 16.3). The median Genotropin dose was 0.23 mg/kg/week in prepubertal children and 0.19 mg/kg/week in pubertal patients. The efficacy results are summarized in Table 2-42, which indicate a height SDS increase of 0.88 in prepubertal and 0.29 in pubertal children, respectively after one year of treatment.($p<0.05$ for each). Height velocity doubled in prepubertal children; in pubertal children the acceleration was less.

Table 2-42 Baseline characteristics and 1-year data for children with PWS treated with GH. Median [10th to 90th percentile].

	Prepubertal children (N=274)		Pubertal children (N=54)	
	Start of treatment	After 1 year	Start of treatment	After 1 year
Height SDS	-1.80 [-3.40 to 0.04]	-0.74 [-2.66 to 0.88]	-1.78 [-3.97 to -0.32]	-1.52 [-3.12 to 0.37]
Height velocity (cm/year)	5.13 [2.73 to 9.36]	10.44 [7.10 to 14.72]	4.51 [1.19 to 7.50]	6.86 [0.78 to 11.80]
Height velocity SDS	-1.40 [-3.50 to 0.95]	4.16 [0.54 to 8.39]	-0.78 [-3.46 to 2.40]	2.28 [-1.37 to 8.97]
Weight SDS	-0.08 [-2.84 to 2.45]	0.39 [-2.03 to 2.68]	0.64 [-2.16 to 3.04]	0.76 [-2.13 to 3.41]
BMI SDS	1.62 [-0.87 to 3.59]	1.28 [-0.73 to 3.19]	2.00 [0.33 to 3.70]	1.86 [-0.37 to 3.72]

Median [10th to 90th percentile]

Data after 2 years of treatment are presented for 161 patients, 127 prepubertal (median age 5 years) and 34 pubertal (median age 11.8). The median Genotropin dose was 0.23 mg/kg/week in prepubertal children and 0.22 mg/kg/week in pubertal patients. Data for the prepubertal subgroup are presented in Table 2-43 by gender. After 2 years of treatment height SDS had a median increase of 1.32 SDS for boys and 1.40 for girls ($p<0.05$ for each).

Table 2-43 Baseline characteristics and 2-year follow-up data for prepubertal children with PWS treated with GH

	Prepubertal children (N=127)			
	Boys (N=71)		Girls (N=56)	
	Start of treatment	After 2 years	Start of treatment	After 2 years
Height SDS	-1.85 [-2.97 to 0.32]	0.24 [-1.93 to 1.59]	-2.15 [-4.20 to -0.73]	-0.71 [-2.82 to 0.86]
Height velocity (cm/year)	5.38 [2.78 to 9.39]	7.90 [5.46 to 9.74]	4.72 [1.68 to 8.03]	8.12 [5.42 to 10.13]
Height velocity SDS	-0.75 [-3.37 to 1.26]	2.50 [-0.91 to 4.60]	-1.86 [-4.71 to 0.70]	2.10 [-1.03 to 3.70]
Weight SDS	-0.12 [-2.62 to 2.45]	0.60 [-0.92 to 2.72]	-0.99 [-4.37 to 1.45]	0.00 [-2.21 to 2.06]
BMI SDS	1.63 [-0.61 to 3.27]	1.34 [-0.22 to 3.34]	1.13 [-1.01 to 2.72]	0.85 [-0.97 to 2.20]

Median [10th to 90th percentile]

Pubertal children showed a smaller increase in height SDS after 2 years of treatment: 0.54 ($p<0.05$; Table 2-44). Consistent with observations made in prepubertal patients.

Table 2-44 Baseline characteristics and 2-year follow-up data for pubertal children with PWS treated with GH

	Pubertal children (N=34)	
	Start of treatment	After 2 years
Height SDS	-1.75 [-3.29 to -0.05]	-1.21[-2.48 to 0.61]
Height velocity (cm/year)	4.25 [3.56 to 7.84]	5.91 [2.45 to 9.46]
Height velocity SDS	-1.06 [-3.46 to 4.12]	1.04 [-3.01 to 5.08]
Weight SDS	0.91 [-1.98 to 3.04]	0.88 [-1.82 to 2.99]
BMI SDS	2.07 [-0.52 to 3.73]	1.80 [-0.40 to 3.59]

Median [10th to 90th percentile]

There were 176 adverse events reported in this study. Of interest, several cases of impaired glucose intolerance, 2 cases of type 1 diabetes and 5 cases of type 2 diabetes were recorded. Five children died at intervals of 2-97 weeks after treatment initiation. Their ages ranged from 2.1 years to 15.8 years. The GH doses were between 0.10 and 0.24 mg/kg/day with only one child receiving a dose of 0.34 mg/kg/day. The suspected cause of death were reported as follows: diarrhea, dehydration, cardiorespiratory arrest (1), found dead in bath (1), died in bed, sleep apnea suspected (1), respiratory insufficiency (1), and pneumonia (1).

Tauber 2007 & Tauber and Cutfield 2007

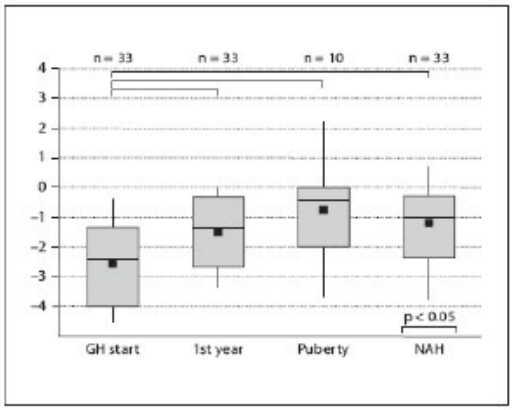
These studies report data on 1135 prepubertal PWS children (mean age of 6.4 years at the beginning of therapy) treated for a mean duration of 1.9 years with Genotropin at an average daily dose of 0.033 mg/kg (range of 0.022 to 0.044). First year data (Table 2-47) indicate an average height SDS gain of one standard deviation and an average height velocity SDS gain of over 5 SD. Of interest, nearly three quarters of patients had low IGF-1 levels at baseline.

Table 2-47 Auxological data at the start and after 1 year of GH treatment (median and 10^{th}-90^{th} percentile)

	Baseline	1 year therapy
Height SDS	-2.2 (-4.1 to 0.4) n=652	-1.2 (-3.2 to 0.6) n=652
Height velocity SDS	-1.4 (-4.1 to 0.9) n=229	4.0 (-0.2 to 9.0) n=651
BMI SDS	1.7 (-1.2 to 3.7) n=652	1.3 (-0.9 to 3.4) n=651
IGF-1SDS	-1.6 (-2.9 to 0.1) n=393	

Near-adult height was obtained in 33 patients (21 boys and 12 girls) and mean values were within the normal range (approximately -1 SDS) as illustrated in Figure 2-13. The mean height SDS gain was 2.4.

Figure 2-13 Height SDS in PWS patients.



At the start of GH therapy (n=33), after 1 year of GH therapy (n=33), at the start of puberty (n=10) and at near-adult height (NAH; n=33).

Lindgren et al 1999
This study describes data obtained from 9 prepubertal children with PWS treated for 6-9 months with 0.033 mg/kg/day of Genotropin. Patients' respiratory function was evaluated. The study concludes that GH treatment increased resting ventilation, central inspiratory drive, and CO2 response (thus partially normalizing the abnormal CO2 sensitivity often found in children with PWS).

Lindgren, Hagenas, and Ritzen 1999
In this single center study 19 prepubertal children with PWS were randomized to 0.033 mg/kg/day of Genotropin for 2 years or no treatment for the first year and 0.066 mg/kg/day of Genotropin for the second year. The study included also a control group of 11 prepubertal obese but otherwise healthy children. As expected, height SDS increased significantly in the GH groups (there were no statistically significant differences between the two regimens tested); lean body mass also increased during GH treatment and the percentage of body fat was reduced. The study also evaluated changes in glucose metabolism. Dose-dependent elevations in insulin levels that reach out of range concentrations in 6/19 patients were reported. One GH treated patient developed type 2 diabetes during the follow-up phase of the study.

Lindgren 2000
This is a report of 101 patients treated with Genotropin for a median time of 3 years (range 0.2 to 6 years) in the postmarketing surveillance study KIGS. One case of type 2 diabetes and 4 cases of scoliosis were reported.

Darendeliler, Karagiannis, and Wilton 2007
This publication discusses the occurrence of three adverse events: headache, idiopathic intracranial hypertension (IIH) and slipped capital femoral epiphysis (SCFE) in the KIGS database in 1368 PWS children treated with Genotropin at an average dose of 0.039 mg/kg/day (range of 0.013 to 0.044 mg/kg/day). The incidence rates for these adverse reactions are presented in Table 2-52. The IIH frequency of 146/100,000 patients) is comparable to that seen in other GH indications such as Turner and GHD. Similarly, headache was seen with a frequency comparable to that previously observed in the SGA and ISS populations (approx. 700/100,000 patients). Slipped capital epiphysis was not reported in this study despite the association between PWS and obesity (a known risk factor for SCFE).

Table 2-52 Safety results from the KIGS Database for patients with PWS

	Total patients	Patients with AE	Years until AE	Incidence/100000 treatment years	Frequency/100000 patients
Headache	1368	9	1.0 (0.01-2.2)	307.4	658.4
IIH	1368	2	0.1 (0.1-0.1)	68.3	146.3
SCFE	1368	0	Not available	0	0

Median (10^{th}-90^{th} percentile) values

Appendix B.

Summary of published Genotropin studies in children with growth failure due to small for gestational age and absence of catch up growth by 2 years of age

Butenandt and Lang 1997

This was an open-label, multicenter clinical trial that evaluated the effect of GH therapy over 2 years in children born small for gestational age (SGA) with short stature (height SDS for chronological age <-2.0) and a height velocity below 1 SD (to exclude children with spontaneous catch-up growth). Sixty-nine prepubertal children aged between 2 and 8 years (mean age around 4-5 years), received Genotropin at either 0.033 mg/kg/day (n=24) or 0.066 mg/day (n=25); there was a third arm including patients who were observed and received no treatment (n=20). Fifty children completed the trial. The results of the study are summarized in applicant's Table 2-2. Mean height velocity increased somewhat in the untreated control group but mean height SDS did not change substantially (-3.9 at baseline; -4.0 after two years). Dose-dependent accelerations in mean height velocity SDS were seen in both Genotropin groups and they resulted in mean height SDS gains of approximately 1.2 in the 0.033 mg/kg/day group and 2.1 in the 0.066 mg/day group. No serious drug-related adverse events were reported.

Table 2-2 Growth results of the children born SGA after at least 2 years of GH treatment (mean plus minus SD)

		Baseline	Year 1	Year 2
Height velocity SDS	Control group	-1.4±1.6	-1.2±1.6	-0.9±1.4
	0.033 mg/kg/day	-0.7±1.8	2.8±2.3	1.6±2.2
	0.066 mg/kg/day	-1.4±1.7	5.5±2.7	2.9±2.1
Height SDS for chronological age	Control group	-3.9±1.5	-	-4.0±2.0
	0.033 mg/kg/day	-3.5±1.0	-	-2.3±0.7
	0.066 mg/kg/day	-4.6±1.4	-	-2.5±1.4
Gain in bone age (years)	Control group	3.7±1.3*	-	1.8±0.9
(*: bone age at study start)	0.033 mg/kg/day	3.9±1.7*	-	2.1±0.8
	0.066 mg/kg/day	3.7±1.4*	-	2.3±1.1
Gain in height SDS for bone age	Control group	-0.5±2.2**	-	-0.5±1.6
(**: height SDS for bone age at study start)	0.033 mg/kg/day	-1.1±1.4**	-	1.1±1.2
	0.066 mg/kg/day	-0.2±1.0**	-	0.8±2.0

Boguszewski et al 1998

In this open-label, multicenter trial conducted in 4 northern European countries 48 prepubertal patients were treated with 0.033 mg/kg/day of Genotropin (n=16), 0.066 mg/day of Genotropin (n=20), or were observed clinically without treatment (n=12). Patients were selected on the basis of the following inclusion criteria: birth weight/height < -2 SD for gestational age, height SDS for age < -2.0, height velocity SDS for age < +1 (to exclude children with spontaneous catch-up growth), chronological age between 2 and 8 years, and a serum GH concentration > 20 mU/L. Forty-two patients received 2 years of treatment and 24 received 3 years of treatment. The study results summarized in applicant's Table 2-4 indicate a continuous and dose-dependent improvement in height SDS through 3 years of treatment in the Genotropin arms (1.9 SDS for the low dose after 3 years, 2.3 SDS for the high dose); in contrast, no change was noted in the control group after 2 years of treatment. A range of individual responses to GH were observed with some patients displaying responses similar to those obtained in patients with GH-deficiency, whereas in others the growth response was more modest. The high Genotropin dose resulted in a height SDS close to the

target height. No undue acceleration in bone age was reported. Genotropin treatment was reported to have been well tolerated. There were no significant changes in fasting serum insulin concentrations in the low dose group; in contrast, a slight rise in mean insulin levels from 5.01±2.94 mU/l t to 8.83±5.41 mU/l after 2 years took place in the high dose group (no changes in mean fasting glucose and glycosylated hemoglobin were observed). Serum thyroxin, free thyroxin and thyrotrophin concentrations remained in the normal range, while dose-dependent expected rises in serum IGF-1 and IGFBP-3 levels were observed.

Table 2-4 Growth results of the children born SGA after at least 2 years of GH treatment. Mean plus minus SD

		Baseline	Year 1	Year 2	Year 3
Height SDS	Control group	-2.78±0.41	-2.71±0.45	-2.73±0.46	----
	0.033 mg/kg/day	-3.21±0.68	-2.11±0.94[1,2]	-1.66±1.01[1,2]	-1.29±0.89
	0.066 mg/kg/day	-3.27±0.81	-1.83±0.80[1,2]	-1.12±0.80[1,2]	-0.90±0.85
Change in height SDS / year	Control group	0.10±0.26	0.07±0.15	-0.03±0.12	----
	0.033 mg/kg/day	0.12±0.33	1.09±0.48[1,2]	0.45±0.23[1,2]	0.18±0.18
	0.066 mg/kg/day	0.20±0.39	1.43±0.54[1,2]	0.70±0.17[1,2]	0.41±0.16
Diff SDS[3]	Control group	-1.74±0.68	-1.67±0.64	-1.70±0.62	----
	0.033 mg/kg/day	-2.23±1.19	-1.13±1.11[1,2]	-0.68±1.18[1,2]	-0.45±1.17[1]
	0.066 mg/kg/day	-2.34±0.95	-0.90±0.75[1,2]	0.20±0.65[1,2]	0.07±0.72[1]
Weight-for-height SDS (WH SDS)	Control group	-0.20±0.92	-0.24±0.82	-0.22±0.88	----
	0.033 mg/kg/day	-0.01±1.11	-0.49±1.06	-0.20±1.02	-0.14±1.18
	0.066 mg/kg/day	-0.44±1.07	-0.70±1.04	-0.59±1.05	-0.44±0.64

(1) statistical difference compared with baseline values

(2) statistical difference compared with untreated group

(3) Difference between the individual HSDS and mid-parental HSDS

De Zegher et al 1996b and De Zegher et al 1999

In this study, 52 prepubertal children between 2 and 8 years of age were enrolled (50 completed the study) on the basis of small birth weight and height (each < -2 SD for gestational age), short stature (defined as height SDS for age < -2.5) and height velocity SDS for age < +1 (to exclude children with spontaneous catch-up growth), and normal GH secretion (defined as stimulated GH concentration >10 ng/ml). Thirteen patients were part of an untreated control group while 39 other children received Genotropin at 0.066 mg/kg/day (n=20) or 0.1 mg/kg/day (n=19). The efficacy results are summarized in applicant's Table 2-6. Following two years of trial participation patients in the control group had a small (1 cm) reduction in mean height velocity from 6.7 cm/yr to 5.7 cm/yr. Both GH treatment groups had an increase in height velocity of approximately 4 cm. At two years, there was a minimal mean height gain in the control group (0.2 SD) and a clear gain in both GH treatment groups without any added benefit for the high dose group (2.1 SD vs. 2.5 SD). No serious adverse events were reported for the duration of the treatment.

Table 2-6 Principal efficacy results

Efficacy parameter		Baseline	2 years of treatment
Height velocity (cm/y)	Control group	6.7±0.7	5.7±0.3
	0.066 mg/kg/day	6.6±0.4	10.2±0.2
	0.1 mg/kg/day	7.0±0.5	11.0±0.4

Height velocity SDS	Control group	-0.6±0.3	-0.9±0.3
	0.066 mg/kg/day	-0.9±0.2	4.3±0.3
	0.1 mg/kg/day	-0.7±0.3	5.2±0.4
Gain in height SDS	Control group	-3.4±0.3 *	0.2±0.1
(* = initial height SDS)	0.066 mg/kg/day	-3.5±0.2 *	2.1±0.1
	0.1 mg/kg/day	-3.7±0.2 *	2.5±0.1
Annual bone age increment (year)	Control group	3.7±0.5 *	0.84±0.07
(* = initial bone age)	0.066 mg/kg/day	4.5±0.5 *	1.35±0.16
	0.1 mg/kg/day	3.7±0.5 *	1.33±0.24

In a follow-up study, a Genotropin dose of 0.066 mg/kg/day administered to a small number of patients from the same cohort after a 2-year treatment-free period demonstrated renewal of catch-up growth over a 1-2 year interval.

De Zegher et al 1996a

This was a meta-analysis of 4 open-labeled controlled multicenter studies conducted between 1990 and 1995 in 7 European countries, which included 244 prepubertal children (mean age: 5.2 years at the beginning of treatment). Patients received Genotropin at doses of 33, 66, and 100 µg/kg/day. The control group received no GH treatment. Patients were analyzed if they met the following criteria: GH sufficiency, birth weight and/or height < -2 SD for gestational age, height SDS for age < -2.0, height velocity SDS for age < +1), and chronological age between 2 and 8 years at study start. Because differences in baseline characteristics between the patients enrolled and France and those from the other European countries, the French patients were analyzed separately. Efficacy data at 24 months of treatment are summarized in applicant's Table 2-10. Height velocity and height SDS gain showed dose-dependent increases for both datasets analyzed. Additional analyses indicated that Genotropin was most efficacious in younger children with low weight and height SDS.

Table 2-10 Growth characteristics after 2 years of GH treatment in SGA children

	Country	Control group	0.033 mg/kg/day	0.066 mg/kg/day	0.1 mg/kg/day
Height velocity (cm/year)	Belg., Germ., Scandin.	5.59±0.14	8.26±0.20	9.88±0.18	11.38±0.30
	France	5.54±0.27	7.46±0.11	8.15±0.17	NT
Gain in height SDS	Belg., Germ., Scandin.	0.12±0.07	1.13±0.09	2.11±0.10	2.64±0.16
	France	0.17±0.10	1.04±0.05	1.33±0.07	NT
Weight gain (kg/year)	Belg., Germ., Scandin.	1.79±0.12	2.61±0.15	3.37±0.16	4.00±0.28
	France	1.44±0.09	2.50±0.09	2.89±0.10	NT
Annual bone age increment (years)	Belg., Germ., Scandin.	0.85±0.06	1.00±0.06	1.20±0.06	1.41±0.13
	France	1.10±0.15	1.31±0.07	1.27±0.08	NT
Gain in height SDS for bone age	Belg., Germ., Scandin.	-0.36±0.27	0.43±0.26	0.93±0.18	1.24±0.44
	France	-0.78±0.58	-0.24±0.23	0.41±0.19	NT

Belgium: 0.2 or 0.3 IU/kg/day; other countries: 0.1 or 0.2 IU/kg/day

Mean±SEM

NT: not tested

Ranke and Lindberg 1996

This study includes an analysis of growth data collected from 593 children with SGA and Silver-Russell syndrome enrolled in the KIGS (Kabi International Growth Study). The patients analyzed received Genotropin treatment for 1 to 4.3 years at doses of approximately 0.033 mg/kg/day. The inclusion criterion was a birth weight <-2 SD. Table 2-12 contains the efficacy data following one year of treatment in a subset of 210 SGA children (mean age at start of treatment: 7.1 years). Height velocity increased by a little

less than 3 cm/yr and height increased by 0.6 SD at the end of one year of treatment. Using multiple regression analysis the authors identified three positive predictors of height velocity during the first year on GH treatment: GH dose, frequency of GH injections, height at start of GH treatment, with the GH dose being by far the major determinant of the response, and one negative predictor: age at start of GH treatment.

Table 2-12 Growth results of prepubertal children born SGA after 1 year of GH treatment

	At start of GH treatment	After 1 year of GH treatment
Chronological age (years)	7.1 [4.0 / 9.9]	-
Height SDS	-3.0 [-4.2 / -2.1]	-2.4 [-3.8 / -1.6]
Weight SDS	-2.9 [-4.4 / -1.3]	-2.5 [-4.0 / -1.6]
Height velocity (cm/year)	4.5 [2.7 / 6.3]	7.1 [5.5 - 9.7]
Height velocity SDS	-1.6 [-3.1 / -0.2]	1.7 [0.2 - 4.1]
Gain in height SDS	-	0.4 [0.1 - 0.9]

Dose of GH: 0.6 IU/kg/week; 5 GH injections/week

n=210. Median values ([10th centile / 90th centile])

Data available from 79 patients treated for 3 years are presented in Table 2-13.The mean height gain over 3 years was 1 SD.

Table 2-13 Longitudinal prepubertal growth for children born SGA

	At start of GH treatment	After 1 year of GH treatment	After 2 years of GH treatment	After 3 years of GH treatment
Chronological age (years)	5.8	6.8	7.8	8.8
GH dose (IU/kg/week)	0.58	0.55	0.50	0.48
Height SDS	-2.9	-2.4	-2.1	-1.9
Gain in height SDS	-	0.5	0.3	0.2
Height SDS minus target height SDS	-1.9	-1.4	-1.2	-0.9
Height velocity (cm/year)	4.7	7.3	6.6	6.1

*p<0.001 compared with previous year

Mean values (n=79)

A total of 16 children reached near-adult height (Table 2-16). They started treatment at a mean age of 12.7 years and received GH for 4.3 years. The height gain was 1 SD. Final height was -1.7, within the statistical range of normal height but still one SD below the target height.

Table 2-16 Characteristics of SGA patients treated with GH to (near) final height

	At start of treatment	At end of treatment
Chronological age (years)	12.7 [11.0 / 14.7]	17.4 [15.9 / 19.2]
Height SDS	-2.7 [-3.7 / -2.1]	-1.7 [-3.2 / -0.7]
Gain in height SDS	-	1.0 [-0.8 / 0.2]
Height SDS minus target height SDS	-2.0 [-4.2 / -0.6]	-1.0 [-3.7 / 0.3]
Height velocity (cm/year)	12.7 [11.0 / 14.7]	17.4 [15.9 / 19.2]

Mean dose of GH: 0.033 mg/kg/day

Median values ([10th centile / 90th centile]) (n=16)

Ranke et al 2003

This study was an analysis of the KIGS data with the goal of developing a prediction model that would allow individualization of GH treatment in children with SGA. It analyzed data from 613 children who received GH treatment for one year and 385 children treated for 2 years. The mean dose of Genotropin for these children was 0.04 mg/kg/day. GH treatment resulted in median height velocity of 8.4 and 6.9

cm/year, corresponding to a median height increment of 0.6 SDS and 0.3 SDS in the first and second year of GH treatment, respectively. The proposed prediction model shows that in the first year of GH treatment the growth response was linearly correlated with the GH dose, weight at the start of GH treatment and midparental height SDS and negatively with age at treatment start. The major response predictor was GH dose followed by age at treatment start. Height velocity during the first year of treatment was the most important predictor of subsequent growth, suggesting that the final height outcome may be indicated by the initial response to GH. The authors propose that this prediction model can be used in normal clinical practice to predict the response to GH treatment in individual short patients born SGA. This model could also be used to provide the basis for a rational discussion between the treating physician and patient's family concerning the expectation of treatment, and it may also help to identify compliance problems.

De Zegher et al 2000

This publication is a meta-analysis of 4 open-labeled studies in which 188 prepubertal children aged 2-8 years (mean age: 5.2 years) were either treated with Genotropin (139 treated continuously or discontinuously for 6 years) or were observed as controls for 2 years (49 children). Genotopin doses ranged between 33 and 66 µg/kg/day (and as high as 100 µg/kg/day in some sites). At the end of 6 years the increment in height SDS was 2 SD for the 33 µg/kg/day (n=35) and 2.7 SD for the 66 µg/kg/day dose (n=27). A group which was treated discontinuously at 32 µg/kg/day (n=77) gained 1.5 SD. The untreated control group had no height gain (0.1) after 2 years. All groups had similar bone age changes of 7.1 to 7.6 years for the duration of treatment.

De Zegher et al 2002

This is a small study that evaluated glucose metabolism in 13 children small for gestational age (11 were treated with 0.1 mg/kg/day of Genotropin and 2 served as controls). As illustrated in Table 2-26, serum glucose, insulin and proinsulin increased on high dose GH after 2 years of treatment, while insulin sensitivity declined. These changes reversed to normal 3 months after discontinuing GH treatment. No child had impaired glucose tolerance.

2.11.3 Safety: glucose tolerance and insulin sensitivity

Table 2-26 Main safety results

	Baseline (n=9)	2 years of treatment (n=8)	3 months post-GH (n=9)
Glucose (mmol/l)	3.7 (3.2-4.1)	*4.4 (3.9-4.7)	4.1 (3.1-4.4)
Insulin (mU/l)	3.8 (3.1-4.2)	*13.9 (7.5-25.8)	**5.2 (2.8-8.9)
Proinsulin (pmol/l)	1.7 (1.5-5.0)	*4.5(2.2-6.7)	1.7 (1.2-2.7)
Insulin sensitivity[1]	26.9 (10.0-69.7)	*4.0 (1.8-17.6)	17.6 (6.7-47.8)
Glucose tolerance[2]	2.62 (1.97-3.21)	2.39 (1.94-2.71)	2.49 (2.10-2.97)

[1]Bergman minimal model (per min/mU/1x10^4)

[2]Slope of glucose decline 10-40 minutes post iv glucose (min^{-1})

*$p<0.005$, **$p<0.05$ on paired t-test versus Baseline*

Cutfield et al 2006

In this study 84 SGA children (mean age 6.6 years) received GH at 0.66 mg/kg/day for 12 months. Glucose metabolism changes (HbA1c, fasting plasma glucose and insulin, HOMA insulin resistance index and QUICKI [insulin sensitivity check index]) were measured for the duration of the study. No patient developed impaired glucose tolerance or overt diabetes on GH therapy. HbA1c did not change significantly (5.2% at baseline and 5.4% at Month 12). HOMA insulin resistance increased from 0.59 at baseline to 1.13 after 1 year (p=0.02) and QUICKI decreased from 0.42 at baseline to 0.38 at Month 12 (p<0.01). The study indicates normal glucose tolerance for SGA patients at baseline followed by an increase in insulin resistance on treatment, which does not appear to be clinically significant. The authors do not recommend regular assessments of insulin sensitivity; instead they suggest that yearly measurements of HbA1c and fasting glucose should be considered, particularly in patients with risk factory for type 2 diabetes (e.g. obesity, positive family history, acanthosis nigricans).

This report includes also a survey containing data obtained from 1909 SGA children treated with Genotropin (64% males; mean age 9.1 years at start of therapy) collected in a post-marketing surveillance study (KIGS database = Pfizer International Growth database). Approximately 27% of children were from US and received Genotropin at doses between 0.032 – 0.037 mg/kg/day; doses between 0.022 and 0.023 mg/kg/day were used at non-US sites. The most common adverse events are summarized in Table 2-29.

Table 2-29 Adverse events reported in KIGS

Adverse event	Number per 1000 patients
Total	187
Serious	14.0
Respiratory	34.3
Musculoskeletal	16.9
Central/peripheral nervous system	15.8
Gastrointestinal	11.4
Endocrine	2.7
Liver/bilary	2.2
Abnormal glucose regulation	2.0
Psychiatric	4.9
Neoplasia	1.0

The authors indicate that there were very few serious adverse events reported in the KIGS survey, with most of them being either common childhood conditions (e.g. respiratory infections, headaches, or signs/symptoms related to the underlying disorder, such as orthopedic and gastrointestinal problems). Two cases of neoplasia were reported (one of leukemia and one of non-specified neoplasia).

Rapaport, Saenger and Wajnrajch 2008

In this single-arm, open-label, multicenter study 139 children (baseline age 6.5 years) were treated with Genotropin for one year starting with dose of 0.033 mg/kg/day for the first month followed by 0.066 mg/kg/day for the rest of the year. The inclusion criteria were standard for SGA studies (short stature, low height velocity, documentation of low birth weight and/or height). The main efficacy results are summarized in Table 2-31. A height gain of 0.78 SD was noted along with a doubling of IGF-1 and IGFBP-3 levels. Although it increased significantly during GH therapy, IGF-1 SDS remained in the normal range (baseline IGF-1 SDS -1.3, rising to +1.2 throughout the 12 month study). . Increases in lean body mass ((median of 3.4 kg, $p<0.0001$), reductions in percent body fat (median of -2.6%, $p<0.0001$) were noted. Other changes included elevations in bone-specific alkaline phosphatase and ($p<0.0001$) and decreased total cholesterol and low-density lipoprotein cholesterol (high-density lipoprotein cholesterol and triglycerides were unaffected).

Table 2-31 Main efficacy results

	Baseline Median [min,max]	Gain after 1 year treatment
Height SDS	-2.7 [-5.8, -1.0]	0.78 ($p<0.0001$)
IGF-1 (ng/ml)	100.0 [27.0,277.0]	98 ($p<0.0001$)
IGFBP-3 (mg/l)	2.4 [0.8,5.1]	0.8 ($p<0.0001$)

De Schepper et al 2008

This is a randomized, controlled, multicenter study in which 25 short children born SGA were treated with 0.066 mg/kg/day of GH for 2 years (n=14) or were observed without treatment (n=11). As indicated by the results displayed in Table 2-38, statistically significant differences were observed for height SDS, weight SDS, lean mass, as well as for triceps skinfold , and mid-upper arm muscle and fat areas.

Table 2-38 Main results (mean plus minus SD)

	Untreated (n=14)		GH treated (n=11)		
	Baseline	2 years	Baseline	2 years	P value*
Height SDS	-3.2 ± 1	-3 ±1	-3.3 ± 0.7	-1.7 ± 0.7	<0.0001
Weight SDS	-3.6 ± 1.5	-3.4 ± 1.6	-3.5 ± 1.2	-1.8 ± 1	<0.0001
Subscapular skinfold (mm)	6.4 ± 2.1	6 ± 2.1	5.4 ± 1.1	5.1 ± 1	NS
Triceps skinfold (mm)	8.3 ± 2.1	7.9 ± 2.4	7.9 ± 1.4	5.5 ± 2.1	<0.001
mid-upper arm muscle area (cm^2)	14.1 ± 3.5	14.1 ± 2.9	12.8 ± 2.5	17 ± 2.7	<0.005
mid-upper arm fat area (cm^2)	5.7 ± 1.7	5.7 ± 1.9	5.5 ± 1.1	4.3 ± 1.9	<0.001
Lean mass (kg)	9.9 ± 2.2	12.2 ± 2.5	10 ± 3	15.5 ± 3.4	<0.0001
Fat mass (kg)	8.3 ± 2.1	7.9 ± 2.4	7.9 ± 1.4	5.5 ± 2.1	NS

*Statistical difference between untreated and treated group (analysis of variance)

NS = not significant

Dunger 2007

This is an analysis of the data obtained from 891 SGA children enrolled in a postmarketing surveillance study (KIGS database) who received Genotropin at a median daily dose of 0.03 mg/kg. Both first year and final height data were analyzed. Increases in height SDS of 0.7 were observed after one year of treatment. Height data for 65 patients who reached final height indicate an overall height gain of 1.5 SD but still in the short stature range (-2.1 SDS)

Table 2-45 Main characteristics of the 65 patients who reached near adult height

	Baseline	Near adult height
Age (years)	7.9 (3.6 ; 11.9)	16.8 (14.7 ; 18.3)
Height SDS (Prader)	-3.6 (-5.0 ; -2.6)	-2.1 (-3.5 ; -1.3)
BMI SDS	-1.1 (-3.3 ; 0.2)	-0.5 (-2.3 ; 1.2)

Darendeliler, Karagiannis, and Wilton 2007

This study investigates the potential effect of Genotropin on three adverse events associated with rhGH treatment: headache, idiopathic intracranial hypertension, and slipped capital femoral epiphysis as observed in the KIGS database. The incidence of these adverse events among 2973 children with short stature and SGA treated with Genotropin (dose range 0.013 – 0.044 mg/kg/day; average dose 0.039 mg/kg/day) is presented in Table 2-47. No cases of slipped capital femoral epiphysis were reported. Only one case of idiopathic intracranial hypertension was reported. The incidence of headache is comparable to that noted in a previous KIGS report from 1999.

Table 2-47 Safety results from the KIGS Database for SGA patients

	Total patients	Patients with AE	Years until AE	Incidence/100'000 treatment years	Frequency/100'000 patients
Headache	2973	20	1.0 (0.01-8.0)	382	673
IIH	2973	1	0.01	19	34
SCFE	2973	0		0	0

Appendix C.

Proposed changes to the Omnitrope label

The proposed changes submitted with this application are acceptable with minor changes. Only the recommended changes to applicant's proposed label are included in the following table. (b) (4)

(b) (4)

1 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21426	SUPPL-8	SANDOZ INC	OMNITROPE(SOMATROPIN[RDNA ORIGIN] FORINJ
NDA-21426	SUPPL-7	SANDOZ INC	OMNITROPE(SOMATROPIN[RDNA ORIGIN] FORINJ

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/s/

DRAGOS G ROMAN
02/24/2010

MARY H PARKS
02/25/2010
concur w/ recommendations

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021426/S-008

CHEMISTRY REVIEW(S)

CHEMISTS REVIEW	1. ORGANIZATION	2. NDA NUMBER
	DMED, HFD-510	21-426
3. NAME AND ADDRESS OF APPLICANT		**4. SUPPLEMENT NUMBER, DATE**
Sandoz Inc. 2555 W. Midway Blvd. P.O. Box 446 Broomfield, CO 80038-0446		SE1 007, 24-Nov-2008 SE1 008, 24-Nov-2008
5. NAME OF THE DRUG	**6. NONPROPRIETARY NAME**	**7. AMENDMENTS, REPORT, DATE**
Omnitrope	Somatropin (rDNA origin) for injection	Correspondence, 17-Mar-2010 Correspondence, 17-Mar-2010
8. SUPPLEMENT PROVIDES FOR:		
21-426/S-007: The addition of a new indication, Prader-Willi Syndrome (PWS). 21-426/S-008: The addition of a new indication, Small for Gestational Age (SGA).		
9. PHARMACOLOGICAL CATEGORY	**10. HOW DISPENSED**	**11. RELATED IND, NDA, DMF**
Human growth hormone	Rx	
12. DOSAGE FORM	**13. POTENCY**	
Solution for injection Injection	1.5/vial and 5.8 mg/vial 5 mg/1.5 mL and 10 mg/1.5 mL Cartridges	
14. CHEMICAL NAME AND STRUCTURE		
See Chemistry Review #1		
15. COMMENTS		

The applicant has requested a categorical exclusion from the requirements to prepare an Environmental Assessment under 21 CFR, part 25 §25.31(b) for somatropin drug substance. This supplement meets the requirements of a categorical exclusion under 21 CFR §25.31(b) since the concentration of the drug substance at the point of entry into the aquatic environment is below 1 part per billion (1 ppb). To the best of Sandoz's knowledge, no extraordinary circumstances exist in regards to these actions. The applicant's request for a categorical exclusion is granted.

There are no CMC labeling changes in sections 3 – Dosage Forms and Strengths, 11 – Description, and 16 –How Supplied/Storage and Handling.

Continued on next page.

16. CONCLUSION AND RECOMMENDATION
The applicant's request for the categorical exclusion under 21 CFR 25.31(b) is granted. There are no CMC labeling changes. From a CMC standpoint, these supplements can be approved.

17. NAME	18. REVIEWERS SIGNATURE	19. DATE COMPLETED
JANICE T. BROWN	See appended electronic signature sheet.	22-Mar-2010

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AP

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21426	SUPPL-7	SANDOZ INC	OMNITROPE(SOMATROPIN[RDNA ORIGIN] FORINJ
NDA-21426	SUPPL-8	SANDOZ INC	OMNITROPE(SOMATROPIN[RDNA ORIGIN] FORINJ

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/s/

JANICE T BROWN
03/22/2010

JAMES D VIDRA
03/22/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021426/S-008

OTHER REVIEW(S)

REGULATORY PROJECT MANAGER LABELING REVIEW

Division of Metabolism and Endocrinology Products

Application Number: NDA 21426/S-007 & S-008

Name of Drug: Omnitrope (somatropin [rDNA origin] injectable)

Applicant: Sandoz Inc.

Material Reviewed:

Submission Date(s): June 26, 2009 (PLR format) & April 23, 2010

Receipt Date(s): June 29, 2009 & April 23, 2010(email)

Submission Date of Structured Product Labeling (SPL): June 26, 2009

Type of Labeling Reviewed: WORD

Background and Summary

Omnitrope was approved pursuant to section 505(b)(2) of the Food, Drug, and Cosmetic Act in 2006, for the indications of short stature in children associated with growth hormone (GH) deficiency and also for growth hormone deficiency (GHD) of adult- or childhood-onset in adults. It is available as a lyophilized powder in two sizes and as a sterile solution (two strengths) for injection via dedicated pens. PLR format labeling had been approved previously.

Supplement-007 (S-007) now seeks to add the indication of non-GH-deficient short stature in children with Prader-Willi Syndrome (PWS). This is a 505(b)(2) supplemental application.

Supplement-008 (S-008) seeks to add the indication of non-GH-deficient short stature in children who were born small for gestational age (SGA) and who fail to manifest catch-up growth by age two years. This is also a 505(b)(2) supplemental application.

As requested by FDA, the sponsor submitted on June 26, 2009, separate labeling for S-007 and S-008 (in SPL, pdf, and Word). The labeling agreed-upon was emailed in Word on April 23, 2010.

Review

Sponsor added text or sections on PWS and SGA to the [redacted] (b) (4) The sponsor added a reference to an OmniSource phone number for information regarding problems with or replacement of the dedicated injector pens, Omnitrope Pen 5 and Omnitrope Pen 10.

FDA combined the labeling for both indications in one package insert (Word), made some adjustments to the language supplied by the sponsor, and [redacted] (b) (4) FDA requested changes to the OmniSource language to reduce the potential for confusion, and the sponsor complied. See attached comparison of pdf of PI for approved Supplement-006 to the combined PI for S-007 and S-008.

The labeling to which Sandoz agreed on April 23, 2010, is the same as requested by FDA.

Recommendations

Content of Labeling dated April 23, 2010 (by secure email) is acceptable for approval.

Enid Galliers
Chief, Project Management Staff, DMEP

ATTACHMENT

Drafted: emg/ 4-23-2010

CSO LABELING REVIEW

110 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21426	SUPPL-8	SANDOZ INC	OMNITROPE(SOMATROPIN[RDNA ORIGIN] FORINJ
NDA-21426	SUPPL-7	SANDOZ INC	OMNITROPE(SOMATROPIN[RDNA ORIGIN] FORINJ

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/s/

ENID M GALLIERS
04/23/2010

505(b)(2) ASSESSMENT

Application Information		
NDA # 21426	NDA Supplement #: S-007 & S-008	Efficacy Supplement Type SE- 1
Proprietary Name: Omnitrope Cartridges / Omnitrope for Injection Established/Proper Name: somatropin (rDNA origin) Injection & for Injection Dosage Form: Injectable (liquid & lyophilized powder) Strengths: 5 mg/1.5 mL & 10 mg/1.5 mL Cartridges; 1.5 mg/vial & 5.8 mg/vial for injection		
Applicant: Sandoz, Inc.		
Date of Receipt: June 23, 2009 (date UF paid)		
PDUFA Goal Date: April 23, 2010	Action Goal Date (if different):	
Proposed Indication(s): S-007: Prader-Willi Syndrome (PWS) S-008: Small for gestational age (SGA)		

GENERAL INFORMATION

1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES ☒ NO ☐

*If "**YES** "contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

INFORMATION PROVIDED VIA RELIANCE (LISTED DRUG OR LITERATURE)

2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of referenced product)	**Information provided (e.g., pharmacokinetic data, or specific sections of labeling)**
Published literature including data obtained with Genotropin in the proposed indications (PWS and SGA)	Scientific justification for shared mechanism of action of somatropin for treatment of pediatric and adult growth hormone deficiency, Prader-Willi Syndrome, and children born Small for Gestational Age
FDA's finding of safety and effectiveness for Genotropin (NDA 20-280)	Additional conditions of use for Omnitrope (Prader-Willi Syndrome and SGA) based on: FDA's determination that Omnitrope is highly similar to Genotropin physicochemically, pharmacokinetically, pharmacodynamically, biologically, and clinically; Sandoz' demonstration of S&E of Omnitrope for use in pediatric GHD in the original 505(b)(2) application; and scientific justification for shared mechanism of action.

*each source of information should be listed on separate rows

3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific "bridge" to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

Previous submission of data demonstrating that Omnitrope is highly similar to Genotropin physicochemically, pharmacokinetically, pharmacodynamically, biologically, and clinically (including clinical data comparing Omnitrope to Genotropin in pediatric patients with growth hormone deficiency (GHD) who have short stature).
Submission of literature-based scientific justification to support a shared mechanism of action by which somatropin treats growth failure in pediatric patients with GHD and growth failure in PWS and SGA.

RELIANCE ON PUBLISHED LITERATURE

4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES ☒ NO ☐
*If "**NO**," proceed to question #5.*

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES ☒ NO ☐

*If "**NO**", proceed to question #5.*
*If "**YES**", list the listed drug(s) identified by name and answer question #4(c).*

The listed drug named in the literature is NDA 20280 Genotropin (somatropin [rDNA origin]).

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES ☒ NO ☐

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES ☒ NO ☐

*If "**NO**," proceed to question #10.*

6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
Genotropin (somatropin [rDNA origin])	NDA 20280	Y

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A ☐ YES ☒ NO ☐

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer **"N/A"**.*
*If "**NO**", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

8) Were any of the listed drug(s) relied upon for this application:

a) Approved in a 505(b)(2) application?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

b) Approved by the DESI process?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved via the DESI process:

c) Described in a monograph?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES ☐ NO ☒

*If "**YES**", please list which drug(s) and answer question d) i. below.*

*If "**NO**", proceed to question #9.*

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES ☐ NO ☒

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

These supplements add two new indications: treatment of Prader-Willi Syndrome and Small for Gestational Age. The listed drug, Genotropin, has been found safe and effective for these indications.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(**Pharmaceutical equivalents** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and** **(3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES ☐ NO ☐

*If "**NO**" to (a) proceed to question #11.*
*If "**YES**" to (a), answer (b) and (c) then proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

YES ☐ NO ☐

*If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(**Pharmaceutical alternatives** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES ☐ NO ☐

*If "**NO**", proceed to question #12.*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES ☐ NO ☐

*If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed ☒ *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES ☐ NO ☐

*If "**NO**", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? *(Check all that apply and identify the patents to which each type of certification was made, as appropriate.)*

☐ No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

☒ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s): Not stated.

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s): Expiry date(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist ***ONLY*** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):
(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the signed certification.*

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the documentation.*

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

Note *that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information* ***UNLESS*** *the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES ☐ NO ☐ Patent owner(s) consent(s) to an immediate effective date of approval ☐

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21426	SUPPL-7	SANDOZ INC	OMNITROPE(SOMATROPIN[RDNA ORIGIN] FORINJ
NDA-21426	SUPPL-8	SANDOZ INC	OMNITROPE(SOMATROPIN[RDNA ORIGIN] FORINJ

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ENID M GALLIERS
04/22/2010

NDA/BLA REGULATORY FILING REVIEW (# 2)

(Including Memo of Filing Meeting)

Application Information		
NDA # 21-426 BLA#	NDA Supplement #:S- 007+- S-008 BLA STN #	Efficacy Supplement Type SE1 New indication
Proprietary Name: Omnitrope Established/Proper Name: somatropin (rDNA origin) injection & for injection Dosage Form: Injectable (lyophilized and solution) Strengths: 5 mg/1.5 mL and 10 mg/1.5 mL Cartridges; 1.5 mg/vial and 5.8 mg/vial Vials		
Applicant: Sandoz Inc. Contact for Applicant: Jean Domenico		
Date of Application: Nov. 24, 2008 Date of Receipt: Nov. 25, 2008 Date clock started after UN: N/A	RESUBMISSION: Date clock started after UF received: June 23, 2009	
PDUFA Goal Date: Apr. 23, 2010	Action Goal Date (if different):	
Filing Date: Aug. 23, 2009 Date of Filing Meeting: July 30, 2009		
Chemical Classification: (1,2,3 etc.) (original NDAs only) N/A		
Proposed Indication(s): **S-007:** adds Prader-Willi syndrome (PWS); **S-008**: adds Small for Gestational Age (SGA)		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***Refer to Appendix A for further information.***		☐ 505(b)(1) ☑505(b)(2) ☐ 505(b)(1) ☑ 505(b)(2) Not yet determined
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease Priority review voucher was submitted, review classification defaults to Priority.***		☑ Standard ☐ Priority ☐ Tropical disease Priority review voucher submitted
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐		
Part 3 Combination Product? ☑		☐ Drug/Biologic ☑ Drug/Device ☐ Biologic/Device
☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:		☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)

Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s):	
PDUFA and Action Goal dates correct in tracking system? ***If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☑ YES ☐ NO
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established name to the supporting IND(s) if not already entered into tracking system.***	☑YES ☐ NO
Are all classification codes/flags (e.g. orphan, OTC drug, pediatric data) entered into tracking system? ***If not, ask the document room staff to make the appropriate entries.***	☒ YES ☐ NO
Application Integrity Policy	
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ora/compliance_ref/aiplist.html*** **If yes**, explain: **If yes**, has OC/DMPQ been notified of the submission? **Comments**:	☐ YES ☑ NO ☐ YES ☐ NO
User Fees	
Form 3397 (User Fee Cover Sheet) submitted	☑ YES PD3009417 (S-007) ☑ YES PD3009418 (S-008) ☐ NO
User Fee Status **Comments:**	☑ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
Note: *505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. It is expected that all 505(b) applications, whether 505(b)(1) or 505(b)(2), will require user fees unless otherwise waived or exempted (e.g., business waiver, orphan exemption).*	
Exclusivity	

Does another product have orphan exclusivity for the same indication? ***Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm***	☐ YES ☑ NO
If yes, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)*** **Comments**:	☐ YES ☐ NO
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.* **Comments**:	☐ YES # years requested: ☑ NO
If the proposed product is a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***): Did the applicant (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b) request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***	☑ Not applicable ☐ YES ☐ NO
505(b)(2) (NDAs/NDA Efficacy Supplements only)	
	☐ **Not applicable**
1. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐ YES ☑ NO
2. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).	☐ YES ☑ NO
3. Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))?	☐ YES ☑ NO

Note: *If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).*	

4. Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.fda.gov/cder/ob/default.htm*** **If yes**, please list below:	☐ YES ☑ NO

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Format and Content	
Do not check mixed submission if the only electronic component is the content of labeling (COL). **Comments**:	☐ All paper (except for COL) ☑ All electronic ☐ Mixed (paper/electronic) ☑ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?	
If electronic submission: paper forms and certifications signed (non-CTD) or electronic forms and certifications signed (scanned or digital signature)(CTD)? ***Forms*** *include: 356h, patent information (3542a), financial disclosure (3454/3455), user fee cover sheet (3542a), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.* **Comments**: Scanned copies of signed forms	☑ YES ☐ NO
If electronic submission, does it follow the eCTD guidance? (*http://www.fda.gov/cder/guidance/7087rev.pdf*) **If not,** explain (e.g., waiver granted): Waiver granted 6/18/08	☐ YES ☑ NO

Form 356h: Is a signed form 356h included? ***If foreign applicant, <u>both</u> the applicant and the U.S. agent must sign the form.*** Are all establishments and their registration numbers listed on the form? **Comments**: The efficacy supplements do not require any mfg site inspections.	☑ YES ☐ NO ☐ YES ☑ NO
Index: Does the submission contain an accurate comprehensive index? **Comments**: The cover letter contains a very abbreviated ToC which does not contain hyperlinks.	☐ YES ☑ NO
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☐ legible ☐ English (or translated into English) ☐ pagination ☐ navigable hyperlinks (electronic submissions only) **If no**, explain: No hyperlinks from ToC to folders and no indices for documents within each folder.	☒ YES ☐ NO
Controlled substance/Product with abuse potential: Abuse Liability Assessment, including a proposal for scheduling, submitted? Consult sent to the Controlled Substance Staff? **Comments**:	☑ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
BLAs/BLA efficacy supplements only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	 ☐ YES ☐ NO
Patent Information (NDAs/NDA efficacy supplements only)	
Patent information submitted on form FDA 3542a? **Comments**: Form FDA 3542a and revised patent certifications were received Oct. 14, 2010.	☒ YES ☐ NO

Debarment Certification	
Correctly worded Debarment Certification with authorized signature? ***If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification.*** ***Note:*** *Debarment Certification should use wording in FD&C Act section 306(k)(l) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"* **Comments**: Not needed for efficacy supplements	☐ YES ☐ NO X N/A
Field Copy Certification (NDAs/NDA efficacy supplements only)	
Field Copy Certification: that it is a true copy of the CMC technical section (***applies to paper submissions only***) ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☑ Not Applicable (*electronic submission or no CMC technical section*) ☐ YES ☐ NO
Financial Disclosure	
Financial Disclosure forms included with authorized signature? ***Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an Agent.*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.* **Comments**: The supplements do not require any studies for which FD is required.	☐ YES ☑ NO
Pediatrics	
<u>PREA</u> ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.* Are the required pediatric assessment studies or a full waiver of pediatric studies included? **If no,** is a request for full waiver of pediatric studies OR a request for partial waiver/deferral and a pediatric plan included? • ***If no, request in 74-day letter.***	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO

• **If yes**, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3) **Comments**:	☐ YES ☐ NO
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, contact PMHS (pediatric exclusivity determination by the Pediatric Exclusivity Board is needed).*** **Comments**:	☐ YES ☑ NO
Prescription Labeling	
Check all types of labeling submitted. **Comments**: PI only submitted in Word and pdf; no xml.	☐ **Not applicable** ☑ Package Insert (PI) ☐ Patient Package Insert (PPI) ☑ Instructions for Use ☐ MedGuide ☐ Carton labels ☐ Immediate container labels ☐ Diluent ☐ Other (specify)
Is electronic Content of Labeling submitted in SPL format? ***If no, request in 74-day letter.*** **Comments**:	☑ YES ☐ NO
Package insert (PI) submitted in PLR format? **If no**, was a waiver or deferral requested before the application was received or in the submission? **If before**, what is the status of the request? ***If no, request in 74-day letter.*** **Comments**:	☑ YES ☐ NO ☐ YES ☐ NO
All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? **Comments**:	☐ YES ☐ NO
MedGuide or PPI (plus PI) consulted to OSE/DRISK? (*send WORD version if available*) **Comments**:	☐ Not Applicable ☐ YES ☐ NO
REMS consulted to OSE/DRISK?	☒ Not Applicable ☐ YES

Comments:	☐ NO
Carton and immediate container labels, PI, PPI, and proprietary name (if any) sent to OSE/DMEDP? **Comments**:	☑ Not Applicable ☐ YES ☐ NO

OTC Labeling	
Check all types of labeling submitted. **Comments**:	☑ **Not Applicable** ☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)
Is electronic content of labeling submitted? ***If no, request in 74-day letter.*** **Comments**:	☐ YES ☐ NO
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.*** **Comments**:	☐ YES ☐ NO
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.*** **Comments**:	☐ YES ☐ NO
Proprietary name, all labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEDP? **Comments**:	☐ YES ☐ NO
Meeting Minutes/SPA Agreements	
End-of Phase 2 meeting(s)? ***If yes, distribute minutes before filing meeting.*** **Comments**:	☐ YES Date(s): ☑ NO
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? ***If yes, distribute minutes before filing meeting.*** **Comments**: Guidance telecon after UN regarding FDA's requirements for the sNDA's	☑ YES Date(s): March 9, 2009 ☐ NO
Any Special Protocol Assessment (SPA) agreements? ***If yes, distribute letter and/or relevant minutes before filing meeting.***	☐ YES Date(s): ☑ NO

Comments:	

ATTACHMENT

MEMO OF FILING MEETING

DATE: July 30, 2009

NDA/BLA #: 21-426/ S-007 & S-008

PROPRIETARY/ESTABLISHED NAMES: Omnitrope (somatropin [rDNA origin]) Injection and for Injection

APPLICANT: Sandoz Inc.

BACKGROUND: The original Omnitrope NDA was approved pursuant to section 505(b)(2) of the FD&C Act on May 30, 2006, for growth hormone (GH) deficiency in children with short stature and in adults. Clinical studies were submitted for the pediatric GH deficiency indication but not for the adult indication. In submissions dated November 24, 2008, (received November 25, 2008) the applicant sought to add two indications (children with short stature associated with Prader-Willi Syndrome [PWS] and children with short stature who are Small for Gestational Age [SGA]) without additional clinical data but with a mode-of-action summary that named literature references (literature not submitted). It was determined that clinical data were required for approval but had not been submitted, and user fees had not been paid for supplements that require clinical data. Therefore, the November submissions were deemed unacceptable for filing (UN). A teleconference was held on March 9, 2009, to describe the information required to support these supplemental applications.

The product is administered as a daily injection and is approved/marketed as a lyophilized powder with separate diluent included and as a solution in cartridges for use with one of two injector pens approved for this NDA.

On June 23, 2009, FDA received notification that user fees had been paid for both supplements. On June 29, 2009, FDA received an amendment to each supplement (dated June 26, 2009) containing literature reports for each indication, the mode of action summary, and copies of the supporting literature. The review clock was started on June 23, 2009; the filing date is August 22, 2009.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Project Management	RPM/CPMS:	Galliers	Y
Cross-Discipline Team Leader (CDTL)	Mary Parks		Y
Clinical	Reviewer:	Dragos Roman	Y

	TL: (Acting)	Dragos Roman	Y
OSE	Reviewer:	N/A	

Clinical Pharmacology	Reviewer:	N/A	
	TL:	N/A	
Biostatistics	Reviewer:	N/A	
	TL:		
Nonclinical (Pharmacology/Toxicology)	Reviewer:	N/A	
	TL:		
Statistics, carcinogenicity	Reviewer:	N/A	
	TL:		
Product Quality (CMC)	Reviewer:	Janice Brown	Y
	TL:	Jim Vidra	N
Microbiology, sterility (*for NDAs/NDA efficacy supplements*)	Reviewer:	N/A	
	TL:		
Bioresearch Monitoring (DSI)	Reviewer:	N/A	
	TL:		
Other reviewers			

OTHER ATTENDEES:
Janice Weiner, MPH, JD, Regulatory Counsel, ORP
Elizabeth Dickinson, JD, OCC
CAPT Michael D. Jones, UF Staff, ORP
Kati Johnson, RPM, DMEP

505(b)(2) filing issues? **If yes,** list issues: Request corrected patent certification for section 505(b) instead of 505(j). (A fine point is that the Paragraph 1 certification should be a Para 2 cert, although a Para 1 can be accepted.)	☐ Not Applicable ☑ YES ☐ NO
Per reviewers, are all parts in English or English	☑ YES

translation? **If no**, explain:	☐ NO

General/ Other Comments: • Form 356h uses two different established names. Request that future 356h forms be submitted with the correct established name. • One clinical review that loosely follows the template will cover both indications, but the studies for each indication will be presented and evaluated separately. No clinical filing template will be archived. • (b) (4) [redacted] • Sandoz certified only for the 5.8 mg strength, but not the 1.5 mg.	**Consults:** Not needed from OSE or SEALD because the NDA has approved PLR labeling, and the growth hormone model labeling (including the new indications) was recently reviewed. ORP & OCC will be notified but consults will not be sent.

Electronic Submission comments **List comments**: No hyperlinks from the abbreviated and only ToC to the folders within the modules.	☑ Not Applicable
CLINICAL **Comments**: (b) (4) [redacted]	☐ Not Applicable ☑ FILE ☐ REFUSE TO FILE ☑ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain: Applications are supported by literature studies.	☐ YES ☑ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an original NME or BLA application, include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***the application did not raise significant public***	☐ YES Date if known: ☑ NO ☐ To be determined Reason:

health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease	
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☑ Not Applicable ☐ YES ☐ NO
CLINICAL PHARMACOLOGY **Comments**:	☑ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☐ NO
BIOSTATISTICS **Comments**:	☑ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☑ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**: Request submission of an EA.	☐ Not Applicable ☑ FILE ☐ REFUSE TO FILE ☑ Review issues for 74-day letter
• Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)?	☐ Not Applicable ☐ YES ☑ NO ☐ YES ☑ NO ☐ YES ☐ NO

Comments: Sandoz submitted a categorical exclusion request on Oct. 18, 2009. It was inadequate and another request justification was submitted March 17, 2010.	
• Establishment(s) ready for inspection?	☑ Not Applicable ☐ YES ☐ NO
▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? **Comments**:	☐ Not Applicable ☐ YES ☐ NO
• Sterile product? **If yes**, was Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**)	☑ YES ☐ NO ☐ YES ☐ NO
FACILITY (BLAs only) **Comments**:	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Mary Parks

GRMP Timeline Milestones: MCR mtg = ~11-23-09
Draft MOR for DD/CDTL = third week February 2010
Communicate labeling to applicant = 3-16-10
Start labeling discussion with applicant = 3-23-10

Action Date = April 23, 2010 ; **UF Date** = April 23, 2010

Comments:

☐	The application is unsuitable for filing. Explain why:
☑	The application, on its face, appears to be suitable for filing. ☐ No review issues have been identified for the 74-day letter. ☑ Review issues have been identified for the 74-day letter. List (optional):

	☑ Standard Review ☐ Priority Review
ACTIONS ITEMS	
☐	Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into tracking system.
☐	If RTF action, notify everybody who already received a consult request, OSE PM., and Product Quality PM. Cancel EER/TBP-EER.
☐	If filed and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	If BLA or priority review NDA, send 60-day letter.
☑	Send review issues/no review issues by day 74
☐	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21426	SUPPL-7	SANDOZ INC	OMNITROPE(SOMATROPIN[RDNA ORIGIN] FORINJ
NDA-21426	SUPPL-8	SANDOZ INC	OMNITROPE(SOMATROPIN[RDNA ORIGIN] FORINJ

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/s/

ENID M GALLIERS
04/20/2010
Filing review was updated to add submission of items requested in 74-day letter.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021426/S-008

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 21426 SUPPL # 007 & 008 HFD # 510/DMEP

Trade Name Omnitrope

Generic Name somatropin (rDNA origin) injectable

Applicant Name Sandoz Inc.

Approval Date, If Known

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(2) SE1

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☐ NO ☒

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

These supplemental applications rely on literature and the previous FDA finding that this product is highly similar to the listed drug cited in the supporting literature. These applications are for Prader Willi Syndrome (PWS)(S-007) and small for gestational age (SGA)(S-008), which were approved previously for the listed drug, Genotropin (NDA 20280).

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☐ NO ☒

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☐

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical

investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☐ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☐ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently

demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
!
IND # YES ☐ ! NO ☐
! Explain:

Investigation #2 !
!
IND # YES ☐ ! NO ☐
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☐

If yes, explain:

==========

Name of person completing form: Enid Galliers
Title: CPMS, DMEP
Date: 4-23-2010

Name of Office/Division Director signing form: Mary Parks, MD
Title: Director, DMEP

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
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NDA-21426	SUPPL-8	SANDOZ INC	OMNITROPE(SOMATROPIN[RDNA ORIGIN] FORINJ

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/s/

ENID M GALLIERS
04/23/2010

MARY H PARKS
04/23/2010

Galliers, Enid M

From: Galliers, Enid M
Sent: Tuesday, April 20, 2010 6:29 PM
To: 'john.pakulski@sandoz.com'
Subject: Revised labeling - NDA 21426/S-007 & S-008 (PWS & SGA)

Importance: High

Attachments: FDA-2-Sandoz.S-007.S-008.Omnitrope.4-20-10.pi_pws.sga.pdf

Dear John:

FDA has some comments and revisions for the combined labeling for Supplements-007 and -008 for Omnitrope. The comment bubbles in the attached labeling indicate FDA's acceptance of or rationale for rejecting the changes proposed by Sandoz in its April 8 emailed version - with one exception. (b) (4)

[redacted]

FDA-2-Sandoz.S
007.S-008.Omnit.

As you know, the goal date for these supplements is Friday, April 23, so we would appreciate your response by tomorrow evening. We will need an official submission of labeling once we agree. Please contact me to discuss the logistics of that submission and if you have any questions or concerns.

Sincerely,

Enid
Enid Galliers
Chief, Project Management Staff
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: 301-796-1211
Fax: 301-796-9712
email: enid.galliers@fda.hhs.gov

Submissions:

FDA CDER
Division of Metabolism and Endocrinology Products
5901-B Ammendale Rd
Beltsville, MD 20705-1266

54 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

ENID M GALLIERS
04/20/2010
Receipt by Mr. Pakulski was confirmed 4/20/2010.

Galliers, Enid M

From: Galliers, Enid M
Sent: Thursday, April 01, 2010 3:29 PM
To: 'john.pakulski@sandoz.com'
Subject: NDA 21426/S-007 & S-008 Labeling

Attachments: S-007.S-008.Omnitrope.4-1-10.pi_pws.sga.doc

Dear Mr. Pakulski:

As discussed in our telephone conversation earlier today, I am enclosing a clean Word version of the revised and combined labeling for the PWS and SGA supplements for Omnitrope. Please note our embedded request to supply actual numbers as well as percentages for Tables 1 & 2. Also per our telecon, we will be looking for your secure email response (of a Word version) to this proposed labeling within a week. If Sandoz proposes changes (other than minor editorial ones), please include the rationale in your response. It will not be necessary to submit SPL at that time.

Please feel free to contact me if you have questions about this application.

S-007.S-008.Om
nitrope.4-1-10.p..

Sincerely,

Enid

Enid Galliers
Chief, Project Management Staff
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: 301-796-1211
Fax: 301-796-9712
email: enid.galliers@fda.hhs.gov

Submissions:

FDA CDER
Division of Metabolism and Endocrinology Products
5901-B Ammendale Rd
Beltsville, MD 20705-1266

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/s/

ENID M GALLIERS
04/02/2010
Emailed to sponsor on 4-1-2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 021426/SUPPL-7 & SUPPL-8 **FILING COMMUNICATION**

Sandoz Inc.
Attention: Jean Domenico
Manager, Regulatory Affairs
2555 West Midway Boulevard
Broomfield, CO 80020

Dear Ms. Domenico:

Please refer to your supplemental new drug applications (NDA) dated November 24, 2008, received June 23, 2009, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for

Omnitrope (somatropin [rDNA origin] Injection 5 mg/1.5 mL and 10 mg/1.5 mL Cartridges and Omnitrope (somatropin [rDNA origin] for Injection 1.5 mg/vial and 5.8 mg/vial.

We also refer to your submissions dated for S-007 and S-008 dated June 26, 2009.

We have completed our filing review and have determined that your supplemental applications are sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this supplemental application is considered filed 60 days after the date we received your supplemental application. The review classification for this supplemental application is **Standard**. Therefore, the user fee goal date is April 23, 2010.

We are reviewing your supplemental application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by March 16, 2010.

During our filing review of your application, we identified the following potential review issues:

1. Your submission dated June 26, 2009, for Supplement-008 refers to an EMEA requirement for a postmarketing immunogenicity study of patients who had been treated for the condition Small for Gestational Age (SGA). Please explain what finding prompted the EMEA to require that study.

2. Submission of an Environmental Assessment (EA) report is required for both supplements.
3. Your Forms FDA 356h list two established names for this product. This introduces unnecessary confusion, and forms submitted in connection with this NDA should only use the name, "somatropin".
4. You have provided a patent certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(I) for each of your supplements. Section 355(j)(2)(A)(vii) describes the patent certifications applicable to abbreviated new drug applications, rather than 505(b)(2) applications. Submit revised patent certifications pursuant to 21 U.S.C. § 355(b)(2) for each of your supplements. Also, we note that a paragraph I certification ("that such patent information has not been filed") would not apply if patent(s) previously have been listed in the Orange Book for the listed drug relied upon (Genotropin) but have expired.
5. You are required to submit patent information on Form FDA 3542a with the filing of an efficacy supplement (see 21 CFR §§ 314.53(d)(2) and 314.70(f)). Submit the required forms.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

If you have not already done so, you must submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html. The content of labeling must be in the Prescribing Information (physician labeling rule) format.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, call Enid Galliers, Chief, Project Management Staff, at (301) 796-1211.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21426	SUPPL-7	SANDOZ INC	OMNITROPE(SOMATROPIN[RDNA ORIGIN] FORINJ
NDA-21426	SUPPL-8	SANDOZ INC	OMNITROPE(SOMATROPIN[RDNA ORIGIN] FORINJ

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/s/

ENID M GALLIERS
09/04/2009
E. Galliers signing on behalf of M. Parks

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 21-426/S-007 & S-008

PRIOR APPROVAL SUPPLEMENTS
RECEIPT OF USER FEES

Sandoz Inc.
Attention: Jean Domenico
Manager, Regulatory Affairs
2555 West Midway Boulevard
Broomfield, CO 80020

Dear Ms. Domenico:

We have received your supplemental drug applications submitted November 24, 2008, pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for
Omnitrope (somatropin [rDNA origin] Injection 5 mg/1.5 mL and 10 mg/1.5 mL Cartridges and
Omnitrope (somatropin [rDNA origin] for Injection 1.5 mg/vial and 5.8 mg/vial.

You were notified in our letter dated January 23, 2009, that your supplemental applications were not accepted for filing due to non-payment of fees. This is to notify you that the Agency has received all fees owed and your supplemental applications have been accepted as of June 23, 2009.

We also acknowledge receipt of your amendments for S-007 and S-008 dated June 26, 2009, on June 29, 2009.

Supplemental application S-007 proposes the following change: the addition of a new indication, Prader-Willi Syndrome (PWS).

Supplemental application S-008 proposes the following change: the addition of a new indication, Small for Gestational Age (SGA).

Unless we notify you within 60 days of the above date that the applications are not sufficiently complete to permit a substantive review, these applications will be filed under section 505(b) of the Act on August 22, 2009, in accordance with 21 CFR 314.101(a).

The receipt date for these submissions (which begins the review for filability) is the date the review division was notified that payment had been received by the bank.

Please cite the application numbers listed above at the top of the first page of all submissions to these applications. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, call me at (301) 796-1211.

Sincerely,

{See appended electronic signature page}

Enid Galliers
Chief, Project Management Staff
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Enid Galliers

7/7/2009 10:30:44 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 21-426/S-007 & S-008

Sandoz Inc.
Attention: Jean Domenico
Manager, Regulatory Affairs
2555 West Midway Boulevard
Broomfield, CO 80020

Dear Ms. Domenico:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Omnitrope (somatropin [rDNA origin]) Injection 5 mg/1.5 mL & 10 mg/1.5 mL and Omnitrope (somatropin [rDNA origin]) for Injection, 1.5 mg/vial & 5.8 mg/vial.

We also refer to the meeting between representatives of your firm and the FDA on March 9, 2009. The purpose of the meeting was to discuss the requirements for resubmission of supplemental applications, S-007 and S-008, for the new indications of Prader-Willi syndrome and Small for Gestational Age (SGA), respectively.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-1211.

Sincerely,

{See appended electronic signature page}

Enid Galliers
Chief, Project Management Staff
Division of Metabolism and Endocrinology Products (DMEP)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

Meeting Type: C

Meeting Category: Guidance

Meeting Date and Time: March 9, 2009,

Meeting Location: Telephone

Application Number: NDA 21-426/S-007 & S-008

Product Name: Omnitrope (somatropin [rDNA origin]) injection & for injection

Received Briefing Package: February 12, 2009

Sponsor Name: Sandoz, Inc.

Meeting Requestor: Jean Domenico, Sandoz, Inc.

Meeting Chair: Mary Parks

Meeting Recorder: Enid Galliers

Meeting Attendees:

FDA Attendees: (Title and Office/Division)

Kim Dettelbach, J.D.), Associate Chief Counsel, Office of Chief Counsel

Center for Drug Evaluation and Research (CDER)
Dragos Roman, MD, Medical Officer, Division of Metabolism and Endocrinology Products (DMEP)
Robert Perlstein, MD, Medical Officer, DMEP
Mary Parks, MD, Director, DMEP
Kati Johnson, Regulatory Project Manager, DMEP
Enid Galliers, Chief, Project Management Staff, DMEP
CAPT Michael Jones, User Fee Staff, Office of Regulatory Policy (ORP)
Janice Weiner, J.D., M.P.H., Regulatory Counsel, Division of Regulatory Policy 1, ORP

Sponsor Attendees:

Jean Domenico, Manager, Regulatory Affairs, Sandoz Inc.
Martha Manning, Vice President, legal and General Counsel, Sandoz, Inc.
Maria Saurwein, Head Regulatory Affairs Group Biopharmaceuticals, Sandoz GmbH
Ingrid Schwarzenberger, Head of Biopharmaceuticals, Sandoz GmbH
Uwe Gosslar, Regulatory Affairs Manager, Omnitrope, Sandoz GmbH
Alexander Berghout, Head Global Clinical Research & Development, Sandoz Biopharmaceuticals
(b) (4)

1.0 BACKGROUND

On May 30, 2006, the Omnitrope NDA was approved for the treatment of pediatric and adult growth hormone deficiency. Omnitrope cited Genotropin as the listed drug upon which it relied pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. At that time, Genotropin had unexpired orphan exclusivity for the indications, treatment of Prader-Willi Syndrome (PWS) and Small for Gestational Age (SGA). Sandoz Inc. submitted supplements dated November 24, 2008, to the Omnitrope NDA requesting approval of PWS (S-007) and SGA (S-008). Sandoz included a summary and a list of references concerning the mechanism of action of growth hormone and stated that Genotropin's exclusivity for those indications had expired.

FDA subsequently determined that clinical data (which includes literature reports) were necessary for the approval of these indications. Since user fees for supplements requiring clinical data for approval had not been paid, the supplemental applications were found unacceptable for filing. FDA issued an "unacceptable for filing" letter on January 23, 2009. On February 12, 2009, Sandoz requested a telephone meeting to explain the requirements for approval of the PWS and SGA supplements, and the meeting was scheduled for March 9, 2009. FDA sent preliminary responses to the sponsor's questions on March 5, 2009.

2.0 DISCUSSION

Sponsor's questions appear in **bold** text. FDA's *preliminary* responses are shown in *italics*. Discussion at the meeting and post-meeting comments appear in non-italicized, non-bolded text.

Question 1. Would the Division concur that it would have been able to grant approval for these two additional indications in the original 505(b)(2) NDA, but for the orphan drug exclusivity, which was still in effect at the time of the original approval?

FDA Response: No, we do not concur. The original 505(b)(2) application for Omnitrope did not seek approval (i.e., tentative approval pending expiration of orphan drug exclusivity) for the Prader-Willi syndrome and Small for Gestational Age (SGA) indications. If a request and supporting data had been submitted with the original 505(b)(2) application for the Prader-Willi syndrome and SGA indications, the Division would have applied the same review standards as for the adult growth hormone deficiency (GHD) indication. Therefore (and consistent with the standards applied for the adult GHD indication in the original Omnitrope application), the Division recommends that your 505(b)(2) supplements seeking approval for the Prader-Willi syndrome and SGA indications include, at a minimum:

- *a summary of the clinical data obtained with the listed drug relied upon (Genotropin) in support of the Prader-Willi syndrome and SGA indications;*
- *a scientific justification supporting the appropriateness of reliance on the Agency's finding of safety and/or effectiveness for Genotropin for these indications to support approval of Omnitrope for these indications (e.g., the "mechanism of action" summary previously submitted, accompanied by cited literature references); and*
- *a summary of the relevant clinical trials involving somatropin conducted in the Prader-Willi syndrome and SGA populations and published to date . (The purpose of this recommendation is to provide context for the data obtained with the listed drug relied upon with respect to safety and effectiveness of somatropin in non-GH deficient short stature syndromes. This information would be considered supportive to the approval of this application.)*

The clinical summary for the listed drug relied upon constitutes "clinical data" for purposes of Prescription Drug User Fees. As a general matter, please note, that clinical data can be either study reports or literature reports. We believe that the data required for approval, see above, meet the definition of clinical data and each supplement should be assessed a full supplement fee.

Issues further discussed during the meeting and clarifications to follow-up questions:

Expanding on the answer provided for Question 1/ bullet 2, and in response to a request for an example of what the NDA supplement should include, the medical reviewer suggested the following: 1) submit a different, individualized section for each indication (i.e. Prader-Willi syndrome and SGA); 2) in each of the two sections (i.e. the Prader-Willi syndrome section and the SGA section, respectively) provide the scientific argument as to why Sandoz may rely on the Agency's finding of safety and effectiveness for Genotropin to support approval of Omnitrope for these indications 3) provide the full text of the references cited in support this argument so that they can be reviewed by the Division.

The review clock will be re-set at the time of the receipt of the user fee (which takes into account the time for the processing of the user fee by the financial institution and subsequent notification to the Agency). Submission of the clinical data discussed above should be made at about the same time as the submission of the user fee; absence of such data at the time of the filing meeting will result in a refuse to file action.

FDA also advised that the proposed supplements would be considered 505(b)(2) supplements that relied on the Agency's finding of safety and effectiveness for Genotropin. Accordingly, the supplements would be required to contain an appropriate patent certification or statement for any listed patents for the listed drug relied upon and comply with applicable regulatory requirements.

Post meeting clarification to the answer provided in Question 1/bullet 1: the summary of the clinical data obtained with the listed drug relied upon in support of the Prader-Willi syndrome and SGA indications is intended to refer to published literature describing studies with Genotropin (i.e., that may be in addition to the studies described in Genotropin product labeling).

Question 2. Does the Division concur that, in the context of a 505(b)(2) application, these are and/or could be routine labeling supplements to add these now-non-exclusive orphan indications to the Omnitrope label, particularly given our reliance on FDA's prior findings of safety and effectiveness of the RLD in treating these orphan indications?

FDA Response: No, we do not concur. Your requests for the addition of a new indication for Omnitrope would be categorized as efficacy supplements (and not "routine labeling supplements") *and will require clinical data for approval, as described in the response to Question 1. The Division is currently applying the same scientific requirements for any new indication (e.g., Prader-Willi syndrome and SGA) for Omnitrope that were applied to the adult GHD indication in the initial Omnitrope 505(b)(2) application.*

Meeting Discussion: Sandoz noted that the responses to questions 2 through 4 were clear and did not require further discussion.

Question 3. We would appreciate the Division please explaining why anything additional beyond what the Division originally indicated we should submit is necessary to add these previously-exclusive indications to the label, and what it is that the Division considers as being required in an sNDA proposing to add these now-non-exclusive orphan indications to the Omnitrope label.

FDA Response: The Division's requirements for the Prader-Willi syndrome and SGA indications are consistent with the type of data that supported the scientific appropriateness of reliance on the Agency's finding of safety and effectiveness for Genotropin for the adult growth hormone deficiency indication. See also responses to Questions 1 and 2.

Question 4. In light of the unique circumstances involving these NDAs, does the Division concur that an expedited review of these sNDAs is warranted?

FDA Response: No.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

Clarify the details of the clinical data/literature that the sponsor should submit to support the additional indications.

4.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Provide more details of required clinical data.	FDA	Issue with meeting minutes. Clarifications have been included in final minutes.
Determine if sponsor will pursue the new indications	Sponsor	By late March 2009, Sandoz confirmed by phone its intention to pay the required user fees for both indications but timelines for preparing the data for each supplement and their submissions would be staggered. As of late May, neither supplement had been resubmitted.

5.0 ATTACHMENTS AND HANDOUTS

There were no attachments or handouts for the meeting minutes.

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/s/

Enid Galliers
7/2/2009 08:58:21 AM

Galliers, Enid M

From: Galliers, Enid M
Sent: Thursday, March 05, 2009 5:03 PM
To: 'jean.domenico@sandoz.com'
Subject: Omnitrope.PWS_SGA meeting - PRELIMINARY RESPONSES
Attachments: Omnitrope.PWS_SGA.PRELIM_ RESP.UF_mtg.pdf

Hi Jean,

The attached document contains the FDA preliminary responses to the questions Sandoz submitted for the telecon that is scheduled for noon (Eastern time) on Monday, March 9, 2009.

Please contact me if you have any questions or want to cancel the telecon.

Thanks,

Enid

Enid Galliers
Chief, Project Management Staff
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: 301-796-1211
Fax: 301-796-9712
email: enid.galliers@fda hhs.gov

FDA PRELIMINARY RESPONSES SENT TO **Sandoz Inc**. on **March 5, 2009**

APPLICATION: NDA 21-426/S-007 & S-008

DRUG PRODUCTS: Omnitrope (somatropin [rDNA origin]) injection & for injection

MEETING TYPE: C - Guidance Meeting

INDUSTRY MEETING DATE: March 9, 2009

INDUSTRY MEETING PLACE: TELEPHONE

RPM: ENID GALLIERS

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for March 9, 2009, at 12 noon Eastern Time between Sandoz Inc. and the Division of Metabolism and Endocrinology Products. This material is shared to promote a collaborative and successful discussion at the meeting. The minutes of the meeting will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments. If these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the RPM). If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face-to-face to teleconference). It is important to remember that some meetings, particularly milestone meetings, are valuable even if the pre-meeting communications are considered sufficient to answer the questions. Note that if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, we may not be prepared to discuss or reach agreement on such changes at the meeting. If any modifications to the development plan or additional questions for which you would like FDA feedback arise prior to the meeting, contact the Regulatory Project Manager to discuss the possibility of including these for discussion at the meeting.

Sponsor's Questions and FDA's Preliminary Responses

Question 1. Would the Division concur that it would have been able to grant approval for these two additional indications in the original 505(b)(2) NDA, but for the orphan drug exclusivity, which was still in effect at the time of the original approval?

FDA Response: No, we do not concur. The original 505(b)(2) application for Omnitrope did not seek approval (i.e., tentative approval pending expiration of orphan drug exclusivity) for the Prader-Willi syndrome and Small for Gestational Age (SGA) indications. If a request and supporting data had been submitted with the original 505(b)(2) application for the Prader-Willi syndrome and SGA indications, the Division would have applied the same review standards as for the adult growth hormone deficiency (GHD) indication. Therefore (and consistent with the standards applied for the adult GHD indication in the original Omnitrope application), the Division recommends that your 505(b)(2) supplements seeking approval for the Prader-Willi syndrome and SGA indications include, at a minimum:

- *a summary of the clinical data obtained with the listed drug relied upon (Genotropin) in support of the Prader-Willi syndrome and SGA indications;*
- *a scientific justification supporting the appropriateness of reliance on the Agency's finding of safety and/or effectiveness for Genotropin for these indications to support approval of Omnitrope for these indications (e.g., the "mechanism of action" summary previously submitted, accompanied by cited literature references); and*
- *a summary of the relevant clinical trials involving somatropin conducted in the Prader-Willi syndrome and SGA populations and published to date . (The purpose of this recommendation is to provide context for the data obtained with the listed drug relied upon with respect to safety and effectiveness of somatropin in non-GH deficient short stature syndromes. This information would be considered supportive to the approval of this application.)*

The clinical summary for the listed drug relied upon constitutes "clinical data" for purposes of Prescription Drug User Fees. As a general matter, please note, that clinical data can be either study reports or literature reports. We believe that the data required for approval, see above, meet the definition of clinical data and each supplement should be assessed a full supplement fee.

Question 2. Does the Division concur that, in the context of a 505(b)(2) application, these are and/or could be routine labeling supplements to add these now-non-exclusive orphan indications to the Omnitrope label, particularly given our reliance on FDA's prior findings of safety and effectiveness of the RLD in treating these orphan indications?

FDA Response: No, we do not concur. Your requests for the addition of a new indication for Omnitrope would be categorized as efficacy supplements (and not "routine labeling supplements") *and will require clinical data for approval, as described in the response to Question 1. The Division is currently applying the same scientific requirements for any new indication (e.g., Prader-Willi syndrome and SGA) for Omnitrope that were applied to the adult GHD indication in the initial Omnitrope 505(b)(2) application.*

Question 3. We would appreciate the Division please explaining why anything additional beyond what the Division originally indicated we should submit is necessary to add these previously-exclusive indications to the label, and what it is that the Division considers as being required in an sNDA proposing to add these now-non-exclusive orphan indications to the Omnitrope label.

FDA Response: The Division's requirements for the Prader-Willi syndrome and SGA indications are consistent with the type of data that supported the scientific appropriateness of reliance on the Agency's finding of safety and effectiveness for Genotropin for the adult growth hormone deficiency indication. See also responses to Questions 1 and 2.

Question 4. In light of the unique circumstances involving these NDAs, does the Division concur that an expedited review of these sNDAs is warranted?

FDA Response: No.

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/s/

Enid Galliers
3/5/2009 05:26:15 PM
CSO

MEMORANDUM OF TELECON

DATES: January 23, 2009; 5:00 PM Eastern Time (VOICE MAIL MESSAGE)
and
January 26, 2009; 4:00 PM Eastern Time (DISCUSSION)

APPLICATION NUMBERS: NDA 21-426/ S-007 & S-008
Omnitrope (somatropin [rDNA origin] Injection and for Injection

BETWEEN:

Name: Jean Pederson
Regulatory Affairs
Phone: 303-438-4242 (Mountain Time Zone)
Representing: Sandoz Inc.

AND

Name: Enid Galliers, CPMS
Division of Metabolism and Endocrinology Products, HFD-510

SUBJECT: UN letters for supplements and potential Refuse to File issues

BACKGROUND: On November 25, 2008, FDA received supplements submitted by Sandoz to add the indications of Prader-Willi Syndrome (PWS)(S-007) and small for gestational age (SGA)(S-008) to its approved 505(b)(2) NDA for recombinant human growth hormone. The only supporting material provided was a summary of information concerning the mechanism of action of growth hormone and a list of literature (without copies of the references). An internal filing meeting was held on January 22, 2009, and additional discussion took place between Mike Jones of CDER's User Fee Staff and me on January 23. Subsequently, the DMEP medical team concluded that mechanism of action (MoA) information is needed to support approval of the supplements. The MoA information needs to be supported by reports of clinical studies (literature or data) and therefore a User Fee (UF) would be required for each supplement. On January 23, 2009, DMEP issued letters stating that the supplements are unacceptable for filing due to non-payment of required UF's.

VOICE MESSAGE (Jan. 23, 2009): A call to the Sandoz receptionist revealed that Ms. Pederson was away from the office for the rest of the afternoon. Therefore, I left the following message for Ms. Pederson.

> Both supplements required mechanism of action (MoA) information to support approval of each supplement. The MoA information would need to be supported by reports of clinical studies (literature or data) and therefore a User Fee (UF) would be required for each supplement. We have issued letters stating that the supplements are unacceptable

for filing due to non-payment of required UF's. The UF for each supplement is $623,600.

If Sandoz chooses to pursue approval, the address for UF payment is on the letters. Also, Sandoz would need to submit some additional information that I would be happy to discuss with her on Monday.

DISCUSSION (Jan. 26, 2009): I called Ms. Pederson to elaborate on the message I had left on Friday and answer any questions. She said she thought that my message indicated that new clinical studies would be needed, and I replied that it appeared literature reports – including reports of clinical studies - could be used to support the mechanism of action proposed to provide the scientific link between the information in the approved NDA and the proposed new indications; i.e., that we were not requesting new clinical studies. I also verified the amount of the user fee per supplement.

Ms. Pederson mentioned that she had had a discussion with another RPM in DMEP prior to submission of the new indications and asked why she had not been told about this then. I told her I knew about those discussions and said that we had not evaluated in detail what would actually be required to approve the new indications or attempted to answer questions regarding user fees until the supplemental applications actually arrived. Because this 505(b)(2) "follow-on" protein NDA was breaking new ground, we had to think through some issues that had not arisen before. I explained that the "unacceptable for filing" letters that were in the mail were different from a refusal to file in that the former is based solely on whether a user fee payment is due.

We also talked about additional information that should be included when the supplements are resubmitted after payment of user fees. I said that the literature reports for the mechanism of action should be submitted (electronically – preferably with hyperlinks from the summary) and that we would appreciate if Sandoz would indicate what listed drug(s) was the subject of the investigation in each report or that no brand names had been indicated. I suggested that the mechanism of action information be located in a folder called "clinical data" instead of "CMC" as described in the old guidance for electronic non-CTD submission. I asked if the firm had obtained a waiver for submission of non-eCTD electronic submissions for this NDA, and she said she would check on that.

I said that the resubmissions should include SPL versions of the labeling, tables of contents that identify electronic and/or paper submissions, valid hyperlinks, appropriate patent certifications (including a statement of no relevant patents, if applicable), Forms 3397 (User Fee Cover Sheet), 3674 (Clinical Trials Registration) and 3542a (Patent Information). I asked Ms. Pederson to call me if Sandoz should decide to pursue approval in case there were any other issues to discuss. She agreed to that and to resubmit the supplements to the same sNDA numbers if the user fees were paid. Since she had not yet received the late-issued acknowledgment letters, I told her the

supplement numbers assigned to the three November 24, 2008, submissions (S-006 was a CMC supplement to extend expiry dating). In response to her asking what information should be in the labeling history, we went over that in detail.

Ms. Pederson asked about what procedure to follow if the decision is to not pay the fees, and I asked for notification in the form of withdrawal letters. She agreed to a written withdrawal as well as telephone notification. She said that the sponsor in Europe would need to be consulted so a decision might not be immediate.

_____

Enid Galliers
Chief, Project Management Staff, DMEP

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/s/

Enid Galliers
2/5/2009 03:50:07 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-426/S-008

Sandoz Inc.
Attention: Jean Pederson
Senior Associate, Regulatory Affairs
2555 West Midway Boulevard
Broomfield, CO 80020

Dear Ms. Pederson:

We have received your supplemental new drug application submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:

Omnitrope (somatropin [rDNA origin] Injection 5 mg/1.5 mL and 10 mg/1.5 mL Cartridges and Omnitrope (somatropin [rDNA origin] for Injection 1.5 mg/vial and 5.8 mg/vial

NDA Number: 21-426

Supplement Number: S-008

Date of Application: November 24, 2008

Date of Receipt: November 25, 2008

This supplemental application proposes the following change: the addition of a new indication, Small for Gestational Age (SGA).

We have not received the appropriate user fee for this application. An application is considered incomplete and cannot be accepted for filing until all fees owed have been paid. Therefore, this application is not accepted for filing. We will not begin a review of this application's adequacy for filing until FDA has been notified that the appropriate fee has been paid. Payment should be submitted to the following address:

Food and Drug Administration
P.O. Box 70963
Charlotte, NC 28262

Checks sent by a courier should be addressed to:

Wachovia Bank
Attn: Food and Drug Administration, Lockbox 70963
1525 West WT Harris Blvd., Room NC0810
Charlotte, NC 28262

NOTE: Please include the User Fee I.D. Number, the Application number, and the FDA P.O. Box number (P.O. Box 70963) on the enclosed check. It would be helpful if you included the user fee cover sheet (Form FDA 3397) with your payment.

Please cite the NDA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you wish to send payment by wire transfer, or if you have any other questions, please call Beverly Friedman or Mike Jones at 301-796-3602.

If you have any questions, call me at (301) 796-1211.

Sincerely,

{See appended electronic signature page}

Enid Galliers
Chief, Project Management Staff
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Enid Galliers

1/23/2009 04:47:10 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-426/S-008

Sandoz Inc.
Attention: Jean Pederson
Senior Associate, Regulatory Affairs
2555 West Midway Boulevard
Broomfield, CO 80020

PRIOR APPROVAL SUPPLEMENT

Dear Ms. Pederson:

We have received your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Products:

Omnitrope (somatropin [rDNA origin] Injection 5 mg/1.5 mL and 10 mg/1.5 mL Cartridges and Omnitrope (somatropin [rDNA origin] for Injection 1.5 mg/vial and 5.8 mg/vial

NDA Number: 21-426

Supplement number: S-008

Review Priority Classification: Standard (S)

Date of supplement: November 24, 2008

Date of receipt: November 25, 2008

This supplemental application proposes the following change: the addition of a new indication, Small for Gestational Age (SGA).

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on **January 24, 2009**, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be **September 25, 2009**.

Please cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products (DMEP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have questions, call me at (301) 796-1211.

Sincerely,

{See appended electronic signature page}

Enid Galliers
Chief, Project Management Staff
Division of Metabolism and Endocrinology Products (DMEP)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Enid Galliers

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