

Serostim[®]

[somatotropin (rDNA origin) for injection]

DESCRIPTION

Serostim[®] [somatotropin (rDNA origin) for injection] is a human growth hormone (hGH) produced by recombinant DNA technology. Serostim[®] 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. Serostim[®] is produced by a mammalian cell line (mouse C127) that has been modified by the addition of the hGH gene. Serostim[®] is secreted directly through the cell membrane into the cell-culture medium for collection and purification.

Serostim[®] is a highly purified preparation. Biological potency is determined by measuring the increase in the body weight induced in hypophysectomized rats.

Serostim[®] is available in 4 mg, 5 mg and 6 mg vials for single dose administration. Serostim[®] is also available in 4 mg and 8.8 mg vials for multi-dose administration. Each 4 mg vial contains 4.0 mg (approximately 12 IU) somatotropin, 27.3 mg sucrose, 0.9 mg phosphoric acid. Each 5 mg vial contains 5.0 mg (approximately 15 IU) somatotropin, 34.2 mg sucrose and 1.2 mg phosphoric acid. Each 6 mg vial contains 6.0 mg (approximately 18 IU) somatotropin, 41.0 mg sucrose and 1.4 mg phosphoric acid. Each 8.8 mg vial contains 8.8 mg (approximately 26.4 IU) somatotropin, 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 with Water for Injection, USP. The pH is adjusted with sodium hydroxide or phosphoric acid to give a pH of 6.5 to 8.5 after reconstitution with Bacteriostatic Water for Injection, USP (0.9% Benzyl Alcohol).

CLINICAL PHARMACOLOGY

Serostim[®] [somatotropin (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).

HIV-associated wasting or cachexia, which commonly involves involuntary loss of lean body mass or body weight, is a metabolic disorder characterized by abnormalities of intermediary metabolism resulting in weight loss, inappropriate depletion of lean body mass (LBM), and paradoxical preservation of body fat. LBM includes primarily skeletal muscle, organ tissue, blood and blood constituents, and both intracellular and extracellular water. Depletion of LBM results in muscle weakness, organ failure, and death. Unlike nutritional intervention for HIV-associated wasting, in which supplemental calories are converted predominantly to body fat, Serostim[®] treatment resulted in a significant increase in LBM and a decrease in fat mass with a significant increase in body weight due to the dominant effect of LBM gain.

Effects on Protein, Lipid, and Carbohydrate Metabolism:

A one-week study in 6 patients with HIV-associated wasting has shown that treatment with Serostim[®] 0.1 mg/kg/day improved nitrogen balance, increased protein-sparing lipid oxidation, and had little effect on overall carbohydrate metabolism.

Effects on Nitrogen and Mineral Retention:

In the one-week study in 6 patients with HIV-associated wasting, treatment with Serostim[®] resulted in the retention of phosphorous, potassium, nitrogen, and sodium. The ratio of retained potassium and nitrogen during Serostim[®] therapy was consistent with retention of these elements in lean tissue.

Physical Performance:

Cycle ergometry work output and treadmill performance were examined in separate 12-week, placebo-controlled trials (see 'Clinical Studies'). In both studies, work output improved significantly in the group receiving Serostim[®] 0.1 mg/kg/day subcutaneously vs placebo. Isometric muscle performance, as measured by grip strength dynamometry, declined, probably as a result of a transient increase in tissue turgor known to occur with Serostim[®] therapy.

PHARMACOKINETICS

Subcutaneous Absorption: The absolute bioavailability of Serostim[®] [somatropin (rDNA origin) for injection] after subcutaneous administration of a formulation not equivalent to the marketed formulation was determined to be 70-90%. The $t_{1/2}$ (Mean \pm 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 \pm SD) following IV administration of Serostim[®] 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 $t_{1/2}$ (Mean \pm 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 HIV.

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 infected with HIV.

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 Serostim[®] 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 HIV+ patients is unknown.

CLINICAL STUDIES

The clinical efficacy of Serostim[®] [somatropin (rDNA origin) for injection] was assessed in two placebo-controlled trials. All study subjects received concomitant antiretroviral therapy.

Clinical Trial 1: A 12-week, randomized, double-blind, placebo-controlled study followed by an open-label extension phase enrolled 178 patients with severe AIDS wasting taking nucleoside analogue therapy (pre-HAART era). The primary endpoint was body weight. Body composition was assessed using dual energy X-ray absorptiometry (DXA) and physical function was assessed by treadmill exercise testing. Patients meeting the inclusion/exclusion criteria were treated with either placebo or Serostim[®] 0.1 mg/kg daily. Ninety-six percent (96%) were male. The average baseline CD4 count/ μ L was 85. The results from one hundred forty (140) evaluable patients were analyzed (those completing the 12-week course of treatment and who were at least 80% compliant with study drug). After 12 weeks of therapy, the mean difference in weight increase between the Serostim[®]-treated group and the placebo-treated group was 1.6 kg (3.5 lb). Mean difference in lean body mass (LBM) change between the Serostim[®]-treated group and the placebo-treated group was 3.1 kg (6.8 lbs) as measured by DXA. Mean increase in weight and LBM, and mean decrease in body fat, were significantly greater in the Serostim[®]-treated group than in the placebo group ($p=0.011$, $p<0.001$, $p<0.001$, respectively) after 12 weeks of treatment (Figure 1). There were no significant changes with continued treatment beyond 12 weeks suggesting that the original gains of weight and LBM were maintained (Figure 1).

Treatment with Serostim[®] resulted in a significant increase in physical function as assessed by treadmill exercise testing. The median treadmill work output increased by 13% ($p=0.039$) at 12 weeks in the group receiving Serostim[®] (Figure 2). There was no improvement in the placebo-treated group at 12 weeks. Changes in treadmill performance were significantly correlated with changes in LBM.

Figure 1: Mean Changes in Body Composition

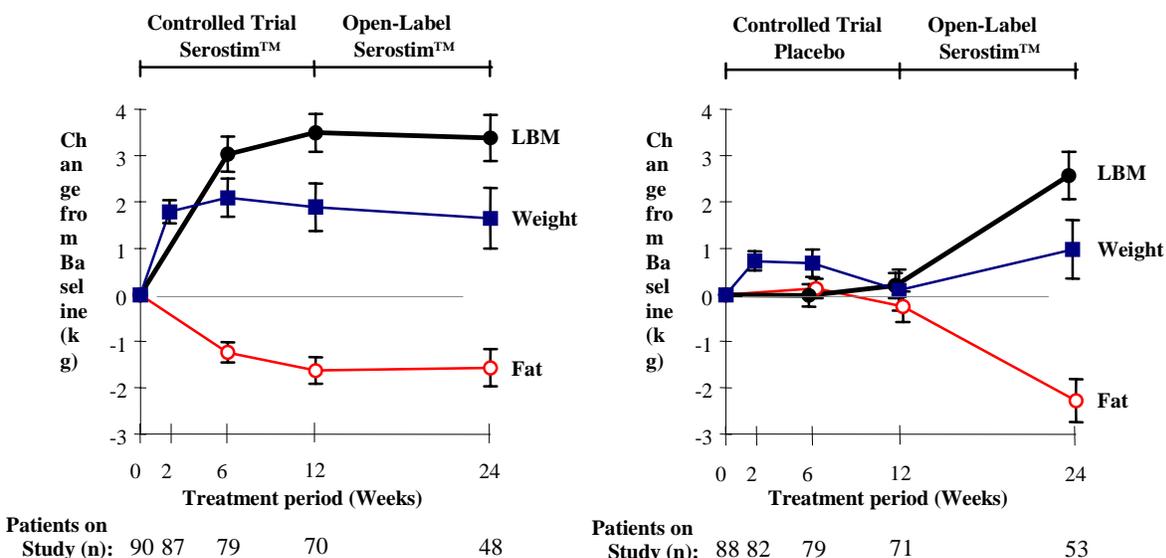
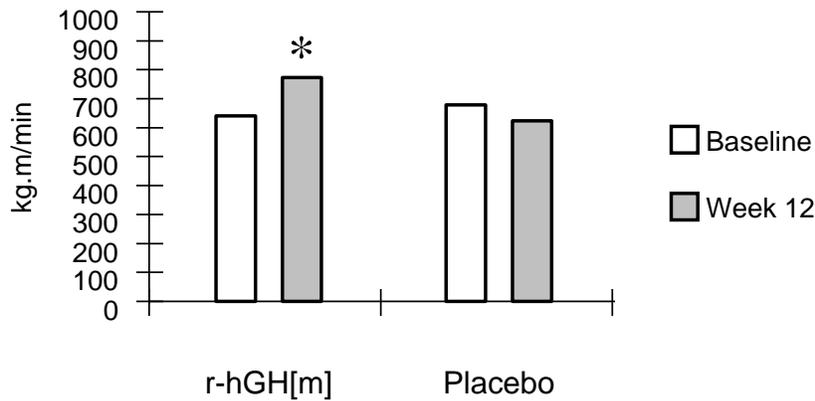


Figure 2: Median Treadmill Work Output



*p = 0.039

Clinical Trial 2: A 12-week, randomized, double-blind, placebo-controlled study enrolled 757 patients with HIV-associated wasting, or cachexia. The primary efficacy endpoint was physical function as measured by cycle ergometry work output. Body composition was assessed using bioelectrical impedance spectroscopy (BIS) and also by dual energy X-ray absorptiometry (DXA) at a subset of centers. Patients meeting the inclusion/exclusion criteria were treated with either placebo, approximately 0.1 mg/kg every other day (qod) of Serostim[®], or approximately 0.1 mg/kg daily (qhs) of Serostim[®]. All results were analyzed in intent-to-treat populations (for cycle ergometry work output, n=670). Ninety-one percent (91%) were male and 88% were on HAART anti-retroviral therapy. The average baseline CD4 count/ μ L was 446. Six hundred forty-six patients (646) completed the 12-week study and continued in the Serostim[®] treatment extension phase of the trial.

Clinical Trial 2 results are summarized in Tables 1 and 2:

**Table 1: Mean (Median) of Cycle Work Output (kJ) Response after 12 weeks of Treatment
ITT Population**

	Placebo	Half-Dose Serostim ^b	Full-Dose Serostim ^a
Cycle work output (kJ)	n=222	n=230	n=218
Baseline	25.92 (25.05)	27.79 (26.65)	27.57 (26.30)
Change from baseline	-0.05 (-0.25)	2.48 (2.30)	2.52 (2.40)
Percent change from baseline	0.2%	8.9%	9.1%
Difference from Placebo			
Mean (2-sided 95% C.I.)		2.53 ^c (0.81, 4.25)	2.57 ^c (0.83, 4.31)
Median		2.55	2.65

^a approximately 0.1 mg/kg daily

^b approximately 0.1 mg/kg every other day

^c p<0.01

Table 2: Mean (Median) Change from Baseline for Lean Body Mass, Fat Mass and Body Weight

	Placebo		Half-Dose Serostim ^b		Full-Dose Serostim ^a	
	n	Mean (Median)	n	Mean (Median)	n	Mean (Median)
Lean body mass (kg) (by BIS)	222	0.97 (0.67)	223	3.89 (3.65)	205	5.84 (5.47)
Fat mass (kg) (by DXA)	94	0.03 (0.01)	100	-1.25 (-1.23)	85	-1.72 (-1.51)
Body weight (kg)	247	0.69 (0.68)	257	2.18 (2.15)	253	2.79 (2.65)

^a approximately 0.1 mg/kg daily

^b approximately 0.1 mg/kg every other day

The mean maximum cycle work output until exhaustion increased after 12 weeks by 2.57 kilojoules (kJ) in the Serostim[®] 0.1 mg/kg daily group (p<0.01) and by 2.53 kJ in the Serostim[®] 0.1 mg/kg every other day group (p<0.01) compared with placebo (Table 1). Cycle work output improved approximately 9% in both active treatment arms and decreased <1% in the placebo group. Lean body mass (LBM) and body weight (BW) increased, and fat mass decreased, in a dose-related fashion after treatment with Serostim[®] and placebo (Table 2). The LBM results obtained by BIS were confirmed with DXA.

Patients' perceptions of the impact of 12 weeks of treatment on their wasting symptoms as assessed by the Bristol-Meyers Anorexia/Cachexia Recovery Instrument improved with both doses of Serostim[®] in Clinical Trial 2.

Extension Phase: All patients (n=646) completing the 12-week placebo-controlled phase of Clinical Trial 2 continued Serostim[®] treatment into an extension phase. Five hundred and forty eight of these patients completed an additional 12 weeks of active treatment. In these patients, changes in cycle ergometry work output, LBM, BW, and fat mass either improved further or were maintained with continued Serostim[®] treatment.

INDICATIONS AND USAGE

Serostim[®] [somatropin (rDNA origin) for injection] is indicated for the treatment of HIV patients with wasting or cachexia to increase lean body mass and body weight, and improve physical endurance. Concomitant antiretroviral therapy is necessary (see PRECAUTIONS).

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).

Serostim[®] is contraindicated in patients with active neoplasia (either newly diagnosed or recurrent). Any anti-tumor therapy should be completed prior to starting therapy with Serostim[®].

Serostim[®] [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).

Serostim[®] 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, Serostim[®] [somatropin (rDNA origin) for injection] may be reconstituted with Sterile Water for Injection, USP. When Serostim[®] 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: Serostim[®] [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 HIV infection. Inadequate nutritional intake, malabsorption and hypogonadism, which are common in individuals with HIV infection and which may contribute to catabolism and weight loss, should be diagnosed and treated.

HIV and Growth Hormone Considerations: In some experimental systems, recombinant human growth hormone (r-hGH) has been shown to potentiate HIV replication in vitro at concentrations ranging from 50-250 ng/ml. There was no increase in virus production when the antiretroviral agents, zidovudine, didanosine or lamivudine were added to the culture medium. Additional in vitro studies have shown that r-hGH does not interfere with the antiviral activity of zalcitabine or stavudine. In the controlled clinical trials, no significant growth hormone-associated increase in viral burden was observed. However, the protocol required all participants to be on concomitant antiretroviral therapy for the duration of the study. In view of the potential for acceleration of virus replication, it is recommended that HIV patients be maintained on antiretroviral therapy for the duration of Serostim[®] treatment.

Increased tissue turgor (swelling, particularly in the hands and feet) and musculoskeletal discomfort (pain, swelling and/or stiffness) may occur during treatment with Serostim[®], 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 Serostim[®]. If the symptoms of carpal tunnel syndrome do not resolve by decreasing the weekly number of doses of Serostim[®], it is recommended that treatment be discontinued.

Patients should be informed that allergic reactions are possible and that prompt medical attention should be sought if an allergic reaction occurs. None of the 651 study participants with HIV-

associated wasting treated with Serostim[®] for the first time developed detectable antibodies to growth hormone (> 4 pg binding). Patients were not rechallenged.

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

Hyperglycemia may occur in HIV infected individuals due to a variety of reasons. Treatment with Serostim[®] 0.1 mg/kg daily and 0.1 mg/kg every other day for 12 weeks were associated with approximately 10mg/dL and 6mg/dL increases of mean blood glucose concentration, respectively. The increases occurred early in treatment. Patients with other risk factors for glucose intolerance should be monitored closely during Serostim[®] therapy.

During post-marketing surveillance, 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 Serostim[®]. Some patients developed diabetic ketoacidosis and diabetic coma. In some patients, these conditions improved when Serostim[®] was discontinued, while in others the glucose intolerance persisted. Some patients necessitated initiation or adjustment of antidiabetic treatment while on Serostim[®].

No cases of intracranial hypertension (IH) have been observed among patients with AIDS wasting treated with Serostim[®]. 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, fundoscopic evaluation of patients is recommended at the initiation and periodically during the course of Serostim[®] therapy.

Kaposi's sarcoma, lymphoma, and other malignancies are common in HIV+ individuals. There was no increase in the incidence of Kaposi's sarcoma, lymphoma, or in the progression of cutaneous Kaposi's sarcoma in clinical studies of Serostim[®]. Patients with internal KS lesions were excluded from the studies. Potential effects on other malignancies are unknown.

Information For Patients: Patients being treated with Serostim[®] 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 Serostim[®].

It is recommended that Serostim[®] 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 in vitro drug interaction studies have not been conducted. No data are available on drug interactions between Serostim[®] and HIV protease inhibitors or the non-nucleoside reverse transcriptase inhibitors.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term animal studies for carcinogenicity have not been performed with Serostim[®]. There is no evidence from animal studies to date of Serostim[®]-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 Serostim[®]. 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 Serostim[®] is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Serostim[®] is administered to a nursing woman.

Pediatric Use: In two small studies, 11 children with HIV-associated failure to thrive were treated subcutaneously with human growth hormone. In one study, five children (age range, 6 to 17 years) were treated with 0.04 mg/kg/day for 26 weeks. In a second study, six children (age range, 8 to 14 years) were treated with 0.07 mg/kg/day for 4 weeks. Treatment appeared to be well tolerated in both studies. The preliminary data collected on a limited number of patients with HIV-associated failure to thrive appear to be consistent with safety observations in growth hormone-treated adults with AIDS wasting.

Geriatric Use : Clinical studies with Serostim[®] 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 the low end of the dosing range.

ADVERSE REACTIONS

In the 12-week, placebo-controlled Clinical Trial 2, 510 patients were treated with Serostim[®] [somatropin (rDNA origin) for injection]. The most common adverse reactions judged to be associated with Serostim[®] were musculoskeletal discomfort and increased tissue turgor (swelling, particularly of the hands or feet), and were more frequently observed when Serostim[®] 0.1 mg/kg was administered on a daily basis (Table 3 and PRECAUTIONS). These symptoms were generally rated by investigators as mild to moderate in severity and often subsided with continued treatment or dose reduction. Approximately 23% of patients receiving Serostim[®] 0.1 mg/kg daily and 11% of patients receiving 0.1 mg/kg every other day required dose reductions. Discontinuations as a result of adverse events occurred in 10.3% of patients receiving Serostim[®] 0.1 mg/kg daily and 6.6% of patients receiving 0.1 mg/kg every other day. The most common reasons for dose reduction and/or drug discontinuation were arthralgia, myalgia, edema, carpal tunnel syndrome, elevated glucose levels, and elevated triglyceride levels.

Clinical adverse events which occurred during the first 12 weeks of study in at least 5% of the patients in any one of the three treatment groups are listed below by treatment group, without regard to causality assessment.

Table 3: Controlled Clinical Trial 2 Adverse Events :

Body System Preferred Term	Placebo	0.1 mg/kg qod Serostim [®]	0.1 mg/kg daily Serostim [®]
	Patients (n=247)	Patients (n=257)	Patients (n=253)
	%	%	%
MUSCULOSKELETAL SYSTEM DISORDERS			
ARTHRALGIA	11.3	24.5	36.4
MYALGIA	11.7	17.9	30.4
ARTHROSIS	3.6	7.8	10.7
GASTRO-INTESTINAL SYSTEM DISORDERS			
DIARRHEA	10.1	10.1	5.5
NAUSEA	4.9	5.4	9.1

PSYCHIATRIC DISORDERS			
INSOMNIA	6.1	3.9	5.9
BODY AS A WHOLE - GENERAL DISORDERS			
EDEMA PERIPHERAL	2.8	11.3	26.1
HEADACHE	9.3	10.1	12.6
FATIGUE	4.5	3.5	5.1
RESPIRATORY SYSTEM DISORDERS			
RHINITIS	6.5	5.1	4.0
UPPER RESP TRACT INFECTION	5.7	4.3	3.6
BRONCHITIS	5.3	2.3	4.7
ENDOCRINE DISORDERS			
GYNECOMASTIA	0.4	3.5	5.5
CENTR & PERIPH NERVOUS SYSTEM DISORDERS			
PARESTHESIA	4.5	7.4	7.9
HYPOESTHESIA	2.4	1.6	5.1
METABOLIC AND NUTRITIONAL DISORDERS			
EDEMA GENERALIZED	1.2	1.2	5.9

Adverse events that occurred in 1% to less than 5% of study participants receiving Serostim[®] during the 12-week, placebo-controlled Clinical Trial 2 are listed below by body system. The list of adverse events has been compiled regardless of causal relationship to Serostim[®].

Body as a Whole: rigors, fever, carpal tunnel syndrome (see PRECAUTIONS), night sweats, edema/face edema (see PRECAUTIONS), pain, flu-like symptoms, leg pain, chest pain, asthenia.

Gastrointestinal System: vomiting, abdominal pain, dyspepsia, gastroenteritis, and constipation.

Musculoskeletal System: back pain, musculoskeletal pain (see PRECAUTIONS), and arthropathy.

Central and Peripheral Nervous System: peripheral neuropathy, dizziness, and hypertonia.

Respiratory System: coughing, sinusitis, pharyngitis, and pneumonia.

White Blood Cell and Reticuloendothelial System Disorders: lymphadenopathy

Skin and Appendages: folliculitis, rash, verruca, and maculopapular rash.

Psychiatric: anorexia, depression, anxiety, and somnolence.

Metabolic and Nutritional: hypertriglyceridemia, hyperglycemia (see PRECAUTIONS), and periorbital edema (see PRECAUTIONS).

Immune System Dysfunction: moniliasis, viral infection, and herpes simplex.

Urinary System: urinary tract infection, renal calculus

Vision: conjunctivitis

Cardiovascular, General: dependent edema (see PRECAUTIONS), hypertension, tachycardia

Secondary Terms: accident not otherwise specified

Neoplasms: male breast neoplasm

During the 12-week, placebo-controlled portion of Clinical Trial 2, the incidence of hyperglycemia reported as an adverse event was 3.6% for the placebo group, 1.9% for the 0.1 mg/kg qod group and 3.2% for the 0.1 mg/kg daily group. One case of diabetes mellitus was noted in the 0.1 mg/kg daily group during the first 12-weeks of therapy. In addition, during the extension phase of Clinical Trial 2, two patients converted from placebo to full dose Serostim[®], and 1 patient converted from placebo to half-dose Serostim[®], were discontinued because of the development of diabetes mellitus.

The types and incidences of adverse events reported during the Clinical Trial 2 extension phase were not different from, or greater in frequency than those observed during the 12-week, placebo-controlled portion of Clinical Trial 2.

During post-marketing surveillance, 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 Serostim[®]. Some patients developed diabetic ketoacidosis and diabetic coma. In some patients, these conditions improved when Serostim[®] was discontinued, while in others the glucose intolerance persisted. Some patients necessitated initiation or adjustment of antidiabetic treatment while on Serostim[®].

OVERDOSAGE

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

DOSAGE AND ADMINISTRATION

The usual starting dose of Serostim[®] [somatropin (rDNA origin) for injection] is 0.1 mg/kg subcutaneously (SC) daily (up to 6 mg). It should be administered SC daily at bedtime according to the following dosage recommendations:

Weight Range	Dose
>55kg (>121 lb)	6 mg* SC daily
45-55 kg (99-121 lb)	5 mg* SC daily
35-45 kg (75-99 lb)	4 mg* SC daily
<35 kg (<75 lb)	0.1 mg/kg SC daily

*Based on an approximate daily dosage of 0.1 mg/kg.

Serostim[®] 8.8 mg and Serostim[®] 4 mg with Bacteriostatic Water for Injection, USP (0.9% Benzyl Alcohol), multi-use vials, should be administered as per the above weight-based dosing table. Serostim 4, 5 or 6 mg with Sterile Water for Injection, USP, single use vials, should be administered to patients requiring 4, 5 or 6 mg daily, respectively, as per the above weight-based dosing table.

Treatment with Serostim[®] 0.1 mg/kg every other day was associated with fewer side effects, and resulted in a similar improvement in work output, as compared with Serostim[®] 0.1 mg/kg daily. Therefore, a starting dose of Serostim[®] 0.1 mg/kg every other day should be considered in patients at increased risk for adverse effects related to recombinant human growth hormone therapy (i.e., glucose intolerance). In general, dose reductions (i.e., reducing the total daily dose or the number of doses per week) should be considered for side effects potentially related to recombinant human growth hormone therapy, which are unresponsive to symptom-directed treatment.

Most of the effect of Serostim[®] on work output and lean body mass was apparent after 12 weeks of treatment. The effect was maintained during an additional 12 weeks of therapy. There are no safety or efficacy data available from controlled studies in which patients were treated with Serostim[®] continuously for more than 48 weeks. There are no safety or efficacy data available from trials in which patients were treated intermittently with Serostim[®].

Injection sites should be rotated.

Safety and effectiveness in pediatric patients with HIV have not been established.

Each vial of Serostim[®] 4 mg, 5 mg or 6 mg is reconstituted with 0.5 to 1 mL Sterile Water for Injection, USP. Each vial of Serostim[®] 8.8 mg is reconstituted in 1 to 2 mL of Bacteriostatic Water for Injection, USP (0.9% Benzyl Alcohol preserved) and each vial of Serostim[®] 4 mg is reconstituted in 0.5 to 1 mL of Bacteriostatic Water for Injection, USP (0.9% Benzyl Alcohol preserved). Approximately 10% mechanical loss can be associated with reconstitution and administration from multi-dose vials. For patients sensitive to this diluent, see WARNINGS.

To reconstitute Serostim[®], inject the diluent into the vial of Serostim[®] aiming the liquid against the glass vial wall. Swirl the vial with a gentle rotary motion until contents are dissolved completely. The Serostim[®] solution should be clear immediately after reconstitution. **DO NOT INJECT** Serostim[®] if the reconstituted product is cloudy immediately after reconstitution or after refrigeration (2-8°C/36-46°F) for up to 14 days. Occasionally, after refrigeration, small colorless particles may be present in the Serostim[®] solution. This is not unusual for proteins like Serostim[®].

STABILITY AND STORAGE

Before reconstitution: Vials of Serostim[®] 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.

After Reconstitution with diluent containing 0.3% (w/v) metacresol in WFI: The reconstituted solution in the Serostim[®] 8.8 mg click.easy[®] cartridge should be stored under refrigeration (2-8°C/36-46°F) for up to 21 days.

Avoid freezing reconstituted vials and cartridges of Serostim[®].

HOW SUPPLIED

Serostim[®] can be administered using (1) a standard sterile, disposable syringe and needle, (2) the Serojet[™] needle-free growth hormone delivery device or (3) the one.click autoinjector pen with the click.easy reconstitution device. For proper use, refer to the Instructions for Use provided with either the Serojet[™] needle-free device or the one.click[™] autoinjector pen / click.easy[™] reconstitution device.

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

Serostim[®] vials containing 4 mg (approximately 12 IU) somatropin (mammalian-cell) with Sterile Water for Injection, USP. Package of 7 vials. NDC 44087-0004-7

Serostim[®] vials containing 5 mg (approximately 15 IU) somatropin (mammalian-cell) with Sterile Water for Injection, USP. Package of 7 vials. NDC 44087-0005-7

Serostim[®] vials containing 6 mg (approximately 18 IU) somatropin (mammalian-cell) with Sterile Water for Injection, USP. Package of 7 vials. NDC 44087-0006-7

Serostim[®] vial containing 4 mg (approximately 12 IU) somatropin (mammalian-cell) with Bacteriostatic Water for Injection, USP (0.9% Benzyl Alcohol). Package of 1 vial. NDC 44087-0014-1

Serostim[®] vials containing 4 mg (approximately 12 IU) somatropin (mammalian-cell) with Bacteriostatic Water for Injection, USP (0.9% Benzyl Alcohol). Package of 7 vials. NDC 44087-0024-7

Serostim[®] vial containing 8.8 mg (approximately 26.4 IU) somatropin (mammalian-cell) with Bacteriostatic Water for Injection, USP (0.9% Benzyl Alcohol). Package of 1 vial. NDC 44087-0088-1

1 click.easy[®] cartridge of 8.8 mg (approximately 26.4 IU) Serostim[®] and 1.51 mL Bacteriostatic Water for Injection (0.3% (w/v) metacresol) NDC 44087-0080-1

5 click.easy[®] cartridges of 8.8 mg (approximately 26.4 IU) Serostim[®] and 1.51 mL Bacteriostatic Water for Injection (0.3% (w/v) metacresol) NDC 44087-0082-5

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

Rx Only BX Rated

October 2006








Manufacturer:
 Serono
 Kenilworth, NJ 07033 USA
 03/05

Serostim® 4 mg
 [somatotropin (rDNA origin) for injection]
 For subcutaneous injection
 Use immediately upon reconstitution. Discard unused material.
 Storage: room temperature (15°-30°C/59°-86°F)

Lot:
Exp:
Code: L6420101B



Papier - ETT-1395 - 194
 Papier - ETT-1395 - 3025
 Papier - ETT-1395 - Noir

Variable data

	Original text	English translation	Approved by RA
1	Lot:	Batch No.	Date:
2	Exp:	Expiry date	Signature:
3			
4			

E64201XXX
E64201XXX
E64201XXX
E64201XXX
E64201XXX

Reconstitute each 4 mg vial with 0.5-1 mL Bacteriostatic Water for Injection, USP (0.9 % Benzyl Alcohol). Approximately 10% mechanical loss can be associated with reconstitution and multi-dose administration.
Storage : Room temperature (15°-30°C/59°-86°F) (2-8°C/26-46°F) and used within 14 days.
Reconstituted vials should be refrigerated

BX Rated

NDC 44087-0014-1

Serostim® 4 mg

[somatropin (rDNA origin) for injection]
4 mg (approximately 12 IU)

Rx Only

- 1 vial Serostim®
- 1 vial Bacteriostatic Water for Injection, USP (0,9 % Benzyl Alcohol)
- For subcutaneous injection



Original text		English translation		Approved by RA	
1	Lot No.:	Batch No.:	Date:	Signature:	
2	Exp. Date:	Expiry date:			
3					
4					

Variable data

Contents :

One vial of Serostim® containing 4 mg somatropin, 27.3 mg sucrose, 0.9 mg phosphoric acid and sodium hydroxide or phosphoric acid to adjust pH.
One vial of Bacteriostatic Water for Injection, USP (0,9 % Benzyl Alcohol) containing 10 mL.

LSA 10-NB
08/06
EDP-1908
USA



Serostim® 4 mg
[somatropin (rDNA origin) for injection]
Manufactured for :
Serono, Inc.
Rockland, MA 02370 USA
Made in Switzerland

Serostim® 4 mg
[somatropin (rDNA origin) for injection]

Lot No.:
Exp. Date:

EDP-1908 Noir
EDP-1908 368

EDP-1908 3025
EDP-1908 Réserve vernie

EDP-1908 194

EDP-1908 306



Reconstitute each 4 mg vial with 0.5-1 mL Bacteriostatic Water for Injection, USP (0.9 % Benzyl Alcohol). Approximately 10% mechanical loss can be associated with reconstitution and multi-dose administration. Storage : Room temperature (15°-30°C/59°-86°F). Reconstituted vials should be refrigerated (2-8°C/36°-46°F) and used within 14 days.

E6420102A
E6420102A
E6420102A
E6420102A
E6420102A

BX Rated

NDC 44087-0024-7

Serostim[®] 4 mg
[somatropin (rDNA origin) for injection]
4 mg (approximately 12 IU)

Rx Only

- 7 vials of Serostim[®]
- 7 vials of Bacteriostatic Water for Injection, USP (0,9 % Benzyl Alcohol)
- For subcutaneous injection



Variable data

Original text	English translation	Approved by RA
1 Lot No.:	Batch No.:	Date:
2 Exp. Date:	Expiry date:	Signature:
3		
4		

Contents :
Seven vials of Serostim[®] each containing 4 mg somatropin, 27.3 mg sucrose, 0.9 mg phosphoric acid and sodium hydroxide or phosphoric acid to adjust pH.
Seven vials Bacteriostatic Water for Injection, USP (0,9 % Benzyl Alcohol) containing 10 mL.

LSA 11-NB
08/06
EDP-1907
USA



Serostim[®] 4 mg
[somatropin (rDNA origin) for injection]

Manufactured for :
Serono, Inc.
Rockland, MA 02370 USA
Made in Switzerland

Serostim[®] 4 mg
[somatropin (rDNA origin) for injection]

Lot No.:
Exp. Date:

NDC 44087-8006-0

SL730110

Each mL contains: Benzyl Alcohol
(as bacteriostat) 0.9% in Water for
Injection q.s. For use as solvent,
vehicle or carrier of drugs for
parenteral use. Pyrogen free.

Sterile 10 mL Multiple Dose Vial

**BACTERIOSTATIC WATER
FOR INJECTION, USP**

NOT FOR USE IN NEWBORNS

Rx Only



Store at controlled room temperature
15°-30° C (59°-86° F).

Manufactured for:

Serono, Inc.
Rockland, MA 02370 USA

Manufactured by:
American Pharmaceutical Partners, Inc.
Schaumburg, IL 60173

401755B