Serostim®
(somatropin) for injection

SEROSTIM®
CLINICAL PROFILE

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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 SAFETY INFORMATION

CONTRAINDICATIONS

Acute Critical Illness: Serostim® 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.

Please see Important Safety Information throughout and on pages 26-27 and accompanying full Prescribing Information.

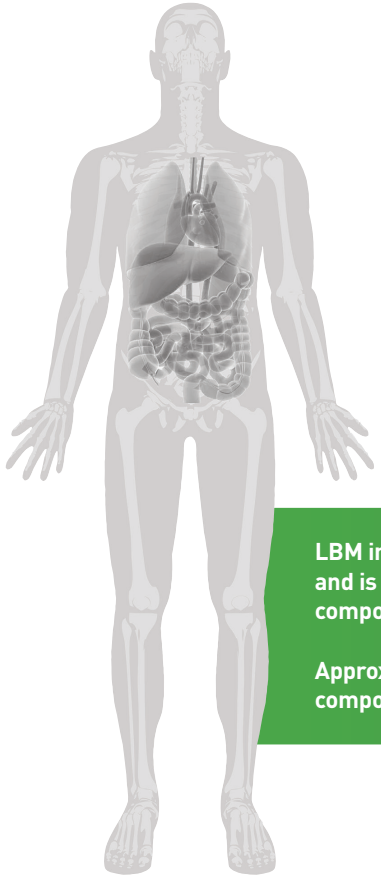
Introduction

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 loss of lean body mass (LBM), involuntary weight loss and decreased physical endurance.[1-4]

Over time, as patients living with HIV lose weight and LBM, physical endurance may be lost

Unintentional weight loss in patients affected with HIV-associated wasting may occur as a preferential loss of LBM, which may be accompanied by a relative preservation of fat.[5,6] As patients unintentionally lose weight, there's loss of LBM, which may be associated with a decline in strength and functional performance.[5]

Reduced functional capacity can decrease the ability to complete tasks requiring a certain level of physical endurance.



LBM includes muscle mass and is a component of total body composition and weight.[7,8]

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

Who May Be at Risk

HIV-associated wasting is a serious condition that can be a concern across a range of patients living with HIV, including those with undetectable viral loads and normal CD4 counts who are well controlled on antiretroviral therapy.

Your patients may experience HIV-associated wasting even when their virus is well controlled on antiretroviral therapy.[5]

HIV-associated wasting can be a concern across a range of patients, which may include:[9-12]

- Newly diagnosed patients
- HIV Long-Term Survivors
- HIV-positive patients with normal CD4 counts and controlled viral loads
- Patients on antiretroviral therapy who fail to gain weight
- Patients on antiretroviral therapy with acute infection
- Patients with advanced HIV disease
- Poor virologic responders
- Patients who have been nonadherent to antiretroviral therapy

More men experience HIV-associated wasting, but it can occur in women, too.[13]

Pathophysiology

The underlying pathogenesis of HIV-associated wasting is not clearly understood.[13] However evidence suggest that altered metabolism and/or reduced caloric intake have an important role in the development of this condition.[13] These may be important individually or collectively in triggering unintentional weight loss, loss of LBM, and reduced physical endurance in HIV-positive patients. HIV-associated wasting is a diagnosis of exclusion and the underlying conditions and comorbidities should be addressed individually as appropriate.[13,14]

HIV/AIDS-related Infections[2,6,12,16]

- Opportunistic infections related to HIV, including but not limited to candidiasis, pneumocystosis, toxoplasmosis, and tuberculosis, have been shown to increase the risk of unintentional weight loss and may:
  - Contribute to a number of complications that interfere with swallowing, which may limit caloric intake
  - Cause anorexia, which can result in reduced nutritional intake during active opportunistic infection
  - Lead to metabolic changes as a result of energy expenditure and energy needs being altered

Inflammatory Response[12,17-23]

- Elevated plasma levels of proinflammatory cytokines characterize HIV infection at all phases, even in patients on antiretroviral therapy. These cytokines exert numerous effects throughout the body, including the mediation of the acute-phase response (APR) of the innate immune system.
- APR is part of the early-defense or innate immune system, which is triggered by stimuli such as trauma, infection, stress, neoplasia, and inflammation.
- In patients living with HIV, this chronic, systemic inflammatory response leads to the ongoing deterioration of muscle, which may lead to unintentional weight loss.
- Even when HIV is well-controlled, a sustained inflammatory state may persist indefinitely.
- Proinflammatory cytokines, including Interleukin-6 (IL-6), also mediate the anorexia that is a component of many acute infections.

VIEW CYTOKINE STORM >

Pathophysiology (continued)

The underlying pathogenesis of HIV-associated wasting is not clearly understood.[13] HIV-associated wasting is a diagnosis of exclusion and the underlying conditions and comorbidities should be addressed individually as appropriate.[13,14]

Metabolic Changes[1-4,6,7,24,25]

- Dysregulation of metabolic pathways can result in inappropriate depletion of LBM, body weight, and a relative preservation of body fat.
- A number of factors may promote catabolism, the metabolic breakdown of complex molecules into simpler ones. Excessive catabolic activity from the following can result in loss of LBM:
  - Proinflammatory cytokines
  - Elevated resting energy expenditure
  - Reduced serum Insulin-like growth factor 1 (IGF-1) levels which leads to increased protein degradation and loss of LBM
  - Shift in endocrine function toward increased levels of the catabolic hormone cortisol may contribute to HIV-associated wasting
- Changes affecting other cellular pathways, such as the phosphoinositide-3-kinase (PI3K) pathway, may also contribute to HIV-associated wasting.

VIEW METABOLIC CHANGES >

Endocrine Dysfunction

Low testosterone[12,16, 26, 27]

- Hypogonadism affects about 20% - 25% of HIV-positive men on combination antiretroviral therapy and is highly correlated with significant loss of LBM.
  - Androgen deficiency appears to be more common in HIV-positive males than in the general population.
- In a study of HIV-positive men, the incidence of hypogonadism varied depending on the criteria used:
  - Using a threshold of free testosterone (FT) < 100 pg/mL found that 64% were hypogonadal with the presence of at least 1 hypogonadal symptom
  - Using the currently accepted threshold of total testosterone (TT) < 300 ng/mL identified only 24% as hypogonadal
- It is unclear whether low testosterone is a consequence or a cause of unintentional weight loss.
- An increased prevalence of metabolic syndrome in HIV-positive men may contribute to the high rates of androgen deficiency.
- Among HIV-positive women, decreased levels of free testosterone are also significantly associated with HIV-associated wasting.

Pathophysiology (continued)

The underlying pathogenesis of HIV-associated wasting is not clearly understood.[13] HIV-associated wasting is a diagnosis of exclusion and the underlying conditions and comorbidities should be addressed individually as appropriate.[13,14]

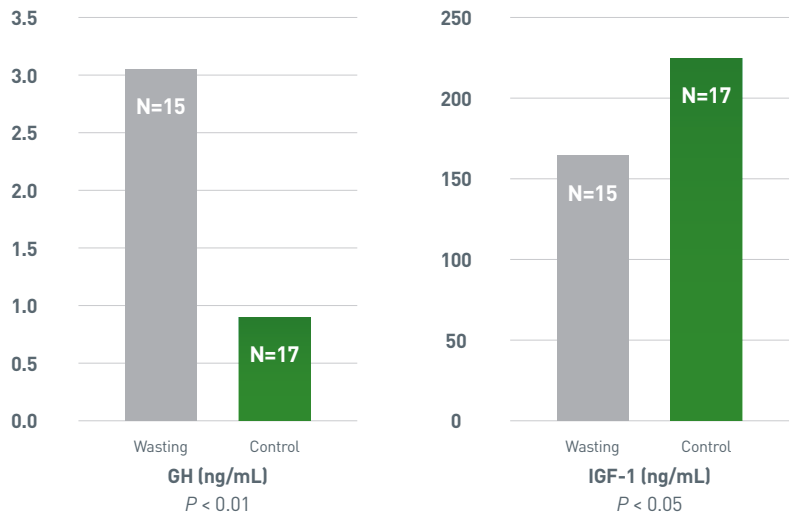
Endocrine Dysfunction (continued)

Growth Hormone (GH) Resistance[11,13,27]

- The GH/IGF-1 axis is one of the regulators of muscle protein metabolism that is altered in patients with HIV-associated wasting.
- Acquired GH resistance may result in decreased production of IGF-1 by the liver.
- Disruptions in the GH/IGF-1 axis can lead to elevated serum GH levels and reduced serum IGF-1 levels.
- Elevated mean overnight GH levels corresponded to decreased mean IGF-1 levels in a study of hypogonadal men with HIV-associated wasting.*
  - These data may support the rationale for pharmacologic use of GH to overcome GH resistance in this population.

VIEW GROWTH HORMONE RESISTANCE >

GH and IGF-1 mean overnight levels in men with HIV-associated wasting* [27]



*Referred to as AIDS wasting in this study.

Twenty hypogonadal male subjects with weight loss (>10% of preillness weight or absolute weight <90% of ideal body weight) were enrolled in the study.

Pathophysiology (continued)

The underlying pathogenesis of HIV-associated wasting is not clearly understood.[13] HIV-associated wasting is a diagnosis of exclusion and the underlying conditions and comorbidities should be addressed individually as appropriate.[13,14]

Gastrointestinal Issues

Gut-associated Lymphoid Tissue (GALT)[11,23]

- GALT is the largest component of the mucosal immune system and the primary target tissue during acute HIV infection.
- Even in patients living with HIV who have undetectable viral loads, GALT can serve as a viral reservoir.
- This may stimulate chronic inflammation and immune activation.

Gastrointestinal Alterations[28,29]

- HIV alters the gut flora which may lead to long-term effects on epithelial barrier and affect T-cell function in the gut.
- Over time, the integrity of the protective mucosal barrier may be diminished.
- Gastrointestinal alterations may be associated with inflammation and malabsorption of vital nutrients.
- Malabsorption of nutrients can lead to unintentional weight loss and LBM.

Diarrhea[14,21,29-31]

- Diarrhea may be caused by:
  - Use of antiretroviral therapy (ART)
  - Opportunistic infections that target the GI tract
  - GI comorbidity
  - Polypharmacy
- Unintentional weight loss may be more likely in HIV-positive patients with clinically significant diarrhea, which can:
  - Affect weight loss through a loss of calories
  - Discourage food intake
  - Make patients living with HIV unable to meet nutritional goals through oral intake

Screening and Evaluating Patients with HIV-associated Wasting

Initiating a Conversation

Proactively asking your HIV-positive patients questions about their symptoms may help you identify HIV-associated wasting and intervene early as your patients may be reluctant to bring them up on their own.

Questions to consider:

- ☐ Have you had unintentional weight loss?
- ☐ Have you recently lost weight without trying?
- ☐ Does your unintentional weight loss affect your health?
- ☐ Do your clothes fit more loosely due to unintentional weight loss?
- ☐ Have friends, family, or coworkers noticed any changes in your weight?
- ☐ Do you have a loss of energy, along with unintentional weight loss?
- ☐ Do you frequently feel tired?
- ☐ Are you exercising less?
- ☐ Do you need to rest more often?
- ☐ Is it more difficult to complete some of your activities?

Other Screening Methods

Measuring and reviewing weight history*, calculating Body Mass Index (BMI), and evaluating muscle tone and physical endurance as well as visual appearance may help you identify HIV-associated wasting.

*A weight history should include a premorbid or prediagnosis weight and changes in weight over time.

Clinically managing patients to assess for HIV-related comorbidities, such as HIV-associated wasting, can add a layer of complexity during visits with limited face-to-face interaction or during telemedine visits.

Some methods you may consider to screen your HIV-positive patients for changes in weight include:

- Asking your patient to keep a record of their weight, and self-reporting them during visits, by:
  - Keeping a scale at home
  - Weighing themselves at their local pharmacy, AIDS Service Organization, during their routine lab visits or wherever a scale is available
- Inquiring about whether patients' clothing fit differently
- Looking for changes in physical appearance during audiovisual telemedicine calls, asking about involuntary changes in body habitus

Screening and Evaluating Patients with HIV-associated Wasting (continued)

The process of monitoring and assessing patients at risk for, or being treated for, HIV-associated wasting, involves both clinical evaluation and an ongoing discussion with your HIV-positive patients. In addition to asking your patients if they are experiencing any symptoms of HIV-associated wasting you may consider the following actions:

Action: Measure Weight / Review Weight History

Questions:

- Is a premorbid weight documented in the medical record?
- How often are you weighing patients?
- How are you assessing changes in weight over time?

Action: Calculate BMI / Review BMI History

Questions:

- How frequently do you calculate your patient's BMI?
- How are you assessing changes in BMI over time?

Action: Visual Examination of Physical Appearance

Questions:

- Are you assessing loose skin or hanging skin folds consistent with weight loss?
- Are you observing changes in body habitus or loose fitting clothing?
- Are you evaluating muscle tone?

Action: Evaluate Physical Endurance

Questions:

- Are you talking to your patients about their level of physical endurance?
- Are your patients bringing up loss of energy associated with unintentional weight loss?

As previously mentioned, evidence suggests that altered metabolism can have an important role in the development of HIV-associated wasting.[13]

Serostim® (somatropin) for Injection

Mechanism of Action[32]

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).

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 SAFETY INFORMATION

CONTRAINDICATIONS

Acute Critical Illness: Serostim® 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.

Please see Important Safety Information throughout and on pages 26-27 and accompanying full Prescribing Information.

Clinical Studies—Efficacy[32]

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.

IMPORTANT SAFETY INFORMATION (continued)

CONTRAINDICATIONS (continued)

Active Malignancy: 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. Discontinue somatropin if there is evidence of recurrent activity.

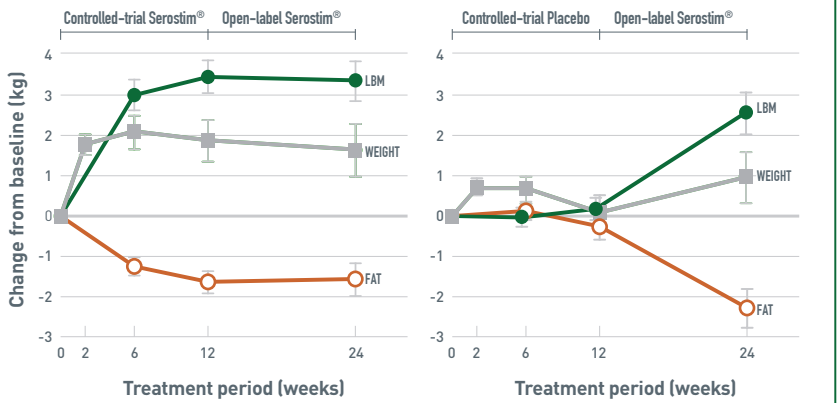
Please see Important Safety Information throughout and on pages 26-27 and accompanying full Prescribing Information.

Clinical Studies—Efficacy[32] (continued)

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

- 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.
- There were no significant changes with continued treatment beyond 12 weeks suggesting the original gains of weight and LBM were maintained.

Figure 1: Mean changes in body composition



IMPORTANT SAFETY INFORMATION (continued)

CONTRAINDICATIONS (continued)

Hypersensitivity: Serostim® is contraindicated in patients with a known hypersensitivity to somatropin or any of its excipients. Systemic hypersensitivity reactions have been reported.

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

WARNINGS AND PRECAUTIONS

Acute Critical Illness: Increased mortality (42% vs. 19% in somatropin compared to placebo treated) 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.

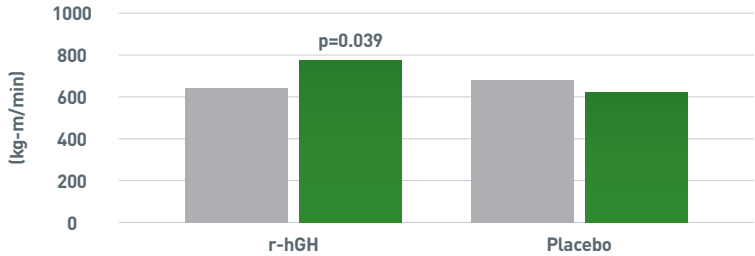
Please see Important Safety Information throughout and on pages 26-27 and accompanying full Prescribing Information.

Clinical Studies—Efficacy[32] (continued)

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

- 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.
- There was no improvement in the placebo-treated group at 12 weeks.
- Changes in treadmill performance were significantly correlated with changes in LBM.

Figure 2: Median treadmill work output



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

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

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

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: Patients with other risk factors for glucose intolerance should be monitored closely during Serostim® therapy. 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 and, in some, improved when Serostim® was discontinued and in others persisted. Some of these patients required initiation or adjustment of antidiabetic treatment.

Please see Important Safety Information throughout and on pages 26-27 and accompanying full Prescribing Information.

Clinical Studies—Efficacy[32] (continued)

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 (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. At study entry, 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.

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.

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

Intracranial Hypertension: Intracranial hypertension (IH) with papilledema, visual changes, headache, nausea, and/or vomiting has been reported usually within the first 8 weeks of somatropin therapy and rapidly resolved after stopping or reducing the somatropin dose. Funduscopic examination should be performed prior to initiating treatment with somatropin and periodically during 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: 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. Carpal tunnel syndrome may occur and if the 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.

Please see Important Safety Information throughout and on pages 26-27 and accompanying full Prescribing Information.

Clinical Studies—Efficacy[32] (continued)

Serostim® treatment significantly increased LBM and weight, and maintained gains with continued treatment

- A statistically significant median increase in LBM and body weight was observed after 12 weeks of treatment with Serostim®.
- Patients taking Serostim® daily had a 5.84 kg (12.8 lb) increase in LBM, 2.79 kg (6.1 lb) increase in body weight, and 1.72 kg (3.8 lb) loss in fat mass.
- Patients taking Serostim® on alternate days had a 3.89 kg (8.6 lb) increase in LBM, 2.18 kg (4.8 lb) increase in body weight, and 1.25 kg (2.8 lb) loss in fat mass.
- Patients taking placebo had a 0.97 kg (2.1 lb) increase in LBM, 0.69 kg (1.5 lb) increase in body weight, and 0.03 kg (0.07 lb) increase in fat mass.

Table 1: 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

Clinical Studies—Efficacy[32] (continued)

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

- After 12 weeks on Serostim®, patients were able to exert statistically significantly more work output (kJ) while cycling compared with those treated with placebo, who experienced a loss of physical endurance.
- Patients made statistically significant gains in physical endurance with increases of 8.9% on qod and 9.1% on daily dose (*P*<0.01 for both groups vs. placebo).
- In an extension phase, improvements were maintained or improved through 24 weeks.

Table 2: 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)
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 daily
(b) approximately 0.1 mg/kg every other day
(c) p<0.01.

IMPORTANT SAFETY INFORMATION (continued)

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 pediatric patients with HIV have not been established. Clinical studies did not include sufficient numbers of subjects ≥ 65 to determine a response different from that of younger patients. Studies have not been conducted in patients with hepatic or renal impairment. Gender-based analysis is not available.

Please see Important Safety Information throughout and on pages 26-27 and accompanying full Prescribing Information.

Clinical Studies—Adverse Events[32]

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.

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 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 Studies—Adverse Events[32] (continued)

Clinical Adverse Reactions

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[32]

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.

Clinical Pharmacology[32] (continued)

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

Pregnancy: There are no adequate and well-controlled studies in pregnant women. Serostim® 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: Safety and effectiveness in pediatric patients with HIV have not been established. Available evidence suggests that r-hGH clearances are similar in adults and children, but no pharmacokinetic studies have been conducted in children with HIV.

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.

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

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.

Please see Important Safety Information throughout and on pages 26-27 and accompanying full Prescribing Information.

Description[32]

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[32]

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.

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.

Please see Important Safety Information throughout and on pages 26-27 and accompanying full Prescribing Information.

Stability, Storage, and Forms[32]

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.

Patient Counseling Information[32]

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.

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

Never Share Serostim® Needles Between Patients

Serostim® (somatropin) for Injection

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 SAFETY INFORMATION

CONTRAINDICATIONS

Acute Critical Illness: Serostim® 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.

Active Malignancy: 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. Discontinue somatropin if there is evidence of recurrent activity.

Hypersensitivity: Serostim® is contraindicated in patients with a known hypersensitivity to somatropin or any of its excipients. Systemic hypersensitivity reactions have been reported.

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

WARNINGS AND PRECAUTIONS

Acute Critical Illness: Increased mortality (42% vs. 19% in somatropin compared to placebo treated) 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, and there was no increase in virus production when antiretroviral agents were added to the culture medium. No significant somatropin-associated increase in viral burden was observed. All patients received antiretroviral therapy for the duration of treatment during Serostim® clinical trials.

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: Patients with other risk factors for glucose intolerance should be monitored closely during Serostim® therapy. 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 and, in some, improved when Serostim® was discontinued and in others persisted. Some of these patients required initiation or adjustment of antidiabetic treatment.

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

Intracranial Hypertension: Intracranial hypertension (IH) with papilledema, visual changes, headache, nausea, and/or vomiting has been reported usually within the first 8 weeks of somatropin therapy and rapidly resolved after stopping or reducing the somatropin dose. Funduscopic examination should be performed prior to initiating treatment with somatropin and periodically during 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: 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. Carpal tunnel syndrome may occur and if the 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 >5%) were arthralgia, myalgia, peripheral edema, arthrosis, nausea, paresthesia, generalized edema, gynecomastia, hypoesthesia and fatigue.

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 pediatric patients with HIV have not been established. Clinical studies did not include sufficient numbers of subjects ≥ 65 to determine a response different from that of younger patients. Studies have not been conducted in patients with hepatic or renal impairment. Gender-based analysis is not available.

For more information about clinical trial adverse reactions, see pages 18-19.
Please see the accompanying full Prescribing Information.

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