Serostim®
Clinical Profile

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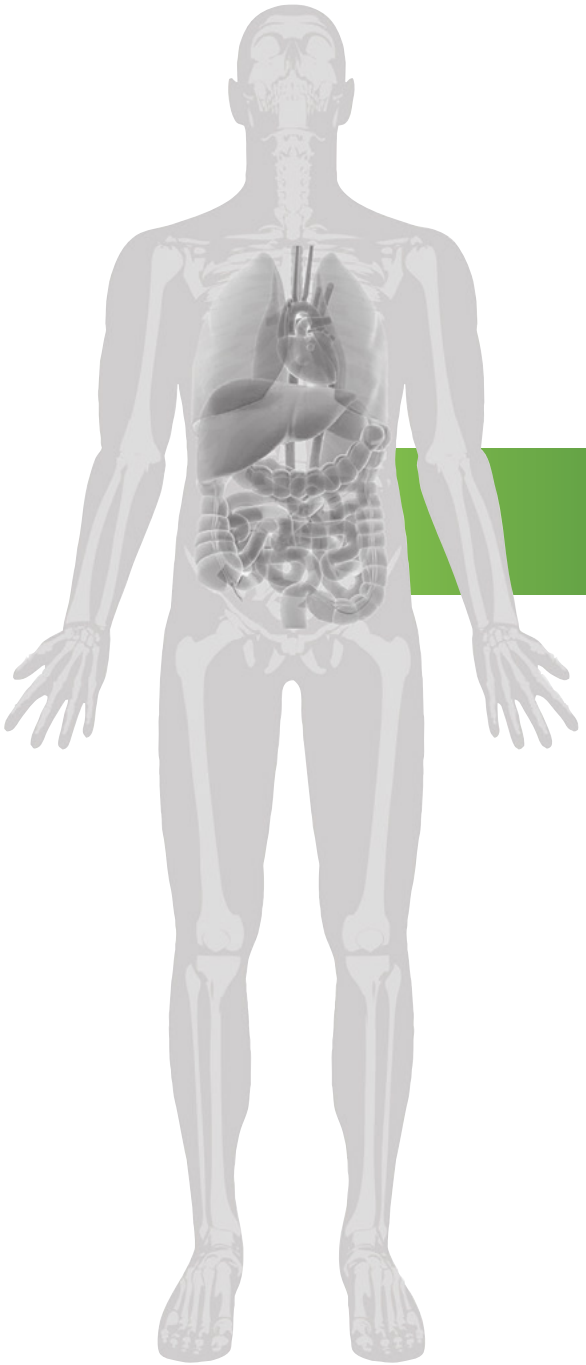
HIV-associated Wasting

Introduction

HIV-associated wasting, or cachexia, is characterized by abnormalities in the way the body uses carbohydrates, fats, and proteins to meet energy and tissue-building needs, which results in decreased physical endurance, involuntary weight loss, and loss of lean body mass (LBM).[1,2]



Energy is drawn from the breakdown of LBM, resulting in depletion of[3,4]:

- Skeletal muscle
- Organ tissue
- Blood and blood constituents
- Intracellular and extracellular water

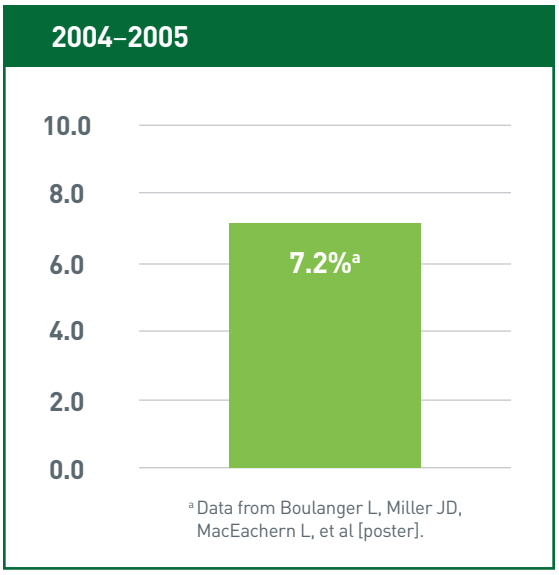
Approximately 50% of LBM is composed of skeletal muscle.[5]

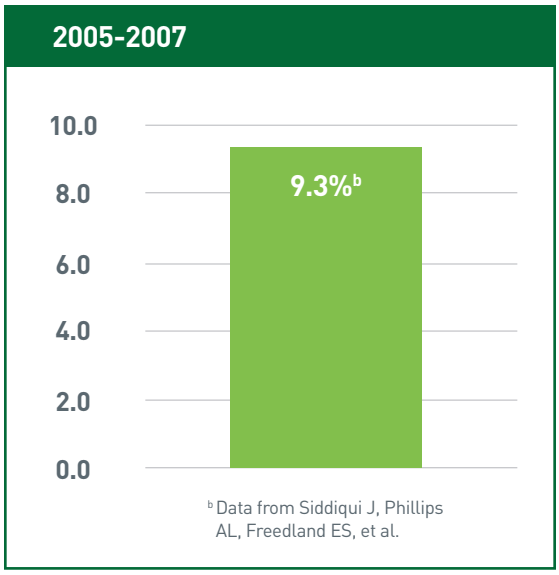
Who May Be at Risk

According to CDC estimates, there were almost one million people living with HIV in the United States in 2016. 39,782 additional people were diagnosed with HIV infection that year.[6] A 2004–2005 retrospective analysis from a scientific poster of a large US-managed care claims database involving 75 health plans of approximately 51 million patient lives reported that 7.2% of patients diagnosed with HIV/AIDS had a concomitant diagnosis of, or treatment for, cachexia. The prevalence was higher in patients over the age of 45.[7]

A similar published retrospective analysis of a managed care database from January 2005 to July 2007 found that more than 9% of commercially insured persons with HIV had evidence of treatment for HIV-associated wasting or cachexia.[8] The prevalence in both analyses underscores the need to identify HIV-associated wasting or cachexia.

Estimated prevalence of HIV-associated wasting or cachexia in 2 retrospective claims database analyses[7,8]





Patients with HIV-associated wasting may include:

- Newly diagnosed patients who have not begun treatment (over one-third of all HIV-infected individuals, if untreated, will experience wasting)[9,10]
- Patients on antiretroviral therapy who fail to gain weight[8]
- Long-term survivors with HIV[11]
- HIV-infected patients with normal CD4 counts and controlled viral loads[11]
- Patients on antiretroviral therapy with acute infection[11]
- Those who have not been adherent to antiretroviral treatment[11]

Pathophysiology

Although it is well known that HIV can disrupt the body's anabolic/catabolic process, the exact cause(s) of HIV-associated wasting remain unknown. Many factors are associated with reduced caloric intake and/or altered metabolism. These may be important individually or collectively in triggering unintentional weight loss, loss of LBM, and reduced physical endurance in HIV-positive individuals. HIV-associated wasting is a diagnosis of exclusion and the underlying conditions and comorbidities should be addressed individually as appropriate.[12,13]

Immune Dysfunction

With the availability of cART, people living with HIV are able to achieve undetectable viral loads. Despite viral suppression, patients can still experience unintentional weight loss, loss of LBM, and loss of physical endurance—the hallmarks of HIV-associated wasting.

- **Proinflammatory cytokines:** The innate immune system releases proinflammatory cytokines upon first exposure to HIV.[14] In the presence of these cytokines, a breakdown of protein known as muscle proteolysis occurs. As this response becomes chronic, the continuing breakdown of muscle can lead to loss of LBM.[15]
- **Infection:** A profound loss of adaptive immune system protection can occur with CD4+ and CD8+ T-cell depletion and dysfunction.[16,17] This loss happens concurrently with an increased resting energy expenditure (REE) and increased protein catabolism, accelerating the loss of LBM.[17,18]

  It is also important to remember that swallowing difficulty can be indicative of some systemic infections.[19] This may lead to prolonged loss of appetite that can result in reduced nutritional intake during active opportunistic infection.[18]

Endocrine Dysfunction

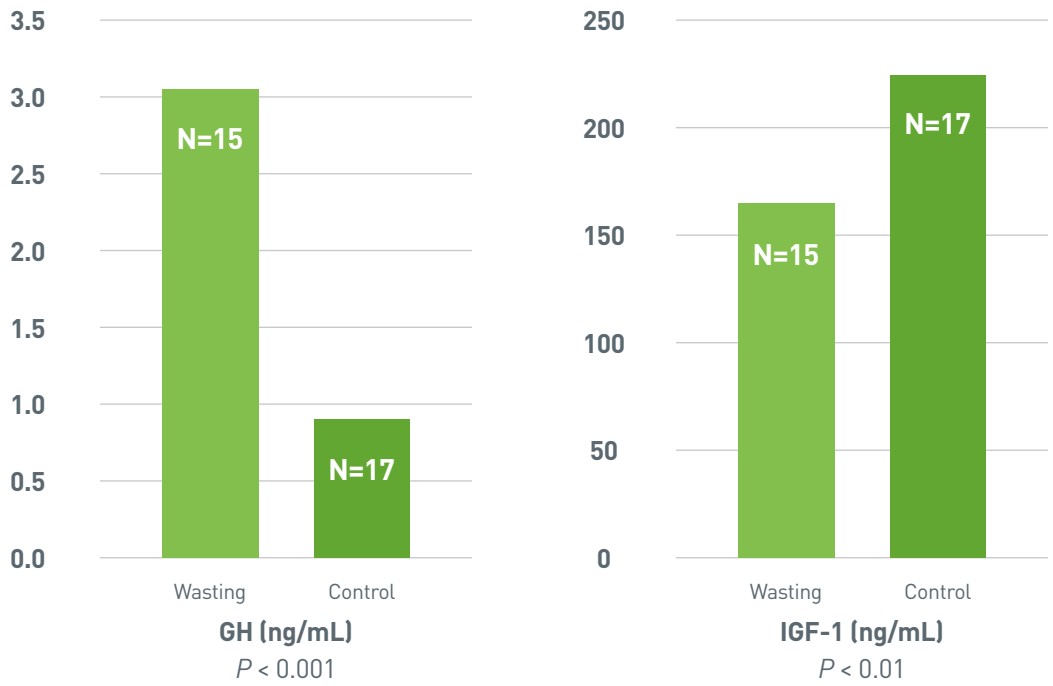
HIV-associated endocrine dysfunction is characterized by disruption of the hormonal regulatory axis and abnormal levels of hormones, such as glucagon, insulin, epinephrine, and glucocorticoids like cortisol, which are involved in regulating the metabolism of proteins, lipids, and carbohydrates.[13]

- **Growth hormone (GH) resistance:** GH is synthesized and secreted in the anterior pituitary gland and stimulates muscle growth and protein synthesis. GH promotes anabolism and accumulation of LBM as well as the metabolism of fat or energy in preference to proteins and glucose. GH receptors are found in most organs and tissues, especially the liver.[5,12]

Pathophysiology (cont.)

Insulin-like growth factor (IGF-1) is mainly secreted by the liver as a result of stimulation by GH. Higher levels of GH/IGF-1 are associated with protein synthesis. Reduced serum IGF-1 levels may lead to increased protein degradation and the loss of LBM.[20] The shift in endocrine function toward increased levels of the catabolic hormone cortisol may also contribute to a higher rate of protein degradation and to increased muscle atrophy.[21]

GH and IGF-1 mean overnight levels in men with AIDS wasting[22]



Twenty hypogonadal male subjects with weight loss (>10% of pre-illness weight or absolute weight <90% of ideal body weight) were enrolled in the study.[22]

- **Testosterone:** Hypogonadism has been shown to impact as high as 29% of HIV-positive men on cART.[23] Among HIV infected women, lower testosterone levels have been found, compared with age- and sex-matched groups.[24]

Metabolic Changes

Multiple cellular pathways are involved in the normal regulation of metabolic function. However, in HIV-infected patients, dysregulation of one or more of these cellular pathways can lead to weight loss, inappropriate depletion of LBM, and paradoxical preservation of body fat.[25] A number of factors may promote excessive catabolic activity, including proinflammatory cytokines, hormonal imbalances, elevated resting energy expenditure, and increased cortisol levels.[26-29] Changes affecting other cellular pathways, such as the phosphoinositide 3-kinase (PI3K) pathway, may also occur and lead to accelerating protein degradation of LBM, loss of muscle strength, and reduced physical endurance.[30]

Gastrointestinal Changes

The largest component of the mucosal immune system is gut-associated lymphoid tissue (GALT), one of the primary target tissues during acute HIV infection. Even in patients with undetectable viral loads, GALT can still serve as a reservoir of the virus, stimulating chronic inflammation and immune activation.[31]

In addition, HIV alters the gut flora and can lead to long-term effects on epithelial barrier and T-cell function in the gut, even after years on antiretroviral treatment. Over time, these changes continue to diminish the integrity of the protective mucosal barrier. These disruptions of the GI tract are associated with inflammation and malabsorption of vital nutrients, which can contribute to HIV-associated wasting.[32]

Other Potential Contributing Factors to Unintentional Weight Loss

Other factors that are associated with reduced caloric intake include:

- **Depression:** In general, depression is one of the strongest predictors of poor adherence and treatment outcomes in the management of HIV, and may cause chronic loss of appetite, which can contribute to malnutrition.[33,34]
- **Drug use:** Substance use is associated with decreased nutritional intake.[35] In one study, among male non-dieters, injection drug users had marginally less protein intake compared to non-drug users.[36]

Screening Patients for HIV-associated Wasting

Initiating a Conversation

Proactively speaking with patients and asking questions about their energy and weight may reveal problems with decreased physical endurance and loss of LBM that are associated with unintentional loss of weight…problems they may be reluctant to bring up on their own.

To help diagnose HIV-associated wasting, begin by asking your patients the following questions:

- ☐ Have you experienced unintentional weight loss and loss of energy?
- ☐ Are any activities more difficult to perform?
- ☐ Are you exercising less?
- ☐ Do you need to rest more often?
- ☐ Do you frequently feel tired after certain activities?
- ☐ Have you recently lost weight without trying?
- ☐ Do any changes in your weight negatively affect your health and how you feel?
- ☐ Do your clothes fit more loosely than normal due to unintentional weight loss?
- ☐ Have friends, family, or coworkers noticed any changes in the way that you look based on changes in your weight?

Other Screening Methods

In addition to speaking with your patients, other methods that can help you screen for gradual, unintentional weight loss include measuring weight, calculating body mass index (BMI), and reviewing weight history, as well as evaluating physical endurance and visually examining physical appearance.

Serostim® (somatropin) for Injection in HIV-associated Wasting

Rationale for Use[37]

Serostim® (somatropin) for injection is the only human growth hormone approved to treat HIV-associated wasting. It has both anabolic and anticatabolic properties. The anabolic properties promote tissue growth. This affects metabolism by increasing protein synthesis which, in turn, promotes growth of LBM.

The anticatabolic properties lead to decreased fat production and increased fat metabolism. When fat is metabolized, protein or muscle is spared, a process known as protein-sparing lipid oxidation. Results from studies have demonstrated improvement in muscle protein synthesis, reduced protein oxidation, and an increase in IGF-1 levels.

Effects of Serostim® (somatropin) for injection on tissue in patients with HIV-associated wasting

	Anabolic (Builds LBM up)	**Anticatabolic** (Prevents LBM from breaking down)
Changes in metabolism	Increases protein synthesis	Decreases fat production and increases fat-burning for energy
How changes in metabolism affect LBM	Promotes growth of LBM, much of which is protein	Burns fat for energy rather than protein (protein-sparing lipid oxidation)
End result	Produces new LBM	Preserves existing LBM

Clinical trials have demonstrated that Serostim® significantly increases body weight and LBM and improves physical endurance in patients with HIV-associated wasting receiving concomitant antiretroviral therapy. Patients also reported improvements in their perceptions of their HIV-associated wasting symptoms.

Clinical trials excluded patients with a history of diabetes, impaired fasting glucose, or impaired glucose.

Serostim® (somatropin) for Injection

Clinical Studies—Efficacy[37]

The clinical efficacy of Serostim® (somatropin) for injection in HIV-associated wasting, or cachexia, was assessed in 2 placebo-controlled trials. All study subjects received concomitant antiretroviral therapy. There was no increase in the incidence of Kaposi sarcoma (KS) or lymphoma, or in the progression of cutaneous KS in clinical studies of Serostim®. Patients with internal KS lesions were excluded from the studies. Potential effects on other malignancies are unknown.

Clinical Trial 1

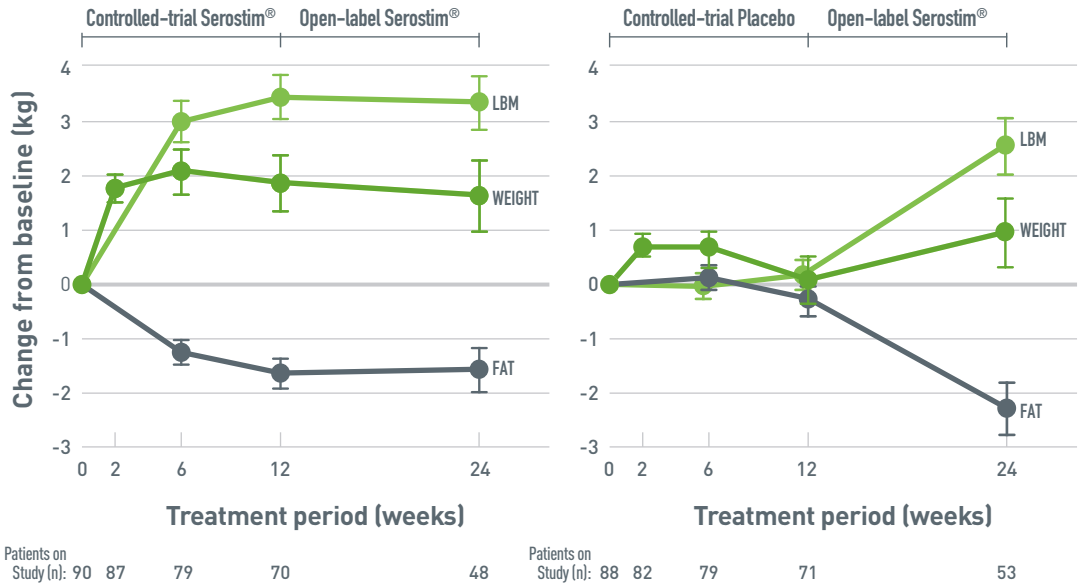
A 12-week, randomized, double-blind, placebo-controlled study followed by an open-label extension phase enrolled 178 patients with severe HIV wasting taking nucleoside analogue therapy (pre-HAART era). The primary endpoint was body weight. Body composition was assessed using dual energy X-ray absorptiometry (DXA) and physical function was assessed by treadmill exercise testing. Patients meeting the inclusion criteria were treated with either placebo or Serostim® 0.1 mg/kg daily. Ninety-six percent (96%) were male. The average baseline CD4 count was 85 cells/mm. The results from 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 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 related with changes in LBM.

Serostim® (somatropin) for injection treatment significantly increased LBM and weight after 12 weeks, suggesting gains were maintained beyond 12 weeks[37]

Figure 1: Mean changes in body composition



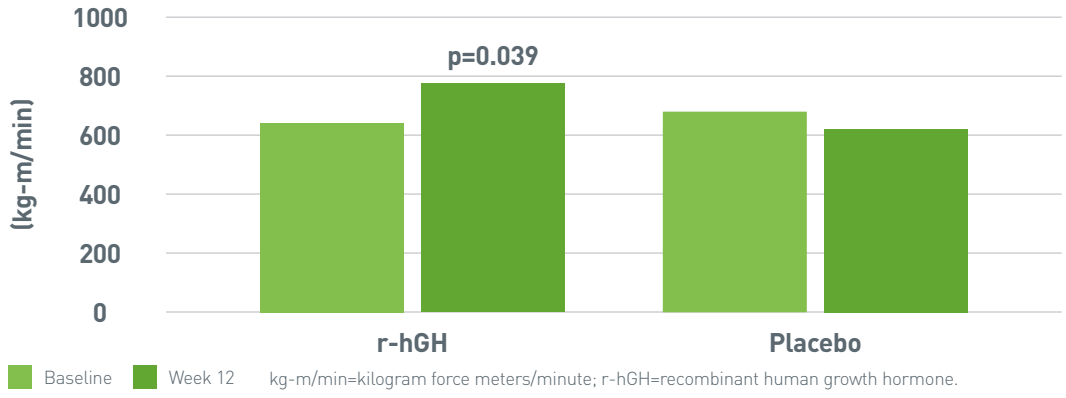
- Serostim® treatment significantly increased physical function as assessed by treadmill exercise
- Median treadmill work output increased by 13% (p=0.039) at 12 weeks in the Serostim® group
- Changes in treadmill performance were significantly correlated with changes in LBM
- There were no significant changes with continued treatment beyond 12 weeks suggesting the original gains of weight and LBM were maintained

Mean increase in weight and LBM and mean decrease in body fat were also 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.

Clinical Studies—Efficacy (cont.)

Serostim® treatment significantly increased physical function as assessed by treadmill exercise testing after 12 weeks[37]

Figure 2: Median treadmill work output



kg-m/min=kilogram force meters/minute; r-hGH=recombinant human growth hormone.

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 DXA at a subset of centers. Patients meeting the inclusion criteria were treated with either placebo, approximately 0.1 mg/kg every other day (AD) of Serostim®, or approximately 0.1 mg/kg daily (DD) at bedtime 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. At study entry, mean body weight for wasting patients was 144 pounds. The average baseline CD4 count/μL was 446. A total of 646 patients 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.[37]

Patients with HIV-associated wasting treated with Serostim® AD or DD completed the Bristol-Myers Anorexia/Cachexia Recovery Instrument (BACRI) questionnaire. The questionnaire measured the patient's perception of the impact of Serostim® therapy on their wasting symptoms. After taking Serostim®, patients reported statistically significant and dose-dependent improvements for each individual question (benefit from treatment, impact on health, change in appearance, change in appetite, eating more or less) as assessed with the BACRI instrument.[37,38]

Serostim® (somatropin) for injection significantly improved physical endurance for patients, as assessed by a stationary bike exercise in a 12-week clinical study[37]

Table 1: Mean (median) of cycle work output (kJ) response after 12 weeks of treatment, ITT population

	Placebo	Alternate-dose Serostim®[a]	Daily-dose Serostim®[b]
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)
Percentage change from baseline	-0.2%	8.9%	9.1%
Difference from placebo			
Mean (2-sided 95% CI)	-	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 every other day. [b] Approximately 0.1 mg/kg daily. [c] p<0.01.

After 12 weeks on Serostim®, patients were able to exert clinically and statistically significantly more work output (kJ) while cycling compared with those treated with placebo, who experienced a loss of physical endurance.

Serostim® treatment significantly increased LBM and weight, and maintained gains with continued treatment[37,38]

Table 2: Mean (median) change from baseline for lean body mass, fat mass, and body weight[37]

	Placebo		Alternate-dose Serostim®[a]		Daily-dose Serostim®[b]	
	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 every other day. [b] Approximately 0.1 mg/kg daily.

A statistically significant median increase in lean body mass after 12 weeks of treatment with Serostim® was 7.3 pounds in the AD group and 11.5 pounds in the DD group vs 1.4 pounds in the placebo group (P<0.0001 for both groups vs placebo; P=0.0173 for DD vs AD).[38]

Clinical Studies—Safety[37]

In the 12-week, placebo-controlled Clinical Trial 2, 510 patients were treated with Serostim®. 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. These symptoms, summarized in Table 3, 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 reactions 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 reactions, which occurred during the first 12 weeks of study in at least 5% of the patients in either active treatment group and at an incidence greater than placebo, are listed below, without regard to causality assessment.

During the 12-week, placebo-controlled portion of Clinical Trial 2, the incidence of hyperglycemia reported as an adverse reaction was 3.6% for the placebo group, 1.9% for the 0.1 mg/kg every other day 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 who converted from placebo to full-dose Serostim®, and 1 patient who converted from placebo to half-dose Serostim®, were discontinued because of the development of diabetes mellitus. The types and incidences of adverse reactions 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.

Clinical Adverse Reactions[37]

Table 3: Controlled Clinical Trial 2 adverse reactions occurring in at least 5% of patients in one of the treatment groups and at an incidence greater than placebo

	Placebo	0.1 mg/kg every other day 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
Gastrointestinal System Disorders			
Nausea	4.9	5.4	9.1
Body as a Whole—General Disorders			
Edema peripheral	2.8	11.3	26.1
Fatigue	4.5	3.5	5.1
Endocrine Disorders			
Gynecomastia	0.4	3.5	5.5
Central and Peripheral 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

Serostim® (somatropin) for Injection

Clinical Pharmacology In-vitro Experiments[37]

Mechanism of Action

Serostim® 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-1 (IGF-1).

Pharmacodynamics

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 HIV lipodystrophy. Serostim® is not approved for the treatment of HIV lipodystrophy.

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. 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.

In some experimental systems, somatropin 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 somatropin does not interfere with the antiviral activity of zalcitabine or stavudine.

Pharmacokinetics

Absorption: The absolute bioavailability after subcutaneous administration was determined to be 70% to 90%. The mean t½ (half life) after subcutaneous administration is significantly longer than that seen after intravenous administration in normal male volunteers down-regulated with somatostatin (approximately 4.0 hrs vs 0.6 hrs), indicating that the subcutaneous absorption of somatropin is a rate-limiting process.

Distribution: The steady-state volume of distribution (Mean ± SD) following intravenous administration of somatropin in normal male 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 (half life) 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 somatropin subcutaneously, was 4.28 ± 2.15 hrs, similar to that observed in normal male volunteers. 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 six weeks of daily dosing as indicated.

Use in Specific 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 studies have been conducted to determine the effect of race on the pharmacokinetics of Serostim®.

Renal Impairment: Subjects with chronic renal failure tend to have decreased somatropin clearance compared to those with normal renal function. However, no studies have been conducted to determine the effect of renal impairment on the pharmacokinetics of Serostim®.

Hepatic Impairment: No studies have been conducted to determine the effect of hepatic impairment on the pharmacokinetics of Serostim®.

Pregnancy/Nursing Mothers: Somatropin should be used during pregnancy only if clearly needed and with caution in nursing mothers because it is not known whether somatropin is excreted in human milk.

Geriatric: 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 the action of somatropin, and therefore, may be more prone to develop adverse reactions. A lower starting dose and smaller dose increments should be considered for older patients.

Serostim® (somatropin) for Injection

Description[37]

Serostim® 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 growth hormone. 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 sterile lyophilized powder intended for subcutaneous injection after reconstitution to its liquid form.

Vials of Serostim® contain either 4 mg, 5 mg, or 6 mg. Each vial contains somatropin, sucrose, and phosphoric acid.

Each 4 mg multi-vial is supplied in a combination package with Bacteriostatic Water for Injection, USP (0.9% Benzyl Alcohol). The pH is adjusted with sodium hydroxide of phosphoric acid to give a pH of 7.4 to 8.5 after reconstitution.

Each 5 mg single-use vial is supplied in a combination package with Sterile 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.

Each 6 mg single-use vial is supplied in a combination package with Sterile Water for Injection, USP. The pH is adjusted with sodium hydroxide of phosphoric acid to give a pH of 7.4 to 8.5 after reconstitution.

Dosage Information[37]

The usual starting dose of Serostim® is 0.1 mg/kg subcutaneously once daily (up to a total dose of 6 mg). Serostim® should be administered subcutaneously once daily at bedtime according to the following body weight-based dosage recommendations:

Weight range	Dosage
→55 kg (→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.

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.

Injection sites should be rotated to avoid localized skin irritation.

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.

BMI Table

This BMI chart is provided as a reference to determine a patient's weight category and should not be used for dosing.

BMI

Height		14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
Feet	**Inches**	**Weight (lb)**														
4'10"	58"	67	72	76	81	86	91	96	100	105	110	115	119	124	129	134
4'11"	59"	69	75	79	84	89	94	99	104	109	114	119	124	128	133	138
5'0"	60"	72	77	82	87	92	97	102	107	112	118	123	128	133	138	143
5'1"	61"	74	79	85	90	95	100	106	111	116	122	127	132	137	143	148
5'2"	62"	76	82	87	93	98	104	109	115	120	126	131	136	142	147	153
5'3"	63"	79	85	90	96	102	107	113	118	124	130	135	141	146	152	158
5'4"	64"	81	87	93	99	105	110	116	122	128	134	140	145	151	157	163
5'5"	65"	84	90	96	102	108	114	120	126	132	138	144	150	156	162	168
5'6"	66"	87	93	99	105	112	118	124	130	136	142	148	155	161	167	173
5'7"	67"	89	96	102	108	115	121	127	134	140	146	153	159	166	172	178
5'8"	68"	92	98	105	112	118	125	131	138	144	151	158	164	171	177	184
5'9"	69"	95	101	108	115	122	128	135	142	149	155	162	169	176	182	189
5'10"	70"	97	104	111	118	126	132	139	146	153	160	167	174	181	188	195
5'11"	71"	100	107	114	122	129	136	143	150	157	165	172	179	186	193	200
6'0"	72"	103	110	118	125	132	140	147	154	162	169	177	184	191	199	206
6'1"	73"	106	113	121	129	136	144	151	159	166	174	182	189	197	204	212
6'2"	74"	109	117	124	132	141	148	155	163	171	179	186	194	202	210	218
6'3"	75"	112	120	128	136	144	152	160	168	176	184	192	200	208	216	224
6'4"	76"	115	123	131	139	148	156	164	172	180	189	197	205	213	221	230
6'5"	77"	118	126	135	143	151	160	168	176	185	193	202	210	218	227	235
6'6"	78"	121	130	138	147	155	164	172	181	190	198	207	216	224	233	241

Source: National Institute of Health (NIH)/National Heart, Lung, and Blood Institute (NHLBI).

Serostim® (somatropin) for Injection

Stability, Storage, and Forms[37]

Storage and Handling

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.

Single-use vials: After reconstitution with Sterile Water for Injection, USP, the reconstituted solution should be used immediately and any unused portion should be discarded.

Multi-use vials: 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® is available in the following forms:

- Serostim® single-use vials containing 5 mg with Sterile Water for Injection, USP. Package of 7 vials.
- Serostim® single-use vials containing 6 mg with Sterile Water for Injection, USP. Package of 7 vials.
- Serostim® multiple-use vials containing 4 mg with Bacteriostatic Water for Injection, USP (0.9% Benzyl Alcohol). Package of 7 vials.

Serostim® (somatropin) for Injection

Patient Considerations[37]

Patient Counseling Information

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.

Never Share Serostim® Needles Between Patients

Counsel patients that they should never share Serostim® or Serostim® needles with another person, even if the needle or nozzle is changed. Sharing of Serostim® between patients may pose a risk of transmission of infection.

Patients should be informed about the management of common side effects related to tissue turgor, glucose intolerance, and musculoskeletal discomfort.

INDICATIONS AND USAGE

Serostim® (somatropin) 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.

IMPORTANT RISK INFORMATION

CONTRAINDICATIONS

Serostim should not be used in patients with acute critical illness, active malignancy, hypersensitivity to somatropin or any of its excipients, or diabetic retinopathy. Increased mortality has been reported in patients with acute critical illness due to complications following surgery, multiple accidental trauma, or acute respiratory failure. Preexisting malignancies should be inactive and treatment completed prior to instituting therapy. Serostim should be discontinued if there is evidence of tumor recurrence. Systemic hypersensitivity reactions have been reported with postmarketing use of somatropin products.

WARNINGS AND PRECAUTIONS

Acute Critical Illness: Increased mortality in patients with acute critical illness due to complications following open heart surgery, abdominal surgery or multiple accidental trauma, or those with acute respiratory failure has been reported after treatment with [pharmacologic amounts of] somatropin.

Concomitant Antiretroviral Therapy: Somatropin has been shown to potentiate HIV replication in vitro, however there was no increase in virus production when antiretroviral agents were added to the culture medium. All patients received antiretroviral therapy for the duration of treatment during Serostim clinical trials and no significant increase in viral burden was observed.

Neoplasms: Patients with preexisting tumors should be monitored for progression or reoccurrence. Monitor patients on somatropin therapy carefully for preexisting nevi.

Impaired Glucose Tolerance/Diabetes: Cases of new onset impaired glucose tolerance, new onset type 2 diabetes, and exacerbation of preexisting diabetes have been reported in patients receiving Serostim. Some patients developed diabetic ketoacidosis and diabetic coma. Patients with risk factors for hyperglycemia and glucose intolerance should be monitored closely and those using antidiabetic agents may require dose adjustment.

Intracranial Hypertension: Intracranial hypertension (IH) with papilledema, visual changes, headache, nausea, and/or vomiting has been reported. Funduscopic examination should be performed prior to initiating treatment with Serostim and periodically during the course of treatment. If papilledema is observed, treatment should be stopped and restarted at a lower dose after IH-associated symptoms have resolved.

Severe Hypersensitivity: Serious systemic hypersensitivity reactions including anaphylactic reactions and angioedema have been reported with postmarketing use of somatropin products. Patients and caregivers should be informed that such reactions are possible and that prompt medical attention should be sought if an allergic reaction occurs.

Fluid Retention/Carpal Tunnel Syndrome: Swelling (particularly in the hands and feet), musculoskeletal discomfort, or carpal tunnel syndrome may occur during treatment with Serostim. Symptoms may resolve spontaneously, with analgesic therapy, or after reducing the frequency of dosing. If symptoms of carpal tunnel do not resolve by decreasing the weekly number of doses, it is recommended that Serostim treatment be discontinued.

Skin Atrophy: Rotate the injection site to avoid tissue atrophy.

Pancreatitis: Cases of pancreatitis have been reported rarely. Consider pancreatitis in patients who develop persistent severe abdominal pain.

ADVERSE REACTIONS

In clinical trials in HIV-associated wasting or cachexia the most common adverse reactions (incidence >10%) were increased tissue turgor, arthralgia, myalgia, and arthrosis, which may be responsive to dose reduction. Other common adverse reactions (incidence >5%) included nausea, fatigue, gynecomastia, paresthesia, generalized edema and hypoesthesia.

SPECIAL POPULATIONS:

Somatropin should be used during pregnancy only if clearly needed and with caution in nursing mothers because it is not known whether somatropin is excreted in human milk. The safety and effectiveness of somatropin in patients with hepatic or renal impairment or in patients aged 65 years and over have not been evaluated in clinical studies.

For more information about clinical trial adverse reactions, see pages 14-15.
Please see the Full Prescribing Information attached.

References

1. Coats AJ. Origin of symptoms in patients with cachexia with special reference to weakness and shortness of breath. *Int J Cardiol*. 2002;85:133-139.
2. Data on file. Study 9037 (r-hGH) Integrated Clinical and Statistical Final Report. Merck KGaA, Darmstadt, Germany. 2002.
3. Roubenoff R, Grinspoon S, Skolnik PR, et al. Role of cytokines and testosterone in regulating lean body mass and resting energy expenditure in HIV-infected men. *Am J Physiol Endocrinol Metab*. 2002;283(1):E138-E145.
4. Kotler DP, Wang J, Pierson RN. Body composition studies in patients with the acquired immunodeficiency syndrome. *Am J Clin Nutr.* 1985;42(6):1255-1265.
5. Dudgeon WD, Phillips KD, Carson JA, et al. Counteracting muscle wasting in HIV-infected individuals. *HIV Med.* 2006;7:299-310.
6. Centers for Disease Control and Prevention. HIV Surveillance Report, 2016; vol. 28. https://www.cdc.gov/hiv/pdf/library/reports/surveillance/cdc-hiv-surveillance-report-2016-vol-28.pdf. Published November 2017. Accessed August 22, 2019.
7. Boulanger L, Miller JD, MacEachern L, et al. Prevalence of cachexia (wasting syndrome) diagnosis and treatment among patients with HIV/AIDS: a medical claims database analysis. Poster presented at: 11th Annual International Meeting of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR); May 19-23, 2007; Arlington, VA.
8. Siddiqui J, Phillips AL, Freedland ES, et al. Prevalence and cost of HIV-associated weight loss in a managed care population. *Curr Med Res Opin.* 2009;25(5):1307-1317.
9. Coodley GO, Loveless MO, Merrill TM. The HIV wasting syndrome: a review. *J Acquir Immune Defic Syndr.* 1994;7(7):681-694.
10. Falutz J. Growth hormone and HIV infection: contribution to disease manifestations and clinical implications. *Best Pract Res Clin Endocrinol Metab.* 2011;25:517-529.
11. Wasserman P, Segal-Maurer S, Webbeh W, et al. Wasting disease, chronic immune activation and inflammation in the HIV-infected patient. *Top Clin Nutr.* 2011;26(1):14-28.
12. Gelato M, McNurlan M, Freedland E. Role of recombinant human growth hormone in HIV-associated wasting and cachexia: pathophysiology and rationale for treatment. *Clin Ther.* 2007;29(11):2269-2288.
13. Grinspoon S, Mulligan K; Department of Health and Human Services Working Group on the Prevention and Treatment of Wasting and Weight Loss. Weight loss and wasting in patients infected with human immunodeficiency virus. *Clin Infect Dis.* 2003;36 (suppl 2):S69-S78.
14. Cray C, Zaias J, Altman NH. Acute phase response in animals: a review. *Comp Med.* 2009;59(6):517-526.
15. Castaneda C. Muscle wasting and protein metabolism. *J Anim Sci.* 2002;80 (suppl 2):E98-E105.
16. Boasso A, Shearer GM, Chougnet C. Immune dysregulation in human immunodeficiency virus infection: know it, fix it, prevent it? *J Intern Med.* 2009;265(1):78-96.
17. Koethe JR, Heimburger DC, PrayGod G, Filteau S. From wasting to obesity: the contribution of nutritional status to immune activation in HIV infection. *J Infect Dis.* 2016;214 (suppl 2):S75-S82.
18. Chang E, Sekhar R, Patel S, Balasubramanyam A. Dysregulated energy expenditure in HIV-infected patients: a mechanistic review. *Clin Infect Dis.* 2007;44(11):1509-1517.
19. Williams B, Waters D, Parker K. Evaluation and treatment of weight loss in adults with HIV disease. *Am Fam Physician.*1999;60(3):843-854.
20. Melmed S. Disorders of the anterior pituitary and hypothalamus. In: Kasper DL, Fauci AS, Hauser SL, Longo DL, Jameson JL, Loscalzo J, eds. *Harrison's Principles of Internal Medicine.* 19th ed. New York, NY: McGraw-Hill; 2015.
21. Morgan SA, Hassan-Smith ZK, Doig CL, et al. Glucocorticoids and 11ß-HSD1 are major regulators of intramyocellular protein metabolism. *J Endocrinol.* 2016;229(3):277-286.
22. Grinspoon S, Corcoran C, Lee K, et al. Loss of lean body and muscle mass correlates with androgen levels in hypogonadal men with acquired immunodeficiency syndrome and wasting. *J Clin Endocrinol Metab.* 1996;81(11):4051-4058.
23. Gomes AR, Souteiro P, Silva CG, et al. Prevalence of testosterone deficiency in HIV-infected men under antiretroviral therapy. *BMC Infect Dis.* 2016;16:628.
24. Grinspoon S, Corcoran C, Miller K, et al. Body composition and endocrine function in women with acquired immunodeficiency syndrome wasting. *J Clin Endocrinol Metab.*1997;82:1332-1337.
25. Perry CM, Wagstaff AJ. Recombinant mammalian cell-derived somatropin: a review of its pharmacological properties and therapeutic potential in the management of wasting associated with HIV infection. *BioDrugs.* 1997;8(5):394-414.
26. Spate U, Schulze PC. Proinflammatory cytokines and skeletal muscle. *Curr Opin Clin Nutr Metab Care.* 2004;7:265–269.
27. Roubenoff R, Grinspoon S, Skolnik PR, et al. Role of cytokines and testosterone in regulating lean body mass and resting energy expenditure in HIV-infected men. *Am J Physiol Endocrinol Metab.* 2002;283:e138–e145.
28. Kosmiski L. Energy expenditure in HIV infection. *Am J Clin Nutr.* 2011;94(suppl):1677s-82s
29. Alberti KG, Johnston DG. Cortisol and Catabolism: A new perspective. *Clin Sci Mol Med.* 1977;52(4):333-336.
30. Cohen S, Nathan JA, Goldberg AL. Muscle wasting in disease: molecular mechanisms and promising therapies. *Nat Rev Drug Discov.* 2015;14(1):58-74.
31. Mehandru S, Poles MA, Tenner-Racz K, et al. Primary HIV-1 infection is associated with preferential depletion of CD4+ T lymphocytes from effector sites in the gastrointestinal tract. *J Exp Med.* 2004;200(6):761-770.
32. Zilberman-Schapira G, Zmora N, Itav S, Bashiardes S, Elinav H, Elinav E. The gut microbiome in human immunodeficiency virus infection. *BMC Med.* 2016;14(1):83.
33. Simoni JM, Safren SA, Manhart LE, et al. Challenges in addressing depression in HIV research: assessment, cultural context, and methods. *AIDS Behav.* 2011;15(2):376–388.
34. Rabkin JG. HIV and depression: 2008 review and update. *Curr HIV/AIDS Rep.* 2008;5(4):163-171.
35. Hendricks K, Gorbach S. Nutrition issues in chronic drug users living with HIV infection. *Addict Sci Clin Pract.* 2009;5(1):16-23.
36. Kim JH, Spiegelman D, Rimm E, Gorbach SL. The correlates of dietary intake among HIV-positive adults. *Am J Clin Nutr.* 2001;74:852-861.
37. Serostim® (somatropin) for injection Prescribing Information. EMD Serono, Inc.
38. Moyle GJ, Daar ES, Gertner JM, et al. Growth hormone improves lean body mass, physical performance, and quality of life in subjects with HIV-associated weight loss or wasting on highly active antiretroviral therapy. *J Acquir Immune Defic Syndr.* 2004;35(4):367-375.

EMD Serono

Serostim®
(somatropin) for injection

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use SEROSTIM® safely and effectively. See full prescribing information for SEROSTIM.

SEROSTIM (somatropin) for injection, for subcutaneous use

Initial U.S. Approval: 1987

INDICATIONS AND USAGE

SEROSTIM is indicated for the treatment of HIV patients with wasting or cachexia to increase lean body mass and body weight, and improve physical endurance (1)

DOSAGE AND ADMINISTRATION

- The recommended dose of SEROSTIM is 0.1 mg/kg subcutaneously (SC) daily (up to 6 mg) at bedtime for HIV patients with wasting or cachexia (2.1)
- Injection sites, which may be located on thigh, upper arm, abdomen or buttock, should be rotated to avoid local irritation (2.2)

DOSAGE FORMS AND STRENGTHS

- Single-dose administration (to be administered with Sterile Water for Injection) (3):
  SEROSTIM 5 mg/ vial
  SEROSTIM 6 mg/ vial
- Multi-dose administration (to be administered with Bacteriostatic Water for Injection):
  SEROSTIM 4 mg/ vial

CONTRAINDICATIONS

- Acute Critical Illness (4)
- Active Malignancy (4)
- Diabetic Retinopathy (4)
- Hypersensitivity to somatropin or excipients (4)

WARNINGS AND PRECAUTIONS

- Acute Critical Illness: Increased mortality in patients with acute critical illness following open heart surgery, abdominal surgery or multiple accidental trauma, or those with acute respiratory failure has been reported after treatment with pharmacologic amounts of somatropin (5.1)
- Concomitant Antiretroviral Therapy: In vitro experimental systems have demonstrated the potential to potentiate HIV replication. No significant somatropin-associated increase in viral load was observed in clinical trials. HIV patients should be maintained on antiretroviral therapy for the duration of SEROSTIM treatment (5.2)
- Neoplasms: Monitor all patients with a history of any neoplasm routinely while on somatropin therapy for progression, recurrences, or development of a tumor (5.3)
- Impaired Glucose Tolerance/Diabetes: May be unmasked. Periodically monitor glucose levels. Dose adjustment of concurrent antihyperglycemic drugs in diabetics may be required (5.4)
- Intracranial Hypertension: Exclude preexisting papilledema. May develop and is usually reversible after discontinuation or dose reduction (5.5)
- Hypersensitivity: Serious hypersensitivity reactions may occur. In the event of an allergic reaction, seek prompt medical attention (5.6)
- Fluid Retention (edema, arthralgia)/Carpal Tunnel Syndrome: May occur frequently. Reduce dose as necessary (5.7)
- Pancreatitis: Consider pancreatitis in patients with persistent severe abdominal pain (5.9)

ADVERSE REACTIONS

Most common adverse reactions include (incidence >10%) tissue turgor (edema, myalgia, hypoesthesia) and musculoskeletal discomfort (arthralgia, pain in extremities) (6)

To report SUSPECTED ADVERSE REACTIONS, contact EMD Serono at 1-800-283-8088 ext 5563 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*

DRUG INTERACTIONS

- Inhibition of 11β-Hydroxysteroid Dehydrogenase Type 1: May require the initiation of glucocorticoid replacement therapy. Patients treated with glucocorticoid replacement for previously diagnosed hypoadrenalism may require an increase in their maintenance doses (7.1)
- Cytochrome P450-Metabolized Drugs: Monitor carefully if used with somatropin (7.2)
- Oral Estrogen: Larger doses of somatropin may be required in women (7.3)
- Insulin and/or Oral/Injectable Hypoglycemic Agents: May require adjustment (7.4)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 06/2019

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

SEROSTIM (somatropin) 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.

2 DOSAGE AND ADMINISTRATION

SEROSTIM is administered by subcutaneous injection.

SEROSTIM therapy should be carried out under the regular guidance of a physician who is experienced in the diagnosis and management of HIV infection.

2.1 HIV-associated wasting or cachexia

The usual starting dose of SEROSTIM is 0.1 mg/kg subcutaneously once daily (up to a total dose of 6 mg). SEROSTIM should be administered subcutaneously once daily at bedtime according to the following body weight-based 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.	

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.

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 with HIV wasting or cachexia were treated intermittently with SEROSTIM.

2.2 Preparation and Administration

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 4 mg is reconstituted in 0.5 to 1 mL of Bacteriostatic Water for Injection, USP (0.9% Benzyl Alcohol preserved). For patients sensitive to Benzyl Alcohol, SEROSTIM may be reconstituted with Sterile Water for Injection, USP *[see Pediatric Use (8.4)]*.

When SEROSTIM is reconstituted with Sterile Water for Injection, USP, the reconstituted solution should be used immediately and any unused portion should be discarded.

When SEROSTIM is reconstituted with Bacteriostatic Water for Injection, USP (0.9% Benzyl Alcohol preserved) the reconstituted solution may be refrigerated (2-8°C/36-46°F) for up to 14 days.

Approximately 10% mechanical loss can be associated with reconstitution and administration from multi-dose vials.

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. DO NOT SHAKE. Parenteral drug products should always be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. SEROSTIM MUST NOT BE INJECTED if the solution is cloudy or contains particulate matter. Use it only if it is clear and colorless.

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.

Injection sites, which may be located on the thigh, upper arm, abdomen or buttock, should be rotated to avoid local irritation.

3 DOSAGE FORMS AND STRENGTHS

Single-use administration (to be reconstituted with Sterile Water for Injection):

- SEROSTIM 5 mg per vial
- SEROSTIM 6 mg per vial

Multi-use administration (to be reconstituted with Bacteriostatic Water for Injection):

- SEROSTIM 4 mg per vial

4 CONTRAINDICATIONS

• Acute Critical Illness

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 *[see Warnings and Precautions (5.1)]*.

• Active Malignancy

In general, somatropin is contraindicated in the presence of active malignancy. Any preexisting malignancy should be inactive and its treatment complete prior to instituting therapy with somatropin. Somatropin should be discontinued if there is evidence of recurrent activity *[see Warnings and Precautions (5.3)]*.

• Hypersensitivity

SEROSTIM is contraindicated in patients with a known hypersensitivity to somatropin or any of its excipients. Systemic hypersensitivity reactions have been reported with postmarketing use of somatropin products *[see Warnings and Precautions (5.6)]*.

• Diabetic Retinopathy

Somatropin is contraindicated in patients with active proliferative or severe non-proliferative diabetic retinopathy.

5 WARNINGS AND PRECAUTIONS

5.1 Acute Critical Illness

Increased mortality in patients with acute critical illness due to complications following open heart surgery, abdominal surgery or multiple accidental trauma, or those with acute respiratory failure has been reported after treatment with pharmacologic amounts of somatropin. Two placebo-controlled clinical trials in non-growth hormone deficient adult patients (n=522) with these conditions revealed a significant increase in mortality (42% vs. 19%) among somatropin-treated patients (doses 5.3-8 mg/day) compared to those receiving placebo *[see Contraindications (4)]*.

5.2 Concomitant Antiretroviral Therapy

In some experimental systems, somatropin 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 somatropin does not interfere with the antiviral activity of zalcitabine or stavudine. In the controlled clinical trials, no significant somatropin-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.

5.3 Neoplasms

Because malignancies are more common in HIV positive individuals, the risks and benefits of starting somatropin in HIV positive patients should be carefully considered before initiating SEROSTIM treatment and patients should be monitored carefully for the development of neoplasms if treatment with somatropin is initiated.

Monitor all patients with a history of any neoplasm routinely while on somatropin therapy for progression or recurrence of the tumor *[see Contraindications (4)]*.

Monitor patients on somatropin therapy carefully for increased growth, or potential malignant changes of preexisting nevi.

5.4 Impaired Glucose Tolerance/Diabetes

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.

During safety surveillance of patients with HIV-associated wasting, cases of new onset impaired glucose tolerance, 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.

In clinical trials of SEROSTIM conducted in HIV patients with lipodystrophy (an unapproved indication), evidence of dose-dependent glucose intolerance and related adverse reaction was observed at doses of 4 mg SEROSTIM daily and 4 mg SEROSTIM every other day for 12 weeks *[see Adverse Reactions (6.1)]*.

5.5 Intracranial Hypertension

Intracranial hypertension (IH) with papilledema, visual changes, headache, nausea, and/or vomiting has been reported in a small number of patients treated with somatropin products. Symptoms usually occurred within the first eight (8) weeks after the initiation of somatropin therapy. In all reported cases, IH-associated signs and symptoms rapidly resolved after cessation of therapy or a reduction of the somatropin dose. Funduscopic examination should be performed routinely before initiating treatment with somatropin to exclude preexisting papilledema, and periodically during the course of somatropin therapy. If papilledema is observed by funduscopy during somatropin treatment, treatment should be stopped. If somatropin-induced IH is diagnosed, treatment with somatropin can be restarted at a lower dose after IH-associated signs and symptoms have resolved.

5.6 Severe Hypersensitivity

Serious systemic hypersensitivity reactions including anaphylactic reactions and angioedema have been reported with postmarketing use of somatropin products. Patients and caregivers should be informed that such reactions are possible and that prompt medical attention should be sought if an allergic reaction occurs *[see Contraindications (4)]*.

5.7 Fluid Retention/Carpal Tunnel Syndrome

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 (2.1)]*.

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.

5.8 Lipoatrophy

When somatropin is administered subcutaneously at the same site over a long period of time, tissue atrophy may result. This can be avoided by rotating the injection site *[see Dosage and Administration (2.2)]*.

5.9 Pancreatitis

Cases of pancreatitis have been reported rarely in children and adults receiving somatropin treatment, with some evidence supporting a greater risk in children compared with adults. Published literature indicates that girls who have Turner syndrome may be at greater risk than other somatropin-treated children. Pancreatitis should be considered in any somatropin-treated patient, especially a child who develops abdominal pain.

6 ADVERSE REACTIONS

The following important adverse reactions are also described elsewhere in the labeling:

Acute Critical Illness *[see Warnings and Precautions (5.1)]*
Neoplasms *[see Warnings and Precautions (5.3)]*
Impaired glucose tolerance and diabetes mellitus *[see Warnings and Precautions (5.4)]*
Intracranial hypertension *[see Warnings and Precautions (5.5)]*
Severe hypersensitivity *[see Warnings and Precautions (5.6)]*
Fluid retention/Carpal tunnel syndrome *[see Warnings and Precautions (5.7)]*
Lipoatrophy *[see Warnings and Precautions (5.8)]*

Pancreatitis *[see Warnings and Precautions (5.9)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Clinical trials in HIV-associated wasting or cachexia:

In the 12-week, placebo-controlled Clinical Trial 2, 510 patients were treated with SEROSTIM. 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 1 and Warnings and Precautions (5)]*. These symptoms 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 reactions 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 reactions which occurred during the first 12 weeks of study in at least 5% of the patients in either active treatment group and at an incidence greater than placebo are listed below, without regard to causality assessment.

Table 1: Controlled Clinical Trial 2 Adverse Reactions Occurring in at least 5% of Patients in one of the Treatment Groups, and at an Incidence Greater than Placebo

	Placebo	0.1 mg/kg every other day 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
Gastrointestinal System Disorders			
Nausea	4.9	5.4	9.1
Body As A Whole - General Disorders			
Edema Peripheral	2.8	11.3	26.1
Fatigue	4.5	3.5	5.1
Endocrine Disorders			
Gynecomastia	0.4	3.5	5.5
Central and Peripheral 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 reactions 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 dose 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 reaction was 3.6% for the placebo group, 1.9% for the 0.1 mg/kg every other day 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 reactions 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.

Adverse reactions from treatment with SEROSTIM in clinical trials in HIV lipodystrophy

SEROSTIM was evaluated for the treatment of patients with HIV lipodystrophy in two double-blind, placebo-controlled trials that excluded patients with a history of diabetes, impaired fasting glucose or impaired glucose (approximately 20% of the patients screened were excluded from study enrollment as a result of a diagnosis of diabetes or glucose intolerance). The studies included a 12-week double-blind, placebo-controlled, parallel group "induction" phase followed by maintenance phases of different durations (12 and 24 weeks, respectively). In the initial 12-week treatment periods of the two, placebo-controlled clinical trials, 406 patients were treated with SEROSTIM. Clinical adverse reactions 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 2, 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 often subsided with dose reduction. During the 12-week induction phase, 1) approximately 26% of patients receiving SEROSTIM 4 mg daily and 19% of patients receiving SEROSTIM 4 mg every other day required

dose reductions; and 2) discontinuations as a result of adverse reactions occurred in 13% of patients receiving SEROSTIM 4 mg daily and 5% of patients receiving SEROSTIM 4 mg every other day. 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 2: Controlled HIV Lipodystrophy Studies 1 and 2 Combined – Adverse Reactions with >5% Incidence in Either Active Treatment Arm

	Placebo	**SEROSTIM 4 mg every other day[1]**	**SEROSTIM 4 mg daily**
	Patients (n=159)	Patients (n=80)	Patients (n=326)
System Organ Class Preferred Term	%	%	%
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
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

[1] Study 22388 only
[2] similar terms were grouped together and reported below

Glucose metabolism related adverse reactions: During the initial 12-week treatment periods of Studies 1 and 2, the incidence of glucose-related adverse reactions was 4% for the placebo group, 13% for the 4 mg every other day group and 22% for the 4 mg daily group.

Twenty-three patients discontinued due to hyperglycemia while receiving SEROSTIM during any phase of these studies (3.2% in the 12-week induction phases and 2.1% in the extension phases).

Breast-Related Terms: When grouped together, breast-related adverse reactions (e.g. nipple pain, gynecomastia, breast pain/mass/tenderness/swelling/edema/hypertrophy) had an incidence of 1% for the placebo group, 3% for the SEROSTIM 4 mg every other day group and 6% for the SEROSTIM 4 mg daily group.

Adverse reactions that occurred in 1% to less than 5% of trial participants receiving SEROSTIM during the first 12 weeks of HIV Lipodystrophy Studies 1 and 2 thought to be related to SEROSTIM include carpal tunnel syndrome, Tinel's sign and facial edema.

The adverse reactions reported for SEROSTIM 4 mg every other day during the maintenance phase of HIV Lipodystrophy Study 1 (Week 12 to Week 24) were similar in frequency and quality to those observed after treatment with SEROSTIM 4 mg every other day during the 12-week induction phase.

IGF-1 serum concentrations increased statistically in SEROSTIM-treated patients when compared to placebo (Table 3). In the SEROSTIM treated patients at baseline, the proportion of subjects with serum IGF-1 SDS levels ≥ +2 was approximately 10 to 20%, while with treatment with either dose regimen of SEROSTIM the percentage increased to 80 to 90% by Week 12.

Table 3: **Change from Baseline to Week 12 in Serum IGF-1 SDS After Treatment with SEROSTIM 4 mg daily vs. Placebo (Modified ITT Population; Studies 1 and 2 Combined)**

		Placebo	**SEROSTIM 4 mg every other day**	**SEROSTIM 4 mg daily**
Time Point	Statistic	(n=145)	(n=79)	(n=290)
Baseline	Mean (SD) Range	0.4 (1.4) (-2.5, 4.8)	1.3 (2.1) (-2.0, 13.7)	0.0 (1.6) (-3.0, 11.9)
Week 12	Mean (SD) Range	0.8 (1.6) (-2.6, 6.7)	5.1 (3.4) (-0.7, 17.2)	6.1 (5.0) (-1.8, 29.2)
Change from Baseline to	Mean (SD) Range	0.4 (1.3) (-2.9, 7.7)	3.9 (3.1) (-9.4, 11.8)	6.1 (4.6) (-2.4, 24.3)
Week 12	p-value[(b)]	<0.001	<0.001	<0.001
	Mean[(a)] diff (SEM)		3.5 (0.5)	5.7 (0.4)
	p-value[(c)]		<0.001	<0.001

(a) Proportionally weighted least squares means from a two-way ANOVA model on raw data including effects for treatment, sex, and the treatment by sex interaction.

(b) P-value from a Wilcoxon Signed Rank test on the change from baseline to Week 12.

(c) P-value from a two-way ANOVA model on ranked data including effects for treatment, sex, and the treatment by sex interaction.

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influences by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to SEROSTIM with the incidence of antibodies to other products may be misleading.

After 12 weeks of treatment, 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. Data beyond 3 months is not available.

6.2 Post-Marketing Experience

The following adverse reactions have been identified during post approval use of SEROSTIM. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Hypersensitivity: Serious systemic hypersensitivity reactions including anaphylactic reactions and angioedema have been reported with postmarketing use of somatropin products *[see Warnings and Precautions (5.6)]*.

Endocrine:

- new onset impaired glucose tolerance
- new onset type 2 diabetes mellitus
- exacerbation of preexisting diabetes mellitus
- diabetic ketoacidosis
- 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 *[see Warnings and Precautions (5.4)]*.

Gastrointestinal: Pancreatitis *[see Warnings and Precautions (5.9)]*.

7 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.

7.1 11β-Hydroxysteroid Dehydrogenase Type 1

The microsomal enzyme 11β-hydroxysteroid dehydrogenase type 1 (11βHSD-1) is required for conversion of cortisone to its active metabolite, cortisol, in hepatic and adipose tissue. Somatropin inhibits 11βHSD-1. Patients treated with glucocorticoid replacement for previously diagnosed hypoadrenalism may require an increase in their maintenance or stress doses following initiation of somatropin treatment; this may be especially true for patients treated with cortisone acetate and prednisone since conversion of these drugs to their biologically active metabolites is dependent on the activity of 11βHSD-1.

7.2 Cytochrome P450-metabolized drugs

Limited published data indicate that somatropin treatment increases cytochrome P450 (CYP450)-mediated antipyrine clearance in man. These data suggest that somatropin administration may alter the clearance of compounds metabolized by CYP450 liver enzymes (e.g., corticosteroids, sex steroids, anticonvulsants, cyclosporine). Therefore, careful monitoring is advised when somatropin is administered in combination with drugs metabolized by CYP450 liver enzymes. However, formal drug interaction studies have not been conducted.

7.3 Oral Estrogen

Because oral estrogens may reduce the serum IGF-1 response to somatropin treatment, girls and women receiving oral estrogen replacement may require greater somatropin dosages *[see Dosage and Administration (2)]*.

7.4 Insulin and/or Other Oral/Injectable Hypoglycemic Agents

Patients with diabetes mellitus who receive concomitant treatment with somatropin may require adjustment of their doses of insulin and/or other hypoglycemic agents *[see Warnings and Precautions (5.4)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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, SEROSTIM should be used during pregnancy only if clearly needed.

8.3 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.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients with HIV have not been established. Available evidence suggests that somatropin clearance is similar in adults and children, but no pharmacokinetic studies have been conducted in children with HIV.

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 HIV wasting.

Benzyl alcohol, a component of this product, has been associated with serious adverse events and death, particularly in pediatric patients. The "gasping syndrome," (characterized by central nervous system depression, metabolic acidosis, gasping respirations, and high levels of benzyl alcohol and its metabolites found in the blood and urine) has been associated with benzyl alcohol dosages >99 mg/kg/day in neonates and low-birth weight neonates. Additional symptoms may include gradual neurological deterioration, seizures, intracranial hemorrhage, hematologic abnormalities, skin breakdown, hepatic and renal failure, hypotension, bradycardia, and cardiovascular collapse. Practitioners administering this and other medications containing benzyl alcohol should consider the combined daily metabolic load of benzyl alcohol from all sources.

8.5 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 the action of somatropin, and therefore, may be more prone to develop adverse reactions. A lower starting dose and smaller dose increments should be considered for older patients *[see Dosage and Administration (2)]*.

8.6 Hepatic Impairment

No studies have been conducted for SEROSTIM in patients with hepatic impairment *[see Clinical Pharmacology (12.3)]*.

8.7 Renal Impairment

Subjects with chronic renal failure tend to have decreased somatropin clearance compared to those with normal renal function. However, no studies have been conducted for SEROSTIM in patients with renal impairment *[see Clinical Pharmacology (12.3)]*.

8.8 Gender Effect

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 for SEROSTIM in normal volunteers or patients infected with HIV.

10 OVERDOSAGE

Short-Term

Acute overdosage could lead initially to hypoglycemia and subsequently to hyperglycemia.

Long-Term

Long-term overdosage could result in signs and symptoms of acromegaly consistent with the known effects of excess growth hormone.

11 DESCRIPTION

SEROSTIM 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 growth hormone. 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 sterile lyophilized powder intended for subcutaneous injection after reconstitution to its liquid form.

Vials of SEROSTIM contain either 4 mg, 5 mg, or 6 mg. Each vial contains the following:

	Vials		
	4 mg	5 mg	6 mg
Component			
Somatropin	4 mg	5 mg	6 mg
Sucrose	27.3 mg	34.2 mg	41 mg
Phosphoric acid	0.9 mg	1.2 mg	1.4 mg

Each 4 mg multi-vial is supplied in a combination package with Bacteriostatic Water for Injection, USP (0.9% Benzyl Alcohol). The pH is adjusted with sodium hydroxide of phosphoric acid to give a pH of 7.4 to 8.5 after reconstitution.

Each 5 mg single-use vial is supplied in a combination package with Sterile 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.

Each 6 mg single-use vial is supplied in a combination package with Sterile Water for Injection, USP. The pH is adjusted with sodium hydroxide of phosphoric acid to give a pH of 7.4 to 8.5 after reconstitution.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

SEROSTIM 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-1 (IGF-1).

12.2 Pharmacodynamics

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 HIV Lipodystrophy *[see Clinical Studies (14)]*.

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 (14)]*. 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.

12.3 Pharmacokinetics

Absorption: The absolute bioavailability after subcutaneous administration was determined to be 70 to 90%. The mean t½ after subcutaneous administration is significantly longer than that seen after intravenous administration in normal male volunteers down-regulated with somatostatin (approximately 4.0 hrs. vs. 0.6 hrs.), indicating that the subcutaneous absorption of somatropin is a rate-limiting process.

Distribution: The steady-state volume of distribution (Mean ± SD) following intravenous administration of somatropin in normal male 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 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 somatropin subcutaneously was 4.28 ± 2.15 hrs, similar to that observed in normal male volunteers. 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 daily dosing as indicated.

Specific 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 studies have been conducted to determine the effect of race on the pharmacokinetics of SEROSTIM.

Renal Impairment: Subjects with chronic renal failure tend to have decreased somatropin clearance compared to those with normal renal function. However, no studies have been conducted to determine the effect of renal impairment on the pharmacokinetics of SEROSTIM.

Hepatic Impairment: No studies have been conducted to determine the effect of hepatic impairment on the pharmacokinetic of SEROSTIM.

13 NONCLINICAL TOXICOLOGY

13.1 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.

14 CLINICAL STUDIES

HIV-Associated Wasting or Cachexia

The clinical efficacy of SEROSTIM in HIV-associated wasting or cachexia was assessed in two placebo-controlled trials. All study subjects received concomitant antiretroviral therapy. There was no increase in the incidence of Kaposi's sarcoma (KS), 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.

Clinical Trial 1:

A 12-week, randomized, double-blind, placebo-controlled study followed by an open-label extension phase enrolled 178 patients with severe HIV 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/microliter 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

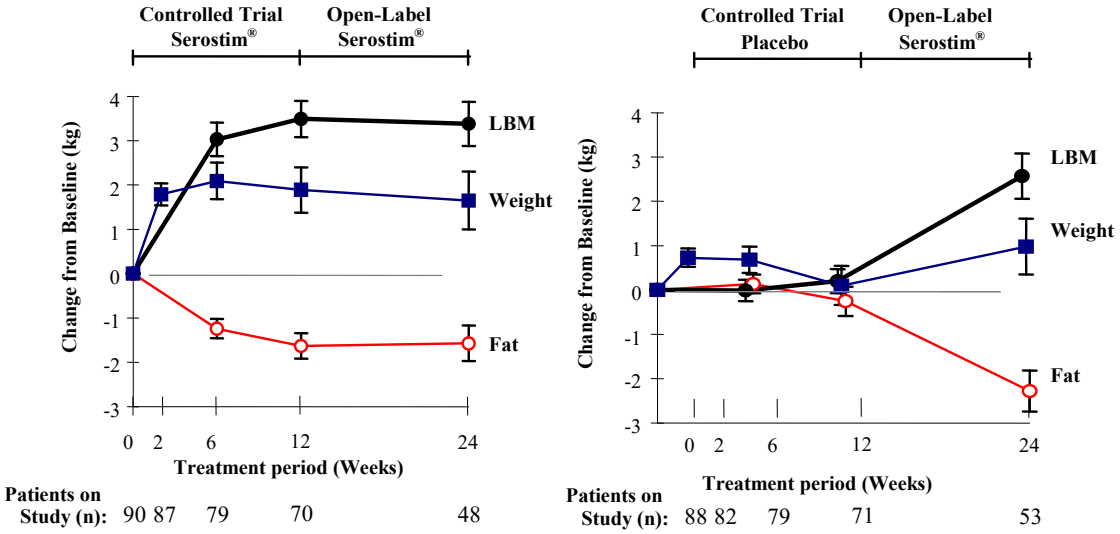
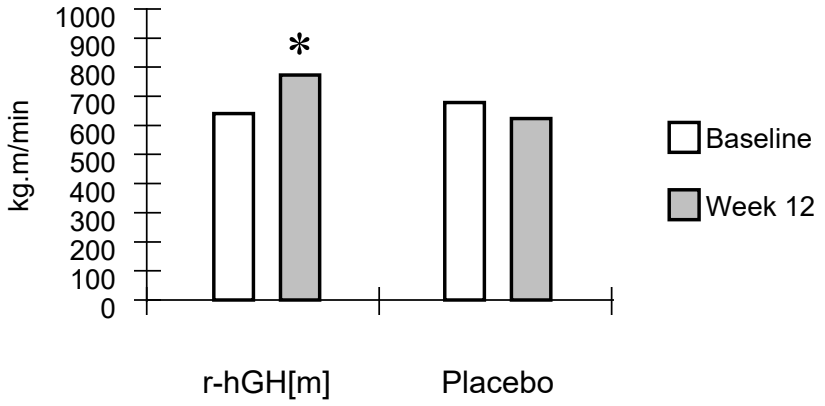


Figure 2: Median Treadmill Work Output



*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 at bedtime 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/µL 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 4 and 5:

Table 4: 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 5: 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 4). 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 5). 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.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

SEROSTIM is available in the following forms:

- SEROSTIM single-use vials containing 5 mg with Sterile Water for Injection, USP. Package of 7 vials. NDC 44087-0005-7
- SEROSTIM single-use vials containing 6 mg with Sterile Water for Injection, USP. Package of 7 vials. NDC 44087-0006-7
- SEROSTIM multiple-use vials containing 4 mg with Bacteriostatic Water for Injection, USP (0.9% Benzyl Alcohol). Package of 7 vials. NDC 44087-0004-7

16.2 Storage and Handling

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.

Single-use vials: After reconstitution with Sterile Water for Injection, USP, the reconstituted solution should be used immediately and any unused portion should be discarded.

Multi-use vials: After reconstitution with Bacteriostatic Water for Injection, USP (0.9% Benzyl Alcohol), the reconstituted solution should be stored under refrigeration (2-8ºC/36-46ºF) for up to 14 days.

Avoid freezing reconstituted vials of SEROSTIM.

17 PATIENT COUNSELING INFORMATION

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.

Never Share a SEROSTIM Pen or Needle Between Patients

Counsel patients that they should never share SEROSTIM or SEROSTIM injection devices with another person, even if the needle or nozzle is changed. Sharing of SEROSTIM or SEROSTIM injection devices between patients may pose a risk of transmission of infection.

Patients should be informed about the management of common side effects related to tissue turgor, glucose intolerance and musculoskeletal discomfort.

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