

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Approval Package for:**

***APPLICATION NUMBER:***

**NDA 21-426/S-004**

***Trade Name:*** Omnitrope

***Generic Name:*** somatropin (rDNA origin) injection

***Sponsor:*** Sandoz, Inc

***Approval Date:*** 8/25/2008

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

- Pediatric: Treatment of children with growth failure due to growth hormone deficiency GHD (1.1)
- Adult: Treatment of adults with either adult onset or childhood onset GHD (1.2)

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*  
**NDA 21-426/S-004**

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**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**NDA 21-426/S-004**

**APPROVAL LETTER**



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-426/S-004

Sandoz, Inc  
Attention: Beth Brannan  
Director, Regulatory Affairs  
2555 W. Midway Blvd., P.O. Box 446  
Broomfield, CO 80038

Dear Ms. Brannan:

Please refer to your supplemental new drug application dated March 28, 2008, received March 31, 2008, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Omnitrope (somatropin [rDNA origin] for injection) and Omnitrope (somatropin [rDNA origin] injection).

We acknowledge receipt of your submissions dated April 22, and July 30, 2008.

This supplemental new drug application provides for a new strength cartridge (10 mg/1.5 mL) of the liquid formulation for use in a new reusable injector pen, Omnitrope Pen 10.

We completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) for the package insert and Instructions for Use must be identical to the enclosed labeling. The FPL for the cartridge label, cartridge cartons, and pen device carton is acceptable.

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

MEDWATCH  
Food and Drug Administration  
Suite 12B05  
5600 Fishers Lane  
Rockville, MD 20857

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 Kati Johnson, Regulatory Project Manager, at (301) 796-1234.

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:    Package Insert  
                  Instructions for Use-Omnitrope Pen 10  
                  Omnitrope Pen 10 Carton  
                  Omnitrope Cartridge (10 mg/1.5 mL) Label  
                  Omnitrope Cartridge (10 mg/1.5 mL) Carton (1-count)  
                  Omnitrope Cartridge (10 mg/1.5 mL) Carton (5-count)  
                  Omnitrope Cartridge (10 mg/1.5 mL) Carton (10-count)

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

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Mary Parks  
8/25/2008 11:56:29 AM

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

***APPLICATION NUMBER:***  
**NDA 21-426/S-004**

**LABELING**

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all of 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

### 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 (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)
- **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)
- 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 (5.2).
- 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 (5.3).
- Intracranial Hypertension: Exclude preexisting papilledema. May develop and is usually reversible after discontinuation or dose reduction (5.4).
- Fluid Retention (i.e., edema, arthralgia, carpal tunnel syndrome - especially in adults): May occur frequently. Reduce dose as necessary (5.5).
- Hypothyroidism: May first become evident or worsen (5.6)
- Slipped Capital Femoral Epiphysis: May develop. Evaluate children with the onset of a limp or hip/knee pain (5.7)
- Progression of Preexisting Scoliosis: May develop (5.8)

### 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 800-525-2492 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).**

### DRUG INTERACTIONS

- Inhibition of 11 $\beta$ -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).
- 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)

### USE IN SPECIFIC POPULATIONS

See 17 for PATIENT COUNSELING INFORMATION and FDA Approved Product Labeling

Approved:

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## FULL PRESCRIBING INFORMATION

Omnitrope (somatropin [rDNA origin]) Cartridges and for Injection

### 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).

#### 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.

In general, confirmation of the diagnosis of adult GHD in both groups usually requires an appropriate GH stimulation test. However, confirmatory GH stimulation testing may not be required in patients with congenital/genetic GHD or multiple pituitary hormone deficiencies due to organic disease.

### 2 DOSAGE AND ADMINISTRATION

For subcutaneous injection.

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 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. Serum insulin-like growth factor I (IGF-I) levels may be useful during dose titration.

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

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

##### *Pediatric Growth Hormone Deficiency (GHD)*

Generally, a dosage of 0.16 - 0.24 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. Omnitrope® is not indicated for the treatment of pediatric patients who have growth failure due to genetically confirmed Prader-Willi syndrome.

#### **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 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.

### **5.3 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 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.

### **5.4 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.

Funduscopy 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.

### **5.5 Fluid Retention**

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

### **5.6 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.

In patients with hypopituitarism (multiple hormone deficiencies), standard hormonal replacement therapy should be monitored closely when somatropin therapy is administered.

### **5.7 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.

### **5.8 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.

### **5.9 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.

### **5.10 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.

### 5.11 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<sup>b</sup> and/or most frequently observed<sup>a</sup> adverse reactions during treatment with somatropin:

- <sup>b</sup>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)]
- <sup>b</sup>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)]
- <sup>a,b</sup>Glucose intolerance including impaired glucose tolerance/impaired fasting glucose as well as overt diabetes mellitus [see *Warnings and Precautions* (5.4)]
- <sup>b</sup>Intracranial hypertension [see *Warnings and Precautions* (5.5)]
- <sup>b</sup>Significant diabetic-retinopathy [see *Contraindications* (4.4)]
- <sup>b</sup>Slipped capital femoral epiphysis in pediatric patients [see *Warnings and Precautions* (5.8)]
- <sup>b</sup>Progression of preexisting scoliosis in pediatric patients [see *Warnings and Precautions* (5.9)]
- <sup>a</sup>Fluid retention manifested by edema, arthralgia, myalgia, nerve compression syndromes including carpal tunnel syndrome/paraesthesias [see *Warnings and Precautions* (5.6)]
- <sup>a</sup>Unmasking of latent central hypothyroidism [see *Warnings and Precautions* (5.7)]
- <sup>a</sup>Injection site reactions/rashes and lipoatrophy (as well as rare generalized hypersensitivity reactions) [see *Warnings and Precautions* (5.11)]

### 6.2 Clinical Trials Experience

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

#### *Clinical Trials in Pediatric GHD Patients*

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.

The following events were observed during clinical studies with OMNITROPE<sup>®</sup> Cartridge conducted in children with GHD:

**Table 1:** Incidence of adverse reactions occurring in  $\geq 5\%$  pediatric patients with GHD during treatment with OMNITROPE<sup>®</sup> Cartridge (n=86)

<u>Adverse Event</u>	<u>Number (%)</u>
Elevated HbA1c	14
Eosinophilia	12

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  $\geq 5\%$  pediatric patients with GHD during treatment with OMNITROPE® for injection (n=44)

<b>Adverse Event</b>	<b>Number (%)</b>
Hypothyroidism	16%
Elevated HbA1c	14%
Eosinophilia	11%
Hematoma	9%
Headache	7%
Hypertriglyceridemia	5%
Leg Pain	5%

#### *Clinical Trials in Adult GHD Patients*

In clinical trials with somatropin in 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.

### **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 (5.2)*].

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 Inhibition of 11 $\beta$ -Hydroxysteroid Dehydrogenase Type 1 (11 $\beta$ HSD-1)**

Somatropin inhibits 11 $\beta$ -hydroxysteroid dehydrogenase type 1 (11 $\beta$ HSD-1) in adipose/hepatic tissue and may significantly impact the metabolism of cortisol and cortisone. As a consequence, in patients treated with somatropin, previously undiagnosed central (secondary) hypoadrenalism may be unmasked requiring glucocorticoid replacement therapy. In addition, patients treated with glucocorticoid replacement therapy for previously diagnosed hypoadrenalism may require an increase in their maintenance or stress doses; 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 the 11 $\beta$ HSD-1 enzyme.

### **7.2 Glucocorticoid Replacement**

Excessive glucocorticoid therapy may attenuate the growth promoting effects of somatropin in children. Therefore, glucocorticoid replacement therapy should be carefully adjusted in children with concomitant GH and glucocorticoid deficiency 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<sup>®</sup>. It is not known whether Omnitrope<sup>®</sup> can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity.-

Reproduction studies carried out with another approved 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, somatropin doses of 0.3, 1, and 3.3 mg/kg/day of another approved 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 offsprings due to another approved 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<sup>®</sup> is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Omnitrope<sup>®</sup> is administered to a nursing woman.

#### **8.5 Geriatric Use**

The safety and effectiveness of Omnitrope<sup>®</sup> 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.



Omnitrope<sup>®</sup> Pen 10

Instructions for Use

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

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**READ FIRST:** Important Safety Information

1. Read the following instructions before using the Omnitrope<sup>®</sup> Pen 10. Ask your healthcare professional if there is something you do not understand.
2. The Omnitrope<sup>®</sup> Pen 10 is a pen injector. It is for use with Omnitrope<sup>®</sup> cartridges 10 mg/1.5 mL (30 IU) and BD<sup>®</sup> 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<sup>®</sup> Pen 10 unless someone with good eyesight is able to help.

## DOS AND DON`TS

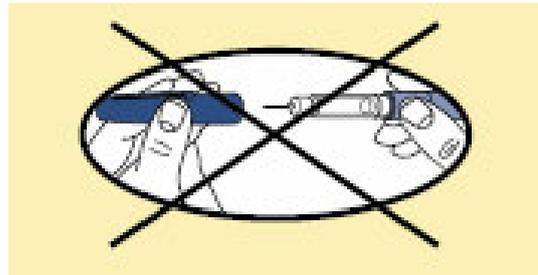
### DOs

1. Always keep Omnitrope<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> Pen 10 with a pen needle attached.**

**Never recap pen with pen needle on.**



Storing or carrying your Omnitrope<sup>®</sup> 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<sup>®</sup> 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.

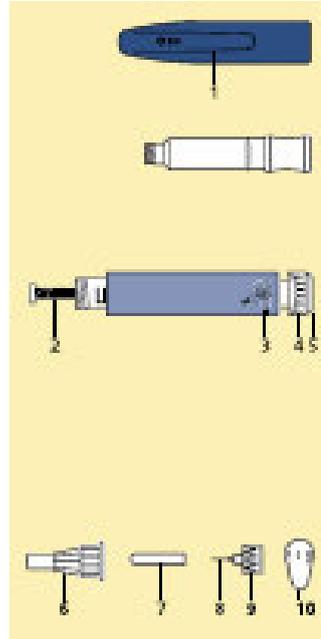
**How it works**

(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**

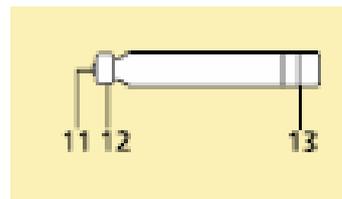
**PEN BODY**

- 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.**

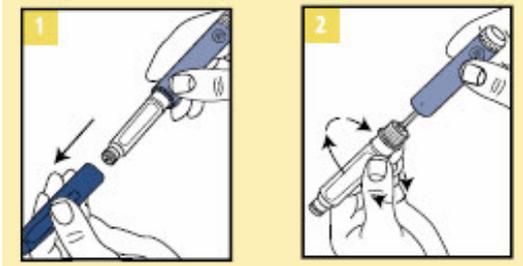


**CARTRIDGE**

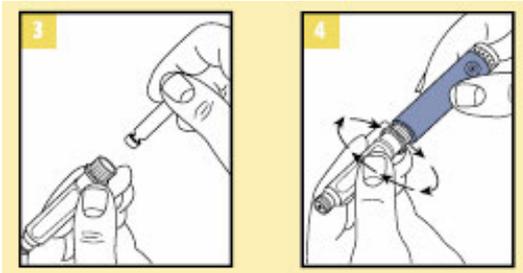
- 11. Rubber septum
- 12. Metal Cap
- 13. Cartridge plunger

## HOW TO USE YOUR OMNITROPE® PEN 10

### LOADING THE CARTRIDGE INTO THE PEN



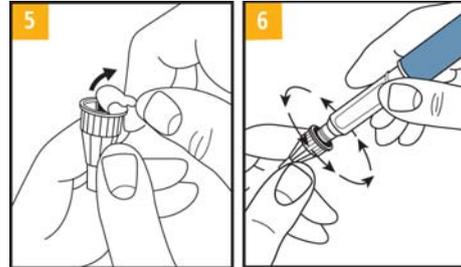
1. Remove the pen cap by pulling it off the pen.
2. Unscrew the cartridge holder from the pen body



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 yellow line mark on the pen body.

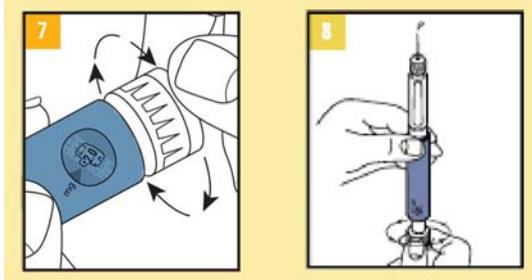
**Note** - Do not overtighten.

### 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<sup>®</sup> Pen 10.

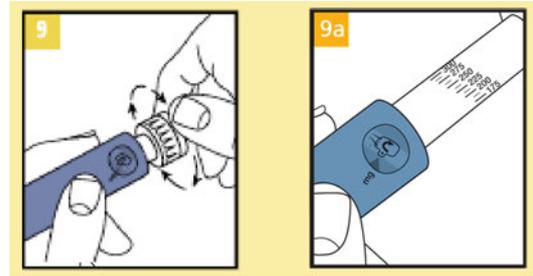
### For a New Cartridge Only

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<sup>®</sup> 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

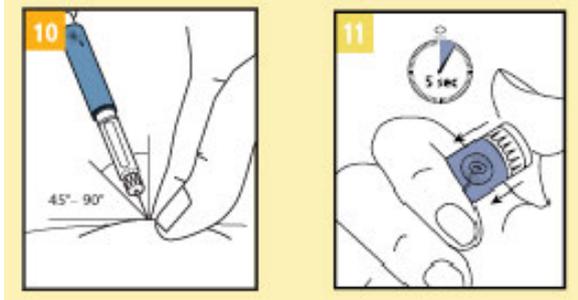
If you turn the dose knob past your dose, **do not dial backwards.**

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 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.

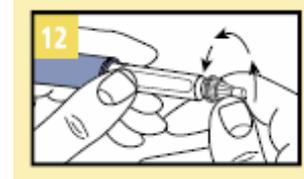
**If medicine continues to drip** from the pen needle after injection, hold the pen needle in your skin for a longer time the next time you inject.

**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<sup>®</sup> 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<sup>®</sup> 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**

<b>PROBLEM</b>	<b>POSSIBLE CAUSE</b>	<b>HOW TO FIX</b>
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<sup>®</sup> Pen 10 contains a somatotropin cartridge, it has to be stored in the refrigerator between 36 and 46°F (2 and 8°C).

Protect your Omnitrope<sup>®</sup> 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<sup>®</sup> Pen 10 can be reloaded with a new cartridge and be used multiple times.

Your Omnitrope<sup>®</sup> 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<sup>®</sup> Pen 10 is damaged or you cannot get it to work contact your local Omnitrope<sup>®</sup> Pen 10 provider (phone 800-525-2492). For questions or additional information please call 1800 525 8747. Do not attempt to repair the pen yourself.

## GUARANTEE

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

If your Omnitrope<sup>®</sup> Pen 10 is defective in materials or workmanship within the period of the guarantee, the local pen provider will replace the Omnitrope<sup>®</sup> Pen 10 and/or rectify the fault at its own cost.

In case of complaints, please contact your local pen provider to report a complaint.

This guarantee is invalid if your Omnitrope<sup>®</sup> 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<sup>®</sup> Pen 10 complies with the accuracy requirements of the International Standard EN ISO11608-1/2000 Pen Injectors for medical use - Requirements and test methods.

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## IMPORTANT PERSONAL NOTES

Date I first used the Omnitrope<sup>®</sup> Pen 10:  
\_\_\_\_\_ (dd/mm/yy)

Pen log no:  
\_\_\_\_\_

Additional Comments:  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

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## SERVICE MATERIALS\*



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



**REFRIGATOR STORAGE BOX** to protect the drug from odors and accidental spills



**COOLBAG** to help maintain Omnitrope<sup>®</sup> at refrigerator temperature when traveling

\* Optional; please check availability with your local Sandoz representative

Produced for:  
Sandoz GmbH  
Biochemiestr. 10  
A-6250 Kundl  
Austria

Authorized representative  
Becton Dickinson France S.A.S.  
38801 Le Pont de Claix Cedex  
France

BD medical-Pharmaceutical Systems  
1 Becton Drive  
Franklin Lanes, NJ 07417  
USA

Omnitrope is a trademark of Novartis.  
BD and BD Logo are trademarks of Becton, Dickinson and  
Company.

OP5.ifU.06.1

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**NDA 21-426/S-004**

**CHEMISTRY REVIEW(S)**

**DIVISION OF POST-MARKETING VALUATION**  
**Review of Chemistry, Manufacturing, and Controls**

**NDA #** 21-426 **SUPPLEMENT:** SCF-004

**REVIEW DATE:** 21-Jul-2008

**SUPPLEMENT(S) PROVIDE(S) FOR:** an addition of an Omnitrope Cartridge 10 mg/1.5 mL glass cartridge

**TYPE of SUPPLEMENT:**

SUPAC  CBE-0  CBE-30  Prior Approval  Bundled Review  Expedited Review

**THE USER FEE GOAL DATE:** 31-Jul-2008

<u>SUBMISSION DATE:</u>	<u>DOC. TYPE</u>	<u>DOC DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
28-Mar-2008	electronic	31-Mar-2008	31-Mar-2008	14-Jul-2008
22-Apr-2008, BL				Labeling

**NAME & ADDRESS OF APPLICANT:**

Beth Brannan, Director, Regulatory Affairs  
Sandoz, Inc.  
2555 W. Midway Blvd, Broomfield, CO 80038  
T: 303-438-4237, F: 303-438-4600  
Sandoz, Inc.  
506 Carnegie Center Drive, Suite 400,  
Princeton, NJ 08540  
T: 609-627-8500, F: 609-627-8684

**DRUG PRODUCT NAME:**

Proprietary:	OMNITROPE™ (Somatropin [rhGH] for injection
Nonproprietary/Established/USAN:	Somatropin, Sotmatotropin
Code Name/#:	
Chem. Type/Therapeutic Class:	5/S

**DESI/PATENT STATUS:** Holder of the approved Application is Pharmacia & Upjohn Company

**PHARMACOL. CATEGORY/INDICATION:**

Human Growth Hormone

**DOSAGE FORM:**

Lyophilized powder, **liquid for injection**

**STRENGTHS:**

1.5 and 5.8 mg, and 5 mg/1.5 mL, **10 mg/1.5 mL**

**ROUTE OF ADMINISTRATION:**

subcutaneous injection

**DISPENSED:**

xx Rx      OTC

**CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA(M.F.), MOLECULAR WEIGHT(M.W.):**

somatropin [rDNA origin], which is a polypeptide hormone of recombinant DNA origin. It has 191 amino acid residues and a molecular weight of 22,124 daltons. The amino acid sequence of the product is identical to that of human growth hormone of pituitary origin (somatropin). GENOTROPIN is synthesized in a strain of *Escherichia coli* that has been modified by the addition of the gene for human growth hormone.

**SUPPORTING DOCUMENTS:** N/A

**RELATED DOCUMENTS (if applicable):** N/A

**CONSULTS:** Microbiology, requested 01-May-2008, review completed: 24-Jun-2008, recommended: Approval by Dr. John Metcalfe.

**REMARKS/COMMENTS:** (see review notes as well)

Manufacturing Omnitrope 6.7 mg/ml Cartridge has been validated by three consecutive validation batches and batch results comply with the preset specifications. The stability data along with the supporting stability data support the claim of 24 month shelf life at  $5\pm 3^{\circ}\text{C}$  and an in-use stability of 28 days.

Overall, from a CMC standpoint, this supplement is recommended for **Approval**.

**CONCLUSIONS & RECOMMENDATIONS: Approval**

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Li-Shan Hsieh, Ph.D., Review Chemist,

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James Vidra, Ph.D., Chief of Branch VII

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

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Li-Shan Hsieh  
7/30/2008 12:42:59 PM  
CHEMIST

Janice Brown  
7/30/2008 02:10:10 PM  
CHEMIST  
Refer to J. Brown's memo to this supplement regarding  
immunogenicity and shelf life.

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**NDA 21-426/S-004**

**PHARMACOLOGY REVIEW(S)**



DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

## PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER: 21-426  
SERIAL NUMBER: S004  
DATE RECEIVED BY CENTER: 3/14/2008  
PRODUCT: Somatropin 10 mg/1.5 ml  
  
INTENDED CLINICAL POPULATION: Growth Hormone deficiencies  
SPONSOR: Sandoz  
  
DOCUMENTS REVIEWED: Vol. 1  
REVIEW DIVISION: Division of Metabolism and Endocrinology  
**Products (HFD-510)**  
PHARM/TOX REVIEWER: Herman Rhee, Ph.D.  
PHARM/TOX SUPERVISOR: Todd Bourcier, Ph.D.  
PROJECT MANAGER: Ms. Kati Johnson

Date of review submission to DARRTs/DFS: 7/31/2008

## ***EXECUTIVE SUMMARY***

### **I. Recommendations**

#### A. Recommendation on approvability: Approval.

Preclinical pharmacology and toxicology recommends approval of NDA21-426, S004, based on preclinical data obtained from local tolerance toxicity study. The sponsor's submission was based on the findings that were reviewed under previous IND#58,980 (Genotropin), NDA19-107(Protropin), NDA19-640(Humatrope), NDA19-721(Norditropin), NDA19-764(Saizen), and NDA20-280(Genotropin).

#### B. Recommendation for nonclinical studies: None

#### C. Recommendations on labeling

The labeling information of pharmacology and toxicology for Omnitrop would be the same as that of other approved human growth hormones.

### **II. Summary of nonclinical findings**

#### A. Brief overview of nonclinical findings

A local tolerance toxicology study of a new formulation containing (b) (4) in Himalayan rabbits produced negative results, comparable to the original local tolerance study conducted in 2000 with the original formulation.

#### B. Pharmacologic activity: Growth Hormone

#### C. Nonclinical safety issues relevant to clinical use: None

## 2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

### 2.6.1 INTRODUCTION AND DRUG HISTORY

**NDA number:** 21-426

**Review number:** 005

**Sequence number/date/type of submission:** S004/Mar. 14, 2008/Commercial

**Information to sponsor:** Yes ( ) No (x)

**Sponsor and/or agent:** Sandoz

**Manufacturer for drug substance:** Biochemie U.S., Inc., Plainsboro, NJ

**Reviewer name:** Herman Rhee, Ph.D.

**Division name:** DMEP

**HFD #:** 510

**Review completion date:** 7/27/2008

**Drug:**

Trade name: Somatropin Cartridge 10 mg/1.5 ml

Generic name: Human Growth Hormone, Somatropin, Somatotropin

Code name: EP2000 and BC rhGH

Chemical name: 191 amino acid residues that are identical to that of human GH

CAS registry number: 12629-01-05

Molecular formula/molecular weight: 22,124 daltons

Structure: 191 amino acid residues that are identical to that of human GH

**Relevant INDs/NDAs/DMFs:** IND 58,980 (Genotropin), NDA19-107(Protropin), NDA19-640(Humatrope), NDA19-721(Norditropin), NDA19-764(Saizen), and NDA20-280(Genotropin)

**Drug class:** Growth Hormone

**Intended clinical population:** Growth Hormone deficiencies

**Clinical formulation:** Drug product (Omnitrope 5 mg/ml powder for solution for injection (batch S0002 (54742301, 6000291864)): Novartis AG, Switzerland; Omnitrope 6.7 mg/ml solution for injection (batch 138035 (54790401)): Sandoz GmbH, Schafteuau, Austria; Genotropin (batch 60300C51, registration number 49530.00.00): purchased from Pfizer Pharma GmbH, Germany) plus (b) (4) (Please see Table 1) below.

**Route of administration:** Subcutaneous

**Disclaimer:** Tabular and graphical information are constructed by the reviewer unless cited otherwise.

**Studies reviewed within this submission:** Local tolerance study in rabbits

**Studies not reviewed within this submission:** None

## 2.6.2 PHARMACOLOGY

### 2.6.2.1 Brief summary

The active ingredient of Omnitrope is human GH manufactured by recombinant DNA technology using the bacterium strain *Escherichia coli* K12. It is composed of 191 amino acids and has an amino acid sequence identical to that of natural hGH produced in the pituitary gland. The protein has a molecular weight of 22,125 daltons. Omnitrope belongs to the pharmacotherapeutic group of anterior pituitary lobe hormones and analogues. The original sponsor (Biochemie GmbH, Kundl, Austria) submitted a local toxicity in New Zealand White rabbit on March 26, 2004 under the NDA 21-426, which is attached below. The sponsor submitted another local toxicity study in Himalayan rabbits to document potential toxicity of low and high impurities of its new excipients (b) (4), compared to genotropin. The second local tolerance study was needed because the formulation was changed as shown below (Table 1). (b) (4)

(b) (4) in the Omnitrope subcutaneous preparation, which is consistent with maximal levels present in currently marketed products according to the FDA Inactive Ingredient Database ( $\leq 0.5\%$ , subcu preparations). Similarly, (b) (4) (b) (4), consistent with levels found in currently marketed products ( $\leq 16\%$ ).



## 2.6.6 TOXICOLOGY

**2. The local tolerance study that was submitted for the original NDA is summarized below.**

### 2.6.6.7 Local tolerance study (Original study, 2000/2001)

#### **Study title: Local Tolerance Study in New Zealand White Rabbits after IV, IM and SC Administration**

Key study findings: The anticipated human therapeutic dose is 0.03 mg/kg/day. The sponsor wished to determine the potential local tolerability of the test article EP 2000 (Growth hormone formulations) following daily intravenous, intramuscular or subcutaneous administration of a higher dose (5 mg/day) in New Zealand White rabbit for 7 consecutive days under GLP conditions. There were no unscheduled deaths and treatment-related effects on body weight and other clinical signs were not evident.

There were signs of mechanical injection trauma in all groups including the control placebo groups. The liquid formulation and its vehicle were associated with slight erythema at the sites of the IV injections and with some local induration. The erythema had disappeared by about D13 (6 days) after the last injection. The incidences were not frequent after administration of the products and erythema was not observed after D8.

**Study no.:** (b) (4) # 21/001-D

**Volume #, and page #:**

**Conducting laboratory and location:** (b) (4)

(b) (4)

**Date of study initiation:** 9/7/2000-3/8/2001

**GLP compliance:** Yes

**QA reports:** yes (x ) no ( )

**Drug, lot #, and % purity:**

**Formulation/vehicle:**

#### **Methods**

Doses: Two formulations (Formulation I = Batch#S00200=rh-GH 5.8 mg and Formulation II = Batch#S0034360) were used in the following experimental design.

Study design: Four male and four female rabbits/group received two formulations of Omnitrope and the vehicles daily for 7 days via im, iv or sc injections at the dose of 5mg/animal. The volume of injection was 1mL (lyophilized formulation) and 1.5mL (liquid formulation). Detailed clinical examinations of general health and of the injection sites were made every day; 2 animals/sex/group were killed on D8 (one day post-dosing) and the remaining two animals on D22 (2 weeks post-dosing).

Morbidity/mortality was examined at least twice daily. Clinical examinations were performed daily and injection sites were examined twice daily (before and 2 hours after

administration) during the treatment period (days 1 to 7) then daily during the treatment-free period. Individual body weights were recorded prior to dosing then twice weekly.

Half of the animals were killed at the end of the treatment period (day 8) and the remaining half of the animals at the end of the treatment-free period (day 22). Injection sites were fixed and preserved at necropsy for all animals. These tissues were examined histopathologically.

Group number	Dosing formulation	Route of administration	Dose level (mg/animal/day)	Dose volume (ml/site/day)	Number of animals	
					Day 8 <sup>(1)</sup>	Day 22 <sup>(2)</sup>
1	Lyophilisate formulation	Intravenous	5	1	4	4
2		Intramuscular	5	1	4	4
3		Subcutaneous	5	1	4	4
4	Liquid formulation	Intravenous	5	1.5	4	4
5		Intramuscular	5	1.5	4	4
6		Subcutaneous	5	1.5	4	4

(1) killed the day after the last administration (day 8).

(2) killed 2 weeks after the last administration (day 22).

## Outline of the local tolerance study

<b>F</b>	Title	EP2000 (Growth hormone formulations) – Local tolerance in rabbits by intravenous, intramuscular and subcutaneous routes
	Investigational product	Omnitrop 5.8 mg lyophilized powder [batch 6000140823 (S00200); diluent 907973] and Omnitrop liquid 5 mg/1.5 mL solution in a cartridge [batch 6000140900 (0034360)]
	Route of administration	Intravenous, intramuscular and subcutaneous injections
	Duration	7 days of treatment
	Dosage	Omnitrop powder for solution for injection: 5 mg/animal/day in a volume of 1 mL. Omnitrop solution for injection: 5 mg/animal/day in a volume of 1.5 mL. Vehicle: 1 or 1.5 mL depending on the dosing formulation.
	Test system	48 male New Zealand White rabbits were divided into 6 groups. The rabbits were randomized using random stratified body weight procedures.
	Observations	Morbidity/mortality: All animals were observed at least twice daily. Clinical signs or reactions to treatment: All animals were examined twice daily during the treatment period. Injection sites: All animals were examined twice daily (before and at least 2 hours after administration) from day 1 to 7 and daily thereafter. Body weight was recorded twice weekly.
	Pathology	Half of the animals were killed on day 8, and the remaining half of the animals on day 22. Necropsies were performed on all animals. The injection sites were sampled of all animals.

### Results:

There were no unscheduled deaths and treatment-related effects on body weight were not evident.

There were signs of mechanical injection trauma in all groups including the control placebo groups. The liquid formulation and its vehicle were associated with slight erythema at the sites of the IV injections and with some local induration. The erythema had disappeared by about D13 (6 days) after the last injection. The incidences were not frequent after administration of the products and erythema was not observed after D8.

No particular reaction was seen at the sites of the IM injections other than the effects of mechanical trauma of injection. The subcutaneous injection sites in all groups showed small hemorrhages attributed to mechanical trauma and minimal edema and erythema, slightly more marked after the lyophilized formulation, and some induration after the vehicle of that formulation.

Both formulations appear to have a slight local effect after intravenous or subcutaneous administrations, but not after repeated IM injections. There was no report of any indication of untoward local reaction at the sites of repeated subcutaneous injections.

### 3. NEW LOCAL TOLERANCE STUDY

#### 2.6.6.7 Local tolerance study - II

#### Study title: Local Tolerance Study in Himalayan Rabbits after IV, IM and SC Administration

Key study findings:

- Overall mean scores from all injection routes indicate an equal or less propensity for the ‘new’ omnitrope formulations to incite local reactions compared to the powder omnitrope or to genotropin.
- Evaluated individually, the data suggests that growth hormone products incite a local reaction when given intravenously or intraarterially, but this is not specific to the new omnitrope formulations.

**Study no.:** (b) (4) # 21/001-D

**Volume #, and page #:** EDR

**Conducting laboratory and location:** (b) (4)

**Date of study initiation:** 9/12/2006

**GLP compliance:** Yes

**QA reports:** yes ( ) no ( x )

**Drug, lot #, and % purity:** Batch#: Omnitrope solutions (138035), Omnitrope powder(6000298739), Genotropin (#62116C92) and Control 0.9% NaCl(6261A101)



**Methods:**

Route of administration: Intravenous, subcutaneous, intraarterial, intramuscular and paravenous injections.

Duration: Single administration by 5 routes (IV, SC, IA, IM, PV) followed by observation for 14 days.

Dosage:

Table 10-1 Volumes administered in each study group

Group	Test item / concentration	Dose level in mg/ animal/administration	Application volume in mL/animal	Animal no./sex
1	Omnitrope 6.7 mg/mL solution for injection (low impurities)	Intravenous: 5.0 Intraarterial: 5.0 Subcutaneous: 5.0 Intramuscular: 2.5	Intravenous: 0.75 Intraarterial: 0.75 Subcutaneous: 0.75 Intramuscular: 0.37	1 – 6 m
2	Omnitrope 6.7 mg/mL solution for injection (high impurities)	Paravenous: 2.5	Paravenous: 0.37	7 – 12 m
3	Omnitrope 5 mg/mL powder for solution for injection	Intravenous: 5.0 Intraarterial: 5.0 Subcutaneous: 5.0 Intramuscular: 2.5	Intravenous: 1.0 Intraarterial: 1.0 Subcutaneous: 1.0 Intramuscular: 0.5	13 – 18 m
4	Genotropin 5 mg/mL	Paravenous: 2.5	Paravenous: 0.5	19 – 24 m

i.v.: Into the marginal vein of the ear

i.a.: Into the central artery of the ear

i.m.: Into the gastrocnemius muscle

p.v.: Beside the vena saphena parva

s.c.: Under the dorsal skin

Note that an equal volume of 0.9% saline was injected into the contralateral (right) side of each animal receiving growth hormone injections to control for intra-animal variability. The saline injections were matched for volume and location.

Study Design:

Male Himalayan rabbits (1.7-2.3 kg from (b) (4)) were given single injections of the test articles by routes and dosages cited in the above table, and saline was injected in the contralateral side of the animal. Observations were carried forward for 14 days post-injection, with interim sacrifices at 48h, 96h, and 14d (2 rabbits/time point).

**Table 1 Outline of the local tolerance study**

Title	EP00-005: Local tolerance test in rabbits after a single intravenous, subcutaneous, intraarterial, intramuscular and paravenous administration of Omnitrope 6.7 mg/ml solution for injection (low impurities), Omnitrope 6.7 mg/ml solution for injection (high impurities), Omnitrope 5 mg/ml powder for solution for injection and Genotropin 5 mg/ml.
Investigational products	Omnitrope 6.7 mg/ml s.f.i. (low impurities; batch 138035), Omnitrope 6.7 mg/ml s.f.i. (high impurities; batch 138035), Omnitrope 5 mg/ml p.f.s.f.i. (batch 6000298739 [S0001]; diluent (batch 135447 [54742301]), Genotropin 5 mg/ml (batch #62116C92)
Characterisation of Omnitrope 6.7 mg/ml s.f.i. in terms of product-related substances	"Low" impurities: Largest individual impurity (b) (4) Sum of product-related substances: (b) (4) "High impurities": Largest individual impurity (b) (4) Sum of product-related substances: (b) (4)
Route of administration	Intravenous, subcutaneous, intraarterial, intramuscular and paravenous injections
Duration	Single administration by 5 routes (IV, SC, IA, IM, PV) followed by observation for 14 days.
Dosage	Omnitrope 6.7 mg/ml s.f.i.: i.v., i.a., s.c. sites: 0.75 ml per injection (5 mg) i.m., p.v. sites: 0.37 ml per injection (2.5 mg)  Omnitrope 5 mg/ml p.f.s.f.i. : i.v., i.a., s.c. sites: 1.0 ml per injection (5 mg) i.m., p.v. sites: 0.5 ml per injection (2.5 mg)  Genotropin 5mg/ml : i.v., i.a., s.c. sites: 1.0 ml per injection (5 mg) i.m., p.v. sites: 0.5 ml per injection (2.5 mg)  Saline control: same volumes as test compounds into corresponding locations on the right side of each animal.
Test system	24 male Himalayan rabbits were divided into 4 groups. The rabbits were randomised using random stratified body weight procedures.
Observations	Morbidity/mortality: All animals were observed daily.  Clinical signs or reactions to treatment: All animals were examined daily during the treatment period.  Injection sites: All injection sites were inspected at 2, 6, 12, 24, 48, 96 hours and 14 days after injection.  Body weight was recorded once a week.
Pathology	Two animals from each group were sacrificed at the following intervals: 48 hours, 96 hours, and 14 days. Necropsies were performed on all animals.  The injection sites were excised and evaluated for all animals.

Observations:

All animals were observed daily to detect eventual clinical signs of systemic toxicity or adverse drug reactions. Animals were weighed before the first application and at weekly intervals, where applicable. Sequential macroscopic examinations of the injection site were performed by the same veterinarian or technician. A second veterinarian was responsible for the histological evaluations. *(from sponsor's submission)*

Morbidity/mortality: All animals were observed daily.

Clinical signs or reactions to treatment: All animals were examined daily during the treatment period.

Injection sites: All injection sites were inspected at 2, 6, 12, 24, 48, 96 hours and 14 days after injection. Body weight was recorded once a week.

Pathology: Two animals from each group were sacrificed at the following intervals: 48 hours, 96 hours, and 14 days. Necropsies were performed on all animals. Injection sites were inspected macroscopically 2, 6, 12, 24, 48, and 96 hours after administration in the appropriate animals by a person not involved in the administration. All pathological findings were recorded. Furthermore, erythema and edema were traced and graded according to Draize et al., 1944 and Draize, 1965 (Table 10-3). The injection sites were excised and evaluated for all animals.

Table 10-3 Grading of skin reactions

Grade	Erythema and eschar formation
0	No erythema
1	Very slight erythema (barely perceptible)
2	Well-defined erythema
3	Moderate to severe erythema
4	Severe erythema (beet redness) to slight eschar formation (injuries in depth) preventing erythema reading
Edema formation	
0	No edema
1	Very slight edema (barely perceptible)
2	Slight edema (edges of area well defined by definite raising)
3	Moderate edema (raised approx. 1 mm)
4	Severe edema (raised more than 1 mm and extending beyond the area of exposure)

Histopathology (from sponsor's submission): After the animals had been sacrificed, the injection sites were excised and evaluated macroscopically. Specimens of 5 mm thickness from the injection sites of both, test/reference item and NaCl, were fixed in 10% buffered formalin, stained with hematoxylin-eosin after preparation of paraffin sections (3 to 5 µm), and examined histologically. The specimens were scored according to Wolven and Levenstein, 1967 (Table 10-4).

Table 10-4 Histopathologic examination

Grade	Epithelium
0	Normal-Intact
1	Cell degeneration or flattening
2	Metaplasia
3	Focal erosion
4	Generalized erosion
<b>Leukocyte infiltration (per high-power field)</b>	
0	Absent
1	Minimal - less than 25
2	Mild - 26 – 50
3	Moderate - 51 – 100
4	Marked - greater than 100
<b>Vascular congestion</b>	
0	Absent
1	Minimal
2	Mild
3	Moderate
4	Marked with disruption of vessels
<b>Edema</b>	
0	Absent
1	Minimal
2	Mild
3	Moderate
4	Marked
<b>Total score of the histopathologic assessment</b>	
0	None
1 to 4	Minimal
5 to 8	Mild
9 to 12	Moderate
13 to 16	Severe

### Results:

Clinical signs and mortality: None.

Body Weight: No effects on BW were observed.

Macroscopic changes: No macroscopic changes were observed at any injection site with the low or high impurity omnitrope formulations up to 14 days. Genotropin (5 mg/ml) and Omnitrope (powder formulation) administration also did not produce any remarkable macroscopic changes. There were no macroscopic changes for any growth hormone injection when compared to the corresponding saline control.

Microscopic changes:

Note, only changes considered possibly related to the drug/formulation are presented. Other injection site reactions observed (e.g., muscle damage, hemorrhage) were present in both the growth hormone and saline injection sites.

Omnitrope ‘low’ impurity:

The only response that may indicate a drug/formulation reaction was by the intraarterial route, which produced mild focal purulent dermatitis at the injection site at 48h and 96h in 1 of 2 rabbits, but not at 14 days. No response was seen at the corresponding saline sites.

Omnitrope ‘high’ impurity:

Again, the only response that suggests a drug/formulation reaction was by the intrarterial route, which produced mild focal hemorrhage and purulent dermatitis at 48h and 96h, but not at 14 days. No response was seen at the corresponding saline sites.

Omnitrope powder formulation:

Intravenous and intrarterial routes suggest a drug/formulation reaction.

Intravenous injection produced purulent dermatitis at 48hrs which was absent at 96h and 14days; no reaction was seen at the saline site.

Intraarterial injection also produced a focal/multifocal purulent dermatitis with mixed cell infiltration with animals effected at 48h and 96h time points, but not at 14 days. The saline site in one animal showed dermatitis at 48h.

Genotropin:

Intravenous and intrarterial routes suggest a drug/formulation reaction.

Intravenous injection produced purulent dermatitis/cell infiltration/hemorrhage in 1 or 2 rabbits at the 48h and 96h time points; the saline control site showed a similar though less ‘severe’ reaction in one rabbit at 48 and 96h.

Intraarterial injection produced a focal/multifocal purulent dermatitis with mixed cell infiltration and hemorrhage with animals effected at 48h and 96h time points, but not at 14 days. The saline site in one animal showed mild hemorrhage at 48h.

The overall mean scores summarized from all injection sites are shown in the table below. The two ‘new’ omnitrope formulations scored less than the powder omnitrope and genotropin. The omnitrope products and the control saline injections scored comparably, whereas the genotropin product scored slightly higher than its respective saline control.

Summary mean score results of histological evaluation

Group	Test item / reference item		Saline control	
	Total score	Mean score per animal per route	Total score	Mean score per animal per route
Group 1: Omnitrope 6.7 mg/mL solution for injection (low impurities)	24	0.8	22	0.7
Group 2: Omnitrope 6.7 mg/mL solution for injection (high impurities)	34	1.1	36	1.2
Group 3: Omnitrope 5 mg/mL powder for solution for injection	43	1.4	40	1.3
Group 4: Genotropin 5 mg/mL	47	1.6	39	1.3

**2.6.6.9 Discussion and Conclusions**

Somatropin Cartridge (Omnitrope 6.7 mg/ml) solution for injection (s.f.i.) had (b) (4) . Levels of the two excipients are consistent with levels present in currently marketed products intended for subcutaneous administration (FDA Inactive Ingredient Database). A local tolerance study conducted in male rabbits indicates that the ‘new’ formulation of omnitrope has equal or less propensity to incite a local injection site reaction vs. the ‘old’ formulation or genotropin, based on summary mean scores of multiple injection routes and specifically on subcutaneous administration. However, there appears to be a dermatitis-type reaction to growth hormone products if given by the intraarterial or intravenous route. This was evident for omnitrope and for genotropin.

**OVERALL CONCLUSIONS AND RECOMMENDATIONS**

The new formulation of omnitrope containing new excipients (b) (4) has an equal or less propensity to produce local injection site reactions via the subcutaneous route compared to the ‘old’ omnitrope formulation or to genotropin.

Unresolved toxicology issues (if any): None

Recommendations: None

Reviewer Signature \_\_\_\_\_

Supervisor Signature \_\_\_\_\_ Concurrence Yes \_\_\_ No \_\_\_

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/s/

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Herman Rhee  
7/31/2008 03:30:12 PM  
PHARMACOLOGIST

Todd Bourcier  
8/1/2008 09:53:50 AM  
PHARMACOLOGIST  
Recommend approval

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**NDA 21-426/S-004**

**MICROBIOLOGY REVIEW(S)**

# Product Quality Microbiology Review

24 June 2008

**NDA:** 21-426/SCF-004

**Drug Product Name**

**Proprietary:** Omnitrope™  
**Non-proprietary:** Somatropin [rhGH] for injection  
**Drug Product Priority Classification:** N/A

**Review Number:** 1

**Dates of Submission(s) Covered by this Review**

Letter	Stamp	Review Request	Assigned to Reviewer
28 MAR 2008	31 MAR 2008	01 MAY 2008	09 MAY 2008

**Applicant/Sponsor**

**Name:** Sandoz Inc.  
**Address:** 506 Carnegie Center Dr.  
Suite 400  
Princeton, NJ 08540  
**Representative:** Beth Brannan  
**Telephone:** 303-438-4237

**Name of Reviewer:** John W. Metcalfe, Ph.D.

**Conclusion:** Recommend Approval.

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## Product Quality Microbiology Data Sheet

- A. 1. TYPE OF SUBMISSION:** Prior Approval CMC Supplement.
- 2. SUBMISSION PROVIDES FOR:**  
The submission provides for an additional presentation of the subject drug product. Currently, the following are approved presentations:
- 1.5 mg & 5.8 mg Vial.
  - 5 mg/1.5 mL Cartridge.
- The proposed new presentation is:
- 10 mg/1.5 mL Cartridge.
- 3. MANUFACTURING SITE:**  
Sandoz GmbH  
Plant Schafftenau  
Biochemiestrasse 10  
A-6336 Langkampfen Austria
- 4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:**
- Solution for injection in glass cartridge.
  - Subcutaneous Injection.
  - 6.7 mg/mL.
- 5. METHOD(S) OF STERILIZATION:** (b) (4)
- 6. PHARMACOLOGICAL CATEGORY:** Hormone.
- B. SUPPORTING/RELATED DOCUMENTS:** None.
- C. REMARKS:**  
The subject submission is provided electronically in the CTD format.

This reviewer contacted the applicant on 18 June 2008 to make the following request for information:

- Provide the filter retention validation report.
- Provide the antimicrobial effectiveness testing report.

The requested reports were provided to this reviewer on 20 June 2008 via electronic mail. The information is summarized and reviewed in appropriate sections of this review. It was decided that the NDA did not need to be amended with the requested reports.

**File Name:** N021426S004R1.doc

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**Executive Summary**

**I. Recommendations**

- A. **Recommendation on Approvability** – NDA 21-426/SCF-004 is recommended for approval on the basis of product quality microbiology.
- B. **Recommendations on Phase 4 Commitments and/or Agreements, if Approvable** – Not applicable.

**II. Summary of Microbiology Assessments**

- A. **Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology** –  (b) (4)
- B. **Brief Description of Microbiology Deficiencies** – There are no microbiology deficiencies identified.
- C. **Assessment of Risk Due to Microbiology Deficiencies** - Not applicable.

**III. Administrative**

- A. **Reviewer's Signature** \_\_\_\_\_  
John W. Metcalfe, Ph.D.
- B. **Endorsement Block** \_\_\_\_\_  
Stephen Langille, Ph.D.
- C. **CC Block**  
N/A

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/s/

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John Metcalfe  
6/25/2008 01:40:56 PM  
MICROBIOLOGIST

Stephen Langille  
6/26/2008 07:51:52 AM  
MICROBIOLOGIST

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**NDA 21-426/S-004**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

## CLINICAL PHARMACOLOGY REVIEW

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<b>NDA</b>	21-426 S-004
<b>Submission Date</b>	March 28, 2008
<b>Brand Name</b>	OMNITROPE™
<b>Generic Name</b>	Somatropin (rDNA origin) for injection
<b>Reviewer</b>	S.W. Johnny Lau, R.Ph., Ph.D.
<b>Team Leader</b>	Sally Y. Choe, Ph.D.
<b>OCP Division</b>	Clinical Pharmacology 2 (HFD-870)
<b>OND Division</b>	Metabolism and Endocrinology Products (HFD-510)
<b>Sponsor</b>	Sandoz Inc.
<b>Formulation; Strength</b>	Solution for injection; 10 mg/1.5 mL
<b>Relevant IND</b>	58,980
<b>Submission Type; Code</b>	Addition of new strength; PAS
<b>Indication</b>	Treatment of children with growth failure due to growth hormone deficiency (GHD) Treatment of adults with either adult onset or childhood onset GHD

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<b>Table of Contents</b>	<b>Page</b>
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### 1 Executive Summary

#### 1.1 Recommendation

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 2 (OCP/DCP2) has reviewed NDA 21-426 S004's Clinical Pharmacology and Biopharmaceutics information for the 10 mg somatropin (rDNA origin)/1.5 mL solution and finds it acceptable.

#### 1.2 Summary of Clinical Pharmacology and Biopharmaceutics Findings

OMNITROPE™ lyophilized powder was approved in 2006. The sponsor is requesting the addition of an OMNITROPE™ Cartridge 10 mg/1.5 mL, which is a different formulation from the previously approved lyophilized powder and solution cartridge. OMNITROPE™ Cartridge 10 mg/1.5mL is a sterile, ready-to use solution filled in a glass cartridge. The drug substance remains the same as in the previously approved NDA and is manufactured at the same manufacturing site. The sponsor conducted a 3-way crossover bioequivalence (BE) study to bridge this new liquid formulation with the approved OMNITROPE™ lyophilized powder and

GENOTROPIN<sup>®</sup> lyophilized powder. To accurately assess the pharmacokinetics (PK) and pharmacodynamics (PD), endogenous growth hormone (GH) was suppressed via a constant IV infusion of 40 µg octreotide/40mL/h for 25 hours, beginning 1 hour before the somatropin administration. The BE study results showed that the ratios (test/reference) for all PK and PD parameters were within the 90% confidence intervals. Hence, OMNITROPE<sup>™</sup> 6.7 mg/mL Solution (10 mg/1.5 mL) for injection is bioequivalent to OMNITROPE<sup>™</sup> 5 mg/mL Powder for Solution for Injection and GENOTROPIN<sup>®</sup> 5 mg/mL powder for solution for injection.

## 2 Question-Based Review

### 2.1 Background

OMNITROPE<sup>™</sup> (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<sup>™</sup> is synthesized in a strain of Escherichia coli that has been modified by the addition of the gene for human growth hormone.

The sponsor submitted NDA 21-426 S-004 to seek approval of the 10 mg somatropin (rDNA) origin/1.5 mL OMNITROPE<sup>™</sup> solution filled in a glass cartridge. Currently, the sponsor has the following approval for OMNITROPE<sup>™</sup>:

- Test Product: 1.5 mg/vial in 2 vials, one containing somatropin powder and the other containing diluent
- Reference Product: 5.8 mg/vial in 2 vials, one containing somatropin powder and the other containing diluent
- Reference Product: 5 mg/1.5 mL prefilled sterile solution in a glass cartridge ready to be administered with the OMNITROPE Pen 5

The Office of Drug Evaluation II approved the somatropin (OMNITROPE<sup>™</sup> [rDNA origin]) injection, 1.5 mg/vial and 5.8 mg/vial on May 30, 2006 for (1) the long-term treatment of pediatric patients who have growth failure due to inadequate secretion of endogenous GH and (2) long-term replacement in adults with GH deficiency of either childhood or adult onset etiology. The Division of Metabolism and Endocrinology Products approved the somatropin (OMNITROPE<sup>™</sup> [rDNA origin]) injection, 5 mg/1.5 mL in a cartridge on January 16, 2008 for the same indications. Dr. Xiaoxiong Wei reviewed the Clinical Pharmacology and Biopharmaceutics information for these 2 submissions.

The sponsor conducted a Phase I BE (PK/PD) study (EP00-105) for the 10 mg somatropin (rDNA origin)/1.5 mL solution cartridge to support NDA 21-426 S004.

### 2.2 General Clinical Pharmacology

Somatropin clinical pharmacology information is available in:

- product labeling
- *Drugs* **64**:1375-81 (2004)

## 2.3 General Biopharmaceutics

Table 1 below details the formulation of the 10 mg somatropin/1.5 mL solution:

Table 1 Composition of Omnitrope 6.7 mg/ml Solution for Injection

(b) (4)



### 2.3.1

**Is the clinically tested formulation in Study EP00-105 identical to the to-be-marketed formulation?**

Yes, per Section 5 (page 8) of 2.5 Clinical Overview.

### 2.3.2

**Is the 10 mg somatropin (rDNA origin) OMNITROPE™/1.5 mL solution bioequivalent to other approved products?**

Yes. The sponsor conducted Study EP00-105 to assess the BE of 10 mg somatropin (rDNA origin)/1.5 mL solution. Briefly, Study EP00-105 is a double-blind, single-dose, 3-way crossover with 3 treatments, 3 periods, and 6 sequences in 36 healthy volunteers (see details in Appendix). This study's objectives follow:

- Compare the GH  $C_{max}$  and  $AUC_{last}$  (PK parameters) among the 3 different treatments.
- Compare the insulin-like growth factor (IGF-1), insulin-like growth factor binding protein 3 (IGFBP-3), and nonesterified fatty acid (NEFA) PD parameters among the 3 treatments.

On Day 1 of each treatment period, randomized and overnight fasted participants received single subcutaneous (SC) dose of 5 mg somatropin (this dose was studied for prior approvals) for either 1 of the following in the lower abdomen:

- 10 mg somatropin (rDNA origin)/1.5 mL (solution in cartridge)
- 5 mg somatropin/mL (powder reconstituted with diluent in vial)
- GENOTROPIN® 5.0 mg (15 IU; 2-chamber cartridge)

All participants received 24-hours constant octreotide infusion (40 µg/40 mL/hour [this dosing regimen was studied for prior approvals] via a peripheral vein started 1 hour before test dose and stopped with the 24-hour blood sample) after the test medication in each treatment period to suppress endogenous GH release during the PK and PD sampling.

Figure 1. Serum GH concentration (mean ± SD) vs. time for all 3 treatment groups.

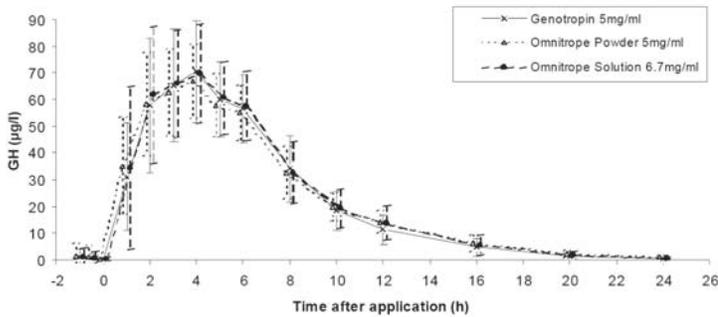


Table 1. PK parameters after a single (SC) administration of 5 mg of OMNITROPE™ 5.0 mg/mL powder for solution for injection, OMNITROPE™ 6.7 mg/mL solution for injection and GENOTROPIN® 5 mg/mL.

	Omnitrope 5 mg/ml Powder for Solution for Injection	Omnitrope 6.7 mg/ml Solution for Injection	Genotropin 5 mg/ml
AUC <sub>last</sub> [h * µg/l]	550 ± 96	558 ± 115	537 ± 110
AUC <sub>0-∞</sub> [h * µg/l]	555 ± 96	561 ± 114	540 ± 110
C <sub>max</sub> [µg/l]	69 ± 16	74 ± 22	73 ± 20
t <sub>max</sub> [h]	4.0* (2.0 - 6.0)	4.0* (2.0 - 6.0)	4.0* (2.0 - 6.0)
t <sub>1/2</sub> [h]	2.9 ± 0.5	2.5 ± 0.7	2.5 ± 0.7

Results are presented as mean ± SD.  
\* median value (min - max)

Table 2. Ratios of the least square means of AUC<sub>last</sub> and C<sub>max</sub> between OMNITROPE™ 5.0 mg/mL powder for solution for injection, OMNITROPE™ 6.7 mg/mL solution for injection and GENOTROPIN®.

	AUC <sub>last</sub> Ratio of LS-Means [90% CI]	C <sub>max</sub> Ratio of LS-Means [90% CI]
Omnitrope 5.0 mg/ml Powder for Solution for Injection vs. Genotropin 5 mg/ml	1.031 [0.997; 1.065]	0.968 [0.920; 1.019]
Omnitrope 6.7 mg/ml Solution for Injection vs. Genotropin 5 mg/ml	1.038 [1.004; 1.073]	1.008 [0.958; 1.061]
Omnitrope 5.0 mg/ml Powder for Solution for Injection vs. Omnitrope 6.7 mg/ml Solution for Injection	0.993 [0.961; 1.026]	0.960 [0.912; 1.011]

Figure 2. Serum IGF-1 concentration (mean ± SD) vs. time for all 3 treatment groups.

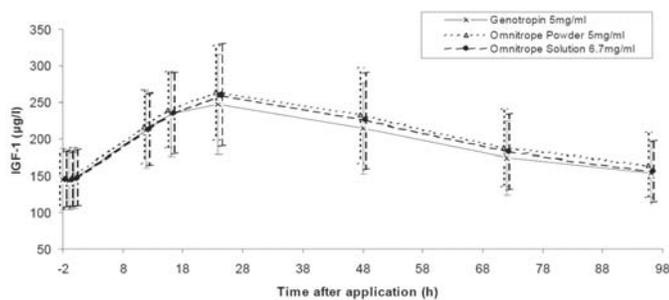


Table 3. IGF-1: AUEC<sub>last</sub>, E<sub>max</sub> and t<sub>max</sub> of OMNITROPE™ 5.0 mg/ml Powder for Solution for Injection, OMNITROPE™ 6.7 mg/ml Solution for Injection and GENOTROPIN® 5 mg/ml.

IGF-1	Omnitrope 5.0 mg/ml Powder for Solution for Injection	Omnitrope 6.7 mg/ml Solution for Injection	Genotropin 5 mg/ml
AUEC <sub>last</sub> [h * µg/l]	20355 ± 5067	19829 ± 5107	19126 ± 5072
E <sub>max</sub> [µg/l]	267 ± 64	265 ± 68	252 ± 67
t <sub>max</sub> [h]	24* (16 - 48)	24* (16 - 24)	24* (12 - 24)

\* median value (min - max)

Table 4. IGF-1: Ratios of the least square means of  $AUEC_{last}$  and  $E_{max}$  between OMNITROPE™ 5.0 mg/ml Powder for Solution for Injection, OMNITROPE™ 6.7 mg/ml Solution for Injection and GENOTROPIN® 5 mg/ml.

IGF-1	$AUEC_{last}$ Ratio of LS-Means [90% CI]	$E_{max}$ Ratio of LS-Means [90% CI]
Omnitrope 5.0 mg/ml Powder for Solution for Injection vs. Genotropin 5.0 mg/ml	1.069 [1.040; 1.099]	1.064 [1.028; 1.100]
Omnitrope 6.7 mg/ml Solution for Injection vs. Genotropin 5 mg/ml	1.042 [1.014; 1.071]	1.057 [1.022; 1.094]
Omnitrope 5.0 mg/ml Powder for Solution for Injection vs. Omnitrope 6.7 mg/ml Solution for Injection	1.026 [0.998; 1.055]	1.006 [0.972; 1.041]

Figure 3. Serum IGFBP-3 concentration (mean ± SD) vs. time for all 3 treatment groups.

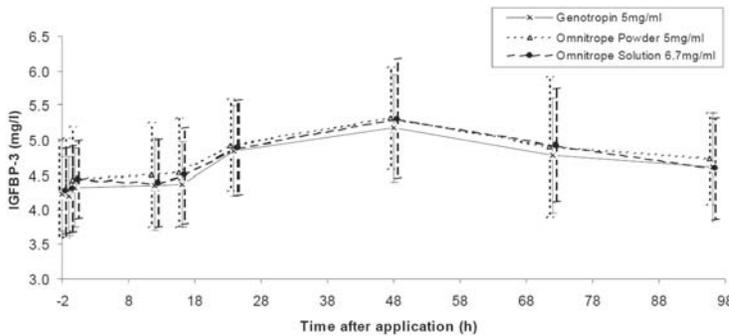


Table 5. IGFBP-3:  $AUEC_{last}$ ,  $E_{max}$  and  $t_{max}$  of OMNITROPE™ 5.0 mg/mL Powder for Solution for Injection, OMNITROPE™ 6.7 mg/ml Solution for Injection and GENOTROPIN® 5 mg/mL.

IGFBP-3	Omnitrope 5.0 mg/ml Powder for Solution for Injection	Omnitrope 6.7 mg/ml Solution for Injection	Genotropin 5 mg/ml
$AUEC_{last}$ [h* mg/l]	471 ± 70	468 ± 67	459 ± 66
$E_{max}$ [mg/l]	5.4 ± 0.8	5.4 ± 0.8	5.3 ± 0.7
$t_{max}$ [h]	48* (16 – 96)	48* (0 – 72)	48* (24 – 72)

\* median value (min - max)

Table 6. IGFBP-3: Ratios of the least square means of  $AUEC_{last}$  and  $E_{max}$  between OMNITROPE™ 5.0 mg/mL powder for solution for injection, OMNITROPE™ 6.7 mg/mL solution for injection and GENOTROPIN® 5 mg/mL.

IGFBP-3	$AUEC_{last}$ Ratio of LS-Means [90% CI]	$E_{max}$ Ratio of LS-Means [90% CI]
Omnitrope 5.0 mg/ml Powder for Solution for Injection vs. Genotropin 5 mg/ml	1.025 [1.007; 1.044]	1.025 [1.001; 1.050]
Omnitrope 6.7 mg/ml Solution for Injection vs. Genotropin 5 mg/ml	1.021 [1.003; 1.039]	1.024 [1.000; 1.049]
Omnitrope 5.0 mg/ml Powder for Solution for Injection vs. Omnitrope 6.7 mg/ml Solution for Injection	1.005 [0.987; 1.023]	1.001 [0.977; 1.025]

Figure 4. Serum NEFA concentration (mean ± SD) vs. time for all 3 treatment groups.

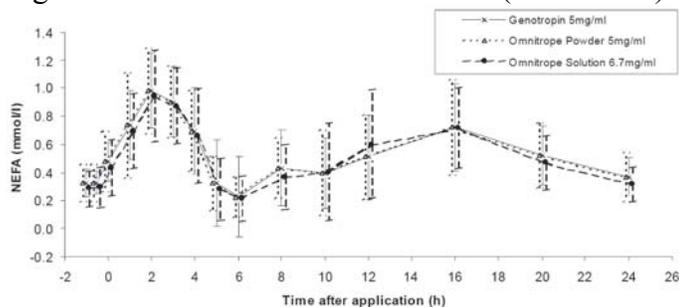


Table 7. NEFA: AUC<sub>last</sub>, E<sub>max</sub> and t<sub>max</sub> of OMNITROPE™ 5.0 mg/mL powder for solution for injection, OMNITROPE™ 6.7 mg/mL solution for injection and GENOTROPIN® 5 mg/mL.

NEFA	Omnitrope 5.0 mg/ml Powder for Solution for Injection	Omnitrope 6.7 mg/ml Solution for Injection	Genotropin 5 mg/ml
AUC <sub>last</sub> [h* mmol/l]	13.1 ± 3.8	12.8 ± 3.7	12.0 ± 4.2
E <sub>max</sub> [mmol/l]	1.1 ± 0.3	1.1 ± 0.3	1.0 ± 0.3
t <sub>max</sub> [h]	3* (1 – 16)	3* (2 – 16)	3* (1 – 20)

\* median value (min - max)

Table 8. NEFA: Ratios of the least square means of AUC<sub>last</sub> and E<sub>max</sub> between OMNITROPE™ 5.0 mg/mL powder for solution for injection, OMNITROPE™ 6.7 mg/mL solution for injection and GENOTROPIN® 5 mg/mL.

NEFA	AUC <sub>last</sub> Ratio of LS-Means [90% CI]	E <sub>max</sub> Ratio of LS-Means [90% CI]
Omnitrope 5.0 mg/ml Powder for Solution for Injection vs. Genotropin 5 mg/ml	1.104 [1.027; 1.186]	1.100 [1.019; 1.188]
Omnitrope Solution 6.7 mg/ml for Injection vs. Genotropin 5 mg/ml	1.077 [1.002; 1.158]	1.120 [1.038; 1.210]
Omnitrope 5.0 mg/ml Powder for Solution for Injection vs. Omnitrope 6.7 mg/ml Solution for Injection	1.025 [0.953; 1.101]	0.982 [0.909; 1.061]

Reviewer’s comment: Per prior experience on other products, hemolysis may interfere with the quantitation of drugs in serum samples and sponsors report modeled PK results rather than observed PK results. Hence, this reviewer also checked these 2 particular aspects and did not find any citing of hemolysis that may interfere with the bioanalytical assays. Additionally, the sponsor used observed serum GH concentrations to perform the PK analysis. For spot-checking, this reviewer repeated the BE analysis for the OMNITROPE™ 10 mg/1.5 mL solution vs. the GENOTROPIN® 5 mg/mL via WinNonlin Version 5.2.1. The ratio (90% CI) for GH C<sub>max</sub> and GH AUC<sub>last</sub> are 101.10 (96.12 – 106.34%) and 103.88 (100.48 – 107.38%), respectively. This analysis is consistent with that of the sponsor’s (see Table 2 above). IGF-1, IGFBP-3, and NEFA are legitimate GH’s clinical biomarkers (*Endocrinology Test Selection and Interpretation*, D.A. Fisher [editor], 3<sup>rd</sup> ed., 2004, Quest Diagnostics Inc.).

The limit of quantitation for serum GH concentration is 0.2 ng/mL. Twelve participants (103, 105, 113, 120, 121, 124, 125, 126, 127, 128, 131, and 132) showed Time 0 serum GH concentrations higher than 0.2 ng/mL. There are 2 protocol violations in octreotide infusion of 3 minutes. Hence, this reviewer eliminated 4 participants (113, 121, 124, and 125) who had the highest Time 0 serum GH concentrations (between 5 – 10% of the next sample at Time 60 minute) from the dataset. This reviewer repeated the BE analysis as before. The ratio (90% CI) for GH C<sub>max</sub> and GH AUC<sub>last</sub> are 103.0 (94.93 – 105.96%) and 102.98 (99.61 – 106.47%), respectively.

Study EP00-105 is acceptable from the Clinical Pharmacology perspective. Per the GH C<sub>max</sub> and AUC<sub>last</sub>, as well as the PD parameters of IGF-1, IGFBP-3, and NEFA, the somatropin (rDNA origin) 10 mg/1.5 mL solution is bioequivalent to the somatropin 5 mg/mL (powder) and bioequivalent to the GENOTROPIN® 5 mg/mL since all ratios (test/reference) for the PK and PD parameters’ 90% CIs are within 80 – 125%.

## 2.4 Bioanalytical

**Are the bioanalytical methods for GH, IGF-1, IGFBP-3, and NEFA used in Study EP00-105 properly validated?**

(b) (4)

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/s/

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S.W. Johnny Lau  
8/1/2008 09:18:47 AM  
BIOPHARMACEUTICS

Sally Choe  
8/1/2008 11:22:30 AM  
BIOPHARMACEUTICS

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

***APPLICATION NUMBER:***  
**NDA 21-426/S-004**

**OTHER REVIEW(S)**

# **REGULATORY PROJECT MANAGER LABELING REVIEW**

## **Division of Metabolism and Endocrinology Products**

**Application Number:** NDA 21-426/S-002, S-004

**Name of Drug:** Omnitrope (somatropin rDNA origin) injection

**Applicant:** Sandoz

### **Material Reviewed:**

#### **Submission Date(s):**

Supplement -002: February 18, 2008

Package Insert (PI), SPL

Cartridge Label, Final Printed Labeling (FPL)

Omnitrope Pen 5 Instructions for Use (IFU), FPL

Cartridge Container, 1 cartridge

Cartridge Container, 5 cartridges

Cartridge Container, 10 cartridges

Supplement -004: September 25, 2008

Package Insert (PI), SPL

Omnitrope Pen 10 Instructions for Use (IFU), FPL

### **Background and Summary**

Omnitrope was approved May 30, 2006 for the treatment of growth hormone deficiency (GHD) in both adult and pediatric patients. It was approved as a lyophilized powder in both a 1.5 mg single dose vial and as a 5.8 mg multi-dose vial. On January 16, 2008, a liquid formulation in a cartridge (5 mg/1.5 ml) was approved for use in a reusable injector pen, Omnitrope Pen 5. On August 25, 2008, a 10 mg/1.5 mL cartridge was approved for used in a reusable injector pen, Omnitrope Pen 10.

### **Review**

#### **Supplement -002**

**Package Insert:** The package insert has been superseded by that approved in S-004

**Cartridge Label:** The FPL (SET-V06-090, 07-2007) was compared to that which was attached to the approval letter. They are identical.

**Omnitrope Pen 5 IFU:** The FPL (OP5.IFU.06.1, 315097) was compared to that which was attached to the approval letter. The following revisions have been made to the last page of the document:

Produced for:  
Sandoz GmbH  
Biochemiestr. 10  
A-6250 Kundl  
Austria

Authorized representative  
Becton Dickinson France S.A.S.  
38801 Le. Pont de Claix Cedex  
France

BD medical-Pharmaceutical Systems  
1 Becton Drive  
Franklin Lanes, NJ 07417  
USA

Omnitrope is a trademark of Novartis  
BD and BD Logo are trademarks of Becton, Dickinson and Company

**has been revised to the following:**

BD  
Omnitrope Pen 5

(b) (4)  
**BD-Medical-Pharmaceutical Systems**  
Franklin Lakes, NJ 07417

(b) (4)

(b) (4)

Omnitrope is a trademark of Novartis  
BD and BD Logo are trademarks of  
Becton, Dickinson and Company

NOTE: these are acceptable editorial revisions.

**Cartridge Container, 1 cartridge:** The FPL (FS-V06-134) was compared to that which was attached to the approval letter. They are identical.

**Cartridge Container, 5 cartridges:** The FPL (FS-V06-135) was compared to that which was attached to the approval letter. They are identical.

**Cartridge Container, 10 cartridges:** The FPL (FS-V06-136) was compared to that which was attached to the approval letter. They are identical.

#### **Supplement -004**

**Package Insert:** The labeling (SPL) was compared to that which was attached to the approval letter. They are identical.

**Omnitrope 10 Pen Carton:** FPL was approved when the supplement was approved, so it was not included in this submission. (b) (4)

**Cartridge Label:** FPL was approved when the supplement was approved, so it was not included in this submission.

**Cartridge Container, 1, 5 and 10-count cartridge cartons:** FPL was approved when the supplement was approved, so it was not included in this submission.

**Omnitrope Pen 10 Instructions for Use (IFU):** FPL (OP10.IFU.07.1, 922610): FPL was compared to that which was attached to the approval letter. They are identical.

### **Recommendations**

An Acknowledge and Retain letter should be drafted.

For S-002 and S-004, the following is the approved labeling for the cartridge products:

Package Insert: that approved with S-004

Omnitrope Pen 5

Cartridge Label (SET-V06-090, 07-2007)

Instructions for Use (OP5.IFU.06.1, 315097)

Cartridge Carton, 1 cartridge: (FS-V06-134)

Cartridge Carton, 5 cartridges (FS-V06-135)

Cartridge Carton, 10 cartridges (FS-V06-136)

Omnitrope Pen 10

Instructions for Use (OP10.IFU.07.1, 922610)

The cartridge label, Omnitrope 10 Pen Device carton and carton labels (for 1, 5 and 10-count cartridges) were approved as FPL in the approval letter.

### **PM LABELING REVIEW**

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/s/

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Kati Johnson  
1/20/2009 03:23:20 PM  
CSO

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**DEPARTMENT OF HEALTH AND HUMAN SERVICES MEMORANDUM**

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CONSULTATION REVIEW

Date: July 22, 2008

To: CDER/DMEP

Attn: Kati Johnson PM

From: LCDR Scott Colburn - HFZ-480

Document No: N 21-426/S-004

Company Name: SANDOZ INC.

Device: Omnitrope Pen 10 - Pen Injector (also known and referred to as (b) (4))

Subject of Consult Request: Consult to Omnitrope Pen 10

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Information used for the consultation of this device:

N 21-426/S-004 files sent with consult request by Kati Johnson

(b) (4) Medical Device Master File for the (b) (4) and Pen Needle System;  
Amendment 8 – File Contents and Attachment 4 - Omnitrope Pen 10 specific testing.

**NOTE TO THE REVIEW TEAM:**

In review of the Omnitrope Pen 10 it is noted that there are very few differences between the Omnitrope Pen 10 and the previously reviewed Omnitrope Pen 5 conducted on March 2, 2007. The main differences between the two devices are the Omnitrope Pen 10's concentration of medication contained in the 1.5 ml cartridge. The difference between the two device concentrations is that the Omnitrope Pen 10 dose increments can be set in 0.1 mg steps to 5.4 mg vs. 0.05mg-2.7mg for the Omnitrope Pen 5.

All other aspects related to design, technical characteristics, performance, materials, sterilization, etc. are identical to that of the Omnitrope Pen 5.

**Device Information:**

Proprietary Name: Omnitrope Pen 10

Common Name: Pen-Injector

Classification Name: Piston Syringe

(b) (4)  
[Redacted]

The Pen Needles are manufactured by:

(b) (4)  
[Redacted]

If there are any questions or comments regarding the content of this consultation or if further clarification is needed on my recommendations please feel free to contact me via email ([scott.colburn@fda.hhs.gov](mailto:scott.colburn@fda.hhs.gov)) or by phone @ 240-276-3707.

*Scott A. Colburn*

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Scott A. Colburn, LCDR USPHS, RN, BSN  
General Hospital Devices Branch

July 22, 2008

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Date

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/s/

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Kati Johnson

7/24/2008 06:35:38 AM

CSO

CDRH review of the pen device (done by Scott  
Colburn) entered into DFS by the OND/DMEP project  
manager

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**NDA 21-426/S-004**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**



**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-426\S-002, S-004

Sandoz, Inc.  
Attention: Jean Pederson  
Manager, Drug Regulatory Affairs  
2555 W. Midway Blvd.  
Broomfield, CO 80038

Dear Ms. Pederson:

We acknowledge receipt of your February 12 and September 25, 2008 submissions containing final printed labeling in response to our January 16, and August 25, 2008 letters approving your supplemental new drug applications for Omnitrope (somatropin [rDNA origin]) Cartridges and for injection.

We have reviewed the labeling that you submitted in accordance with our January 16 and August 25, 2008 letters and we find it acceptable.

If you have any questions, call Kati Johnson, Project Manager, at (301) 796-1234.

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

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/s/

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Kati Johnson  
1/20/2009 03:30:02 PM  
signing for Mary Parks, M.D.

## **Memorandum**

**Date:** 31-Jul-2008  
**From:** Janice Brown, Pharmaceutical Assessment Lead, Branch VII/DPME/ONDQA  
**To:** NDA 21-426/S-004 file for Omnitrope (somatropin [rDNA origin] for injection) 1.5mg & 5.8 mg vial (lyophilized) and 5 mg/1.5mL cartridge (liquid)

**Supplement provides for:** The addition of an Omnitrope Cartridge 10 mg/1.5 mL glass cartridge

### **Background:**

Sandoz has developed four presentations of Omnitrope drug product that are manufactured using the same drug substance:

1. Omnitrope 5 mg/mL powder for solution for injection to be dissolved with the diluent 1.5% Cartridge Benzyl Alcohol prior to subcutaneous administration – multi-dose use.
2. Omnitrope 1.3 mg/mL powder for solution for injection to be dissolved with the diluent Water for Injection prior to subcutaneous administration – single-dose use.
3. Omnitrope 3.3 mg/mL injection – multi-dose use for subcutaneous administration.
4. Omnitrope 6.7 mg/mL injection – multi-dose use for subcutaneous administration.

The two lyophilized powders containing 1.3 mg and 5.0 mg somatropin (described in the original NDA) and the 3.3mg/mL solution for injection (described in S-002) are currently approved. The 6.7 mg/mL solution for injection is a pending supplement and is the subject of this memorandum. Both 3.3 mg/mL and 6.7 mg/mL presentations are solutions however, they do not have the same composition (see table 1 for a comparison of all Omnitrope presentations). To support the new 6.7 mg/mL strength the applicant submitted full CMC data, a bioequivalence study and a local tolerance study.

A 3-way crossover bioequivalence (BE) study to bridge the new liquid formulation with the approved Omnitrope lyophilized powder and Genotropin lyophilized powder was performed by Dr. S.W. Johnny Lau, clinical pharmacology reviewer on 01-Aug-2008 and found acceptable.

A local tolerance toxicology study using the new formulation containing [REDACTED] (b) (4) [REDACTED] was evaluated by Herman Rhee, Ph.D., 510 pharmacology-toxicology reviewer on 31-Jul-2008 and found acceptable.

**Secondary review comments:**

1. Immunogenicity – Levels of product related substances in Omnitrope drug product described in this supplement (S-004, 6.7 mg/mL injection) and S-002 (3.3 mg/mL injection) are significantly higher in the liquid form than the lyophilized powder. Table 1 is a summary of the purity profile of the lyophilized powder and the two liquid formulations. The level of product related substances measured by RP-HPLC and CZE has increased by (b) (4), respectively, from the lyophilized product. The primary degradant in the liquid presentation is the (b) (4)

Based on this observation, on 25-Jul-2008 the PAL contacted Jean Pederson, Sr. Associate, Regulatory Affairs at Sandoz and requested information to support the differences in the impurity profile specifically the increased level of product related substances in the liquid formulations. On 29-Jul-2008, the applicant responded to the information request and provided comparative impurity profiles of the different Omnitrope presentations and related substance levels for batches that were used in clinical immunogenicity trials. Reproduced below is a summary of levels of product related substances for batches of liquid Omnitrope used in Phase III clinical study EP2K-00-PhIIIAQ. Table 8 shows, the batches used during the clinical study exhibited total product-related substance levels ranging from (b) (4) and largest (b) (4) levels ranging from (b) (4) which supports the (b) (4) (by RP-HPLC) and (b) (4) (by CZE) of product related substances proposed in the stability specification. Dr. Dragos Roman, 510 Medical Officer reviewed the clinical trial EP2K-00-PHIIIAQ and did not recommend an immunogenicity trial (see attachment 1). PAL determined that the batches used in this trial contained product related substances at levels (b) (4) the proposed specification.



It should be noted that the formulation of the batches used in study EP2K-00-PhIIIA is not identical to the 6.7 mg/mL injection formulation; however, based on comparability of the physicochemical/biological properties extrapolation of immunogenicity studies to support the current related substances specification is reasonable.

2. Stability – Dr. Hsieh’s primary review of this supplement granted a 24 month shelf life at  $5\pm 3^{\circ}\text{C}$  and an in-use stability of 28 days. Stability data does not support this shelf life.

The applicant has requested (section 3.2.P.8.1, table 8, p. 11, reproduced below) and is granted an (b) (4) stored in the carton and an in-use stability of 28 days at  $5\pm 3^{\circ}\text{C}$  of the cartridge stored in the pen. (b) (4)

(b) (4)

(b) (4)

**Table 9 In-use storage conditions**

Primary Packaging Material	In-use Shelf Life	Storage Condition
Clear glass cartridges stoppered with plunger and cartridge seal in Pen10 device	28 days	Store in a refrigerator ( $5 \pm 3^{\circ}\text{C}$ ) Cartridge should remain in the Pen. Do not freeze.

3. Labeling – The labeling submitted on 22-Apr-2008 for the Omnitrope Pen 10 should be corrected

(b) (4)

**Conclusion:**

**One the labeling change has been made, the final CMC recommendation for NDA 21-426/S-004 is APPROVAL. Alternatively, an AE letter can be issued requesting changes described above to the carton.**

## Attachment 1: Dr. Roman's e-mail regarding immunogenicity

**Brown, Janice**

---

**From:** Roman, Dragos  
**Sent:** Thursday, July 31, 2008 2:25 PM  
**To:** Brown, Janice  
**Cc:** Parks, Mary H; Johnson, Kati; Hsieh, Li Shan; Vidra, James D; Galliers, Enid M  
**Subject:** RE: NDA 21-426/S-004

Hi Janice,

I looked at the July 29, 2008 Response to FDA inquiry/Supplement S-004 that you have received from Sandoz and forwarded to me the other day. As I indicated to you previously, the immunogenicity observed with the Liquid Omnitrope drug product in the original NDA and in subsequent submissions from the clinical trial EP2K-00-PHIIIQA was acceptable. Table 8 of the current submission lists four batches used in the clinical trial EP2K-00-PHIIIQA (0026069, 012899, 0143156, 0151686) with their impurity profile. If in your judgment the levels and profile of impurities described in Table 8 are comparable to that observed for the liquid Omnitrope cartridges of the current Supplement 004, I do not foresee a clinical need for an immunogenicity trial.

Dragos

---

**From:** Brown, Janice  
**Sent:** Wednesday, July 23, 2008 2:30 PM  
**To:** Roman, Dragos  
**Cc:** Parks, Mary H; Johnson, Kati; Hsieh, Li Shan; Vidra, James D; Galliers, Enid M  
**Subject:** RE: NDA 21-426/S-004

Yes, the liquid formulations have a higher level of related substances when compared to the lyophilized form. The only question is whether the purity/impurity levels in the liquid formulation in the original NDA and those listed in supplement 2 and 4 are similar.

Janice

---

**From:** Roman, Dragos  
**Sent:** Wednesday, July 23, 2008 2:20 PM  
**To:** Brown, Janice  
**Cc:** Parks, Mary H; Johnson, Kati; Hsieh, Li Shan; Vidra, James D; Galliers, Enid M  
**Subject:** RE: NDA 21-426/S-004

Janice,

Just to make sure I understand the attached table clearly: supplement 2 (liquid Omnitrope injection) and supplement 4 (liquid Omnitrope cartridge) have similar levels of product-related impurities but both are higher than the lyophilized product by (b) (4) by some assays.

A few reminders for everybody regarding Omnitrope approval:

Omnitrope lyophilized has been approved first (no immunogenicity problems in the marketed formulation).

Omnitrope liquid has been approved in Supplement 2 via a bioequivalence single dose study and CMC data.

Omnitrope cartridge is currently under your review as Supplement 4 and contains a bioequivalence single dose study and CMC.

In the original NDA liquid Omnitrope was used as a comparator for lyophilized Omnitrope. Without going into details regarding the trial design, the immunogenicity with liquid Omnitrope has been between 2-5% for up to 21 Months (per DFS review). Later, a safety update (in DFS) indicated that the immunogenicity for liquid Omnitrope stayed between 3-6% for up to Month 51 in the same cohort of patients. Thus, if my understanding that the two liquid Omnitropes have more or less the same impurity profile is correct, and taking into consideration that Supplement 2 was OK per chemistry (no change in drug substance, i.e. manufacturing site, protocol, etc), I would assume that we are OK clinically at this point. Please me know if there are other opinions regarding this issue.

dragos

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**From:** Brown, Janice  
**Sent:** Wednesday, July 23, 2008 1:34 PM  
**To:** Roman, Dragos  
**Cc:** Parks, Mary H; Johnson, Kati; Hsieh, Li Shan; Vidra, James D  
**Subject:** NDA 21-426/5-004

Dragos - I summarized the issue in the attachment. I will be out of the office Thurs and Friday attending a conference at NIH. You can call me on my cell phone at (b) (6)

Janice

<< File: Purity comparison.doc >>

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/s/

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Janice Brown  
9/15/2008 01:06:59 PM  
CHEMIST



NDA 21-426/S-004

**PRIOR APPROVAL SUPPLEMENT**

Sandoz, Inc.  
Attention: Beth Brannan  
Director, Regulatory Affairs  
2555 W. Midway Blvd., P.O. Box 446  
Broomfield, CO 80038-0446

Dear Ms. Brannan:

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 Product: Omnitrope (somatropin [rDNA origin] for injection, 1.5 mg and 5.8 mg vials, and 5 mg/1.5 ml cartridge

NDA Number: 21-426

Supplement number: S-004

Date of supplement: March 28, 2008

Date of receipt: March 31, 2008

This supplemental application proposes to market a 10 mg/1.5 ml cartridge for use in a new Omnitrope 10 pen injector for self administration of human growth hormone.

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 May 30, 2008 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be July 31, 2008.

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  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

NDA 21-426/S-004

Page 2

If you have any question, call me at 301-796-1234.

Sincerely,

*{See appended electronic signature page}*

Kati Johnson  
Project Manager  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/

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Kati Johnson

5/6/2008 06:02:40 AM

**For Consulting Center Use Only:**

Date Received: \_\_\_\_\_

Assigned to: \_\_\_\_\_

Date Assigned: \_\_\_\_\_

Assigned by: \_\_\_\_\_

Completed date: \_\_\_\_\_

Reviewer Initials: \_\_\_\_\_

Supervisory Concurrence: \_\_\_\_\_

## Intercenter Request for Consultative or Collaborative Review Form

**To (Consulting Center):**

Center: CDRH

Division: ODE

Mail Code: HF Z-480

Consulting Reviewer Name: Anthony Watcon

Building/Room #: CORP Room 340D

Phone #: (b) (6)

Fax #:

Email Address: anthony.watson@fda.hhs.gov

RPM/CSO Name and Mail Code:

**From (Originating Center):**

Center: CDER

Division: Division of Metabolism & Endocrinology Products

Mail Code: HFD-510

Requesting Reviewer Name: Kati Johnson, PM

Building/Room #: WO Room 3366

Phone #: 301-796-1234

Fax #:

Email Address: kati.johnson@fda.hhs.gov

RPM/CSO Name and Mail Code:

Requesting Reviewer's Concurring

Supervisor's Name:

**Receiving Division: If you have received this request in error, you must contact the request originator by phone immediately to alert the request originator to the error.**

Date of Request: 5/2/08

Requested Completion Date: 7/31/08

Submission/Application Number: NDA 21-426/S-004  
(Not Barcode Number)

Submission Type: NDA supplement  
(510(k), PMA, NDA, BLA, IND, IDE, etc.)

Type of Product:  Drug-device combination  Drug-biologic combination  Device-biologic combination  
 Drug-device-biologic combination  Not a combination product

Submission Receipt Date: 3/28/08

Official Submission Due Date: 7/31/08

Name of Product: Omnitrope 10

Name of Firm: Sandoz

Intended Use: The Omnitrope 10 pen-injector is for the self-injection of human growth hormone. The patient loads a cartridge into the device. According to the sponsor, a similar pen was approved (Omnitrope 5) using a different strength cartridge. The reviewer on the Omnitrope 5 pen device was Scott Colburn. I will provide a copy of that review in the package I will send to you.

Brief Description of Documents Being Provided (e.g., clinical data -- include submission dates if appropriate):

Paper copies of the CDER EDR submission.  
  
PLEASE RETURN THE PEN WHEN THE REVIEW IS COMPLETED. THANK YOU  
WHITE OAK, BUILDING 22, ROOM 3366

Documents to be returned to Requesting Reviewer?  Yes  No

**Complete description of the request.** Include history and specific issues, (e.g., risks, concerns), if any, and specific question(s) to be answered by the consulted reviewer. The consulted reviewer should contact the request originator if questions/concerns are not clear. Attach extra sheet(s) if necessary:

Type of Request:  Consultative Review  Collaborative Review

Sections of the electronic document will be copied and provided to you in paper.  
There is a Letter of Authorization for the (b) (4) that contains the device information.  
We are NOT asking for a review of the user manual, as it is identical (except for the concentration of the cartridge) to the Omnitrop 5 pen that was approved 1/18/08 in Supplement -002.

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/s/

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Kati Johnson

5/1/2008 03:02:10 PM

## REQUEST FOR CONSULTATION

TO (Office/Division): **Jim McVey, HFD-805, 301-796-1572**

FROM (Name, Office/Division, and Phone Number of Requestor): **Teshara G. Bouie, ONDQA, Division of Post-Marketing Assessment, 301-796-1649**

DATE  
**May 1, 2008**

IND NO.

NDA NO.  
**21-426**

TYPE OF DOCUMENT  
**SCF-004**

DATE OF DOCUMENT  
**March 28, 2008**

NAME OF DRUG  
**Omnitrope**

PRIORITY CONSIDERATION

CLASSIFICATION OF DRUG

DESIRED COMPLETION DATE  
**July 15, 2008**

NAME OF FIRM: **Sandoz**

### REASON FOR REQUEST

#### I. GENERAL

- |   |  |  |
|---|--|--|
| <input type="checkbox"/> NEW PROTOCOL                               | <input type="checkbox"/> PRE-NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT                            | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING        |
| <input type="checkbox"/> NEW CORRESPONDENCE                         | <input type="checkbox"/> END-OF-PHASE 2 MEETING  | <input type="checkbox"/> LABELING REVISION             |
| <input type="checkbox"/> DRUG ADVERTISING                           | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE   |
| <input type="checkbox"/> ADVERSE REACTION REPORT                    | <input type="checkbox"/> SAFETY / EFFICACY       | <input type="checkbox"/> FORMULATIVE REVIEW            |
| <input checked="" type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA               | <input type="checkbox"/> OTHER (SPECIFY BELOW):        |
| <input type="checkbox"/> MEETING PLANNED BY                         | <input type="checkbox"/> CONTROL SUPPLEMENT      |  |

#### II. BIOMETRICS

- |   |   |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW  | <input type="checkbox"/> CHEMISTRY REVIEW       |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY           |
| <input type="checkbox"/> CONTROLLED STUDIES     | <input type="checkbox"/> BIOPHARMACEUTICS       |
| <input type="checkbox"/> PROTOCOL REVIEW        | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): |   |

#### III. BIOPHARMACEUTICS

- |  |  |
|--|--|
| <input type="checkbox"/> DISSOLUTION             | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE  |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES         | <input type="checkbox"/> IN-VIVO WAIVER REQUEST      |

#### IV. DRUG SAFETY

- |  |  |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL                | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)           | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP         |  |

#### V. SCIENTIFIC INVESTIGATIONS

- |                                   |                                      |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

**COMMENTS / SPECIAL INSTRUCTIONS:** This supplement provides for the addition of an Omnitrope Cartridge 10 mg/1.5 mL. Please review. This supplement is located in the EDR.

PDUFA Goal Date: July 31, 2008

SIGNATURE OF REQUESTOR  
**Teshara G. Bouie**

METHOD OF DELIVERY (Check one)  
 DFS     EMAIL     MAIL     HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

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Teshara Bouie  
5/1/2008 12:29:30 PM