

# MONOGRAPH

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**Serostim<sup>®</sup>**  
[somatropin (rDNA origin) for injection]

Product Monograph



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## Introduction

Wasting is one of the most public and relentless manifestations of HIV infection. As the AIDS epidemic has entered its second decade, and our ability to treat and prophylax against many of the opportunistic infections (OIs) that also characterize HIV infection has improved, wasting has emerged as a major cause of morbidity, mortality, and healthcare utilization. Studies by Kotler and others confirm that the impact of wasting on survival is independent of other factors such as infection or malignancy.<sup>1</sup> These data demonstrate that even a 5% weight loss correlates strongly with decreased survival.<sup>2</sup> More recent studies confirm the relationship between AIDS wasting and increased hospitalization<sup>3</sup> as well as diminished quality of life.<sup>4</sup>

Treatable weight loss can result from inadequate nutrition, whether due to anorexia, obstruction, or malabsorption, and complications of AIDS, such as opportunistic infections and neoplasms. In contrast, AIDS wasting appears to be caused by a derangement of intermediary metabolism. In a failure of normal adaptive mechanisms, the body meets its energy needs by breaking down lean body mass (LBM), a process known as catabolism. This deranged metabolism results in muscle wasting and weakness, organ failure, further immune compromise, inanition, increased hospitalization, deteriorated quality of life and, ultimately, death.<sup>5-8</sup>

Serostim<sup>®</sup>, a human growth hormone produced by recombinant DNA technology, has been shown to exert anticatabolic and anabolic effects in individuals with AIDS wasting. Specifically, during a controlled clinical trial of 12 weeks' duration, Serostim<sup>®</sup> was found to do the following:

- Induce a significant increase in LBM;
- Decrease body fat;
- Increase overall body weight due to the dominant effect of LBM gain; and
- Increase physical functioning as measured by treadmill performance.

This improvement in physical function was correlated with LBM. No such correlation was seen with body fat. 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 r-hGH therapy. There were decreases in serum albumin in both Serostim<sup>®</sup> and placebo groups. In placebo-controlled trials of 12 weeks' duration, no difference in survival between groups was found. In a one-week study in six patients with HIV wasting, Serostim<sup>®</sup> improved nitrogen balance, increased protein-sparing lipid oxidation, and had little overall effect on carbohydrate metabolism.

**While depletion of body weight and LBM has been associated with increased morbidity and mortality, the clinical significance of treatment-induced weight gain and LBM accrual has yet to be established.**

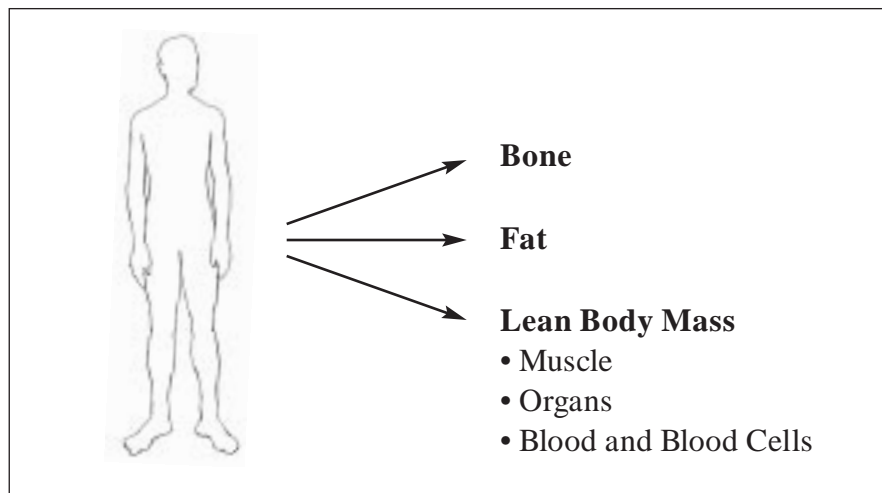
Serostim<sup>®</sup> is indicated for the treatment of AIDS wasting or cachexia. This indication is based on analyses of surrogate endpoints in studies of up to 12 weeks in duration. Concomitant antiviral therapy is necessary. The continued use of Serostim<sup>®</sup> treatment should be reevaluated in patients who continue to lose weight in the first 2 weeks of treatment.

# Pathophysiology of AIDS Wasting

## THE MECHANISM

An understanding of AIDS wasting requires a knowledge of body composition. There are three compartments in the body: bone, fat, and lean body mass (LBM) (Figure 1). The bone compartment gives the body structural support and maintains mineral balance. As a storage compartment, fat serves as an energy reserve. During long-term calorie deprivation or starvation, the body uses fat as a fuel for energy. The vast majority of metabolic activity in the body takes place in the LBM compartment. It is composed of the body's muscles, organs, hematopoietic and lymphoid tissues, and other body fluids. Measuring LBM, therefore, is an excellent measure of nutritional status and the amount of functional protoplasm.<sup>9</sup> Dual-energy X-ray absorptiometry (DEXA) has shown that patients with AIDS wasting are depleted in LBM.<sup>10</sup>

**Figure 1. A Schematic Representation of Body Composition**



During a normal response to weight loss, the body experiences a host of clinical effects, including nitrogen sparing, lowering metabolic rate to conserve energy, and the use of fat as a principal source of energy.<sup>11</sup> LBM is preserved at all cost until fat reserves are depleted.

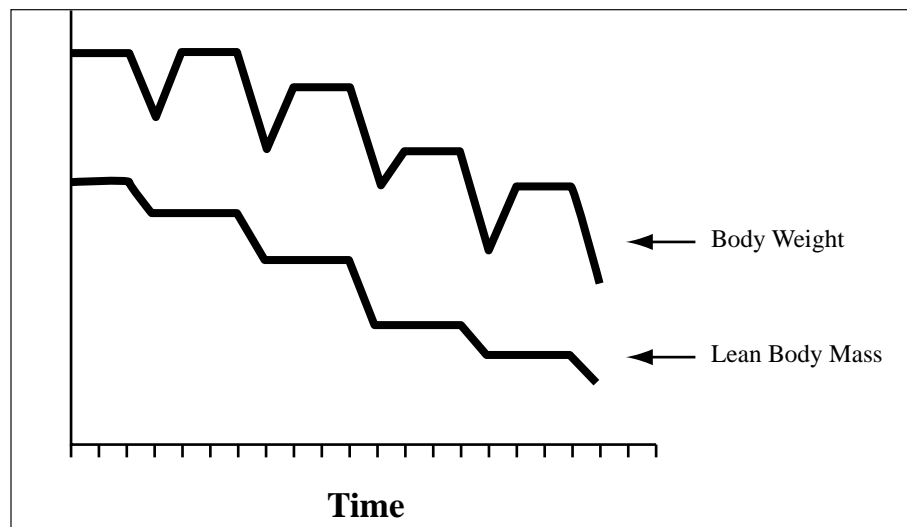
AIDS wasting is different in that these normal adaptive mechanisms fail. Metabolic alterations result in higher rates of resting energy expenditure, even in the absence of acute, concomitant infections.<sup>12</sup> In addition, the process known as futile cycling of lipids drives the paradoxical storage of fat reserves in the wake of increased energy expenditure.<sup>13</sup> Rather than being oxidized, fatty acids mobilized from fat are re-esterified into triglycerides. These are secreted from the liver and stored again in fat. Apart from short-term, 24-hour glycogen stored in the liver, the only other energy source in this situation is LBM, which is catabolized by the body. Depletion of LBM results in muscle weakness, organ failure, and death.

## NATURAL HISTORY OF AIDS WASTING

Allowed to take its course, the natural history of AIDS results in muscle wasting, weakness, immune compromise, organ failure and, ultimately, death. While weight loss and its attendant consequences are a major manifestation of AIDS, the degree of weight loss varies throughout the course of disease progression. Most individuals experience periods of relative weight stability. Such stability is interrupted by bouts of rapid weight loss as may be seen during secondary infection. Following effective therapy for these infections or complications, the individual gains weight again.<sup>7</sup> Body weight is then maintained until another episode occurs. During the early course of HIV infection, an individual's body weight may return to its original, baseline level. As the disease progresses, weight gain is less and less complete until recovery is impossible.

Recovery is much less evident when examining the loss of LBM over time. As with body weight, LBM is lost during episodes of infection or complications. During the recovery phase, weight is regained primarily in the form of body fat. LBM, however, is not recovered. Instead, it remains at the reduced level for a period of time until another episode occurs, as illustrated below. This relentless decline in LBM continues as the disease progresses, placing the individual at increased risk for developing an opportunistic infection.<sup>14</sup>

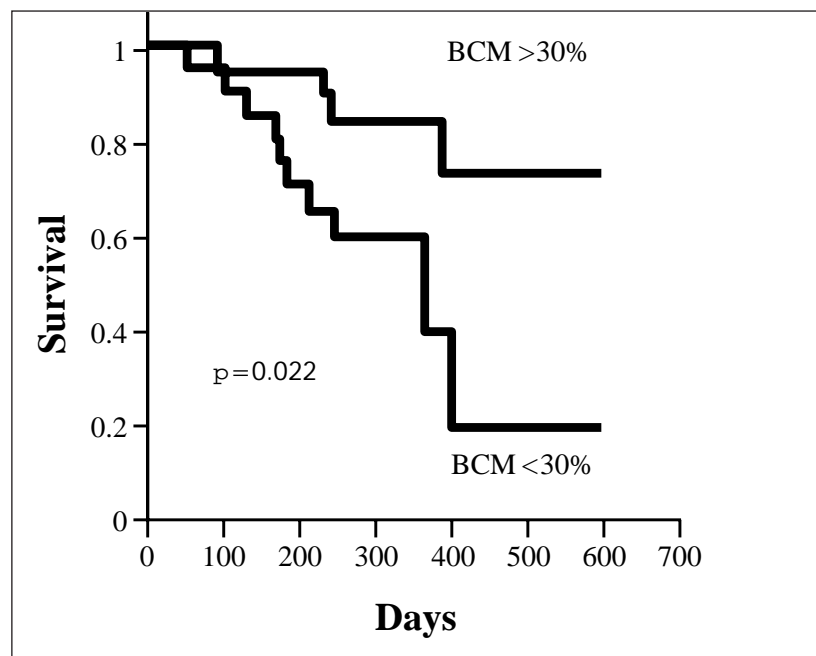
**Illustration of Progressive Loss of Lean Body Mass  
During AIDS Wasting**



## AIDS WASTING AND MORTALITY

Progressive wasting of body-cell mass occurs independently of changes in body fat. Body mass index (BMI) decreases significantly in individuals who deteriorate clinically or die.<sup>15</sup> The timing of death from AIDS wasting is related to the magnitude of body-cell mass depletion observed in these individuals.<sup>1</sup> Survival depends upon a certain, critical level of LBM. A body cell mass of <30%, which corresponds to a 10% to 15% loss of LBM, results in a mortality rate of 80% after 1 year (Figure 2).<sup>16</sup> Survival is significantly prolonged, independent of CD4+ lymphocyte counts, in individuals with a body-cell mass >30% of body weight. They have <30% mortality at the end of 2 years.

**Figure 2. Influence of Body-Cell Mass\* on Long-Term Survival (Kaplan-Meier life table)**



\*Body-cell mass (BCM) is proportionally reflective of LBM.  
(Adapted from Süttmann et al.<sup>16</sup>)

## Rationale for the Use of Growth Hormone in AIDS Wasting

Wasting is a primary manifestation of HIV infection that is an independent predictor of morbidity and mortality.<sup>1,5,7,17,20</sup> AIDS-associated wasting is a metabolic disorder characterized by abnormalities of intermediary metabolism resulting in weight loss, inappropriate depletion of lean body mass (LBM), and paradoxical preservation of body fat.<sup>12,21-26</sup> Endogenous growth hormone (GH) interacts with a broad range of cell types in a variety of tissues, including myocytes, hepatocytes, adipocytes, lymphocytes, and hematopoietic cells. The activities of GH were well characterized in the literature and were recognized as a logical candidate for study in the treatment of AIDS-associated wasting.

In vitro studies defined a range of anabolic and anticatabolic actions. GH increases the cellular uptake of amino acids, decreases amino acid catabolism and promotes their incorporation into functional and structural proteins. Conversely, GH increases lipid catabolism. Increased lipid mobilization, increased fatty acid oxidation, increased protein synthesis and growth have all been demonstrated in vivo. However, the long-term effects of Serostim<sup>®</sup> on these metabolic actions are not known.

The rationale for exploring use of GH for AIDS-associated wasting was further supported in the literature<sup>27-36</sup> by studies in catabolic states in humans, including injury, surgery, critical illness, and burns, which showed the protein-sparing effects of growth hormone. Thus, data from in vitro, in vivo and clinical studies all implied that GH could be the basis for an effective therapeutic intervention in AIDS-associated wasting.

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## Serostim<sup>®</sup>: A New Treatment for AIDS Wasting

Serostim<sup>®</sup> is the first therapy that addresses the underlying metabolic derangements found in AIDS wasting by both replenishing and maintaining lean body mass (LBM). It is a human growth hormone produced by mammalian-cell recombinant DNA technology. Serostim<sup>®</sup> has both anticatabolic and anabolic effects on the body's metabolism. It increases protein synthesis and lipid mobilization. In addition, Serostim<sup>®</sup> does not increase HIV replication or viral burden or alter the anti-HIV effects of commonly used antiretroviral agents, such as AZT. However, since recombinant human growth hormone (r-hGH) has been shown to potentiate HIV replication in vitro in some experimental systems, concomitant antiviral therapy is required for the duration of Serostim<sup>®</sup> treatment.

Safety analysis shows that Serostim<sup>®</sup> is well tolerated in individuals with HIV infection. The most common adverse events reported during clinical trials were musculoskeletal discomfort (pain, swelling, and/or stiffness) and increased tissue turgor (swelling, particularly in the hands and feet). Overall, these symptoms were rated as mild to moderate in severity. They usually subsided with continued treatment, analgesic therapy, or a reduction in the total daily dose or frequency of dosing.

## Clinical Pharmacology of Serostim<sup>®</sup>

Serostim<sup>®</sup> is the trade name for somatotropin, a human growth hormone produced by recombinant DNA technology. Serostim<sup>®</sup> is produced by a mammalian cell line (mouse C127) that has been modified by the addition of the human growth hormone gene. Serostim<sup>®</sup> is secreted directly through the cell membrane into the cell-culture medium for collection and purification. Serostim<sup>®</sup> has 191 amino acid residues and a molecular weight of 22,125 daltons.<sup>37</sup> Its amino acid sequence and structure are identical to the dominant form of human pituitary growth hormone.

### ***Metabolic Activity***

Serostim<sup>®</sup> has both anticatabolic and anabolic properties in individuals with HIV infection. Early clinical research examined this potential in a metabolic ward study of HIV+ men with an average weight loss of 19%. After 7 days of treatment with Serostim<sup>®</sup> (0.1 mg/kg/day), there was prompt and progressive increase in body weight. There was a decrease in protein oxidation, whereas lipid oxidation increased significantly.<sup>23</sup> As an anticatabolic agent, Serostim<sup>®</sup> increases lipolysis and fatty acid oxidation.<sup>38</sup>

Serostim<sup>®</sup> also exerts an anabolic effect by increasing protein synthesis. The transport and cellular uptake of amino acids are increased, as are their rates of efficient synthesis into protein. Serostim<sup>®</sup> also promotes a positive nitrogen balance and a decrease in urinary nitrogen. These promising results from in vitro studies and one seven-day study of 6 patients with HIV wasting provided the basis for further clinical trials to determine if 12-week therapy with Serostim<sup>®</sup> could address the metabolic derangement in these individuals.<sup>39</sup>

## Pharmacokinetics

### ***Subcutaneous Absorption***

The absolute bioavailability of Serostim<sup>®</sup> after subcutaneous administration was determined to be 70-90%. The  $t_{1/2}$  (Mean  $\pm$  SD) after subcutaneous administration is significantly longer than that seen after intravenous administration to normal male volunteers, down-regulated with somatostatin ( $3.94 \pm 3.44$  hrs vs  $0.58 \pm 0.08$  hrs), indicating that the subcutaneous absorption of the compound is slow and rate-limiting.

### ***Renal Insufficiency***

It has been reported that individuals with chronic renal failure tend to have decreased hGH clearance compared to normals, but there are no data on Serostim<sup>®</sup> use in the presence of renal insufficiency.

### ***Hepatic Insufficiency***

A reduction in r-hGH clearance has been noted in patients with severe liver dysfunction. However, the clinical significance of this in HIV+ patients is unknown.

## Clinical Efficacy of Serostim<sup>®</sup>

Based on encouraging results from the metabolic ward study, Serono Laboratories evaluated the safety and clinical efficacy of Serostim<sup>®</sup> in individuals with AIDS wasting. These clinical trials are summarized in Table 1.

**Table 1. Major Clinical Studies Assessing Serostim<sup>®</sup> Safety and Efficacy**

Clinical Trial Number	Phase and Status	Study Design	Dose Regimen of Serostim <sup>®</sup>	No. Treated/Evaluable	Age Range (years)	Outcome Measures
1	Phase III complete, open-label ongoing	1:1 randomization, double-blind, placebo-control, multicenter with open-label continuation	0.1 mg/kg/day (6 mg avg. daily dose SC for 12 weeks)	178/140	26-73	Weight LBM Physical function
2	Phase III complete, open-label ongoing	2:1 randomization, double-blind, placebo-control, multicenter with open-label continuation	6 mg/day SC for 12 weeks	177/129	24-69	Weight Subjective assessment of treatment
3	Phase III complete	Baseline controlled, open-label	6 mg/day SC for 12 weeks	24/20	15-65	Weight LBM

In these clinical trials, study participants were HIV+ and had an unintentional weight loss of at least 10% or weighed less than 90% of the lower limit of ideal body weight. Major assessments for safety and efficacy were carried out at baseline and at weeks 6 and 12 during treatment. The primary outcome parameters were changes in body weight and composition, functional capacity, and tolerability. Body composition was measured by dual-energy X-ray absorptiometry (DEXA)<sup>40</sup> in Clinical Trial #1 and bioimpedance analysis in Clinical Trial #3. Body water measurements were used to assess the physiological relevance of body weight change.<sup>41</sup>

## CLINICAL TRIAL 1<sup>42</sup>

A multicenter, double-blind, placebo-controlled study compared Serostim<sup>®</sup>, at an average daily dose of 0.1 mg/kg/day administered subcutaneously, to placebo in 178 patients with AIDS wasting. The study participants had unintentional weight loss of at least 10% or weighed less than 90% of the lower limit of ideal body weight. In the 140 evaluable patients (those completing a 12-week course of treatment and who were at least 80% compliant with study drug; Serostim<sup>®</sup> = 69, placebo = 71), the mean increase in weight in the Serostim<sup>®</sup>-treated group was 1.6 kg (3.5 lb). For those patients who had a week 2 assessment, 76% had weight gain. After 12 weeks of treatment, 74% of the patients treated with Serostim<sup>®</sup> gained weight ( $p=0.002$ ). Mean increase in LBM in the Serostim<sup>®</sup>-treated group was 3.1 kg (6.8 lb) as measured by DEXA. Significant LBM gain ( $p<0.05$ ) was achieved in 70% of the patients treated with Serostim<sup>®</sup> after 12 weeks (see Table 2). No change in LBM was observed in placebo-treated patients. Mean increase in weight and LBM and mean decrease in body fat (see Figure 3) were significantly greater in the Serostim<sup>®</sup>-treated group than in the placebo-treated group ( $p=0.011$ ,  $p<0.001$ ,  $p<0.001$ , respectively). While depletion of body weight and LBM has been associated with increased morbidity and mortality, the clinical significance of treatment-induced weight gain and LBM accrual have yet to be established.

Figure 3. Trial 1. Mean Changes in Body Composition<sup>42</sup>

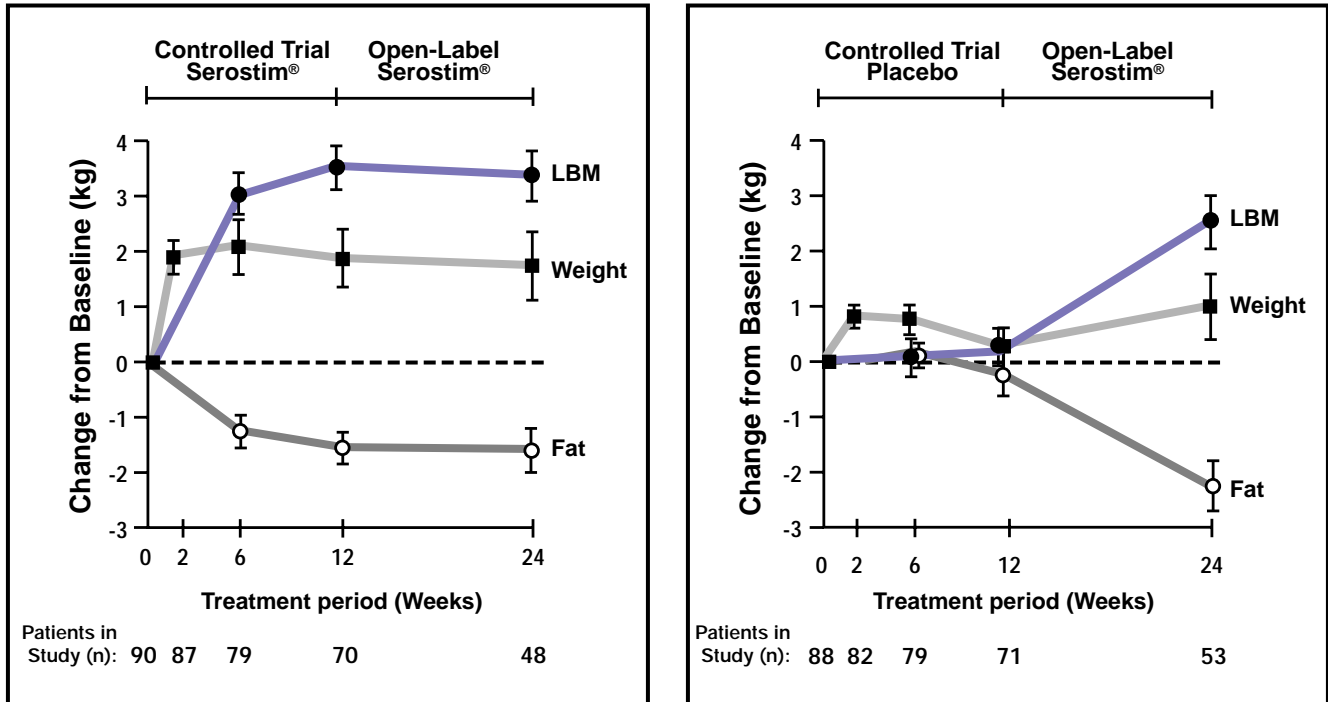


Table 2. Trial 1. Change from Baseline of LBM 12-Week Efficacy Results<sup>42</sup>

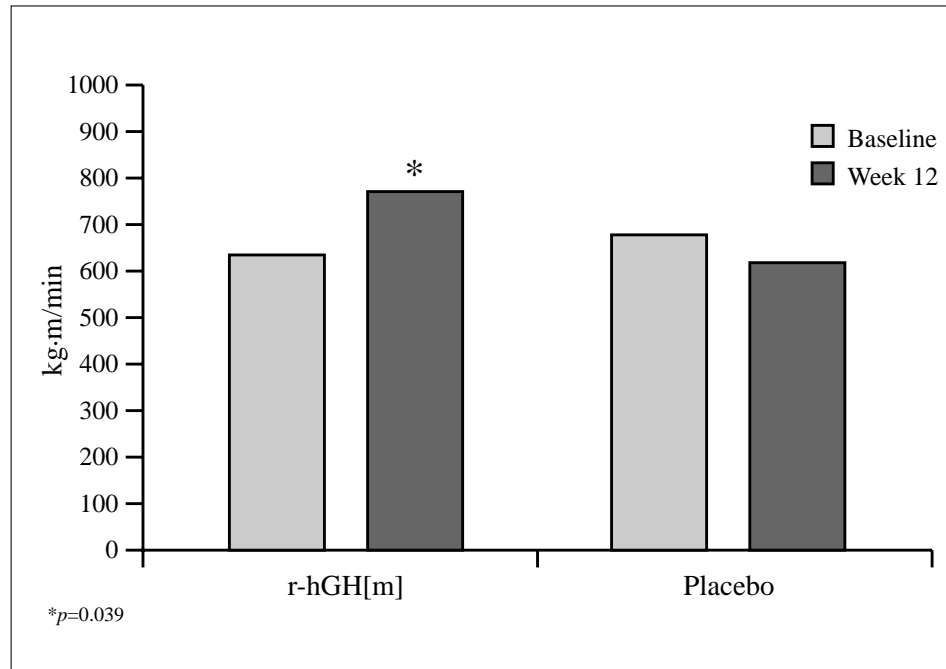
	Serostim <sup>®</sup>		Placebo	
	n	Results	n	Results
Lean Body Mass (kg)	69	+3.1*	69	-0.1
LBM Responders <sup>†</sup>	69	70%*	69	12%

\*Statistically significantly different from placebo at  $p < 0.05$

<sup>†</sup>Major LBM response defined as >4% increase of LBM

Treatment with Serostim<sup>®</sup> resulted in a significant increase of 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<sup>®</sup> (see Figure 4). There was no improvement in the placebo-treated group at 12 weeks. Changes in treadmill performance were significantly correlated with changes in LBM. 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 r-hGH therapy.

**Figure 4. Change in Physical Function as Measured by Median Treadmill Work Output<sup>42,43</sup>**



The most common reason for patient drop-out was concurrent medical events including opportunistic infections. There were decreases in serum albumin in both Serostim<sup>®</sup> and placebo groups. There was up to a 2.7-fold increase in serum IGF-1 levels. No patients developed antibodies to growth hormone.

Patients completing the 12-week placebo-controlled portion of the study were eligible to receive open-label Serostim<sup>®</sup> therapy, and 96% (n=136) chose to participate. Since this phase of the trial was open-label, and due to limited numbers of evaluable patients, it is difficult to interpret weight and LBM changes. The patients who initially received placebo had significant increases in median weight (1.4 kg,  $p=0.012$ ) and LBM (2.4 kg,  $p<0.001$ ) compared to baseline, during their first 12 weeks on Serostim<sup>®</sup>. These changes were similar in magnitude to those observed in patients initially treated with Serostim<sup>®</sup>. For those patients who had initially received Serostim<sup>®</sup> in the placebo-controlled trials, the median weight change during 12 weeks of open-label treatment with Serostim<sup>®</sup> (-0.2 kg), and the LBM change (-0.3 kg), were not significant ( $p=0.700$  and  $p=0.661$ , respectively), suggesting that the gains of weight and LBM were not lost.

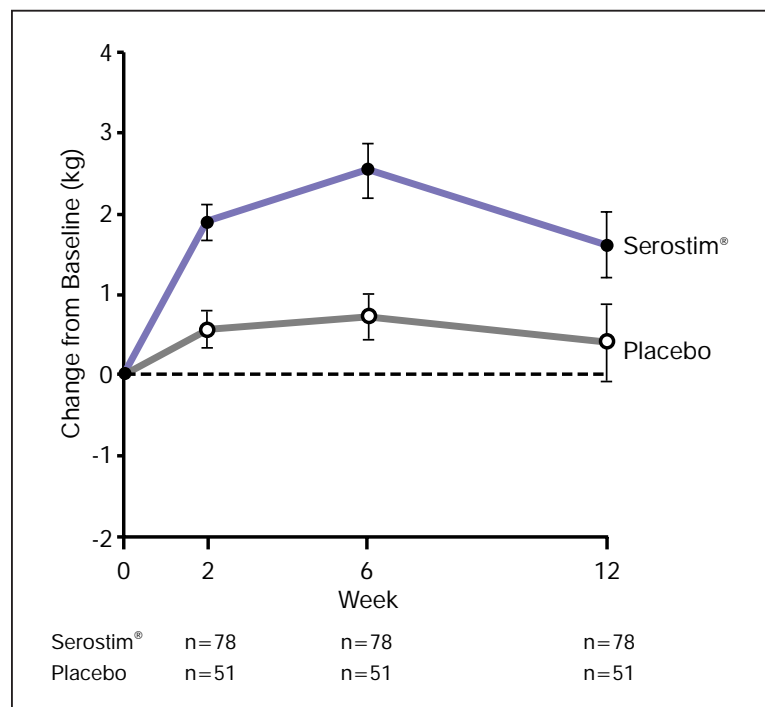
The types and incidences of adverse events reported in an open-label extension trial and in a single foreign trial, for up to one year, were not different from, or greater in frequency than, those observed in the primary placebo-controlled clinical trials.

*Survival Analyses:* The two placebo-controlled clinical trials of Serostim<sup>®</sup> in patients with AIDS wasting up to 12 weeks in length found no difference in survival between groups.

## CLINICAL TRIAL 2<sup>42</sup>

Additional efficacy and safety parameters were evaluated in a second multicenter, double-blind, placebo-controlled study comparing Serostim<sup>®</sup>, 6 mg/day administered subcutaneously, vs placebo, in AIDS patients with wasting. There were 177 patients enrolled and they were randomized in a 2:1 ratio to receive Serostim<sup>®</sup> or placebo. In the 78 evaluable Serostim<sup>®</sup> patients (those completing a 12-week course of treatment and who were at least 80% compliant with study drug), there was a mean increase in body weight in the Serostim<sup>®</sup>-treated group of 1.6 kg, but this change was not significant compared to placebo ( $p=0.110$ ) (see Figure 5). The most common reason for patient drop-out was concurrent medical events including opportunistic infections.

**Figure 5. Trial 2. Mean Changes in Body Weight<sup>42</sup>**



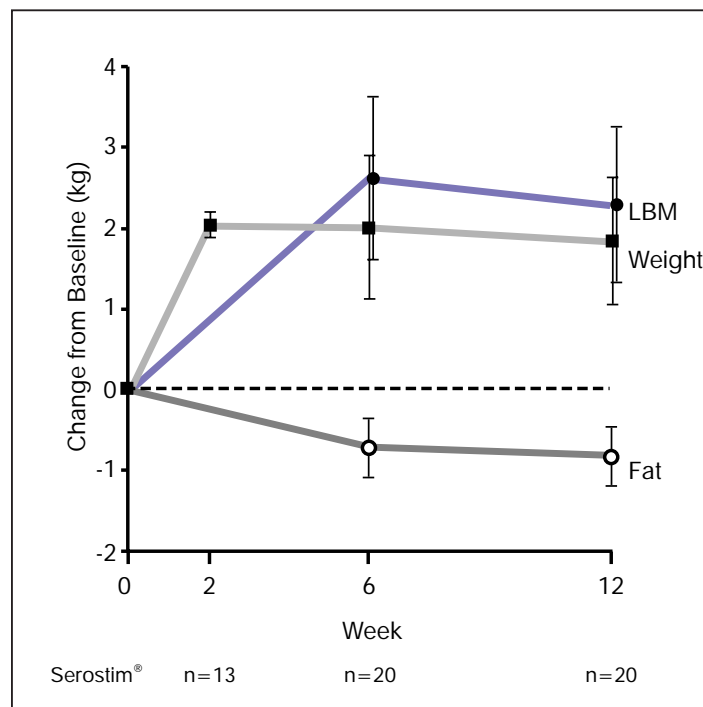
Patients were asked to respond to a nine-item survey that measured subjective assessments of treatment. Positive findings at 6 and 12 weeks were observed in two of the nine items (change in appearance and overall benefit of treatment). Results of other measures were inconclusive.

*Survival Analyses:* The two placebo-controlled clinical trials of Serostim<sup>®</sup> in patients with AIDS wasting up to 12 weeks in length found no difference in survival between groups.

## CLINICAL TRIAL 3<sup>42</sup>

A third open-label, baseline-controlled, multicenter study conducted in Europe administering Serostim<sup>®</sup>, 6 mg/day subcutaneously, enrolled 24 patients with AIDS wasting. Twenty patients completed the 12-week treatment regimen and had body composition measurements using bioimpedance analysis. The mean increase over baseline for body weight was 1.6 kg ( $p=0.137$ , NS) and for lean body mass was 2.3 kg ( $p=0.037$ ) (see Figure 6).

**Figure 6. Trial 3. Mean Changes in Body Composition<sup>42</sup>**



The types and incidences of adverse events reported in an open-label extension trial and in a single foreign trial, for up to one year, were not different from, or greater in frequency, than those observed in the primary placebo-controlled clinical trials.

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## EFFICACY CONCLUSIONS

Serostim<sup>®</sup> has demonstrated a significant effect in overcoming the loss of LBM in individuals with AIDS wasting. Treatment with Serostim<sup>®</sup> in controlled clinical studies was found to do the following:

- Significantly increase LBM and body weight
- Significantly increase physical function as measured by treadmill work output
- Improve change in appearance and overall benefit of treatment
  - Results of other measures were inconclusive

Individuals completing 12 weeks of Serostim<sup>®</sup> therapy, who then received an additional 3 months of open-label therapy, were able to maintain their earlier gains of LBM and weight. However, due to limited numbers of evaluable patients, it is difficult to interpret weight and LBM changes. The clinical significance of treatment-induced weight gain and LBM accrual has yet to be established.

Treatment with Serostim<sup>®</sup> was also well tolerated in these individuals. Dropouts were infrequent. When they did occur, the most common reason was concurrent medical events, including opportunistic infections. Serostim<sup>®</sup> has a favorable safety profile when used at suggested doses. A discussion of adverse events follows.

## Clinical Safety of Serostim<sup>®</sup>

### ADVERSE REACTIONS

In two placebo-controlled clinical trials in which 205 patients were treated with Serostim<sup>®</sup>, the most common adverse reactions judged to be associated with Serostim<sup>®</sup> were musculoskeletal discomfort and increased tissue turgor (swelling, particularly of the hands or feet). These symptoms were generally rated by investigators as mild to moderate in severity and usually subsided with continued treatment. Discontinuations as a result of these events were rare.

Because of the diverse clinical manifestations of AIDS, and the frequent occurrence of adverse events associated with underlying disease process, it was often difficult to distinguish adverse events possibly associated with the administration of Serostim<sup>®</sup> from underlying signs or symptoms of AIDS or associated intercurrent illnesses.

Clinical adverse events which occurred during the first 12 weeks of study in at least 10% of those who received Serostim<sup>®</sup> during the two placebo-controlled trials are listed below (Table 3) by treatment group, without regard to causality assessment.

**Table 3. Most Common Adverse Events Reported During Placebo-Controlled Trials<sup>42</sup>**

<b>Adverse Event</b>	<b>Serostim<sup>®</sup> Group (%) n=205</b>	<b>Placebo Group (%) n=150</b>
Musculoskeletal discomfort	53.7	33.3
Fever	31.2	29.3
Increased tissue turgor	27.3	2.7
Diarrhea	25.9	20.0
Neuropathy	25.9	17.3
Nausea	25.9	16.0
Headache	19.0	20.7
Abdominal pain	17.1	18.7
Fatigue	17.1	16.0
Leukopenia	15.1	24.7
Albuminuria	15.1	9.3
Granulocytopenia	14.1	21.3
Lymphadenopathy	14.1	16.0
Increased sweating	14.1	8.7
Anorexia	12.2	9.3
Anemia	12.2	8.7
Vomiting	11.7	12.0
SGOT increased	11.7	6.0
Insomnia	11.2	9.3
Tachycardia	11.2	6.0
Hyperglycemia	10.2	6.0
SGPT increased	10.2	5.3

## PRECAUTIONS, CONTRAINDICATIONS AND WARNINGS

Serostim<sup>®</sup> therapy should be carried out under the regular guidance of a physician who is experienced in the diagnosis and management of AIDS. Inadequate nutritional intake, malabsorption and hypogonadism, which are common in individuals with AIDS and which may contribute to catabolism and weight loss, should also be monitored and treated.

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

Increased tissue turgor (swelling, particularly in the hands and feet) and musculoskeletal discomfort (pain, swelling and/or stiffness) may occur during treatment with Serostim<sup>®</sup>, but may resolve spontaneously, with analgesic therapy, or after reducing the frequency of dosing.

Carpal tunnel syndrome may occur during treatment with Serostim<sup>®</sup>. If the symptoms of carpal tunnel syndrome do not resolve by decreasing the weekly number of doses of Serostim<sup>®</sup>, it is recommended that treatment be discontinued.

Patients should be informed that allergic reactions are possible and that prompt medical attention should be sought if an allergic reaction occurs. None of the 188 study participants with AIDS wasting who were evaluable for antibody assessments and who were treated with Serostim<sup>®</sup> for the first time developed detectable antibodies to growth hormone (> 4 pg binding). Patients were not rechallenged.

Recombinant human growth hormone has been associated with acute pancreatitis.

Hyperglycemia may occur in HIV-infected individuals due to a variety of reasons. Serostim<sup>®</sup> use was associated with a minimal increase of mean blood glucose concentration. Patients with other risk factors for glucose intolerance should be monitored closely during Serostim<sup>®</sup> therapy.

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

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

*Information For Patients:* Patients being treated with Serostim<sup>®</sup> 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<sup>®</sup>.

It is recommended that Serostim<sup>®</sup> 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 lipodystrophy.

*Drug Interactions:* Formal in vitro drug interaction studies have not been conducted. No data are available on drug interactions between Serostim<sup>®</sup> and HIV protease inhibitors or the non-nucleoside reverse transcriptase inhibitors.

*Carcinogenesis, Mutagenesis, Impairment of Fertility:* Long-term animal studies for carcinogenicity have not been performed with Serostim<sup>®</sup>. There is no evidence from animal studies to date of Serostim<sup>®</sup>-induced mutagenicity or impairment of fertility.

*Pregnancy:* Pregnancy Category B. Reproduction studies have been performed in rats and rabbits. Doses up to 5 to 10 times the human dose, based on body surface area, have revealed no evidence of impaired fertility or harm to the fetus due to Serostim<sup>®</sup>. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

*Nursing Women:* It is not known whether Serostim<sup>®</sup> is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Serostim<sup>®</sup> is administered to a nursing woman.

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

Growth hormone should not be initiated to treat patients with acute critical illness due to complications following open heart or abdominal surgery, multiple accidental trauma or to patients having acute respiratory failure. Two placebo-controlled clinical trials in non-growth hormone deficient adult patients (n=522) with these conditions revealed a significant increase in mortality (41.9% vs 19.3%) among E.coli-derived somatropin treated patients (doses 5.3-8 mg/day) compared to those receiving placebo. The safety of continuing growth hormone treatment in patients receiving replacement doses for approved indications who concurrently develop these illnesses has not been established. Therefore, the potential benefit of treatment continuation with growth hormone in patients having acute critical illness should be weighed against the potential risk.

## SAFETY CONCLUSIONS

Serostim<sup>®</sup>, when taken as prescribed, is generally well tolerated. The most common adverse reactions to Serostim<sup>®</sup> are increased tissue turgor and musculoskeletal discomfort. Generally mild to moderate in their severity, these symptoms usually resolve spontaneously with continued treatment or are effectively managed with analgesic therapy. When unresponsive to symptomatic therapy, these side effects may also be managed by reducing the total daily dose of Serostim<sup>®</sup> or the number of doses given per week.

Serostim<sup>®</sup> should be given with concomitant antiviral therapy. There is no evidence of HIV replication with Serostim<sup>®</sup> therapy in the presence of any of the currently available nucleoside analogues in vitro. In the controlled clinical trials, no significant growth hormone-associated increase in viral burden was observed. However, GH has been shown to potentiate HIV replication in some experimental systems.

## Dosage and Administration

Serostim<sup>®</sup> should be administered subcutaneously daily at bedtime according to the following dosage recommendations:

<b>Weight Range</b>	<b>Dose*</b>
>55 kg	6 mg SC daily
45-55 kg	5 mg SC daily
35-45 kg	4 mg SC daily

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

In patients who weigh less than 35 kg, Serostim<sup>®</sup> should be administered at a dose of 0.1 mg/kg subcutaneously daily at bedtime.

Dose reductions for side effects felt to be related to treatment with Serostim<sup>®</sup>, which are unresponsive to symptomatic treatment, may be effected by reducing the total daily dose or the number of doses given per week.

In patients who continue to lose weight at week 2, reevaluate for concurrent opportunistic infections or other clinical events.

Injection sites should be rotated.

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

Each vial of Serostim<sup>®</sup> 4 mg, 5 mg or 6 mg is reconstituted with 1 mL sterile water for injection.

To reconstitute Serostim<sup>®</sup>, inject the diluent into the vial of Serostim<sup>®</sup>, aiming the liquid against the glass vial wall. Swirl the vial with a gentle rotary motion until contents are dissolved completely. The Serostim<sup>®</sup> solution should be clear immediately after reconstitution. **DO NOT INJECT** Serostim<sup>®</sup> if the reconstituted product is cloudy immediately after reconstitution or refrigeration. Occasionally, after refrigeration, small colorless particles may be present in the Serostim<sup>®</sup> solution. This is not unusual for proteins like Serostim<sup>®</sup>.

## Stability and Storage

*Before reconstitution:* Serostim<sup>®</sup> should be stored at room temperature, 59° to 86°F (15° to 30°C). Expiration dates are stated on product labels.

*After reconstitution:* Use within 24 hours after reconstitution with diluent. The reconstituted solution should be stored under refrigerated conditions (36° to 46°F / 2° to 8°C).

Sterile Diluent, 1 mL (Sterile Water for Injection, USP) should be stored at room temperature, 59° to 86°F (15° to 30°C). Avoid freezing vials of Serostim<sup>®</sup> and Sterile Diluent.

## How Supplied

Serostim<sup>®</sup> is available in the following forms:

Serostim<sup>®</sup> vials containing 6 mg (approximately 18 IU)  
somatotropin (mammalian-cell) with Sterile Water for Injection, USP.

Package of 7 vials.                      NDC 44087-0006-7

Serostim<sup>®</sup> vials containing 5 mg (approximately 15 IU)  
somatotropin (mammalian-cell) with Sterile Water for Injection, USP.

Package of 7 vials.                      NDC 44087-0005-7

Serostim<sup>®</sup> vials containing 4 mg (approximately 12 IU)  
somatotropin (mammalian-cell) with Sterile Water for Injection, USP.

Package of 7 vials.                      NDC 44087-0004-7

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## DESCRIPTION

Serostim® [somatotropin (rDNA origin) for injection] is a human growth hormone 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 human growth hormone gene. Serostim® is secreted directly through the cell membrane into the cell-culture medium for collection and purification.

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

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

## CLINICAL PHARMACOLOGY

Serostim® [somatotropin (rDNA origin) for injection] is an anabolic and anticatabolic agent which exerts its influence by interacting with specific receptors on a variety of cell types including myocytes, hepatocytes, adipocytes, lymphocytes, and hematopoietic cells. Some, but not all, of its effects are mediated by another class of hormones known as somatomedins (IGF-1 and IGF-2).

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

### Effects on Protein, Lipid, and Carbohydrate Metabolism:

A one-week study in 6 patients with HIV-associated wasting has shown that treatment with Serostim® improves nitrogen balance, increases protein-sparing lipid oxidation, and has little effect on overall carbohydrate metabolism.

### Lean Body Mass Accrual:

In the same study, treatment with Serostim® resulted in the retention of phosphorus, potassium, nitrogen, and sodium. The ratio of retained potassium and nitrogen during Serostim® therapy was consistent with retention of these elements in lean tissue. In clinical studies (12 weeks), Serostim® significantly increased lean body mass. There was also a proportionate increase in intracellular and extracellular fluid during Serostim® therapy suggesting accretion of normally hydrated lean body tissue.

### Physical Performance:

Treadmill performance was examined in a 12-week placebo-controlled study. Work output improved significantly in the Serostim®-treated group after 12 weeks of therapy and was correlated with LBM. No such correlation was seen with body fat. 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 r-hGH therapy.

## PHARMACOKINETICS:

**Subcutaneous Absorption:** The absolute bioavailability of Serostim® [somatotropin (rDNA origin) for injection] after subcutaneous administration of a formulation not equivalent to the marketed formulation was determined to be 70-90%. The  $t_{1/2}$  (Mean  $\pm$  SD) after subcutaneous administration is significantly longer than that seen after intravenous administration to normal male volunteers, down-regulated with somatostatin ( $3.94 \pm 3.44$  hrs. vs.  $0.58 \pm 0.08$  hrs.), indicating that the subcutaneous absorption of the clinically tested formulation of the compound is slow and rate-limiting.

**Distribution:** The steady-state volume of distribution (Mean  $\pm$  SD) following IV administration of Serostim® in healthy volunteers is  $12.0 \pm 1.08$  L.

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

**Elimination:** The  $t_{1/2}$  (Mean  $\pm$  SD) in nine patients with AIDS related wasting with an average weight of  $56.7 \pm 6.8$  kg, given a fixed dose of 6.0 mg r-hGH subcutaneously was  $4.28 \pm 2.15$  hrs. The renal clearance of r-hGH after subcutaneous administration in nine patients with AIDS-related wasting was  $0.0015 \pm 0.0037$  L/h. No significant accumulation of r-hGH appears to occur after 6 weeks of dosing as indicated.

### Special Populations:

**Pediatric:** Available evidence suggests that r-hGH clearances are similar in adults and children, but no clinical studies were conducted in children with acquired immune deficiency syndrome or AIDS-related complex.

**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 on Serostim® in normal volunteers or patients infected with HIV.

**Race:** No data are available.

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

**Hepatic insufficiency:** A reduction in r-hGH clearance has been noted in patients with severe liver dysfunction. However, the clinical significance of this in HIV+ patients is unknown.

## CLINICAL STUDIES

The clinical efficacy of Serostim® [somatotropin (rDNA origin) for injection] was assessed in two placebo-controlled clinical trials. Of the 205 AIDS subjects exposed to GH, only 5 were women. All study subjects received concomitant anti-HIV therapy.

**Clinical Trial 1:** A multicenter, double-blind, placebo-controlled study compared Serostim® at an average daily dose of 0.1 mg/kg/day administered subcutaneously to placebo in 178 patients with AIDS wasting. The study participants had unintentional weight loss of at least 10% or weighed less than 90% of the lower limit of ideal body weight. In the 140 evaluable patients (those completing a 12-week course of treatment and who were at least 80% compliant with study drug; Serostim® = 69, Placebo = 71), the mean difference in weight increase in the Serostim®-treated group was 1.6 kg (3.5 lb.). For those patients that had a week two assessment, 76% had weight gain. After 12 weeks of treatment, 74% of the patients treated with Serostim® gained weight while only 48% of the placebo-treated patients gained weight ( $p=0.002$ ). Mean differences in lean body mass change between the Serostim®-treated group and the placebo-treated group was 3.1 kg (6.8 lbs) as measured by DEXA. Significant lean body mass gain ( $p<0.05$ ) was achieved in 70% of the patients treated with Serostim® after 12 weeks (see Table 1). No change in LBM was observed in placebo-treated patients. Mean increase in weight and lean body mass and mean decrease in body fat (see Figure 1) were significantly greater in the Serostim®-treated group than in the placebo group ( $p<0.01$ ,  $p<0.001$ ,  $p<0.001$ , respectively). While depletion of body weight and lean body mass has been associated with increased morbidity and mortality, the clinical significance of treatment-induced weight gain and LBM accrual has yet to be established.

Treatment with Serostim® resulted in a significant increase of 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® (see Figure 2). There was no improvement in the placebo-treated group at 12 weeks. Changes in treadmill performance were significantly correlated with changes of lean body mass.

The most common reason for patient drop-out was concurrent medical events including opportunistic infections. There were decreases in serum albumin in both Serostim® and placebo groups. There was up to a 2.7 fold increase in serum IGF-1 levels. No patients developed antibodies to growth hormone.

Patients completing the 12-week placebo-controlled portion of the study were eligible to receive open-label Serostim® therapy, and 96% ( $n=136$ ) chose to participate. Since this phase of the trial was open-label, and due to limited numbers of evaluable patients, it is difficult to interpret weight and LBM changes. The patients who initially received placebo had significant increases in median weight (1.4 kg,  $p=0.012$ ) and lean body mass (2.4 kg,  $p<0.001$ ) compared to baseline, during their first 12-weeks on Serostim®. These changes were similar in magnitude to those observed in patients initially treated with Serostim®. For those patients who had initially received Serostim® in the

placebo-controlled trials, the median weight change during 12-weeks of open label treatment with Serostim® (-0.2 kg) and LBM change (-0.3 kg) were not significant ( $p=0.700$  and  $p=0.661$ , respectively), suggesting that the gains of weight and LBM were not lost.

Figure 1: Trial 1: Mean Changes in Body Composition

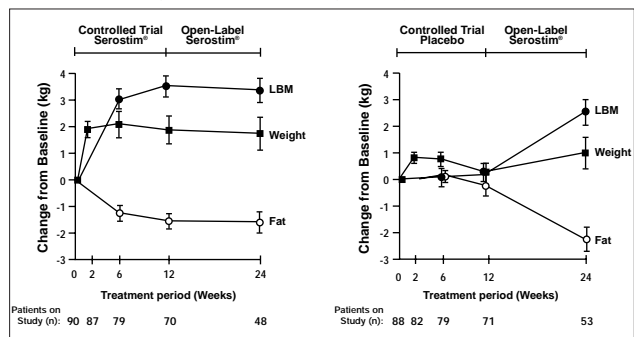


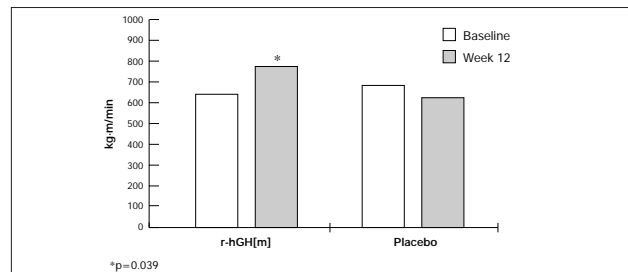
Table 1: Trial 1: Change from Baseline of LBM 12-Week Efficacy Results

	Serostim®		Placebo	
	n	Results	n	Results
Lean Body Mass (kg)	69	+3.1*	69	-0.1
LBM Responders <sup>‡</sup>	69	70%*	69	12%

<sup>‡</sup> Major LBM response defined as > 4% increase of LBM

\* Statistically significantly different from placebo at  $p<0.05$

Figure 2: Median Treadmill Work Output



**Clinical Trial 2:** Additional efficacy and safety parameters were evaluated in a second multicenter, double-blind, placebo-controlled study comparing Serostim®, 6 mg/day administered subcutaneously vs. placebo, in AIDS patients with wasting enrolled 1:1 ratio, to receive Serostim® or placebo. In the 78 evaluable patients (those completing a 12-week course of treatment and who were at least 80% compliant with study drug), there was a mean increase in body weight of 1.6 kg, but this change was not significant compared to placebo ( $p=0.110$ ). The most common reason for patient drop-out was concurrent medical events including opportunistic infections.

Patients were asked to respond to a nine item survey that measured subjective assessments of treatment. Positive findings at 6 and 12 weeks were observed in two of the nine items (change in appearance and overall benefit of treatment). Results of other measures were inconclusive.

**Survival Analyses:** The two placebo-controlled clinical trials of Serostim® in patients with AIDS wasting up to 12 weeks in length found no difference in survival between groups.

**Clinical Trial 3:** A third open-label, baseline-controlled, multicenter study conducted in Europe administering Serostim®, 6 mg/day subcutaneously, enrolled 24 patients with AIDS wasting. Twenty patients completed the 12-week treatment regimen and had body composition measurements using bioimpedance analysis. The mean increase over baseline for body weight was 1.6 kg ( $p=0.137$ , NS) and for lean body mass was 2.3 kg ( $p=0.037$ ).

## INDICATIONS AND USAGE

Serostim® [somatotropin (rDNA origin) for injection] is indicated for the treatment of AIDS wasting or cachexia. This indication is based on analyses of surrogate endpoints in studies of up to 12 weeks in duration. Concomitant antiviral therapy is necessary (see PRECAUTIONS: General). The continued use of Serostim® treatment should be reevaluated in patients who continue to lose weight in the first two weeks of treatment.

## CONTRAINDICATIONS

Growth hormone should not be initiated to treat patients with acute critical illness due to complications following open heart or abdominal surgery, multiple accidental trauma or to patients having acute respiratory failure. Two placebo-controlled clinical trials in non-growth hormone deficient adult patients ( $n=522$ ) with these conditions revealed a significant increase in mortality (41.9% vs 19.3%) among somatotropin treated patients (doses 5.3-8 mg/day) compared to those receiving placebo (see WARNINGS).

Serostim® [somatotropin (rDNA origin) for injection] is contraindicated in patients with a known hypersensitivity to growth hormone.

## WARNINGS

See CONTRAINDICATIONS for information on increased mortality in patients with acute critical illnesses in intensive care units due to complications following open heart or abdominal surgery, multiple accidental trauma or acute respiratory failure. The safety of continuing growth hormone treatment in patients receiving replacement doses for approved indications who concurrently develop these illnesses has not been established. Therefore, the potential benefit of treatment continuation with growth hormone in patients having acute critical illnesses should be weighed against the potential risk.

## PRECAUTIONS

**General:** Serostim® [somatotropin (rDNA origin) for injection] therapy should be carried out under the regular guidance of a physician who is experienced in the diagnosis and management of AIDS. Inadequate nutritional intake, malabsorption and hypogonadism, which are common in individuals with AIDS and which may contribute to catabolism and weight loss, should also be monitored and treated.

**HIV and Growth Hormone Considerations:** In some experimental systems, recombinant human Growth Hormone (r-hGH) has been shown to potentiate HIV replication in vitro at concentrations ranging from 50-250 ng/ml. There was no increase in virus production when the antiretroviral agents, zidovudine, didanosine or lamivudine were added to the culture medium. Additional in vitro studies have shown that r-hGH does not interfere with the antiviral activity of zalcitabine or stavudine. In the controlled clinical trials, no significant growth hormone-associated increase in viral burden was observed. However, the protocol required all participants to be on concomitant nucleoside analogue 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 nucleoside analogue therapy for the duration of Serostim® treatment. Increased tissue turgor (swelling, particularly in the hands and feet) and musculoskeletal discomfort (pain, swelling and/or stiffness) may occur during treatment with Serostim®, but may resolve spontaneously, with

analgesic therapy, or after reducing the frequency of dosing (see dosage and administration).

Carpal tunnel syndrome may occur during treatment with Serostim<sup>®</sup>. If the symptoms of carpal tunnel syndrome do not resolve by decreasing the weekly number of doses of Serostim<sup>®</sup>, it is recommended that treatment be discontinued.

Patients should be informed that allergic reactions are possible and that prompt medical attention should be sought if an allergic reaction occurs. None of the 188 study participants with AIDS wasting who were evaluable for antibody assessments and who were treated with Serostim<sup>®</sup> for the first time developed detectable antibodies to growth hormone (> 4 pg binding). Patients were not rechallenged.

Recombinant Human Growth Hormone (r-hGH) has been associated with acute pancreatitis.

Hyperglycemia may occur in HIV-infected individuals due to a variety of reasons. Serostim<sup>®</sup> use was associated with a minimal increase of mean blood glucose concentration. Patients with other risk factors for glucose intolerance should be monitored closely during Serostim<sup>®</sup> therapy.

No cases of intracranial hypertension (IH) have been observed among patients with AIDS wasting treated with Serostim<sup>®</sup>. The syndrome of IH, with papilledema, visual changes, headache, and nausea and/or vomiting has never been reported in a small number of children with growth failure treated with growth hormone products. Nevertheless, fundoscopic evaluation of patients is recommended at the initiation and periodically during the course of Serostim<sup>®</sup> therapy.

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

**Information For Patients:** Patients being treated with Serostim<sup>®</sup> 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<sup>®</sup>.

It is recommended that Serostim<sup>®</sup> 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 lipodystrophy.

**Drug Interactions:** Formal in vitro drug interaction studies have not been conducted. No data are available on drug interactions between Serostim<sup>®</sup> and HIV protease inhibitors or the non-nucleoside reverse transcriptase inhibitors.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** Long-term animal studies for carcinogenicity have not been performed with Serostim<sup>®</sup>. There is no evidence from animal studies to date of Serostim<sup>®</sup>-induced mutagenicity or impairment of fertility.

**Pregnancy:** Pregnancy Category B. Reproduction studies have been performed in rats and rabbits. Doses up to 5 to 10 times the human dose, based on body surface area, have revealed no evidence of impaired fertility or harm to the fetus due to Serostim<sup>®</sup>. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

**Nursing Women:** It is not known whether Serostim<sup>®</sup> is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Serostim<sup>®</sup> is administered to a nursing woman.

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

#### ADVERSE REACTIONS

In two placebo-controlled clinical trials in which 205 patients were treated with Serostim<sup>®</sup> [somatotropin (rDNA origin) for injection] the most common adverse reactions judged to be associated with Serostim<sup>®</sup> were musculoskeletal discomfort and increased tissue turgor (swelling, particularly of the hands or feet) (see PRECAUTIONS: General). These symptoms were generally rated by investigators as mild to moderate in severity and usually subsided with continued treatment. Discontinuations as a result of these events were rare.

Because of the diverse clinical manifestations of AIDS, and the frequent occurrence of adverse events associated with underlying disease process, it was often difficult to distinguish adverse events possibly associated with the administration of Serostim<sup>®</sup> from underlying signs or symptoms of AIDS or associated intercurrent illnesses.

Clinical adverse events which occurred during the first 12 weeks of study in at least 10% of those who received Serostim<sup>®</sup> during the two placebo-controlled trials are listed below by treatment group, without regard to causality assessment.

**Table 2: Controlled Trials Adverse Events**

Adverse Event	Serostim <sup>®</sup> (n=205)	Placebo (n=150)
	%	%
Musculoskeletal discomfort	53.7	33.3
Fever	31.2	29.3
Increased tissue turgor	27.3	2.7
Diarrhea	25.9	20.0
Neuropathy	25.9	17.3
Nausea	25.9	16.0
Headache	19.0	20.7
Abdominal pain	17.1	18.7
Fatigue	17.1	16.0
Leukopenia	15.1	24.7
Albuminuria	15.1	9.3
Granulocytopenia	14.1	21.3
Lymphadenopathy	14.1	16.0
Increased sweating	14.1	8.7
Anorexia	12.2	9.3
Anemia	12.2	8.7
Vomiting	11.7	12.0
SGOT increased	11.7	6.0
Insomnia	11.2	9.3
Tachycardia	11.2	6.0
Hyperglycemia	10.2	6.0
SGPT increased	10.2	5.3

Adverse events that occurred in 1% to less than 10% of study participants receiving Serostim<sup>®</sup> in the two placebo-controlled clinical efficacy studies are listed below by body system. The list of adverse events has been compiled regardless of causal relationship to Serostim<sup>®</sup>.

**Body as a Whole:** rigors, flu-like symptoms, back pain, malaise, asthenia, carpal tunnel syndrome (see PRECAUTIONS: General), chest pain, hot flashes, allergic reaction.

**Gastrointestinal System:** oral leukoplakia, flatulence, dyspepsia, dry mouth, constipation, ulcerative stomatitis, increased amylase, dysphagia, esophagitis, colitis, pancreatitis, rectal disorder, gastritis, tongue ulceration, gingivitis

**Musculoskeletal System:** muscle weakness

**Central and Peripheral Nervous System:** dizziness, convulsions, hypertonia, neuralgia, tremor, encephalopathy, nystagmus, meningism

**Respiratory System:** dyspnea, coughing, sinusitis, upper respiratory tract infection, pharyngitis, rhinitis, pneumonia, bronchitis, increased sputum, respiratory disorder, bronchospasm, pneumonitis, pleurisy

**White Blood Cell and Reticuloendothelial System Disorders:** cervical lymphadenopathy, eosinophilia

**Skin and appendages:** skin disorder, folliculitis, rash, alopecia, photosensitivity reaction, erythematous rash, pruritus, abnormal pigmentation, seborrhea, dermatitis, skin ulceration, acne, skin discoloration, verruca

**Psychiatric:** depression, anxiety, somnolence, nervousness, appetite increased, amnesia, abnormal thinking

**Metabolic and Nutritional:** hypertriglyceridemia, increased alkaline phosphatase, dehydration, increased creatinine phosphokinase, increased LDH, glycosuria, hypokalemia, cachexia, thirst, acidosis

**Immune System Dysfunction:** moniliasis, bacterial infection, Pneumocystis carinii infection, viral infection, infection, Herpes simplex, sepsis, abscess, fungal infection, Herpes zoster

**Urinary System:** hematuria, urinary tract infection, nocturia

**Liver and Biliary System:** abnormal hepatic function, hepatomegaly, hepatitis

**Vision:** retinitis, abnormal vision, photophobia

**Platelet, Bleeding and Clotting:** thrombocytopenia, purpura

**Cardiovascular, General:** abnormal ECG, heart murmur, hypertension, hypotension

**Application Site:** injection site pain, injection site reaction

**Neoplasms:** Kaposi's sarcoma

**Male Reproductive:** Epididymitis, penis disorder, inguinal hernia

**Hearing and Vestibular:** earache, ear disorder, decreasing hearing

**Endocrine:** gynecomastia, male breast pain

The types and incidences of adverse events reported in an open-label, extension trial and in a single, foreign trial, for up to one year, were not different from, or greater in frequency, than those observed in the primary, placebo-controlled, clinical trials.

#### OVERDOSAGE

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

#### DOSE AND ADMINISTRATION

Serostim<sup>®</sup> [somatotropin (rDNA origin) for injection] should be administered subcutaneously daily at bedtime according to the following dosage recommendations:

Weight Range	Dose*
>55 kg	6 mg SC daily
45-55 kg	5 mg SC daily
35-45 kg	4 mg SC daily

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

In patients who weigh less than 35 kg, Serostim<sup>®</sup> should be administered at a dose of 0.1 mg/kg subcutaneously daily at bedtime.

Dose reductions for side effects felt to be related to treatment with Serostim<sup>®</sup>, which are unresponsive to symptomatic treatment, may be effected by reducing the total daily dose or the number of doses given per week.

In patients who continue to lose weight at week 2, reevaluate for concurrent opportunistic infections or other clinical events.

Injection sites should be rotated.

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

Each vial of Serostim<sup>®</sup> 4 mg, 5 mg or 6 mg is reconstituted with 1 mL sterile water for injection. To reconstitute Serostim<sup>®</sup>, inject the diluent into the vial of Serostim<sup>®</sup> aiming the liquid against the glass vial wall. Swirl the vial with a gentle rotary motion until contents are dissolved completely. The Serostim<sup>®</sup> solution should be clear immediately after reconstitution. **DO NOT INJECT** Serostim<sup>®</sup> if the reconstituted product is cloudy immediately after reconstitution or refrigeration. Occasionally, after refrigeration, small colorless particles may be present in the Serostim<sup>®</sup> solution. This is not unusual for proteins like Serostim<sup>®</sup>.

#### STABILITY AND STORAGE

**Before reconstitution:** Serostim<sup>®</sup> [somatotropin (rDNA origin) for injection] should be stored at room temperature, 59° - 86°F (15° - 30°C). Expiration dates are stated on product labels.

**After reconstitution:** Use within 24 hours after reconstitution with diluent. The reconstituted solution should be stored under refrigerated conditions (36° - 46°F/2° - 8°C).

Sterile Diluent, 1 mL (Sterile Water for Injection, USP) should be stored at room temperature, 59° - 86°F (15° - 30° C). Avoid freezing vials of Serostim<sup>®</sup> and Sterile Diluent.

#### HOW SUPPLIED

Serostim<sup>®</sup> [somatotropin (rDNA origin) for injection] is available in the following forms:

Serostim<sup>®</sup> vials containing 4 mg (approximately 12 IU) somatotropin (mammalian-cell) with Sterile Water for Injection, USP. Package of 7 vials. NDC 44087-0004-7

Serostim<sup>®</sup> vials containing 5 mg (approximately 15 IU) somatotropin (mammalian-cell) with Sterile Water for Injection, USP. Package of 7 vials. NDC 44087-0005-7

Serostim<sup>®</sup> vials containing 6 mg (approximately 18 IU) somatotropin (mammalian-cell) with Sterile Water for Injection, USP. Package of 7 vials. NDC 44087-0006-7

Manufactured for: Sero Laboratories, Inc., Randolph, MA 02368

Rx Only

March 1999



**Serostim<sup>®</sup>**  
[somatropin (rDNA origin) for injection]

Information: (800) 714-2437

FAX: (800) 214-8698

Internet: [www.serono-usa.com](http://www.serono-usa.com)

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