

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 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).

Human immunodeficiency virus (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.

HIV-associated adipose redistribution syndrome (HARS) is characterized by abnormal accumulation of trunk fat, including visceral adipose tissue (VAT), in patients infected with HIV/acquired immune deficiency disorder (AIDS), the vast majority of whom have been treated with highly active antiretroviral therapy (HAART). VAT is comprised of the deep fat in the abdomen in the omental-mesenteric and retroperitoneal compartments. HARS, a subset of HIV lipodystrophy, is more specifically defined as maldistribution of body fat characterized by central fat accumulation (lipohypertrophy) with or without lipoatrophy (subcutaneous fat depletion primarily in the face and limbs). In HARS patients, fat may additionally accumulate in the upper body subcutaneous area such as the dorsocervical area (i.e., "buffalo

hump"). These changes may be accompanied by metabolic disturbances including insulin resistance, glucose intolerance, and dyslipidemia, as well as belly image distress. Initial 12-week treatment with Serostim® resulted in decreases in VAT, trunk fat, and patient-reported belly appearance distress (see CLINICAL STUDIES). The clinical significance of these changes with respect to improved cardiovascular risk profile or compliance with HAART has not been studied.

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.

Decreases in trunk fat and total body fat, and increases in lean body mass were observed during two double-blind, placebo-controlled studies wherein Serostim® vs. placebo were administered daily for 12 weeks to patients with HARS. (see CLINICAL STUDIES).

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

HIV-Associated Wasting or Cachexia

The clinical efficacy of Serostim[®] [somatropin (rDNA origin) for injection] in HIV-associated wasting or cachexia 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

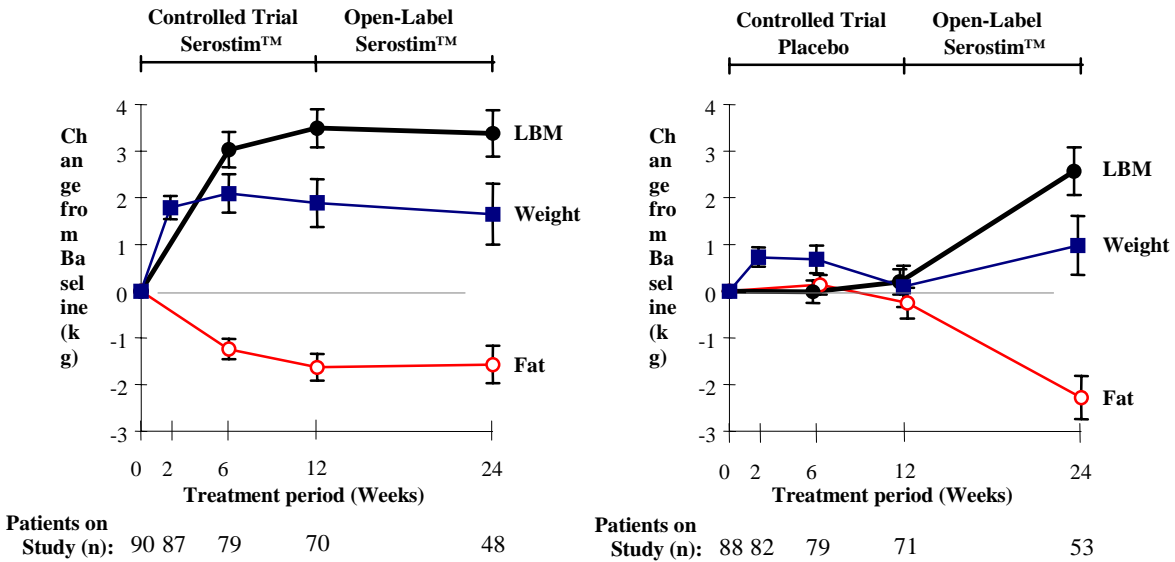
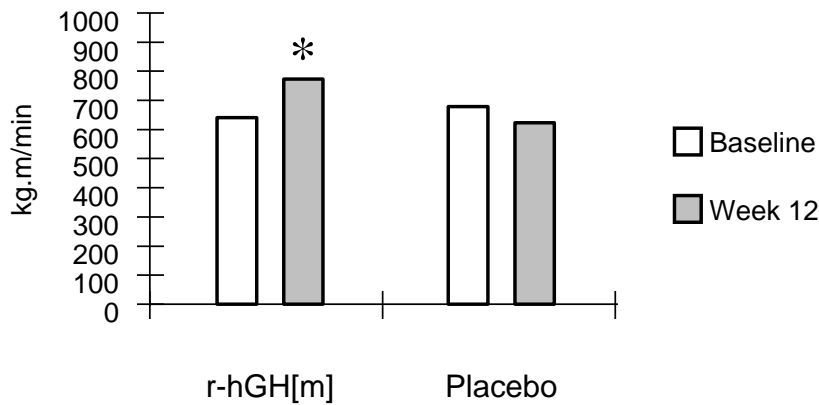


Figure 2: Median Treadmill Work Output



*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.

HIV-Associated Adipose Redistribution Syndrome (HARS)

The clinical efficacy of Serostim[®] [somatropin (rDNA origin) for injection] for the treatment of patients with HARS was assessed in two double-blind, placebo-controlled trials. The inclusion and exclusion

criteria were essentially identical in both studies. Patients with a history of diabetes, impaired fasting glucose or impaired glucose tolerance were excluded. Approximately 20% of the patients screened were excluded from study enrollment as a result of a diagnosis of diabetes or glucose intolerance. Study subjects received concomitant antiretroviral therapy and met the generally accepted criteria for excess central adipose tissue deposition assessed by anthropometric methodology (e.g., waist circumference, waist:hip ratio).

HARS Study 1 (24 weeks)

Induction Phase (12 weeks): A double-blind, placebo-controlled, parallel group study randomized 245 patients with HARS. The co-primary efficacy endpoints were change in visceral adipose tissue (VAT) and trunk:limb fat ratio after 12 weeks of treatment. Secondary efficacy endpoints included changes from baseline to Week 12 in trunk fat, abdominal subcutaneous adipose tissue (SAT), total body fat, lean body mass, various lipid parameters and patient reported outcome (PRO) scores. Patients meeting the inclusion/exclusion criteria were treated with either placebo, Serostim® 4 mg every other day (qod) or Serostim® 4 mg daily qhs. Eighty seven percent (87%) of patients were male, 80% were Caucasian, 97% were receiving treatment with nucleoside reverse transcriptase inhibitors (NRTIs), and 30% were receiving treatment for dyslipidemia.

Maintenance Phase (12 Weeks): Patients completing the 12-week induction phase who were treated with Serostim® 4 mg daily were rerandomized to therapy with either Serostim® 4 mg qod or placebo for an additional 12 weeks. Patients completing the 12 week induction phase who were treated with Serostim® 4 mg qod received Serostim® 4 mg qod for an additional 12 weeks, while patients who were treated with placebo received Serostim® 4 mg daily for an additional 12 weeks. Two hundred and eight patients received study drug and had a maintenance phase visit. The primary and secondary efficacy endpoints were the same as described above.

HARS Study 2 (36 weeks)

Induction Phase (12 Weeks): A double-blind, placebo-controlled, parallel group study randomized 326 patients with HARS. The primary efficacy endpoint was change in VAT after 12 weeks of treatment. The secondary endpoints were similar to those in HARS Study 1. Patients meeting the inclusion/exclusion criteria were treated with either placebo or Serostim® 4 mg daily qhs. Baseline demographic characteristics were very similar to Study 1.

Maintenance Phase (24 Weeks): Patients completing the 12-week induction phase were rerandomized to treatment with either Serostim® 2 mg qod or placebo for an additional 24 weeks. Two hundred fifty six patients received study drug and had a maintenance phase visit. The primary and secondary efficacy endpoints were the same as described above.

Induction Phase (Weeks 0-12) Results For Both Studies

The difference in the change from baseline to Week 12 in VAT (approximately -20 cm^2) was statistically significant after treatment with Serostim® 4 mg qod vs. placebo in Study 1 (Table 3). As seen in Tables 3 and 4, the differences in the change from baseline to Week 12 in VAT (approximately $-17-18 \text{ cm}^2$) were also statistically significant after treatment with Serostim® 4 mg daily vs. placebo in both studies. The VAT response to treatment with Serostim® 4 mg qod vs. placebo in Study 1 was very similar to the response observed after treatment with Serostim® 4 mg daily (Table 3). Patients with the largest VAT levels at baseline manifested the largest reductions in VAT in response to Serostim® treatment (data not shown).

Table 3: HARS Study 1 Induction Phase – Mean Change from Baseline to Week 12 in Visceral Adipose Tissue (cm²)^a by Treatment Group (Modified ITT Population with LOCF)

	Placebo n=57	Serostim® 4 mg qod n=58	Serostim® 4 mg daily n=61
Baseline (SE) ^b	133 (12)	130 (14)	138 (12)
Change from Baseline (SE) ^c	-9 (6)	-28 (7)	-27 (6)
Difference from Placebo for Change (95% CI) ^c		-20 (-38, -2) p=0.034	-18 (-35, -2) p=0.031

(a) Measured by computed tomography (CT) scan; (b) Analysis of variance model with terms for treatment group, gender, and treatment-by-gender interaction; (c) Analysis of covariance model with terms for treatment group, gender, and treatment-by-gender interaction, and baseline VAT as covariate; (d) CI = confidence interval and SE = standard error

Table 4: HARS Study 2 Induction Phase – Mean Change from Baseline to Week 12 in Visceral Adipose Tissue (cm²)^a by Treatment Group (Modified ITT Population with LOCF)

	Placebo n=74	Serostim® 4 mg daily n=210
Baseline (SE) ^b	110 (11)	116 (6)
Change from Baseline (SE) ^c	-12 (5)	-29 (3)
Difference from Placebo for Change (95% CI) ^c		-17 (-29, -5) p=0.005

(a) through (d) Same as Table 3

Subgroup analysis by gender revealed that women did not have a significant reduction in VAT in response to Serostim® 4 mg daily as indicated by the descriptive statistics by gender in Table 5 (only results from Study 2 are shown, but the results from Study 1 were similar).

Table 5: HARS Study 2 Induction Phase – VAT (cm²)^a Descriptive Statistics by Gender

Variable as Mean (SD) ^b	Female		Male	
	Placebo	Serostim® 4 mg daily	Placebo	Serostim® 4 mg daily
Baseline	n=9 77 (50)	n=31 87 (34)	n=65 143 (54)	n=179 144 (65)
Change from Baseline	-7 (44)	-7 (19)	2 (33)	-37 (39)

(a) Measured by computed tomography (CT) scan; (b) SD = standard deviation

Improvements in some secondary body composition endpoints (trunk fat, abdominal SAT, total body fat, and lean body mass) were observed in both Serostim® dose groups regardless of gender. Although a greater response was observed with 4 mg daily dosing, this dose was associated with a higher rate of adverse events, dose reductions and study discontinuation (see PRECAUTIONS and ADVERSE REACTIONS). Improvements were not observed in other secondary endpoints including non-HDL cholesterol.

Maintenance Phase Results

In Study 2, VAT reaccumulated to the same extent in patients treated with Serostim® 2 mg qod and placebo.

The maintenance phase results from Study 1 are summarized in Table 6. In patients initially treated with Serostim® 4 mg daily during the induction phase, rerandomization to Serostim® 4 mg qod (vs. placebo) resulted in less reaccumulation of VAT, trunk fat and total body fat.

Table 6: HARS Study 1 Maintenance Phase: Descriptive Statistics for Mean Changes from Week 12 to Week 24 in Various Body Composition Endpoints in Patients Randomized to Placebo vs. Serostim® 4 mg qod After 12 Weeks of Induction Therapy with Serostim® 4 mg Daily

Variable as Mean (SD) ^c		Placebo	Serostim® 4 mg qod
Visceral Adipose Tissue ^a (cm ²)	Week 12	138.7 (46.2) (n=25)	114.1 (75.0) (n=27)
	Change	17.7 (32.3) (n=25)	5.7 (41.4) (n=27)
Trunk Fat ^b (kg)	Week 12	8.3 (3.7) (n=27)	6.6 (3.3) (n=23)
	Change	1.2 (1.5) (n=27)	0.3 (1.2) (n=23)
Total Body Fat ^b (kg)	Week 12	13.9 (7.1) (n=27)	10.7 (5.5) (n=23)
	Change	1.3 (2.2) (n=27)	0.2 (1.9) (n=23)

(a) Measured by computed tomography (CT) scan; (b) Assessed by dual energy X-Ray absorptiometry (DEXA) scan; (c) SD = standard deviation

Patient Reported Outcomes

Belly appearance distress, belly size estimation and belly profile assessment (the essential PRO secondary efficacy endpoints) were measured using a validated PRO instrument, the Body Image Impact Module (BIIM) in both studies. Only results for belly appearance distress and belly size estimation are discussed in that the belly profile assessment was used to establish responder criteria for the belly appearance distress and the belly size estimation. Both Serostim® treatment groups manifested more improvement in belly appearance distress and belly size estimation than placebo-treated patients. Although a greater response was observed with 4 mg daily dosing during the induction phase, this dose was associated with a higher rate of adverse events, dose reductions and study discontinuation (see PRECAUTIONS and ADVERSE REACTIONS). The improvements in belly appearance distress and belly size estimation were sustained during the maintenance phase of Study 1.

The clinical significance of the changes described above in the HARS subsection of the CLINICAL STUDIES section with respect to improved cardiovascular risk profile or compliance with HAART has not been studied.

INDICATIONS AND USAGE

HIV-Associated Wasting or Cachexia

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.

There are limited data in women with HARS, especially those taking estrogen. The 47 women treated with Serostim®, 6 of whom were taking estrogen, showed no difference from placebo with respect to reduction in VAT after 12 weeks of induction treatment. It is well established that GH deficient women concomitantly treated with oral estrogen replacement therapy require substantially more rhGH to obtain comparable rhGH-related treatment effects. In addition, women with HARS have lower baseline VAT levels; lower baseline VAT levels have been demonstrated by several authors to predict a lesser reduction in VAT in response to treatment with rhGH.

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. None of the Serostim[®]-treated HARS study participants with available test results developed detectable antibodies to rhGH during the induction or maintenance phases of treatment.

Recombinant human growth hormone (rhGH) has been associated with acute pancreatitis.

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

In HARS patients who had normal fasting glucose levels at screening, treatment with Serostim[®] 4 mg daily and 4 mg qod for 12 weeks (vs. placebo) was associated with approximately 7 and 6 mg/dL increases in mean fasting blood glucose concentrations, respectively. With respect to the induction phase, peak sugars on-study usually occurred early after initiation of Serostim[®] treatment, and, most often decreased spontaneously with continued Serostim[®] therapy or responded to dose reduction. Transient and occasionally sustained peak sugars between 100 and 126 mg/dL (and transient sugars in excess of 126 mg/dL) occurred in a substantial minority of patients (including patients with normal fasting blood glucose levels at baseline). Treatment with Serostim[®] 4 mg daily resulted in a greater number of glucose intolerance-related adverse reactions than treatment with Serostim[®] 4 mg qod (see ADVERSE REACTIONS). In HARS Study 2, hemoglobin A1c increased from a mean of 5.0% at baseline to 5.3% at Week 12 after treatment with Serostim[®] 4 mg daily, but it remained in the desirable range (less than 7.0%) in all patients. HARS patients are often insulin resistant and even glucose intolerant to some degree at baseline, and therefore are very susceptible to more overt glucose intolerance after treatment with large pharmacologic amounts of rhGH. Therefore, if HARS patients are treated with Serostim[®], they should be very closely monitored for glucose intolerance.

During safety surveillance of patients with HIV-associated wasting and HARS, 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 of these patients required initiation or adjustment of antidiabetic treatment while on Serostim[®].

No cases of intracranial hypertension (IH) have been observed among patients 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, funduscopic 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 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.

Published *in vitro* data indicate that growth hormone may be an inducer of cytochrome P450 3A4. In clinical trials of HIV-infected patients with wasting or HARS who were receiving antiretroviral therapy, Serostim[®] did not adversely alter antiretroviral effectiveness, such as mean circulating levels of CD4 counts or HIV-1 RNA (viral load). When Serostim[®] is administered in combination with drugs known to be metabolized by CYP P450 3A4 hepatic enzymes, such as some antiretroviral drugs, it is advisable to monitor the clinical effectiveness of these drugs.

Somatropin inhibits 11 β -hydroxysteroid dehydrogenase type 1 (11 β 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 primary (and 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 β HSD-1 enzyme.

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

HIV-Associated Wasting or Cachexia

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 7 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 7: Controlled Clinical Trial 2 Adverse Events

	Placebo	0.1 mg/kg qod Serostim [®]	0.1 mg/kg daily Serostim [®]
	Patients (n=247)	Patients (n=257)	Patients (n=253)
Body System			
Preferred Term	%	%	%
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 trial participants receiving Serostim[®] during the first 12 weeks of Clinical Trial 2 thought to be related to Serostim[®] included dependent edema, periorbital edema, carpal tunnel syndrome, hyperglycemia and hypertriglyceridemia.

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.

HIV-Associated Adipose Redistribution Syndrome (HARS)

In the initial 12-week treatment periods of the two HARS, placebo-controlled clinical trials, 406 patients were treated with Serostim[®]. Clinical adverse events which occurred during the first 12 weeks of both studies combined in at least 5% of the patients in either of the two active treatment groups are listed by treatment group in Table 8, without regard to causality assessment. The most common adverse reactions judged to be associated with Serostim[®] were edema, arthralgia, pain in extremity, hypoesthesia, myalgia, and blood glucose increased, all of which were more frequently observed when Serostim[®] 4 mg was administered on a daily basis compared with alternate days. These symptoms were generally rated by investigators as mild to moderate in severity and often subsided with dose reduction. In addition, during the 12-week induction phase, 1) approximately 26% of patients receiving Serostim[®] 4 mg daily and 19% of patients receiving Serostim[®] 4 mg qod required dose reductions; and 2) discontinuations as a result of adverse events occurred in 13% of patients receiving Serostim[®] 4 mg daily and 5% of patients receiving Serostim[®] 4 mg qod. Once again, the most common reasons for dose reduction and/or drug discontinuation were peripheral edema, hyperglycemia (including blood glucose increased, blood glucose abnormal, and hyperglycemia), and arthralgia.

Table 8: Controlled HARS Studies 1 and 2 Combined - Adverse Events with >5% Incidence in Either Active Treatment Arm

System Organ Class Preferred Term	Placebo	Serostim® 4 mg qod ¹	Serostim® 4 mg daily
	Patients (n=159)	Patients (n=80)	Patients (n=326)
	%	%	%
Musculoskeletal and connective tissue disorders			
Arthralgia	11.9	27.8	37.1
Pain in extremity	3.8	5.0	19.3
Myalgia	3.8	2.5	12.6
Musculoskeletal stiffness	1.9	3.8	8.0
Joint stiffness	1.3	3.8	7.7
Joint swelling	0.6	5.0	6.1
General disorders and administration site conditions			
Edema peripheral	3.8	18.8	45.4
Fatigue	1.9	6.3	8.9
Nervous system disorders			
Hypoesthesia	0.6	8.8	15.0
Headache	3.1	3.8	14.1
Paraesthesia	2.5	12.5	11.0
Investigations (Laboratory Evaluations)			
Blood glucose increased ²	2.5	3.8	13.8
Metabolism and nutrition disorders			
Hyperglycemia ²	0.6	8.8	7.1
Fluid retention	0.6	2.5	5.2
Gastrointestinal disorders			
Nausea	2.5	1.3	6.1
Psychiatric disorders			
Insomnia	1.9	7.5	8.3
Infections and infestations			
Upper respiratory tract infection	5.0	10.0	5.2

¹ Study 22388 only

² similar terms were grouped together and reported below

Glucose-Related Terms: Similar glucose-related adverse event terms (including hyperglycemia, blood glucose increased, blood glucose abnormal) were grouped together which resulted in a greater than 5% incidence in Serostim®-treated patients. During the initial 12-week treatment periods of HARS Studies 1 and 2, the incidence of glucose-related adverse events was 4% for the placebo group, 13% for the 4 mg qod group and 22% for the 4 mg daily group. No patients required treatment for hyperglycemia. Of the 23 patients who discontinued due to hyperglycemia during any phase of these studies, 13 were being treated with induction therapy with Serostim® 4 mg daily (and 9 of these 13 during the 12 week induction phases of HARS Studies 1 and 2). One of these patients whose baseline fasting blood glucose was 95 mg/dL demonstrated substantial hyperglycemia (384 mg/dL) 12 days after treatment with Serostim® 4 mg daily was begun; however, the patient was normoglycemic 1 month after Serostim® was discontinued without treatment for hyperglycemia. A second patient in HARS Study 2 whose fasting blood glucose was 89 mg/dL at baseline manifested a fasting blood glucose of 404 mg/dl 21 days after treatment with Serostim® 4 mg daily was begun. His last known fasting blood glucose 1 week after Serostim® had been

discontinued was 224 mg/dl and then he was lost to follow-up. Whether sustained overt diabetes mellitus persisted is therefore unknown.

Breast-Related Terms: Similar breast-related adverse event terms (including nipple pain, gynecomastia, breast pain/mass/tenderness/swelling/edema/hypertrophy) were grouped together which resulted in a greater than 5% incidence in Serostim®-treated patients. The incidence of breast-related adverse event reports was 1% for the placebo group, 3% for the 4 mg qod group and 6% for the 4 mg daily group.

Adverse events that occurred in 1% to less than 5% of trial participants receiving Serostim® during the first 12 weeks of HARS Studies 1 and 2 thought to be related to Serostim® include carpal tunnel syndrome, tinel's sign and facial edema.

The adverse events reported for Serostim® 4 mg qod during the maintenance phase of HARS Study 1 (Week 12 to Week 24) were similar in frequency and quality to those observed after treatment with Serostim® 4 mg qod during the 12-week induction phase.

During safety surveillance of patients with HIV-associated wasting and HARS, 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 of these patients required 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

HIV-Associated Wasting or Cachexia

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® 5 or 6 mg with Sterile Water for Injection, USP, single use vials, should be administered to patients requiring 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 to avoid local irritation.

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

Each vial of Serostim[®] 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.

Avoid freezing reconstituted vials of Serostim[®].

HOW SUPPLIED

Serostim[®] can be administered using (1) a standard sterile, disposable syringe and needle, (2) a compatible Serostim[®] needle-free injection device or (3) a compatible Serostim[®] needle injection device. For proper use, refer to the Instructions for Use provided with the administration device.

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

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[®] 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 44087-0004-7

Serostim[®] vials 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

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

Rx Only BX Rated

July 2007