# CENTER FOR DRUG EVALUATION AND RESEARCH

## Approval Package for:

## *APPLICATION NUMBER:*

# 20-604/S-026

***Trade Name:*** Zorbitive

***Generic Name:*** [somatotropin (rDNA origin) for injection]

***Sponsor:*** Serono, Inc.

***Approval Date:*** December 1, 2003

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

# 20-604/S-026

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# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**20-604/S-026**

# APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-597
NDA 20-604/S-026

Serono, Inc.
Attention: Pamela Williamson-Joyce
One Technology Place
Rockland, MA 02370

Dear Ms. Williamson-Joyce:

Please refer to your new drug application (NDA) dated October 31, 2002, received November 1, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zorbtive® [somatotropin (rDNA origin) for injection].

We acknowledge receipt of your submissions to NDA 21-597 dated December 19, 2002, February 14, April 15, May 2, May 21, May 22, May 30, June 10, June 11, July 15, July 22, August 5, August 27, September 3, September 24, October 15, October, 20, November 12, November 18, November 24, November 25, and November 26, 2003.

We also acknowledge receipt of your submissions to NDA 20-604/S-026 dated October 31, 2002, September 24, November 24, and November 25, 2003.

This new drug application provides for the use of Zorbtive® [somatotropin (rDNA origin) for injection] for the treatment of Short Bowel Syndrome in patients receiving specialized nutritional support.

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

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert) and to the submitted labeling (text for the vial labels and cartons submitted on November 24, 2003). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the Guidance for Industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved NDA 21-597**." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your postmarketing commitment in your submission dated November 24, 2003. This commitment is listed below.

Description: educational plan for caregivers who treat Short Bowel Syndrome (SBS) patients and for SBS patients

| | |
|---|---|
| Submission of program final forms: | Within 3 months of the date of this letter |
| Program start: | Within 4 months of the date of this letter |
| Program follow-up final report submission: | Within 24 months of the date of this letter |

(including interim reports to assess program success every 6 months during this 24 month period).

Submit clinical protocols to your IND for this product. Submit the final educational program, nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to NDA 20-604. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to NDA 20-604. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to this postmarketing study commitment must be prominently labeled **"Postmarketing Study Protocol", "Postmarketing Study Final Report", or "Postmarketing Study Correspondence."**

We also remind you of your agreement on November 25, 2003, to develop a patient package insert (PPI) and to submit the PPI within 30 days of the date of this letter. The PPI should be submitted as a labeling supplement.

FDA's Pediatric Rule [at 21 CFR 314.55/21 CFR 601.27] was challenged in court. On October 17, 2002, the court ruled that FDA did not have the authority to issue the Pediatric Rule and has barred FDA from enforcing it. Although the government decided not to pursue an appeal in the courts, it will work with Congress in an effort to enact legislation requiring pharmaceutical manufacturers to conduct appropriate pediatric clinical trials. In addition, third party interveners have decided to appeal the court's decision striking down the rule. Therefore, we encourage you to submit a pediatric plan that describes development of your product in the pediatric population where it may be used. Please be aware that whether or not this pediatric plan and subsequent submission of pediatric data will be required depends upon passage of legislation or the success of the third party appeal. In any event, we hope you will decide to submit a pediatric plan and conduct the appropriate pediatric studies to provide important information on the safe and effective use of this drug in the relevant pediatric populations.

The pediatric exclusivity provisions of FDAMA as reauthorized by the Best Pharmaceuticals for Children Act are not affected by the court's ruling. Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products. You should refer to the Guidance for Industry on Qualifying for Pediatric Exclusivity (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request". FDA generally does not consider studies submitted to an NDA before issuance of a Written Request as responsive to the Written Request. Applicants should obtain a Written Request before submitting pediatric studies to an NDA.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Metabolic and Endocrine Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Please submit one market package of the drug product when it is available.

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

All 15-day alert reports, periodic (including quarterly) adverse drug experience reports, field alerts, annual reports, supplements, and other submissions should be addressed to the original NDA 20-604 for this drug product, not to this NDA. In the future, do not make submissions to this NDA except for the final printed labeling requested above.

If you have any questions, call Alice Kacuba, RN, MSN, RAC, Regulatory Health Project Manager, at (301) 827-9334.

Sincerely,

*{See appended electronic signature page}*

Robert L. Justice, M.D., M.S.
Director
Division of Gastrointestinal & Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

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

/s/

Robert Justice
12/1/03 04:43:17 PM

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**20-604/S-026**

# LABELING

**Zorbtive™**
**[somatropin (rDNA origin) for injection]**

DESCRIPTION

Zorbtive™[somatropin (rDNA origin) for injection] is a human growth hormone (hGH) produced by recombinant DNA technology. Zorbtive™ has 191 amino acid residues and a molecular weight of 22,125 daltons. Its amino acid sequence and structure are identical to the dominant form of human pituitary GH. Zorbtive™ is produced by a mammalian cell line (mouse C127) that has been modified by the addition of the hGH gene. Zorbtive™ is secreted directly through the cell membrane into the cell-culture medium for collection and purification.

Zorbtive™ is a highly purified preparation. Biological potency is determined by measuring the increase in the body weight induced in hypophysectomized rats.

Zorbtive™ is available in 4 mg, 5 mg and 6 mg vials for single dose administration. Zorbtive™ is also available in 8.8 mg vials for multi-dose administration. Each 4 mg vial contains 4.0 mg (approximately 12 IU) somatropin, 27.3 mg sucrose, 0.9 mg phosphoric acid. Each 5 mg vial contains 5.0 mg (approximately 15 IU) somatropin, 34.2 mg sucrose and 1.2 mg phosphoric acid. Each 6 mg vial contains 6.0 mg (approximately 18 IU) somatropin, 41.0 mg sucrose and 1.4 mg phosphoric acid. Each 8.8 mg vial contains 8.8 mg (approximately 26.4 IU) somatropin, 60.19 mg sucrose and 2.05 mg phosphoric acid. The pH is adjusted with sodium hydroxide or phosphoric acid to give a pH of 7.4 to 8.5 after reconstitution.

CLINICAL PHARMACOLOGY

Zorbtive™ [somatropin (rDNA origin) for injection] is an anabolic and anticatabolic agent which exerts its influence by interacting with specific receptors on a variety of cell types including myocytes, hepatocytes, adipocytes, lymphocytes, and hematopoietic cells. Some, but not all of its effects, are mediated by insulin-like growth factor-I (IGF-I).

MECHANISM OF ACTION IN SHORT BOWEL SYNDROME (SBS) PATIENTS

Intestinal mucosa contains receptors for growth hormone and for insulin-like growth factor-I (IGF-I), which is known to mediate many of the cellular actions of growth hormone. Thus, the actions of growth hormone on the gut may be direct or mediated via the local or systemic production of IGF

In human clinical studies the administration of growth hormone has been shown to enhance the transmucosal transport of water, electrolytes, and nutrients.

PHARMACOKINETICS

Subcutaneous Absorption: The absolute bioavailability of Zorbtive™ [somatropin (rDNA origin) for injection] after subcutaneous administration of a formulation not equivalent to the marketed formulation was determined to be 70-90%. The t½ (Mean ± SD) after subcutaneous administration is significantly longer than that seen after intravenous administration in normal male volunteers down-regulated with somatostatin (3.94 ± 3.44 hrs. vs. 0.58 ± 0.08 hrs.), indicating that the subcutaneous absorption of the clinically tested formulation of the compound is slow and rate-limiting.

Distribution: The steady-state volume of distribution (Mean ± SD) following IV administration of Zorbtive™ in healthy volunteers is 12.0 ± 1.08 L.

Metabolism: Although the liver plays a role in the metabolism of GH, GH is primarily cleaved in the kidney. GH undergoes glomerular filtration and, after cleavage within the renal cells, the peptides and amino acids are returned to the systemic circulation.

Elimination: The t½ (Mean ± SD) in nine patients with HIV-associated wasting with an average weight of 56.7 ± 6.8 kg, given a fixed dose of 6.0 mg recombinant hGH (r-hGH) subcutaneously was 4.28 ± 2.15 hrs. The renal clearance of r-hGH after subcutaneous administration in nine patients with HIV-associated wasting was 0.0015 ± 0.0037 L/h. No significant accumulation of r-hGH appears to occur after 6 weeks of dosing as indicated.

Special Populations:
Pediatric: Available evidence suggests that r-hGH clearances are similar in adults and children, but no pharmacokinetic studies have been conducted in children with short bowel syndrome.

Gender: Biomedical literature indicates that a gender-related difference in the mean clearance of r-hGH could exist (clearance of r-hGH in males > clearance of r-hGH in females). However, no gender-based analysis is available in normal volunteers or patients with short bowel syndrome.

Race: No data are available.

Renal Insufficiency: It has been reported that individuals with chronic renal failure tend to have decreased r-hGH clearance compared to normals, but there are no data on Zorbtive™ use in the presence of renal insufficiency.

Hepatic Insufficiency: A reduction in r-hGH clearance has been noted in patients with severe liver dysfunction. However, the clinical significance of this in short bowel syndrome patients is unknown.

CLINICAL STUDIES
A randomized, double blind, controlled, parallel-group Phase III clinical study evaluated the efficacy and safety of the administration of Zorbtive™ in subjects with Short Bowel Syndrome (SBS) who were dependent on intravenous parenteral nutrition (IPN) for nutritional support. The primary endpoint was the change in weekly total IPN volume defined as the sum of the volumes of IPN, supplemental lipid emulsion (SLE), and intravenous hydration fluid. The secondary endpoints were the change in weekly IPN caloric content and the change in the frequency of IPN administration per week. Subjects received either Zorbtive™ placebo with the nutritional supplement, glutamine (n=9), Zorbtive™ without glutamine (n=16) or Zorbtive™ with glutamine (n=16). All 3 groups received a specialized diet. Following a two-week equilibration period, treatment was administered in a double blind manner over a further period of four weeks. The dosing of Zorbtive™ was approximately 0.1mg/kg/day for 4 weeks. During the double-blind treatment portion of the trial, the glutamine was given at a daily dose of 30g. The mean baseline IPN volume, mean IPN caloric content, and mean frequency of IPN administration are provided in Table 1. Mean reductions in IPN volume, IPN caloric content and the frequency of IPN administration in each patient group were significantly greater in

both Zorbtive™-treated groups than in group treated with Zorbtive™ placebo. These changes are tabulated in Table 1.

Table 1 Results for Endpoints after 4 weeks of Treatment

| | SOD[GLN] [1] | rhGH + SOD [1] | rhGH + SOD[GLN] [1] |
|---|---|---|---|
| Total IPN volume (L/wk) | | | |
| **Mean at Baseline** | **13.5** | **10.3** | **10.5** |
| **Mean Change** | **-3.8** | **-5.9** | **-7.7** |
| **Treatment differences (with GLN)** | | **-2.1*** | **-3.9**** |
| Total IPN Calories (kcal/wk) | | | |
| **Mean at Baseline** | **8570.4** | **7634.7** | **7895.0** |
| **Mean Change** | **-2633.3** | **-4338.3** | **-5751.2** |
| **Treatment differences (with GLN)** | | **-1705.0** | **-3117.9** |
| Frequency of IPN or SLE (days/week) | | | |
| **Mean at Baseline** | **5.9** | **5.1** | **5.4** |
| **Mean Change** | **-2.0** | **-3.0** | **-4.2** |
| **Treatment differences (with GLN)** | | **-1.0** | **-2.2** |

**[1] SOD[GLN] = Specialized Oral Diet supplemented with Glutamine ; rhGH + SOD = Human Growth Hormone plus Specialized Oral Diet; rhGH + SOD[GLN] = Human Growth Hormone plus Specialized Oral Diet supplemented with Glutamine**

*** p = 0.043, treatment comparison between rhGH + SOD versus SOD[GLN]**

**** p <0.001, treatment comparison between rhGH + SOD[GLN] versus SOD[GLN]**

## INDICATIONS AND USAGE

Zorbtive™ [somatropin (rDNA origin) for injection] is indicated for the treatment of Short Bowel Syndrome in patients receiving specialized nutritional support. Zorbtive™ therapy should be used in conjunction with optimal management of Short Bowel Syndrome.

Specialized nutritional support may consist of a high carbohydrate, low-fat diet, adjusted for individual patient requirements and preferences. Nutritional supplements may be added according to the discretion of the treating physician. Optimal management of Short Bowel Syndrome may include dietary adjustments, enteral feedings, parenteral nutrition, fluid and micronutrient supplements, as needed.

## CONTRAINDICATIONS

Growth hormone therapy should not be initiated in patients with acute critical illness due to complications following open heart or abdominal surgery, multiple accidental trauma or acute respiratory failure. Two placebo-controlled clinical trials in non-growth hormone deficient adult patients (n=522) with these conditions 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).

Zorbtive™ is contraindicated in patients with active neoplasia (either newly diagnosed or recurrent). Any anti-tumor therapy should be completed prior to starting therapy with Zorbtive™. Zorbtive™ [somatropin (rDNA origin) for injection] reconstituted with Bacteriostatic Water for Injection, USP

(0.9% Benzyl Alcohol) should not be administered to patients with a known sensitivity to Benzyl Alcohol. (See « WARNINGS »).

Zorbtive™ is contraindicated in patients with a known hypersensitivity to growth hormone.

WARNINGS

Benzyl Alcohol as a preservative in Bacteriostatic Water for Injection, USP has been associated with toxicity in newborns. If sensitivity to the diluent occurs, Zorbtive™ [somatropin (rDNA origin) for injection] may be reconstituted with Sterile Water for Injection, USP. When Zorbtive™ is reconstituted in this manner, the reconstituted solution should be used immediately and any unused portion should be discarded.

See CONTRAINDICATIONS for information regarding increased mortality in growth hormone-treated patients with acute critical illnesses in intensive care units due to complications following open heart or abdominal surgery, multiple accidental trauma or acute respiratory failure. The safety of continuing growth hormone 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 growth hormone in patients developing acute critical illnesses should be weighed against the potential risk.

PRECAUTIONS

General: Zorbtive™ [somatropin (rDNA origin) for injection] therapy should be carried out under the regular guidance of a physician who is experienced in the diagnosis and management of short bowel syndrome.

Patients should be informed that allergic reactions are possible and that prompt medical attention should be sought if an allergic reaction occurs.

Recombinant human growth hormone (r-hGH) has been associated with acute pancreatitis.

The use of somatropin has been associated with cases of new onset impaired glucose intolerance, new onset type 2 diabetes mellitus and exacerbation of preexisting diabetes mellitus have been reported in patients receiving somatropin. Some patients developed diabetic ketoacidosis and diabetic coma. In some patients, these conditions improved when somatropin was discontinued, while in others the glucose intolerance persisted. Some patients necessitated initiation or adjustment of antidiabetic treatment while on somatropin. Patients with other risk factors for glucose intolerance should be monitored closely during Zorbtive™ therapy.

No cases of intracranial hypertension (IH) have been observed among patients with short bowel syndrome treated with Zorbtive™. The syndrome of IH, with papilledema, visual changes, headache, and nausea and/or vomiting has been reported in a small number of children with growth failure treated with growth hormone products. Nevertheless, funduscopic evaluation of patients is recommended at the initiation and periodically during the course of Zorbtive™ therapy.

Increased tissue turgor (swelling, particularly in the hands and feet) and musculoskeletal discomfort (pain, swelling and/or stiffness) may occur during treatment with Zorbtive™, but may resolve spontaneously, with analgesic therapy, or after reducing the frequency of dosing (see DOSAGE AND ADMINISTRATION).

Carpal tunnel syndrome may occur during treatment with somatropin. If the symptoms of carpal tunnel syndrome do not resolve by decreasing the dose or frequency of somatropin, it is recommended that treatment be discontinued.

Information For Patients: Patients being treated with Zorbtive™ should be informed of the potential benefits and risks associated with treatment. Patients should be instructed to contact their physician should they experience any side effects or discomfort during treatment with Zorbtive™.

It is recommended that Zorbtive™ be administered using sterile, disposable syringes and needles. Patients should be thoroughly instructed in the importance of proper disposal and cautioned against any reuse of needles and syringes. An appropriate container for the disposal of used syringes and needles should be employed.

Patients should be instructed to rotate injection sites to avoid localized tissue atrophy.

Drug Interactions: Formal drug interaction studies have not been conducted.
Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term animal studies for carcinogenicity have not been performed with Zorbtive™. There is no evidence from animal studies to date of Zorbtive™-induced mutagenicity or impairment of fertility.

Pregnancy: Pregnancy Category B. Reproduction studies have been performed in rats and rabbits. Doses up to 5 to 10 times the human dose, based on body surface area, have revealed no evidence of impaired fertility or harm to the fetus due to Zorbtive™. 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.

Nursing Women: It is not known whether Zorbtive™ is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Zorbtive™ is administered to a nursing woman.

Pediatric Use: There are no formal studies in pediatric patients with short bowel syndrome.

Geriatric Use : Clinical studies with Zorbtive™ did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Elderly patients may be more sensitive to growth hormone action, and may be more prone to develop adverse reactions. Thus, dose selection for an elderly patient should be cautious, usually starting at a lower dose.

ADVERSE REACTIONS

Table 2 summarizes the number of subjects by system-organ class who experienced an adverse event during the 4-week treatment period of the Phase 3 SBS study. To be listed in Table 2, an adverse event must have occurred in more than 10% of subjects in any treatment group.

Table 2: Controlled Trial Adverse Events – 4 Week Treatment Period

| Adverse Experiences* | SOD[GLN][1] N=9 n (%) | rhGH+SOD[1] N=16 n (%) | rhGH+SOD[GLN][1] N=16 n (%) |
|---|---|---|---|
| **Total Number of Subjects with At Least One AE** | 8 (89) | 16 (100) | 16 (100) |
| **Body as a Whole: General Disorders** | **4 (44)** | **15 (94)** | **15 (94)** |
| Edema, Peripheral | 1 (11) | 11 (69) | 13 (81) |
| Edema, Facial | 0 (0) | 8 (50) | 7 (44) |
| Pain | 1 (11) | 3 (19) | 1 (6) |
| Chest Pain | 0 (0) | 3 (19) | 0 (0) |
| Fever | 2 (22) | 0 (0) | 1 (6) |
| Back Pain | 1 (11) | 1 (6) | 0 (0) |
| Flu-like Disorder | 1 (11) | 0 (0) | 1 (6) |
| Malaise | 0 (0) | 2 (13) | 0 (0) |
| Edema, Generalized | 0 (0) | 2 (13) | 0 (0) |
| Abdomen Enlarged | 1 (11) | 0 (0) | 0 (0) |
| Allergic Reaction | 1 (11) | 0 (0) | 0 (0) |
| Rigors (Chills) | 1 (11) | 0 (0) | 0 (0) |
| **Gastrointestinal System Disorders** | **6 (67)** | **12 (75)** | **12 (75)** |
| Flatulence | 2 (22) | 4 (25) | 4 (25) |
| Abdominal Pain | 1 (11) | 4 (25) | 2 (13) |
| Nausea | 0 (0) | 2 (13) | 5 (31) |
| Tenesmus | 3 (33) | 1 (6) | 3 (19) |
| Vomiting | 1 (11) | 3 (19) | 3 (19) |
| Hemorrhoids | 1 (11) | 1 (6) | 0 (0) |
| Mouth Dry | 1(11) | 1 (6) | 0 (0) |
| **Musculoskeletal System Disorders** | **1 (11)** | **7 (44)** | **7 (44)** |
| Arthralgia | 0 (0) | 7 (44) | 5 (31) |
| Myalgia | 1 (11) | 2 (13) | 0 (0) |
| **Resistance Mechanism Disorders** | **4 (44)** | **6 (38)** | **3 (19)** |
| Infection | 3 (33) | 0 (0) | 1 (6) |
| Infection Bacterial | 1 (11) | 3 (19) | 0 (0) |
| Infection Viral | 0 (0) | 1 (6) | 2 (13) |
| Moniliasis | 0 (0) | 2 (13) | 0 (0) |
| **Application Site Disorders** | **1 (11)** | **5 (31)** | **4 (25)** |
| Injection Site Reaction | 1 (11) | 3 (19) | 4 (25) |
| Injection Site Pain | 0 (0) | 5 (31) | 0 (0) |
| **Central and Peripheral Nervous System Disorders** | **2 (22)** | **4 (25)** | **4 (25)** |
| Dizziness | 0 (0) | 1 (6) | 2 (13) |
| Headache | 1 (11) | 1 (6) | 1 (6) |
| Hypoasthesia | 1 (11) | 1 (6) | 1 (6) |
| **Skin and Appendages Disorders** | **2 (22)** | **4 (25)** | **4 (25)** |
| Rash | 0 (0) | 1 (6) | 2 (13) |
| Pruritis | 1 (11) | 0 (0) | 1 (6) |
| Sweating Increased | 0 (0) | 2 (13) | 0 (0) |
| Nail Disorder | 1 (11) | 0 (0) | 0 (0) |

| Adverse Experiences* | SOD[GLN][1] N=9 n (%) | rhGH+SOD[1] N=16 n (%) | rhGH+SOD[GLN][1] N=16 n (%) |
|---|---|---|---|
| **Respiratory System Disorders** | **1 (11)** | **1 (6)** | **5 (31)** |
| Rhinitis | 1 (11) | 0 (0) | 3 (19) |
| **Metabolic and Nutritional Disorders** | **1 (11)** | **3 (19)** | **1 (6)** |
| Dehydration | 1 (11) | 3 (19) | 0 (0) |
| Thirst | 1 (11) | 0 (0) | 0 (0) |
| **Urinary System Disorders** | **1 (11)** | **2 (13)** | **1 (6)** |
| Pyelonephritis | 1 (11) | 0 (0) | 0 (0) |
| **Psychiatric Disorders** | **2 (22)** | **1 (6)** | **0 (0)** |
| Depression | 2 (22) | 0 (0) | 0 (0) |
| **Reproductive Disorders, Female** | **1 (11)** | **2 (13)** | **0 (0)** |
| Breast Pain Female | 1 (11) | 1 (6) | 0 (0) |
| **Hearing and Vestibular Disorders** | **0 (0)** | **0 (0)** | **2 (13)** |
| Ear or Hearing Symptoms | 0 (0) | 0 (0) | 2 (13) |

[1] SOD[GLN] = Specialized Oral Diet supplemented with Glutamine; rhGH + SOD = Human Growth Hormone plus Specialized Oral Diet; rhGH + SOD[GLN] = Human Growth Hormone plus Specialized Oral Diet supplemented with Glutamine

Table 3 summarizes the number of subjects by system-organ class who experienced an adverse event during the 12-week follow-up period of the Phase 3 SBS study. To be listed in Table 3, an adverse event must have occurred in more than 10% of subjects in any treatment group.

Table 3: Controlled Trial Adverse Events – 12 Week Follow-Up Period

| Adverse Experiences | SOD[GLN][1] N=9 n (%) | rhGH+SOD[1] N=15 n (%) | rhGH+SOD[GLN][1] N=16 n (%) |
|---|---|---|---|
| **Total Number of Subjects with At Least One AE** | **7 (78)** | **12 (80)** | **13 (81)** |
| **Gastrointestinal System Disorders** | **3 (33)** | **7 (47)** | **7 (44)** |
| Nausea | 2 (22) | 3 (20) | 0 (0) |
| Vomiting | 0 (0) | 2 (13) | 3 (19) |
| Abdominal Pain | 0 (0) | 3 (20) | 1 (6) |
| Tenesmus | 1 (11) | 0 (0) | 3 (19) |
| Pancreatitis | 1 (11) | 0 (0) | 1 (6) |
| Constipation | 1 (11) | 0 (0) | 0 (0) |
| Crohn's Disease Aggravated | 1 (11) | 0 (0) | 0 (0) |
| Gastric Ulcer | 1 (11) | 0 (0) | 0 (0) |
| Gastrointestinal Fistula | 1 (11) | 0 (0) | 0 (0) |
| **Resistance Mechanism Disorders** | **5 (56)** | **6 (40)** | **5 (31)** |
| Infection Bacterial | 3 (33) | 0 (0) | 2 (13) |
| Infection Viral | 1 (11) | 3 (20) | 1 (6) |
| Infection | 1 (11) | 1 (7) | 2 (13) |
| Sepsis | 0 (0) | 3 (20) | 1 (6) |
| **Body as a Whole: General Disorders** | **1 (11)** | **4 (27)** | **2 (13)** |
| Fever | 1 (11) | 2 (13) | 1 (6) |
| Fatigue | 0 (0) | 2 (13) | 0 (0) |
| **Respiratory System Disorders** | **1 (11)** | **2 (13)** | **4 (25)** |
| Rhinitis | 0 (0) | 1 (7) | 3 (19) |
| Laryngitis | 1 (11) | 0 (0) | 0 (0) |
| Pharyngitis | 1 (11) | 0 (0) | 0 (0) |

| | | | |
|---|---|---|---|
| **Reproductive Disorders, Female** | **1 (11)** | **0 (0)** | **4 (25)** |
| Vaginal Fungal Infection | 1 (11) | 0 (0) | 0 (0) |
| Skin and Appendages Disorders | 1 (11) | 2 (13) | 2 (13) |
| Rash | 1 (11) | 1 (7) | 0 (0) |
| **Musculoskeletal System Disorders** | **0 (0)** | **2 (13)** | **2 (13)** |
| Arthralgia | 0 (0) | 2 (13) | 2 (13) |
| **Psychiatric Disorders** | **1 (11)** | **0 (0)** | **1 (6)** |
| Depression | 1 (11) | 0 (0) | 0 (0) |
| Insomnia | 1 (11) | 0 (0) | 0 (0) |
| **Urinary System Disorders** | **2 (22)** | **0 (0)** | **0 (0)** |
| Pyelonephritis | 1 (11) | 0 (0) | 0 (0) |
| Renal Calculus | 1 (11) | 0 (0) | 0 (0) |
| **Application Site Disorders** | **1 (11)** | **0 (0)** | **0 (0)** |
| Injection Site Reaction | 1 (11) | 0 (0) | 0 (0) |
| **Liver and Biliary System Disorders** | **1 (11)** | **0 (0)** | **0 (0)** |
| Hepatic Function Abnormal | 1 (11) | 0 (0) | 0 (0) |
| **Vascular Extracardiac Disorders** | **1 (11)** | **0 (0)** | **0 (0)** |
| Vascular Disorder | 1 (11) | 0 (0) | 0 (0) |

**[1] SOD[GLN] = Specialized Oral Diet supplemented with Glutamine ;rhGH + SOD = Human Growth Hormone plus Specialized Oral Diet; rhGH + SOD[GLN] = Human Growth Hormone plus Specialized Oral Diet supplemented with Glutamine**

Adverse events that occurred in 1% to less than 10% of study participants receiving Zorbtive™ in the placebo-controlled clinical efficacy trial are listed below by body system. The list of adverse events has been compiled regardless of casual relationship to Zorbtive™.

*Body as a Whole, General:* edema, periorbital edema
*Gastrointestinal System:* melena, rectal hemorrhage, mouth disorder, steatorrhea
*Musculoskeletal System:* arthritis, arthropathy, bursitis, cramps
*Resistance Mechanism Disorders:* fungal infection
*Application Site Disorders:* reaction pain, inflammation at injection sites
*Central and Peripheral Nervous System:* parasthesia, phantom pain, visual field defect
*Respiratory System:* bronchospasm, dyspnea, pharyngitis, respiratory disorder, respiratory infection
*Platelet Bleeding and Clotting Disorders:* purpura, prothrombin decrease
*Skin and Appendages:* skin disorder, increased sweating, alopecia, bullous eruption
*Psychiatric:* insomnia
*Metabolic and Nutritional:* hypomagnesemia,
*Urinary System Disorders:* dysuria, urinary tract infection, abnormal urine
*Reproduction Disorders Female:* breast enlargement, vaginal fungal infection
*Heart Rate and Rhythm Disorders:* tachycardia
*Vascular (Extra Cardiac) Disorders:* vasodilatation

The safety profile of patients receiving Zorbtive™ with glutamine was similar to the safety profile of patients receiving Zorbtive™ without glutamine. During the baseline period, 88% of patients receiving Zorbtive™ with glutamine, 88% of patients receiving Zorbtive™ without glutamine, and 78% of patients receiving Zorbtive™ placebo with glutamine reported baseline signs and symptoms (BSS). During the treatment period, 100% of patients receiving Zorbtive™ with and without glutamine reported at least one adverse event (AE), whereas 89% of patients receiving Zorbtive™

placebo with glutamine reported at least one AE. During the follow-up period 81% of patients receiving Zorbtive™ with glutamine, 80% of patients receiving Zorbtive™ without glutamine and 78% of patients receiving Zorbtive™ placebo with glutamine experienced at least one AE. Comparison of the number of serious adverse events (SAEs) before and during treatment demonstrates that this subject population experiences numerous BSSs and AEs due to their underlying conditions and parenteral nutrition complications. Four subjects (25%) receiving Zorbtive™ without glutamine and one subject (11%) in receiving Zorbtive™ placebo with glutamine experienced at least one SAE during the treatment period (Zorbtive™ without glutamine: chest pain, purpura, fungal infection, pharyngitis ; Zorbtive™ placebo with glutamine: hemorrhoids). None of the subjects receiving Zorbtive™ with glutamine experienced SAEs during the treatment period. During the follow-up period, 3 subjects (19%) receiving Zorbtive™ with glutamine, 5 subjects (33%) receiving Zorbtive™ without glutamine and 3 subjects (33%) receiving Zorbtive™ placebo with glutamine experienced at least one SAE. There were no deaths in this study.

## OVERDOSAGE

Glucose intolerance can occur with overdosage. Long-term overdosage with growth hormone could result in signs and symptoms of acromegaly.

## DOSAGE AND ADMINISTRATION

Zorbtive™ should be administered to patients with short bowel syndrome (SBS) at a dose of approximately 0.1 mg/kg subcutaneously daily to a maximum of 8 mg daily. Administration for more than 4 weeks has not been adequately studied.

Injections should be administered daily for 4 weeks. Changes to concomitant medications should be avoided. Patients and physicians should monitor for adverse events. Treat moderate fluid retention and arthralgias symptomatically or dose reduce by 50%. Discontinue Zorbtive™ for up to 5 days for severe toxicities. Upon resolution of symptoms, resume at 50% of original dose. Permanently discontinue treatment if severe toxicity recurs or does not disappear within 5 days.

Injection sites should be rotated.

Safety and effectiveness in pediatric patients with short bowel syndrome have not been established.

Each vial of Zorbtive™ 4 mg, 5 mg or 6 mg is reconstituted with 0.5 to 1 mL Sterile Water for Injection, USP. Each vial of Zorbtive™ 8.8 mg is reconstituted in 1 to 2 mL of Bacteriostatic Water for Injection, USP (0.9% Benzyl Alcohol preserved). See Table 4 below for expected concentration after reconstitution. Approximately 10% mechanical loss can be associated with reconstitution and administration from multi-dose vials. For patients sensitive to benzyl alcohol, see « WARNINGS » .

Table 4: Expected Concentration After Reconstitution (mg/mL)

| | 0.5 mL | 1 mL | 2 mL |
|---|---|---|---|
| **4 mg** | 8 | 4 | -- |
| **5 mg** | 10 | 5 | -- |
| **6 mg** | 12 | 6 | -- |
| **8.8 mg** | -- | 8.8 | 4.4 |

To reconstitute Zorbtive™, inject the diluent into the vial of Zorbtive™ aiming the liquid against the glass vial wall. Swirl the vial with a gentle rotary motion until contents are dissolved completely. The Zorbtive™ solution should be clear immediately after reconstitution. **DO NOT INJECT** Zorbtive™ if the reconstituted product is cloudy immediately after reconstitution (Zorbtive™ 4 mg, 5 mg, 6 mg or 8.8 mg) or after refrigeration (only Zorbtive™ 8.8 mg). The reconstituted Zorbtive™ 8.8 mg can be refrigerated (2-8°C/36-46°F) for up to 14 days. Occasionally, after refrigeration, small colorless particles may be present in the Zorbtive™ 8.8 mg solution. This is not unusual for proteins like Zorbtive™. Allow refrigerated solution to come to room temperature prior to administration. A standard insulin-type subcutaneous syringe is recommended for administration.

STABILITY AND STORAGE

Before reconstitution: Vials of Zorbtive™ and diluent should be stored at room temperature, (15°-30°C/59°-86°F). Expiration dates are stated on product labels.

After Reconstitution with Sterile Water for Injection, USP: The reconstituted solution should be used immediately and any unused portion should be discarded .

After Reconstitution with Bacteriostatic Water for Injection, USP (0.9% Benzyl Alcohol): The reconstituted solution should be stored under refrigeration (2-8°C/36-46°F) for up to 14 days. Avoid freezing reconstituted vials of Zorbtive™.

HOW SUPPLIED

Zorbtive™ [somatropin (rDNA origin) for injection] is available in the following forms:

Zorbtive™ vials containing 4 mg (approximately 12 IU) somatropin (mammalian-cell) with Sterile Water for Injection, USP, 1mL. Package of 7 vials. NDC 44087-0004-7

Zorbtive™ vials containing 5 mg (approximately 15 IU) somatropin (mammalian-cell) with Sterile Water for Injection, USP, 1mL. Package of 7 vials. NDC 44087-0005-7

Zorbtive™ vials containing 6 mg (approximately 18 IU) somatropin (mammalian-cell) with Sterile Water for Injection, USP, 1mL. Package of 7 vials. NDC 44087-0006-7

Zorbtive™ vial containing 8.8 mg (approximately 26.4 IU) somatropin (mammalian-cell) with Bacteriostatic Water for Injection, USP (0.9% Benzyl Alcohol), 10mL. Package of 1 vial. NDC 44087-0088-1

Manufactured for: Serono, Inc., Rockland, MA 02370

**Rx Only** **BX Rated**

Revised November 2003

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**20-604/S-026**

# ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

**Food and Drug Administration**
**Center for Drug Evaluation and Research**
**Office of Drug Evaluation III**

# FACSIMILE TRANSMITTAL SHEET

**DATE:** December 1, 2003

| | |
|---|---|
| **To:** Laurie A. Ridener<br>Senior Manager, Regulatory Affairs | **From:** Alice Kacuba, R.N., MSN, RAC<br>Certified Regulatory Health Project Manager |
| **Company:** Serono, Inc. | Division of Gastrointestinal and Coagulation Drug Products |
| **Fax number:** 781-681-2947 (per your request) | **Fax number:** 301-443-9285 |
| **Phone number:** 781-681-2384 | **Phone number:** (301) 827-1602 or 7310 |

**Subject:** NDA 21-597/20-604/SLR-026

**Total no. of pages including cover:** ___

**Comments:** Attached is some information from the Division of Surveillance, Research, and Communications Support (DSRCS) that will assist you in developing the patient package insert (PPI) and patient handbook.

**Documents to be mailed:** ☐ YES ☑ NO

The following are some comments from DSRCS to assist you in the development of the patient package insert (PPI) and patient handbook.

The Zorbtive PPI should:

- contain comprehensive information based on the prescribing information (PI).
- be written in a Medication Guide question and answer type format (see 21 CFR 208). This format has research and experience to support its communication effectiveness.
- be written at a 6th to 8th grade reading comprehension level. This is an optimal comprehension level for all patient materials.
- be non-promotional.
- have instructions for use appended at the end of the PPI and be clearly written. Refer to *Guidance on Medical Device Patient Labeling; Final Guidance for Industry and FDA Reviewers* for more information on writing instructions for patients.

The patient handbook appears to provide comprehensive information on the disease, management, and treatment with Zorbtive. The patient handbook should:

- be written at a 6th to 8th grade reading comprehension level. Keep sentences shorts, words simplified, explain any medical or technical term, and bullet information when possible.
- have a font size of at least 10 point to aid in ease of readability.
- have adequate background contrast and white space to aid in ease of readability; not be overwhelmed by background pictures or artwork.
- be non-promotional in tone.

Ideally, the patient handbook would be tested for comprehension among a cross section (varying educational levels, including those with low literacy) of Zorbtive treated SBS patients.

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/s/

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## Division of Metabolic and Endocrine Drug Products

# REGULATORY PROJECT MANAGER REVIEW

**Application Number:** 20-604/S-026

**Name of Drug:** Serostim (somatropin [rDNA origin] for injection)

**Applicant:** Serono, Inc.

## Material Reviewed:

**Submission Date(s):** September 24, 2003 (Draft Labeling)

**Receipt Date(s):** September 25, 2003

## Background and Summary

Serostim is indicated for the treatment of treatment of AIDS wasting or cachexia. Supplement -026 proposes an additional indication for the treatment of short bowel syndrome in patients receiving specialized nutritional support. The acknowledgement letter to the sponsor explained that the short bowel indication would be reviewed in the Division of Gastrointestinal and Coagulation Drug Products (DGCDP), HFD-180.

A new trade name, other than Serostim, has been proposed for the short bowel syndrome indication, which will necessitate a separate package insert, vial and carton labels, which will be reviewed in DGCDP.

## Review

The package insert, submitted on September 24, 2003, was compared to the currently approved package insert (August 21, 2003, approved with supplement -027) and only minor editorial changes were made.

## Conclusions

Supplement -026 should be approved with NDA 21-597 (type 6).

Monika Johnson, PharmD
Regulatory Project Manager

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/s/

Monika Johnson
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CSO