

A Guide to Treatment with Serostim[®]



If you have been diagnosed with HIV-associated wasting and prescribed Serostim[®] (somatropin) for injection, this guide has been designed to help educate and assist you with your treatment. Please read this booklet before you begin taking Serostim[®]. If you have any questions or concerns about your Serostim[®] therapy, ask your healthcare provider or pharmacist.

Provider contact info:

Pharmacy name:

Pharmacy number:

Notes:

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Please see Important Risk Information on pages 6–7 and accompanying Full Prescribing Information for Serostim[®].

I. Questions about HIV-associated wasting

Have you noticed a loss of energy associated with unintentional weight loss? To determine whether you are experiencing symptoms of this condition, you may have discussed the following questions with your healthcare provider:

- Do I have a loss of physical endurance along with an unintentional loss of weight?
- Are any activities difficult to perform?
- Am I exercising less?
- Do I need to rest more often?
- Do I frequently feel tired after certain activities?
- Do I have unintentional weight loss?
- Do the changes in my weight negatively affect my health and how I feel?
- Do my clothes fit more loosely than normal due to unintentional weight loss?
- Have I lost weight without trying?
- Have my family, friends or co-workers noticed any changes in the way I look or my body based on changes in my weight?

Answering yes to one or more of these questions may be the reason your healthcare provider has prescribed Serostim® (somatropin) for injection. Only your healthcare provider can diagnose HIV-associated wasting and prescribe Serostim®.

II. Understanding HIV-associated wasting

What is happening to my body and why?

Unintentional weight loss may cause you to feel that you have less physical endurance than you used to have. You may be losing weight without trying. But, it is more than just a loss of weight; it is a loss of lean body mass, which is made up of muscles, organs, blood and water. This loss of lean body mass may impact your ability to complete tasks that need a certain level of physical endurance.

There isn't one direct cause for HIV-associated wasting. For some it could be an issue that develops with the way the body uses energy; instead of drawing energy from fat, the body begins to draw energy from lean body mass.

Who can be affected by HIV-associated wasting?

Unintentional weight loss and decreased physical endurance can impact anyone with HIV, including:

- Newly diagnosed patients on antiretroviral therapy
- Long-term survivors with HIV
- HIV-positive individuals with normal CD4 counts and undetectable viral loads
- Patients on antiretroviral therapy with acute infection

Even though a person's medications, diet, and activity haven't changed, they still may be at risk.

How common is HIV-associated wasting?

A 2004-2005 analysis of a managed care database involving 55 million patients and 75 health plans found that 7% to 8% of HIV/AIDS patients had a diagnosis of, or were receiving treatment for, cachexia, or HIV-associated wasting. In another analysis of a commercial managed care database from 2005-2007 consisting of 22,535 patients with an HIV/AIDS diagnosis, 9.3% of the patients met the criteria for weight loss.

III. What is Serostim[®] (somatropin) for injection and how can it help me?

What is Serostim[®]?

Serostim[®] is an injectable prescription medicine used for the treatment of HIV-positive patients with wasting or cachexia to increase lean body mass and body weight, and improve physical endurance. Treatment with antiretroviral therapy at the same time is necessary.

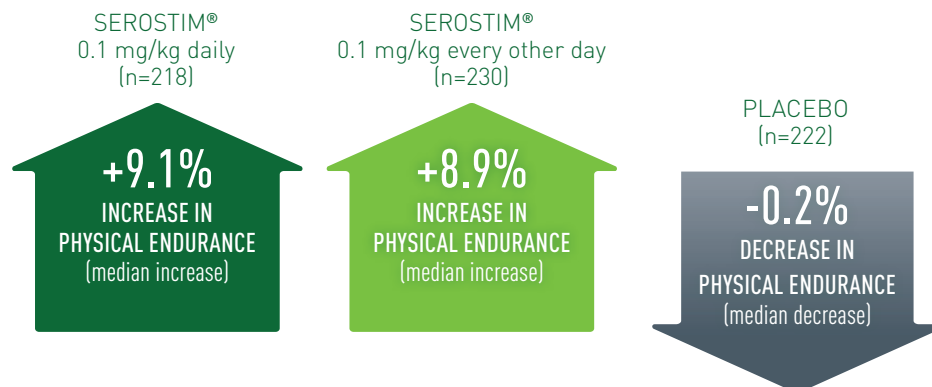
You should not take Serostim[®] if you have:

- A critical illness from surgery, serious injuries, or a severe breathing problem
- Cancer or undergoing treatment for cancer
- Eye problems caused by diabetes
- Allergies to growth hormone or other ingredients in Serostim[®] vials

Serostim[®] Clinical Trial Results

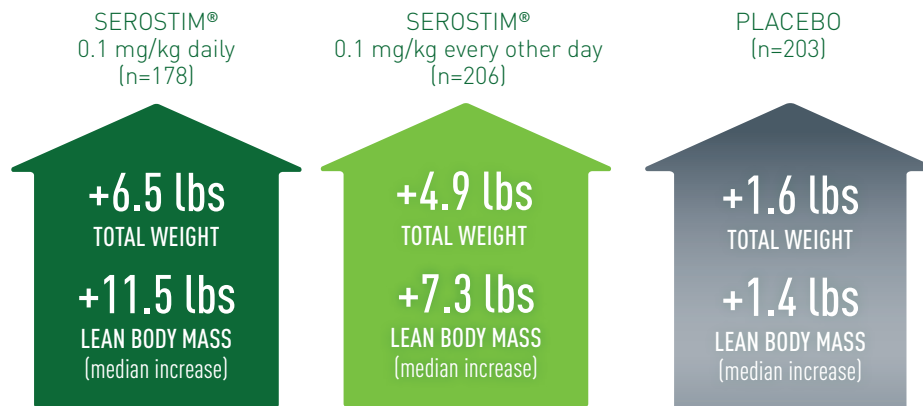
To determine its effectiveness and safety, Serostim[®] was studied in 757 people with HIV-associated wasting. This clinical trial took place across multiple sites in 8 countries. Participants in the study received Serostim[®] every day, every other day, or a placebo (an inactive substance) for 12 weeks. A subset of patients continued on treatment to 24 or 48 weeks. Serostim[®] improved physical endurance and increased lean body mass and weight.

Serostim[®] improved physical endurance in people with HIV-associated wasting



In this study, people taking Serostim[®] significantly improved their physical endurance as assessed by a stationary bike exercise after 12 weeks of treatment. On average, those patients who received Serostim[®] daily had a 9.1% increase in physical endurance, and those who received the drug every other day increased physical endurance by 8.9%. Participants that were given a placebo had an average 0.2% decrease in their physical endurance.

Serostim® (somatropin) for injection increased lean body mass and weight in people with HIV-associated wasting



In the same study, those who were treated daily with Serostim® experienced a median increase of 6.5 pounds in total weight and 11.5 pounds in lean body mass after 12 weeks. Those treated with Serostim® every other day experienced a median increase of 4.9 pounds in total weight and 7.3 pounds in lean body mass.

The placebo-treated group experienced a median increase of 1.6 pounds in total weight and 1.4 pounds in lean body mass. The average increase in weight and lean body mass were significantly greater in both Serostim® treatment groups compared to the placebo group after 12 weeks of treatment. Results based on a subset who completed the 12 week study and took at least 80% of their medicine (PI contains entire study population results). Increases in lean body mass and weight were maintained through 24 weeks in study patients who completed an additional 12 weeks of active treatment.

Patients with HIV-associated wasting treated with Serostim® completed a questionnaire called the BACRI. Their perception of the impact of Serostim® therapy on their wasting symptoms was reported. Patients with Serostim® reported improvements in their symptoms. After taking Serostim®, patients' perceptions included:

- Having a better appetite
- More enjoyment in eating
- Positive changes in appearance
- Improvements in how they felt
- That increases in weight significantly improved their health

What are the most common side effects of Serostim® reported in clinical trials in patients treated for HIV-associated wasting or cachexia?

- Swelling, especially in the hands or feet or around the eyes
- Bone, muscle, and joint pain or stiffness
- Tingling, numbness and pain in the fingers, thumb or wrist
- Unusual skin sensations
- Breast enlargement in men
- Nausea
- Extreme tiredness

Please see Important Risk Information on pages 6–7 and accompanying Full Prescribing Information for Serostim®.

IV. Important Risk Information

Indication

What is Serostim® (somatropin) for injection?

Serostim® is an injectable prescription medicine used for the treatment of HIV-positive patients with wasting or cachexia to increase lean body mass and body weight, and improve physical endurance. Treatment with antiretroviral therapy at the same time is necessary.

Important Risk Information

You should not take Serostim® if you have:

- A critical illness from surgery, serious injuries, or a severe breathing problem
- Cancer or undergoing treatment for cancer
- Eye problems caused by diabetes
- Allergies to growth hormone or other ingredients in Serostim vials

What should I tell my doctor before using Serostim®?

- If you have cancer or had cancer in the past.
- If you have diabetes, are at risk for getting diabetes, or have blood sugar levels that are higher than normal. New cases of type 2 diabetes have been reported in patients taking Serostim®.
- If you are allergic to growth hormone, benzyl alcohol, sucrose, phosphoric acid or sodium hydroxide.
- If you are taking any other medicines (both prescription or over the counter), vitamins, or supplements because these medicines may affect each other. Your doctor may need to adjust the dose of Serostim® or other medicines you are taking.
- If you are nursing, pregnant, or plan to become pregnant. It is not known if Serostim® passes into your breast milk or could harm your unborn baby.

What are the most common side effects of Serostim® reported in clinical trials in patients treated for HIV-associated wasting or cachexia?

- Swelling, especially in the hands or feet or around the eyes
- Bone, muscle, and joint pain or stiffness
- Tingling, numbness and pain in the fingers, thumb or wrist
- Unusual skin sensations
- Breast enlargement in men
- Nausea
- Extreme tiredness

Other less common but serious side effects of Serostim® (somatropin) for injection are:

- High blood sugar (hyperglycemia/diabetes) which can include symptoms of increased thirst and urination, tiredness, or trouble concentrating
- Headaches, changes in vision, nausea or vomiting, which requires immediate medical attention
- Serious allergic reactions that require immediate medical attention
- Pain and tenderness in the abdomen

These are not all of the possible side effects. Let your doctor know about any side effects you experience. Your doctor may prescribe a pain reliever or may decrease your dose of Serostim® to help manage some side effects.

How should you administer Serostim®?

Patients and caregivers should be trained by a healthcare professional on how to mix and inject Serostim® prior to use. Never share Serostim® with another person, even if the needle is changed. Injection sites can include arms, legs, abdomen and should be changed daily. Avoid injecting Serostim® in areas that are sore or bruised.

Please see the Prescribing Information enclosed for complete Serostim® Risk Information.

V. Your Serostim[®] (somatropin) for injection prescription and insurance coverage

How do I get my prescription filled?

If your healthcare provider has prescribed Serostim[®], the AXIS Center[®] can help guide you by assisting with the insurance process, helping navigate the prior authorization process, locating a pharmacy that can dispense Serostim[®] and offering and arranging injection training.

Will my insurance cover Serostim[®]?

Serostim[®] is covered by most insurance plans. The AXIS Center[®] offers trained reimbursement specialists who can help you verify your insurance benefits, determine coverage options, and locate pharmacies in your area.

Will I be able to afford Serostim[®]?

Patient Assistance Program

If you don't have health insurance or are underinsured, the Serostim[®] Patient Assistance Program (PAP) may help people who have HIV-associated wasting get the Serostim[®] treatment they have been prescribed. Eligible patients who meet certain financial and medical criteria may receive Serostim[®] free of charge.

Serostim[®] Copay Assistance Program

The Copay Assistance Program can decrease or potentially eliminate out-of-pocket costs for eligible, commercially or privately insured patients. Ask your healthcare provider for information about the Serostim[®] Copay Assistance Program. For eligibility requirements and to sign up for the Copay Assistance Program, visit SerostimCopay.com.

- You must have a prescription drug benefit that covers Serostim[®] and a valid Serostim[®] prescription.
- **You may not use the copay card if you receive drug benefits from Medicaid, a Medicare drug benefit plan, or other federal or state programs (includes state Medicaid assistance program and/or pharmaceutical patient assistance programs).**

Ask your healthcare provider for more information about any of these assistance programs or call the AXIS Center[®] at 877-714-AXIS.



VI. How do I take Serostim[®] (somatropin) for injection?

This section is intended to assist with Serostim[®] injection training. Your healthcare provider or injection trainer will show you how to prepare and inject Serostim[®] before you use it for the first time. Serostim[®] is injected under the skin, subcutaneously, through a short and thin needle. Serostim[®] can be self administered every day or every other day, usually at bedtime.

Depending on your weight, your doctor will prescribe one of three dosage strengths for you: 4 mg, 5 mg, or 6 mg. Serostim[®] comes in packages containing vials of Serostim[®] powder and diluent for mixing. The 5-mg and 6-mg single-dose vials come with Sterile Water for Injection, USP; the 4-mg multidose vial comes with Bacteriostatic Water for Injection, USP.

You will also need sterile syringes and mixing needles.

Please read all instructions before taking Serostim[®] and inject Serostim[®] exactly as your healthcare provider tells you. Do not change your Serostim[®] dose unless instructed to by your healthcare provider.

What if I need help injecting Serostim[®]?

The AXIS Center[®] offers in-home or in-office injection training provided through a national network of nurse injection trainers. Patient support is available 24/7 to assist patients with treatment education and support.

How do I store Serostim[®]?

Before reconstitution:

Keep your Serostim[®] vials at room temperature—between 59°F and 86°F.

After reconstitution with Sterile Water for Injection, USP:

The reconstituted solution should be used immediately and any unused portion should be discarded.

After reconstitution with Bacteriostatic Water for Injection, USP (0.9% Benzyl Alcohol):

The reconstituted solution should be stored under refrigeration (between 36°F and 46°F) for up to 14 days. Avoid freezing reconstituted vials of Serostim[®].

Please see Important Risk Information on pages 6–7 and accompanying Full Prescribing Information for Serostim[®].

VII. Injecting Serostim[®] (somatropin) for injection using a needle and syringe

The 6-mg single-dose vial is displayed in the instructions below. Please note that the characteristics may vary.

What do I need for my Serostim[®] injection?

The Serostim[®] vial containing the medication in a freeze-dried powder.



Diluent for injection vial holding the liquid you will mix with the Serostim[®] powder.

A syringe used to mix the diluent with the Serostim[®] powder.

Two needles, a longer, 20-gauge needle to add the diluent to the Serostim[®] vial and withdraw the solution prior to your injection, and a shorter, 29-gauge needle to give yourself the injection.



* NOT shown at actual size.

* You may be given a different gauge needle

Alcohol swabs to clean the skin before you inject and to wipe the vial tops.



A bandage or gauze pad to cover the injection site after you inject.



Sharps container to dispose of your used needles and syringes.



Disposable gloves if someone else is giving you the injection. You do not need them if you are injecting yourself.

* Sharps containers may vary in appearance

Note: Not all materials used for the injection are provided. Make sure all injection items are unopened prior to use. If you find an open needle or syringe packet, do not use it. Dispose of it in your sharps container. **Needles and syringes should never be shared or reused. Check the expiration date and do not use if the medication is expired.**

How do I inject Serostim® (somatropin) for injection?

Before each injection, gather the materials outlined on the previous page. Place them on a clean, flat surface, in a place with good light. Make sure to wash your hands with soap and water before you begin. If someone else is giving you the injection, this person should put on a pair of disposable gloves now.

- 1 Remove the flip tops from the drug and diluent vials, and throw them away.**



- 2 Clean both rubber stoppers with a fresh alcohol swab, then throw the swab away. Do not touch the vial tops with your hands or gloves after cleaning them.** If you do, wipe the tops again with a fresh alcohol swab.



- 3 Prepare your needle.**

Unwrap the syringe and the larger needle without touching the hub of the needle where it connects to the syringe. Remove the plastic tip protector from the syringe.

Keeping the needle in its cap, attach it securely to the syringe.

If you touch the hub of the needle or the bottom of the syringe where the needle attaches, or if you drop the needle or syringe, dispose of them in your sharps container and use new ones.



Please see Important Risk Information on pages 6–7 and accompanying Full Prescribing Information for Serostim®.

VII. Injecting Serostim[®] (somatropin) for injection using a needle and syringe (continued)

4 Prepare your syringe.

Pull back on the syringe plunger until it reaches the 1cc/1mL point on the syringe barrel, or to the volume indicated by your healthcare provider.

While holding the syringe in one hand, pull the needle cap straight off with the other hand. Set the needle cap aside for use later.

If the needle and syringe come apart and they have not touched anything, simply put them back together again. If the needle or syringe has touched anything, dispose of them in your sharps container, and start over again from Step 3.



5 Fill your syringe with diluent.

Place the vial of diluent on your clean work surface.

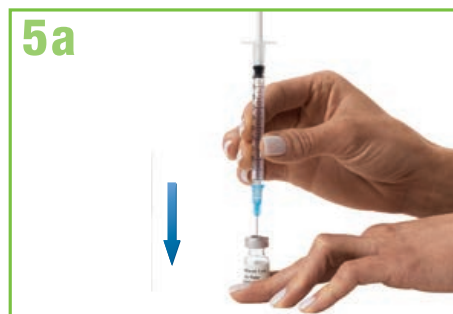
Carefully insert the needle straight down through the center of the rubber stopper into the vial of diluent. (See Step 5a.)

Gently inject all the air from the syringe into the vial by pushing down on the plunger. (The injected air will make it easier to withdraw the solution.) (See Step 5b.)

Without removing the needle, hold the plunger with one hand and turn the vial upside down. Pull back the syringe to make sure that the needle tip is below the diluent level in the vial. Pull the plunger to allow the diluent to fill the barrel of the syringe to the appropriate level as instructed by your healthcare provider. (See Step 5c.)

When you have the right amount of diluent in the syringe, remove the needle from the vial, being careful not to touch the needle or allow it to touch any surface.

Throw the vial of diluent away.



6 Prepare your Serostim® (somatropin) for injection for injection.

Place the vial containing Serostim® powder on your work surface.

Using the same syringe and needle, insert the needle through the center of the rubber stopper into the Serostim® vial. Slowly and gently push the plunger, allowing the diluent to flow down the side of the vial.



Do not squirt the diluent because this will make the solution foamy. If it becomes foamy, let it sit until the bubbles disappear and the liquid becomes clear.

Keeping the needle in the vial, gently swirl the vial until the powder is dissolved. Do not shake or turn the vial upside down.

Once the medication has been mixed, give yourself the injection as indicated in the instructions in the next steps. Do not inject Serostim® if the product is cloudy immediately after reconstitution or refrigeration (with the 4-mg multidose vial only). In this case, prepare another vial and contact your healthcare provider.

The solution from the single-dose 5-mg and 6-mg vials, reconstituted with Water for Injection, USP, must be used immediately. Any unused solution must be discarded.

The solution from the 4-mg multidose vial, reconstituted with Bacteriostatic Water for Injection, USP, can be stored refrigerated for up to 14 days. Occasionally, after refrigeration, small colorless particles may appear in the Serostim® liquid. This is not unusual and does not prevent its use.

7 Fill the syringe with the solution.

Turn the vial upside down, making sure the tip of the needle is below the fluid level.

Slowly pull the plunger back until the syringe fills to slightly more than the unit marking that corresponds to your prescribed dose.

Make sure that the tip of the needle remains in the solution while slowly backing the needle out of the vial to withdraw as much solution as possible.



Carefully remove the needle from the vial without touching the needle or allowing it to touch any surface.

Please see Important Risk Information on pages 6–7 and accompanying Full Prescribing Information for Serostim®.

VII. Injecting Serostim[®] (somatropin) for injection using a needle and syringe (continued)

8 Change the needle.

Before you give yourself the injection, you must replace the larger needle with the smaller one.

Take the needle cap you set aside, place it on your work surface, and recap the needle with a scooping movement, as indicated in the photo on the right. The cap should snap down on the needle. Do not touch the needle or allow it to touch any surface.

Once the cap is on the needle, gently twist the needle and cap off of the syringe and place them in your sharps container.

Do not squirt any of the solution out of the syringe.



9 Put on the smaller needle.

Unwrap the smaller needle and twist it onto the syringe, then carefully remove the needle cap.

Hold the syringe straight with the needle facing up.

To remove any air from the syringe barrel and the needle, gently tap the side of the syringe with your fingertips until the bubbles float to the top of the syringe. Then gently push the plunger until a small drop of liquid appears on the tip of the needle.



10 Pick an injection site.

Find a place on your body where it will be easy for you to give yourself an injection. Your healthcare provider will recommend the appropriate injection site. Examples of common injection sites include: the top side of the thigh, the areas around the belly button, the rear end, and the fleshy part of your arm. Make sure to change the location of your injection each day so that one area does not get injected too many times.

Before you inject, take an alcohol swab and carefully clean a four-inch-square area around your injection site. Throw the swab away and let the skin dry.



11 Inject Serostim® (somatropin) for injection.

Hold the syringe in one hand and remove the cap from the needle.

With your other hand gently pinch a three-inch fold of skin.

Point the needle downward, with the slanted, cutting edge of the needle facing up, about an inch away from the area you plan to inject.

Push the needle tip into the pinched skin as far as it will go. Hold the syringe steady and let go of the skin.

Push the plunger down slowly and gently as far as it will go.

When the syringe is empty, pull the syringe and attached needle straight out of the skin and put it in your sharps container.



Please see Important Risk Information on pages 6–7 and accompanying Full Prescribing Information for Serostim®.

VII. Injecting Serostim[®] (somatropin) for injection using a needle and syringe (continued)

If you accidentally stick yourself with the needle, clean the stuck area carefully with soap and water to prevent infection. Then place a 2" x 2" gauze patch over the area and apply gentle pressure to stop any bleeding.

If someone else gets pricked by the needle after your injection, let the area bleed freely. Then wash the area thoroughly with soap and water and call their doctor immediately to explain what happened.



12 Clean up after injecting.

Immediately discard the injection needle, needle cap, syringe and used gauze patches in your sharps container.



If you have questions about your injection, talk to your healthcare provider or contact the AXIS Center[®] toll free at 1-877-714-AXIS (2947).

VIII. Glossary

Alcohol swab. A soft, antiseptic pad used to clean an area of the body before giving an injection.

Diluent. The liquid used to dissolve Serostim[®] powder.

Disposable gloves. Rubber gloves that are thrown away after one use. These are used when giving someone else an injection.

Gauge. The diameter or thickness of a slender object (as a wire or needle).

HIV-associated wasting. A loss of weight without trying, or involuntary loss of lean body mass (LBM) and body weight in persons infected with HIV.

Injection site. The place on the body where one chooses to inject.

Lean body mass. Lean body mass is made up of muscles, organ tissue, blood, and water.

Metabolism. The process by which the body turns the food we eat into the reserves of energy we need to function and then uses these reserves to release the energy we need to live.

Needle. A thin, hollow, sharp-pointed instrument used for injection.

Longer needle. The 20-gauge needle used to mix the Serostim[®] solution.

Shorter needle. The 27-, 29- or 30-gauge needle used to inject Serostim[®].

Needle cap. The protective, removable covering on a needle.

Physical Endurance. The time that it takes from the start of a physical activity to completion of the activity because of exhaustion.

Reconstitution. The process of mixing the dry Serostim[®] powder with diluent.

Sharps container. The sealed container used for disposing of used syringes and needles.

Sterile. Free from live bacteria or other microorganisms.

Subcutaneous. The area directly under the skin.

Syringe. A medical instrument used for injecting or withdrawing fluids.

Barrel. The hollow shaft of the syringe that is filled with liquids.

Plunger. The part of the syringe that pushes fluid or air out of the barrel.

Vial. A small, closed, disposable container.

Please see Important Risk Information on pages 6–7 and accompanying Full Prescribing Information for Serostim[®].

IX. My Personal Tracker

If you feel you have been experiencing unintentional weight loss and a decrease in physical endurance, use this tracker to keep a weekly record of your weight, your level of physical activity and other important symptoms. This could be helpful information to supply to your healthcare provider at your next appointment.

_____ / _____ / _____
 NAME INITIAL WEIGHT INITIAL DATE

Keep a record of the changes you experience and share it with your healthcare provider at your next visit.

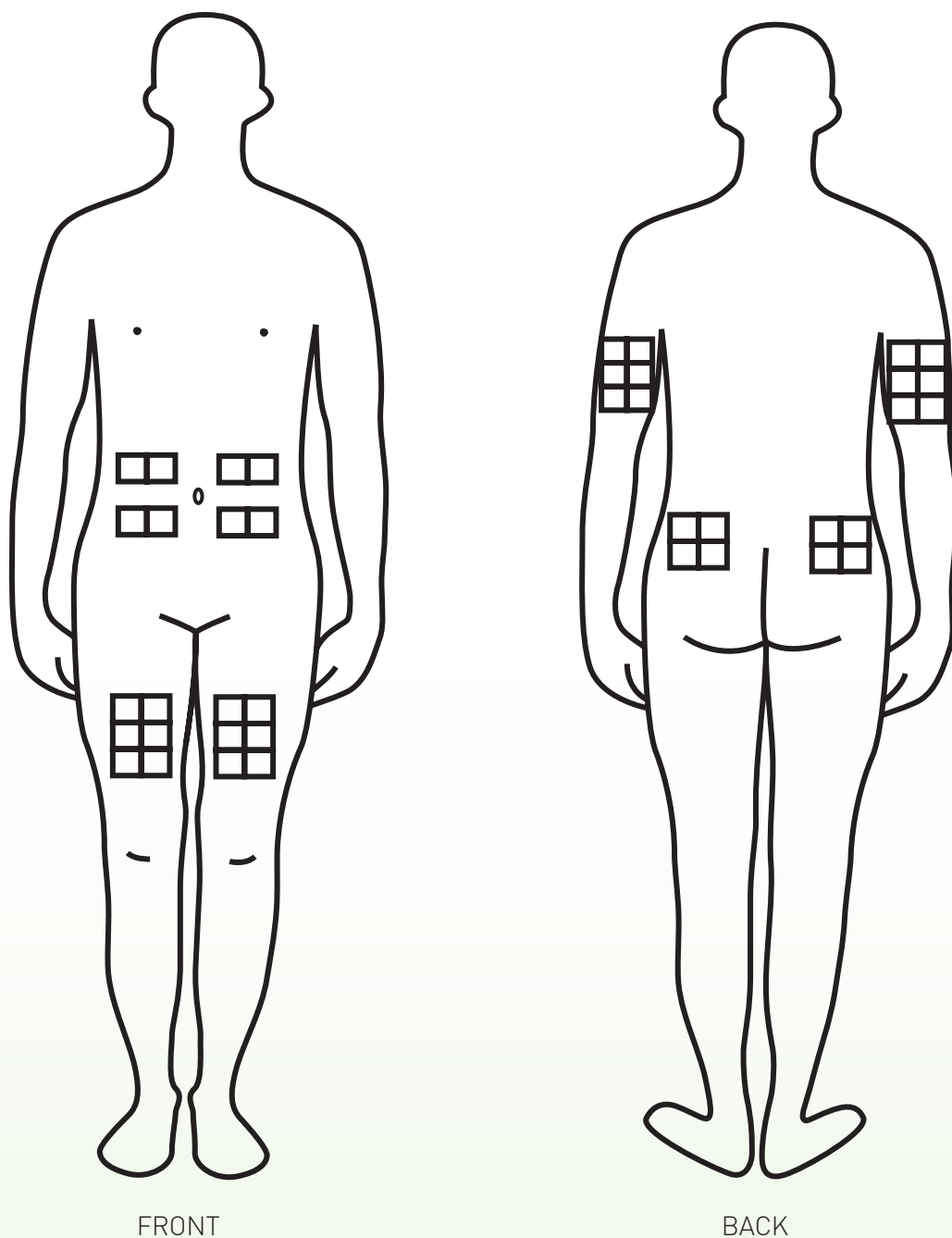
Date						
Weight						
Physical endurance For example: Are any activities more difficult? Are you exercising less? Do you need to rest more frequently?						

Use this space for any additional information or notes that you would like to share.



X. My Injection Tracker

Serostim® (somatropin) for injection should be injected subcutaneously (under the skin) at the sites recommended by your health care provider. Examples of common injection sites include: the top side of the thigh, the areas around the belly button, the rear end, and the fleshy part of your arm. Use a different site each time you inject to help avoid tissue damage.



Please see Important Risk Information on pages 6–7 and accompanying Full Prescribing Information for Serostim®.



Serostim[®]
(somatropin) for injection

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HIGHLIGHTS OF PRESCRIBING INFORMATION

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

SEROSTIM (somatropin) for injection, for subcutaneous use

Initial U.S. Approval: 1987

RECENT MAJOR CHANGES

Contraindications (4)	12/2016
Warnings and Precautions (5)	12/2016

INDICATIONS AND USAGE

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

DOSAGE AND ADMINISTRATION

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

DOSAGE FORMS AND STRENGTHS

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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

ADVERSE REACTIONS

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

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

DRUG INTERACTIONS

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

See 17 for PATIENT COUNSELING INFORMATION

Revised: 05/2018

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

SEROSTIM (somatotropin) is indicated for the treatment of HIV patients with wasting or cachexia to increase lean body mass and body weight, and improve physical endurance. Concomitant antiretroviral therapy is necessary.

2 DOSAGE AND ADMINISTRATION

SEROSTIM is administered by subcutaneous injection.

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

2.1 HIV-associated wasting or cachexia

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

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

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

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

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

2.2 Preparation and Administration

Each vial of SEROSTIM 5 mg or 6 mg is reconstituted with 0.5 to 1 mL Sterile Water for Injection, USP.

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

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

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

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

To reconstitute SEROSTIM, inject the diluent into the vial of SEROSTIM aiming the liquid against the glass vial wall. Swirl the vial with a GENTLE rotary motion until contents are dissolved completely. DO NOT SHAKE. Parenteral drug products should always be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. SEROSTIM MUST NOT BE INJECTED if the solution is cloudy or contains particulate matter. Use it only if it is clear and colorless.

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

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

3 DOSAGE FORMS AND STRENGTHS

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

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

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

- SEROSTIM 4 mg per vial

4 CONTRAINDICATIONS

• Acute Critical Illness

Growth hormone therapy should not be initiated in patients with acute critical illness due to complications following open heart or abdominal surgery, multiple accidental trauma or acute respiratory failure [*see Warnings and Precautions (5.1)*].

• Active Malignancy

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

• Hypersensitivity

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

• Diabetic Retinopathy

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

5 WARNINGS AND PRECAUTIONS

5.1 Acute Critical Illness

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

5.2 Concomitant Antiretroviral Therapy

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

5.3 Neoplasms

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

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

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

5.4 Impaired Glucose Tolerance/Diabetes

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

During safety surveillance of patients with HIV-associated wasting, cases of new onset impaired glucose tolerance, new onset type 2 diabetes mellitus and exacerbation of preexisting diabetes mellitus have been reported in patients receiving SEROSTIM. Some patients developed diabetic ketoacidosis and diabetic coma. In some patients, these conditions improved when SEROSTIM was discontinued, while in others, the glucose intolerance persisted. Some of these patients required initiation or adjustment of antidiabetic treatment while on SEROSTIM.

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

5.5 Intracranial Hypertension

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

5.6 Severe Hypersensitivity

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

5.7 Fluid Retention/Carpal Tunnel Syndrome

Increased tissue turgor (swelling, particularly in the hands and feet) and musculoskeletal discomfort (pain, swelling and/or stiffness) may occur during treatment with SEROSTIM, but may resolve spontaneously, with analgesic therapy, or after reducing the frequency of dosing [see *Dosage and Administration (2.1)*].

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

5.8 Lipoatrophy

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

5.9 Pancreatitis

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

6 ADVERSE REACTIONS

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

Acute Critical Illness [see *Warnings and Precautions (5.1)*]

Neoplasms [see *Warnings and Precautions (5.3)*]

Impaired glucose tolerance and diabetes mellitus [see *Warnings and Precautions (5.4)*]

Intracranial hypertension [see *Warnings and Precautions (5.5)*]

Severe hypersensitivity [see *Warnings and Precautions (5.6)*]

Fluid retention/Carpal tunnel syndrome [see *Warnings and Precautions (5.7)*]

Lipoatrophy [see *Warnings and Precautions (5.8)*]

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

6.1 Clinical Trials Experience

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

Clinical trials in HIV-associated wasting or cachexia:

In the 12-week, placebo-controlled Clinical Trial 2, 510 patients were treated with SEROSTIM. The most common adverse reactions judged to be associated with SEROSTIM were musculoskeletal discomfort and increased tissue turgor (swelling, particularly of the hands or feet), and were more frequently observed when SEROSTIM 0.1 mg/kg was administered on a daily basis [Table 1 and *Warnings and Precautions (5)*]. These symptoms often subsided with continued treatment or dose reduction. Approximately 23% of patients receiving SEROSTIM 0.1 mg/kg daily and 11% of patients receiving 0.1 mg/kg every other day required dose reductions. Discontinuations as a result of adverse reactions occurred in 10.3% of patients receiving SEROSTIM 0.1 mg/kg daily and 6.6% of patients receiving 0.1 mg/kg every other day. The most common reasons for dose reduction and/or drug discontinuation were arthralgia, myalgia, edema, carpal tunnel syndrome, elevated glucose levels, and elevated triglyceride levels.

Clinical adverse reactions which occurred during the first 12 weeks of study in at least 5% of the patients in either active treatment group and at an incidence greater than placebo are listed below, without regard to causality assessment.

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

	Placebo	0.1 mg/kg every other day SEROSTIM	0.1 mg/kg daily SEROSTIM
	Patients (n=247)	Patients (n=257)	Patients (n=253)
Body System	%	%	%
Preferred Term			
Musculoskeletal System Disorders			
Arthralgia	11.3	24.5	36.4
Myalgia	11.7	17.9	30.4
Arthrosis	3.6	7.8	10.7
Gastrointestinal System Disorders			
Nausea	4.9	5.4	9.1
Body As A Whole - General Disorders			
Edema Peripheral	2.8	11.3	26.1
Fatigue	4.5	3.5	5.1
Endocrine Disorders			
Gynecomastia	0.4	3.5	5.5
Central and Peripheral Nervous System Disorders			
Paresthesia	4.5	7.4	7.9
Hypoesthesia	2.4	1.6	5.1
Metabolic and Nutritional Disorders			
Edema Generalized	1.2	1.2	5.9

Adverse reactions that occurred in 1% to less than 5% of trial participants receiving SEROSTIM during the first 12 weeks of Clinical Trial 2 thought to be related to SEROSTIM included dose dependent edema, periorbital edema, carpal tunnel syndrome, hyperglycemia and hypertriglyceridemia.

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

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

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

SEROSTIM was evaluated for the treatment of patients with HIV lipodystrophy in two double-blind, placebo-controlled trials that excluded patients with a history of diabetes, impaired fasting glucose or impaired glucose (approximately 20% of the patients screened were excluded from study enrollment as a result of a diagnosis of diabetes or glucose intolerance). The studies included a 12-week double-blind, placebo-controlled, parallel group “induction” phase followed by maintenance phases of different durations (12 and 24 weeks, respectively). In the initial 12-week treatment periods of the two, placebo-controlled clinical trials, 406 patients were treated with SEROSTIM. Clinical adverse reactions which occurred during the first 12 weeks of both studies combined in at least 5% of the patients in either of the two active treatment groups are listed by treatment group in Table 2, without regard to causality assessment. The most common adverse reactions judged to be associated with SEROSTIM were edema, arthralgia, pain in extremity, hypoesthesia, myalgia, and blood glucose increased, all of which were more frequently observed when SEROSTIM 4 mg was administered on a daily basis compared with alternate days. These symptoms often subsided with dose reduction. During the 12-week induction phase, 1) approximately 26% of patients receiving SEROSTIM 4 mg daily and 19% of patients receiving SEROSTIM 4 mg every other day required

dose reductions; and 2) discontinuations as a result of adverse reactions occurred in 13% of patients receiving SEROSTIM 4 mg daily and 5% of patients receiving SEROSTIM 4 mg every other day. The most common reasons for dose reduction and/or drug discontinuation were peripheral edema, hyperglycemia (including blood glucose increased, blood glucose abnormal, and hyperglycemia), and arthralgia.

Table 2: Controlled HIV Lipodystrophy Studies 1 and 2 Combined – Adverse Reactions with >5% Incidence in Either Active Treatment Arm

	Placebo	SEROSTIM 4 mg every other day ¹	SEROSTIM 4 mg daily
	Patients (n=159)	Patients (n=80)	Patients (n=326)
System Organ Class Preferred Term	%	%	%
Musculoskeletal and connective tissue disorders			
Arthralgia	11.9	27.8	37.1
Pain in extremity	3.8	5.0	19.3
Myalgia	3.8	2.5	12.6
Musculoskeletal stiffness	1.9	3.8	8.0
Joint stiffness	1.3	3.8	7.7
Joint swelling	0.6	5.0	6.1
General disorders and administration site conditions			
Edema peripheral	3.8	18.8	45.4
Fatigue	1.9	6.3	8.9
Nervous system disorders			
Hypoesthesia	0.6	8.8	15.0
Paraesthesia	2.5	12.5	11.0
Investigations (Laboratory Evaluations)			
Blood glucose increased ²	2.5	3.8	13.8
Metabolism and nutrition disorders			
Hyperglycemia ²	0.6	8.8	7.1
Fluid retention	0.6	2.5	5.2
Gastrointestinal disorders			
Nausea	2.5	1.3	6.1

¹ Study 22388 only

² similar terms were grouped together and reported below

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

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

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

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

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

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

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

		Placebo	SEROSTIM 4 mg every other day	SEROSTIM 4 mg daily
Time Point	Statistic	(n=145)	(n=79)	(n=290)
Baseline	Mean (SD) Range	0.4 (1.4) (-2.5, 4.8)	1.3 (2.1) (-2.0, 13.7)	0.0 (1.6) (-3.0, 11.9)
Week 12	Mean (SD) Range	0.8 (1.6) (-2.6, 6.7)	5.1 (3.4) (-0.7, 17.2)	6.1 (5.0) (-1.8, 29.2)
Change from Baseline to	Mean (SD) Range	0.4 (1.3) (-2.9, 7.7)	3.9 (3.1) (-9.4, 11.8)	6.1 (4.6) (-2.4, 24.3)
Week 12	p-value ^(b)	<0.001	<0.001	<0.001
	Mean ^(a) diff (SEM)		3.5 (0.5)	5.7 (0.4)
	p-value ^(c)		<0.001	<0.001
<p>(a) Proportionally weighted least squares means from a two-way ANOVA model on raw data including effects for treatment, sex, and the treatment by sex interaction.</p> <p>(b) P-value from a Wilcoxon Signed Rank test on the change from baseline to Week 12.</p> <p>(c) P-value from a two-way ANOVA model on ranked data including effects for treatment, sex, and the treatment by sex interaction.</p>				

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

After 12 weeks of treatment, none of the 651 study participants with HIV-associated wasting treated with SEROSTIM for the first time developed detectable antibodies to growth hormone (> 4 pg binding). Patients were not rechallenged. Data beyond 3 months is not available.

6.2 Post-Marketing Experience

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

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

Endocrine:

- new onset impaired glucose tolerance
- new onset type 2 diabetes mellitus
- exacerbation of preexisting diabetes mellitus
- diabetic ketoacidosis
- diabetic coma

In some patients, these conditions improved when SEROSTIM was discontinued, while in others the glucose intolerance persisted. Some of these patients required initiation or adjustment of antidiabetic treatment while on SEROSTIM [*see Warnings and Precautions (5.4)*].

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

7 DRUG INTERACTIONS

Formal drug interaction studies have not been conducted. No data are available on drug interactions between SEROSTIM and HIV protease inhibitors or the non-nucleoside reverse transcriptase inhibitors.

7.1 11 β -Hydroxysteroid Dehydrogenase Type 1

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

7.2 Cytochrome P450-metabolized drugs

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

7.3 Oral Estrogen

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

7.4 Insulin and/or Other Oral/Injectable Hypoglycemic Agents

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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

8.3 Nursing Women

It is not known whether SEROSTIM is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SEROSTIM is administered to a nursing woman.

8.4 Pediatric Use

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

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

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

8.5 Geriatric Use

Clinical studies with SEROSTIM did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Elderly patients may be more sensitive to the action of somatropin, and therefore, may be more prone to develop adverse reactions. A lower starting dose and smaller dose increments should be considered for older patients [see *Dosage and Administration (2)*].

8.6 Hepatic Impairment

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

8.7 Renal Impairment

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

8.8 Gender Effect

Biomedical literature indicates that a gender-related difference in the mean clearance of r-hGH could exist (clearance of r-hGH in males > clearance of r-hGH in females). However, no gender-based analysis is available for SEROSTIM in normal volunteers or patients infected with HIV.

10 OVERDOSAGE

Short-Term

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

Long-Term

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

11 DESCRIPTION

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

SEROSTIM is a sterile lyophilized powder intended for subcutaneous injection after reconstitution to its liquid form.

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

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

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

SEROSTIM is an anabolic and anticatabolic agent which exerts its influence by interacting with specific receptors on a variety of cell types including myocytes, hepatocytes, adipocytes, lymphocytes, and hematopoietic cells. Some, but not all of its effects, are mediated by insulin-like growth factor-1 (IGF-1).

12.2 Pharmacodynamics

Effects on Protein, Lipid and Carbohydrate Metabolism

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

Decreases in trunk fat and total body fat, and increases in lean body mass were observed during two double-blind, placebo-controlled studies wherein SEROSTIM vs. placebo were administered daily for 12 weeks to patients with HIV Lipodystrophy [see *Clinical Studies (14)*].

Effects on Nitrogen and Mineral Retention

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

Physical Performance

Cycle ergometry work output and treadmill performance were examined in separate 12-week, placebo-controlled trials [see *Clinical Studies (14)*]. In both studies, work output improved significantly in the group receiving SEROSTIM 0.1 mg/kg/day subcutaneously vs placebo. Isometric muscle performance, as measured by grip strength dynamometry, declined, probably as a result of a transient increase in tissue turgor known to occur with SEROSTIM therapy.

12.3 Pharmacokinetics

Absorption: The absolute bioavailability after subcutaneous administration was determined to be 70 to 90%. The mean $t_{1/2}$ 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 somatotropin is a rate-limiting process.

Distribution: The steady-state volume of distribution (Mean \pm SD) following intravenous administration of somatotropin 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 $t_{1/2}$ 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 somatotropin subcutaneously was 4.28 ± 2.15 hrs, similar to that observed in normal male volunteers. The renal clearance of r-hGH after subcutaneous administration in nine patients with HIV-associated wasting was 0.0015 ± 0.0037 L/h. No significant accumulation of r-hGH appears to occur after 6 weeks of daily dosing as indicated.

Specific Populations:

Pediatric: Available evidence suggests that r-hGH clearances are similar in adults and children, but no pharmacokinetic studies have been conducted in children with HIV.

Gender: Biomedical literature indicates that a gender-related difference in the mean clearance of r-hGH could exist (clearance of r-hGH in males > clearance of r-hGH in females). However, no gender-based analysis is available in normal volunteers or patients infected with HIV.

Race: No studies have been conducted to determine the effect of race on the pharmacokinetics of SEROSTIM.

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

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies for carcinogenicity have not been performed with SEROSTIM. There is no evidence from animal studies to date of SEROSTIM-induced mutagenicity or impairment of fertility.

14 CLINICAL STUDIES

HIV-Associated Wasting or Cachexia

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

Clinical Trial 1:

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

Treatment with SEROSTIM resulted in a significant increase in physical function as assessed by treadmill exercise testing. The median treadmill work output increased by 13% ($p=0.039$) at 12 weeks in the group

receiving SEROSTIM (Figure 2). There was no improvement in the placebo-treated group at 12 weeks. Changes in treadmill performance were significantly correlated with changes in LBM.

Figure 1: Mean Changes in Body Composition

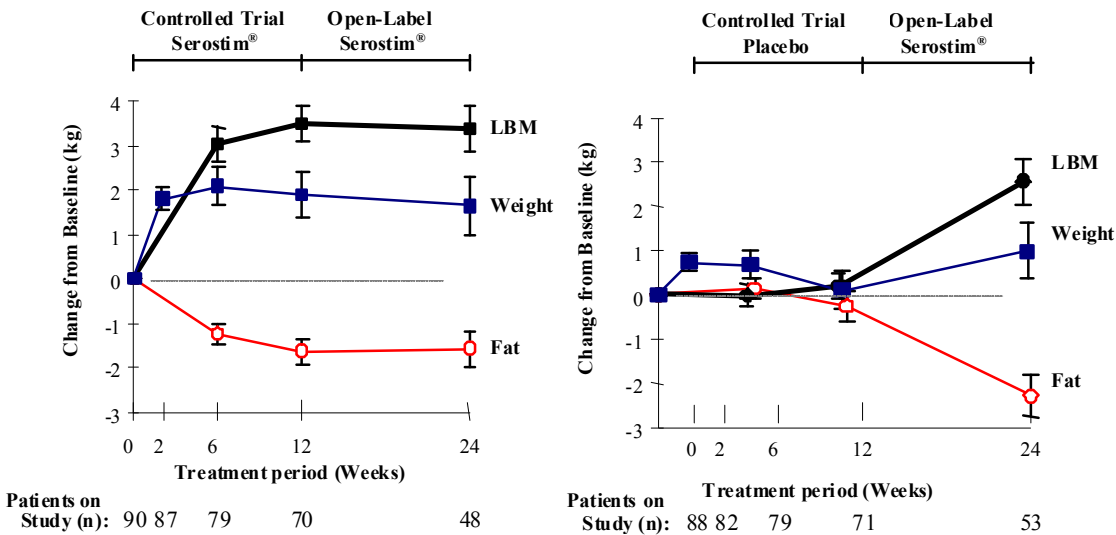
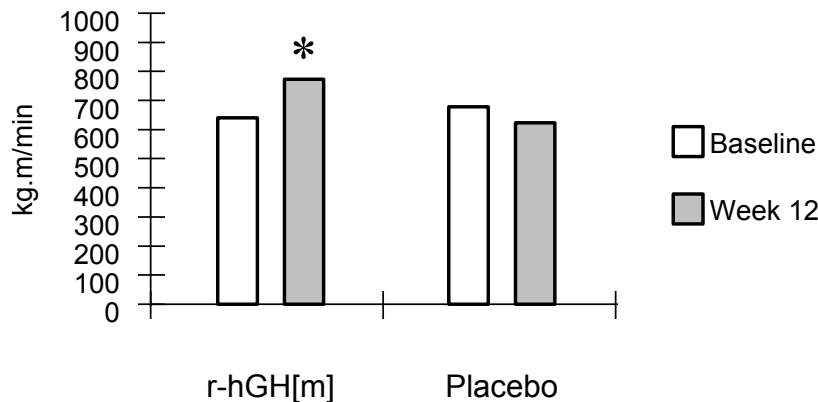


Figure 2: Median Treadmill Work Output



*p = 0.039

Clinical Trial 2:

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

patients (646) completed the 12-week study and continued in the SEROSTIM treatment extension phase of the trial.

Clinical Trial 2 results are summarized in Tables 4 and 5:

Table 4: Mean (Median) of Cycle Work Output (kJ) Response after 12 weeks of Treatment ITT Population

	Placebo	Half-Dose SEROSTIM ^(b)	Full-Dose SEROSTIM ^(a)
Cycle work output (kJ)	n=222	n=230	n=218
Baseline	25.92 (25.05)	27.79 (26.65)	27.57 (26.30)
Change from baseline	-0.05 (-0.25)	2.48 (2.30)	2.52 (2.40)
Percent change from baseline	0.2%	8.9%	9.1%
Difference from Placebo			
Mean (2-sided 95% C.I.)	-	2.53 ^(c) (0.81, 4.25)	2.57 ^(c) (0.83, 4.31)
Median	-	2.55	2.65
^(a) approximately 0.1 mg/kg daily ^(b) approximately 0.1 mg/kg every other day ^(c) p<0.01			

Table 5: Mean (Median) Change from Baseline for Lean Body Mass, Fat Mass and Body Weight

	Placebo		Half-Dose SEROSTIM ^(b)		Full-Dose SEROSTIM ^(a)	
	N	Mean (Median)	n	Mean (Median)	n	Mean (Median)
Lean body mass (kg) (by BIS)	222	0.97 (0.67)	223	3.89 (3.65)	205	5.84 (5.47)
Fat mass (kg) (by DXA)	94	0.03 (0.01)	100	-1.25 (-1.23)	85	-1.72 (-1.51)
Body weight (kg)	247	0.69 (0.68)	257	2.18 (2.15)	253	2.79 (2.65)
^(a) approximately 0.1 mg/kg daily ^(b) approximately 0.1 mg/kg every other day						

The mean maximum cycle work output until exhaustion increased after 12 weeks by 2.57 kilojoules (kJ) in the SEROSTIM 0.1 mg/kg daily group ($p < 0.01$) and by 2.53 kJ in the SEROSTIM 0.1 mg/kg every other day group ($p < 0.01$) compared with placebo (Table 4). Cycle work output improved approximately 9% in both active treatment arms and decreased $< 1\%$ in the placebo group. Lean body mass (LBM) and body weight (BW) increased, and fat mass decreased, in a dose-related fashion after treatment with SEROSTIM and placebo (Table 5). The LBM results obtained by BIS were confirmed with DXA.

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

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

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

SEROSTIM is available in the following forms:

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

16.2 Storage and Handling

Before reconstitution: Vials of SEROSTIM and diluent should be stored at room temperature, ($15^{\circ}\text{C}/59^{\circ}\text{F}$ to $30^{\circ}\text{C}/86^{\circ}\text{F}$). 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 ($2^{\circ}\text{C}/36^{\circ}\text{F}$ to $8^{\circ}\text{C}/46^{\circ}\text{F}$) for up to 14 days.

Avoid freezing reconstituted vials of SEROSTIM.

17 PATIENT COUNSELING INFORMATION

Patients being treated with SEROSTIM should be informed of the potential benefits and risks associated with treatment. Patients should be instructed to contact their physician should they experience any side effects or discomfort during treatment with SEROSTIM.

It is recommended that SEROSTIM be administered using sterile, disposable syringes and needles. Patients should be thoroughly instructed in the importance of proper disposal and cautioned against any reuse of needles and syringes. An appropriate container for the disposal of used syringes and needles should be employed.

Patients should be instructed to rotate injection sites to avoid localized tissue atrophy.

Never Share a SEROSTIM Pen or Needle Between Patients

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

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

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