PRODUCT MONOGRAPH

Pr SEROSTIM®
Somatropin for Injection
Lyophilized Powder for reconstitution

5 mg/vial

Pharmaceutical Standard: Professed

Therapeutic Classification: Human Growth Hormone

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Subcutaneous injection	Lyophilized powder for reconstitution /5 mg/vial	For a complete listing see DOSAGE FORMS, COMPOSITION and PACKAGING section.

DESCRIPTION
SEROSTIM (somatropin for injection, recombinant human growth hormone) is available in a 5 mg/vial dose.

Somatropin is a polypeptide hormone consisting of 191 amino acid residues and its structure is identical to that of growth hormone extracted from human pituitary glands. It is produced by recombinant (rDNA) technology in a mammalian cell expression system.

SEROSTIM is an anabolic and anti-catabolic 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-I and IGF-II).

INDICATIONS AND CLINICAL USE

SEROSTIM (somatropin for injection) is indicated for the treatment of HIV wasting associated with catabolism, weight loss or cachexia.

Geriatrics:
The dosage and administration schedule in the elderly should be the same as for adults (see also WARNINGS AND PRECAUTIONS section).

Pediatrics:
There is limited experience with SEROSTIM in patients under 18 years of age. SEROSTIM should not be used in the pediatric age group until further data becomes available.

CONTRAINDICATIONS

SEROSTIM (somatropin for injection) is contraindicated and should not be administered in the following cases:

- In patients with acute critical illness due to complications following open heart or abdominal surgery, multiple accidental trauma or patients having acute respiratory failure. Clinical studies demonstrated that high doses of growth hormone were associated with a significantly increased morbidity and mortality in those patients (see WARNINGS AND PRECAUTIONS).
- In the presence of any progression of underlying intracranial tumour. Intracranial tumour should be inactive and anti-malignancy treatment must be completed with evidence of remission prior to instituting therapy. SEROSTIM should be discontinued if there is evidence of recurrent activity. Patients should be examined frequently for progression or recurrence of the underlying disease process.
- In patients who are hypersensitive to or have a history of previous allergic reaction to somatropin or to any of the excipients.
- In patients with active neoplasia (either newly diagnosed or recurrent). Any anti-tumour therapy should be completed prior to starting therapy with SEROSTIM, and should be discontinued if there is evidence of recurrent tumor growth.
- In patients with diabetes mellitus.
- In patients with proliferative or preproliferative diabetic retinopathy.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- SEROSTIM (somatropin 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 and hypogonadism, which are common in individuals with AIDS and which may contribute to catabolism and weight loss, should be corrected prior to initiation of SEROSTIM therapy.
- Any substitution of Growth Hormone products should be made cautiously and only under medical supervision
- SEROSTIM shall only be used if, once reconstituted, the resulting solution is water-clear and devoid of particulate matter

General

A significant increase in mortality was reported among growth hormone treated patients with acute critical illnesses in intensive care units due to complications following open heart surgery or abdominal surgery, multiple accidental trauma or acute respiratory failure compared with those receiving placebo (see CONTRAINDICATIONS and ADVERSE REACTIONS).

Fluid retention is expected during growth hormone therapy. Oedema, joint swelling, arthralgias, myalgias, paresthesias may be clinical manifestations of fluid retention. However, these effects are dose dependent, and may resolve spontaneously with analgesic therapy, they usually resolve by reducing the total daily dose by 50% or the number of doses given per week.

It is recommended that SEROSTIM be administered using sterile, disposable syringes and needles(see PART III: CONSUMER INFORMATION). 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 needles and syringes should be used. To avoid transmission of disease, cartridge and prefilled syringe shall not be used by more than one person.

When SEROSTIM is administered subcutaneously at the same site over a long period, local tissue atrophy may result. This can be avoided by rotating the injection site daily.

Carcinogenicity and Mutagenesis

Carcinogenicity studies have not been conducted. There is no evidence from animal studies to date of SEROSTIM-induced mutagenicity.

Treatment with growth hormone may have an increased risk of developing neoplasm. Patients on SEROSTIM treatment should be monitored for the emergence of any new malignancy, particularly if they have a history of any neoplasm, and the product discontinued if a new tumour, signs of relapse or tumour progression are detected.

Kaposi's sarcoma, lymphoma, cervical cancer in women and other malignancies are common in AIDS patients. In clinical studies, the risk of developing new Kaposi sarcoma lesions and lymphomas were not found to be increased. The effect of SEROSTIM on the incidence of cervical cancer has not been assessed in clinical trials since the majority of patients included were male. The potential effects of growth hormone on other malignancies are unknown. Evidence is available suggesting the possibility that growth hormone might increase the risk of development of cancers other than lymphoma, in particular colorectal cancer. Although this evidence is not conclusive, the advisability of a regular screening program for colorectal cancer should be discussed with patients having known risk factors for this malignancy.

Intracranial Hypertension (IH)

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

Idiopathic Intracranial Hypertension

Idiopathic intracranial hypertension has been recognized as a complication (early in treatment usually) of growth hormone treatment. The diagnosis is made on the basis of clinical symptoms

such as severe, persistent or recurrent headache, visual problems, nausea and/or vomiting, papilloedema and temporal relationship to growth hormone. Physicians and parents should be attentive to relevant symptoms such as headache and visual problems in patients under growth hormone therapy. Fundoscopic examination should be performed routinely before initiating treatment with growth hormones to exclude pre-existent papilloedema regularly assessed during treatment. If papilloedema is confirmed by fundoscopy, growth hormone treatment should be stopped. It can be restarted at a lower dose after idiopathic-intracranial hypertension has resolved which occurs rapidly when treatment is withdrawn. If growth hormone treatment is restarted, careful monitoring for symptoms of intracranial hypertension is necessary, and treatment should be discontinued if intracranial hypertension recurs. At present, there is insufficient evidence to guide clinical decision making in patients with resolved intracranial hypertension. Fundoscopic evaluation of patients is therefore recommended at the initiation and periodically during the course of SEROSTIM therapy.

Dependence/Tolerance:
Inappropriate use of SEROSTIM by individuals who do not have indications for which growth hormone is approved, may result in clinically significant negative health consequences (see ADVERSE REACTIONS). SEROSTIM is not a drug of dependence.

Endocrine and Metabolism
Hyperglycemia may occur in HIV-infected individuals due to a variety of reasons. SEROSTIM use was associated with a minimal increase of mean blood glucose concentration. Patients with diabetes mellitus or other risk factors for glucose intolerance should be monitored closely during SEROSTIM therapy.

In adults with risk factors for insulin resistance or glucose intolerance, such as obesity, a family history of diabetes mellitus and those on high dose corticosteroid therapy, growth hormone therapy may induce Type II Diabetes Mellitus if the insulin secretory capacity is impaired.

Hypothyroidism may develop during treatment with SEROSTIM. Growth hormone can affect the metabolism of thyroid hormones by increasing the extrathyroidal conversion of T4 to T3. Thyroid function should be evaluated before starting SEROSTIM therapy and regularly assessed during treatment.

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.

Concomitant Medical Conditions:
Patients with significant cardiac, hepatic or renal diseases were excluded from clinical studies. Therefore, the potential benefit of SEROSTIM treatment for these patients should be weighed against the possible risks.

Diagnosis and treatment of any identifiable factor attributing to weight loss such as opportunistic infection, malabsorption and inadequate nutritional intake and hypogonadism, which are common in individuals with AIDS disease should be monitored.

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.

Immune
As for any recombinant product, SEROSTIM is potentially immunogenic. Consequently, if any serious hypersensitivity or allergic reaction occurs, SEROSTIM should be discontinued immediately and appropriate therapy initiated.

Local allergic reactions:
With growth hormone therapies SEROSTIM patients may experience redness, swelling, pain, inflammation, or itching at the site of injection. (see ADVERSE REACTIONS). Most of these minor reactions usually resolve in a few days to a few weeks. They may occur if the injection is not properly made (irritants in the skin cleansing agent or poor injection technique), or if the patient is allergic to the growth hormone or any excipients. (see CONTRAINDICATIONS).

Rarely, SC administration of growth hormone products can result in lipoatrophy (depression in the skin). Patients should be advised to consult their doctor if they notice any of these conditions. Continuous rotation of the injection site within a given area may help reduce or prevent these reactions. On rare occasion, injection site reactions may require discontinuation of SEROSTIM therapy.

Systemic allergic reactions:
Systemic allergic reactions have rarely occurred with SEROSTIM. If any serious hypersensitivity or allergic reactions occurs, SEROSTIM therapy should be discontinued immediately and appropriate therapy initiated as per general guidelines.

Antibody production:
As with all protein pharmaceuticals, a small percentage of patients may develop antibodies during treatment with growth hormones. Patients who have demonstrated an allergic reaction to other growth hormone products may demonstrate an allergic reaction to SEROSTIM (see ADVERSE REACTIONS). None of the study participants with AIDS wasting who were treated with SEROSTIM for the first time developed detectable antibodies to SEROSTIM.

Musculoskeletal

Increased tissue turgor (non-edematous swelling, particularly in the hands and feet) and musculoskeletal discomfort (pain, swelling and/or stiffness) may occur during treatment with SEROSTIM, but may resolve spontaneously, with analgesic therapy, or after reducing the frequency of dosing (see DOSAGE AND ADMINISTRATION).

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

Pancreatitis in Children:
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.

Renal / Hepatic / Biliary / Pancreatic impairments.
A reduction in somatropin clearance has been noted in patients with hepatic dysfunction as compared with normal controls. Whether the clearance of the product is affected in patients with biliary or pancreatic impairment is unknown. The safety of SEROSTIM has not been established in patients with renal, hepatic, biliary or pancreatic impairments. Growth hormone requirements may need to be adjusted in patients with renal and/or hepatic and/or biliary and/or pancreatic impairments.

Sexual Function/Reproduction
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 (see TOXICOLOGY).

Information for patients
Patients should be informed about potential advantages and disadvantages of growth hormone therapy including the possible side effects. If home use is determined to be desirable by the physician, patients should also be offered instruction for use of injection devices, storage, travelling and other pertinent information. (see PART III: CONSUMER INFORMATION). Female patients should be advised to inform their doctor if they are pregnant or are contemplating pregnancy. Careful monitoring, as well as general health is essential in pregnant patients. (see Special Populations and PART III: CONSUMER INFORMATION).

Special Populations

Adult: Experience with prolonged treatment in adults is limited. Adverse events such as peripheral edema, myalgia, arthralgia, and paresthesia were reported during post-marketing studies (see ADVERSE REACTIONS).

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

Nursing Women: It is not known whether this drug is excreted in human milk. However, a study done on lactating rats showed that the concentration in milk 24 h after administration were 30 times higher than blood concentration at the same time point. Because many drugs are excreted in human milk, caution should be exercised when somatropin is administered to a nursing mother. SEROSTIM is not recommended for use during lactation.

There have been no studies with somatropin in lactating women. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SEROSTIM is administered to lactating women.

Pediatrics: There is limited experience with SEROSTIM in patients under 18 years of age. SEROSTIM should not be used in the pediatric group until further data becomes available.

Geriatrics: Clinical studies with SEROSTIM did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Elderly patients may be more sensitive to growth hormone action, and may be more prone to develop adverse reactions. Thus, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range.

Monitoring and Laboratory Tests

SEROSTIM therapy should be carried out under the regular guidance of a physician who is experienced in the diagnosis and management of AIDS. Monitoring is advisable when SEROSTIM is administered in combination with drugs known to be metabolised by cytochrome 3A4 hepatic enzymes, such as some anti-retroviral drugs (see DRUG INTERACTIONS).

Thyroid function should be evaluated before starting SEROSTIM therapy and regularly assessed during treatment.

Patients on SEROSTIM therapy should be monitored for the emergence of any new malignancy and the treatment discontinued if a new tumour or signs of relapse are detected.

With Growth Hormone therapy the need for regular IGF-1 monitoring shall be considered to maintain IGF-1 within the normal range for age and sex. Glucose levels should be determined before starting SEROSTIM therapy and closely monitored during therapy. Because human growth hormone may induce a state of insulin resistance, patients should be observed for evidence of glucose intolerance. Patients with diabetes or glucose intolerance should be monitored closely during therapy with human growth hormone.

Growth hormone administration is followed by a transient phase of hypoglycemia of approximately 2 hours, then from 2-4 hours onward by an increase in blood glucose levels despite high insulin concentrations.

Serum levels of inorganic phosphorus, alkaline phophatase, and parathyroid hormone (PTH) may increase with growth hormone therapy.

In case of persistent oedema or severe paraesthesia the dosage should be decreased in order to avoid the development of carpal tunnel syndrome.

Clinical manifestations of fluid retention are usually transient and dose dependent.

Occupational Hazards
SEROSTIM is not expected to interfere with the patient's ability to drive or use machinery. No formal studies on the effects on the ability to drive and use machinery have been performed.

ADVERSE REACTIONS

Adverse Drug Reaction Overview
The most commonly reported adverse events reported in clinical studies conducted with SEROSTIM (somatropin for injection) were: musculoskeletal discomfort, fever, increased tissue turgor, diarrhoea, neuropathy, nausea, headache, abdominal pain, fatigue, leucopenia and albuminuria. Among these, increased tissue turgor, nausea and musculoskeletal discomfort were more frequent in the SEROSTIM group as compared to the placebo group (statistically significant, $p \leq 0.05$).

The most frequently reported adverse reactions resulting in clinical intervention (e.g., discontinuation of SEROSTIM, adjustment in dosage, or the need for concomitant medication to treat an adverse reaction symptom) were increased tissue turgor and musculoskeletal discomfort.

Clinical Trial Adverse Drug Reactions
> *Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.*

In two placebo-controlled clinical trials in which 205 patients were treated with SEROSTIM the most common adverse reactions felt to be associated with SEROSTIM were musculoskeletal discomfort and increased tissue turgor (non-edematous swelling, particularly of the hands or feet) (see WARNINGS AND PRECAUTIONS). 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 from underlying signs or symptoms of AIDS or associated intercurrent illnesses.

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 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.

Common Clinical Trial Adverse Events

Clinical adverse events which occurred during the first 12 weeks of study in at least 1% of those who received SEROSTIM during the two placebo-controlled trials are listed below by treatment group.

Body System Preferred Term	SEROSTIM (n=205) %	Placebo (n=150) %
BODY AS A WHOLE – GENERAL		
Fever	31.2	29.3
Increased Tissue Turgor*	27.3	2.7
Fatigue	17.1	16.0
Rigors	9.3	6.7
Influenza-like Symptoms	5.4	8.0
Malaise	4.9	3.3
Asthenia	3.9	4.0
Carpal Tunnel Syndrome	2.9	0.0
Tolerance Increased	2.9	0.0
Death	2.4	2.0
Chest Pain	2.4	0.7
Pain	1.0	2.7
Hot Flashes	1.0	0.7
Allergic Reaction	1.0	0.0
GASTRO-INTESTINAL SYSTEM		
Diarrhoea	25.9	20.0
Nausea*	25.9	16.0
Abdominal Pain	17.1	18.7
Vomiting	11.7	12.0
Flatulence	5.9	2.7
Leukoplakia Oral	5.4	4.0
Mouth Dry	4.4	1.3
Constipation	2.9	2.7
Dyspepsia	2.4	4.7
Dysphagia	2.0	1.3
Oesophagitis	2.0	0.7
Pancreatitis	1.5	0.7
Stomatitis Ulcerative	1.0	3.3
Colitis	1.0	1.3
Rectal Disorder	1.0	1.3
Gastritis	1.0	0.7

Tongue Ulceration	1.0	0.7
Gingivitis	1.0	0.0
Tongue Disorder	1.0	0.0
MUSCULO-SKELETAL SYSTEM		
Musculoskeletal Discomfort*	53.7	33.3
Muscle Weakness	2.4	0.7
CENTRAL&PERIPHERAL NERVOUS SYSTEM		
Neuropathy	25.9	17.3
Headache	19.0	20.7
Dizziness	3.4	4.7
Convulsions	1.5	1.3
Encephalopathy	1.5	0.0
Tremor	1.0	1.3
Nystagmus	1.0	0.7
Meningism	1.0	0.0
RESPIRATORY SYSTEM		
Dyspnoea	9.8	6.0
Coughing	9.3	13.3
Sinusitis	8.8	10.0
Upper Resp Tract Infection	7.8	6.0
Pharyngitis	5.9	4.7
Rhinitis	3.9	6.0
Pneumonia	3.9	2.7
Bronchitis	2.4	4.0
Sputum Increased	2.4	0.0
Respiratory Disorder	2.0	0.7
Bronchospasm	1.5	2.0
Pneumonitis	1.5	0.7
Pleurisy	1.5	0.0
WHITE CELL AND RETICULOENDOTHELIAL SYSTEM DISORDERS		
Lymphadenopathy	14.1	16.0
Lymphadenopathy Cervical	2.0	3.3
Eosinophilia	1.0	2.7
SKIN AND APPENDAGES		
Sweating Increased	14.1	8.7
Rash*	5.9	13.3
Skin Disorder	5.9	6.0
Folliculitis	4.9	2.7
Alopecia	2.0	0.7
Photosensitivity Reaction	2.0	0.7
Pigmentation Abnormal	1.5	1.3
Seborrhoea	1.5	0.7
Dermatitis	1.0	1.3
Skin Ulceration	1.0	1.3
Acne	1.0	0.0
Skin Discolouration	1.0	0.0
Verruca	1.0	0.0
PSYCHIATRIC		
Anorexia	12.2	9.3
Insomnia	11.2	9.3
Depression	8.8	6.0

Anxiety	5.4	6.0
Somnolence	2.4	0.7
Nervousness	2.0	0.7
Appetite Increased	1,5	2.0
Amnesia	1,0	0.7
Thinking Abnormal	1.0	0.0
METABOLIC AND NUTRITIONAL		
Hyperglycaemia	10.2	6.0
Hypertriglyceridaemia	9.3	7.3
Dehydration	3.4	4.0
Cachexia	1.5	2.7
Hypokalaemia	1.5	0.7
Glycosuria	1.0	2.0
Thirst	1.0	0.7
Acidosis	1.0	0.0
RESISTANCE MECHANISM DISORDERS		
Moniliasis	9.3	8.0
Infection Bacterial	6.8	2.0
Pneumocystis Carinii Infection	4.4	5.3
Infection Viral	4.4	1.3
Infection	2.9	2.0
Herpes Simplex	2.4	5.3
Sepsis	1.5	2.0
Abscess	1.5	1.3
Infection Fungal	1.5	0.7
Herpes Zoster	1.0	0.7
URINARY SYSTEM		
Albuminuria	15.1	9.3
Haematuria	6.8	4.7
Urinary Tract Infection	1.0	0.7
Nocturia	1.0	0.0
LIVER AND BILIARY SYSTEM		
Hepatic Function Abnormal	2.0	0.7
Hepatomegaly	1.5	2.7
Hepatitis	1.0	0.0
RED BLOOD CELL		
Anaemia	12.2	8.7
HEART RATE AND RHYTHM		
Tachycardia	11.2	6.0
VISION		
Retinitis	3.4	2.7
Vision Abnormal	2.9	3.3
Photophobia	1.0	0.0
PLATELET, BLEEDING & CLOTTING		
Thrombocytopenia	5.9	6.0
Purpura	1.0	4.7
CARDIOVASCULAR, GENERAL		
ECG Abnormal	1.5	2.7
Heart Murmur	1.5	1.3
Hypertension	1.5	0.7
Hypotension	1.0	1.3
APPLICATION SITE		
Injection Site Pain	2.9	1.3

Injection Site Reaction	2.0	2.7
NEOPLASMS		
Sarcoma	3.4	2.7
REPRODUCTIVE, MALE		
Epididymitis	1.0	0.7
Penis Disorder	1.0	0.7
Hernia Inguinal	1.0	0.0
HEARING AND VESTIBULAR		
Ear Disorder	2.0	2.0
Earache	2.0	1.3
Hearing Decreased	1.0	0.0
ENDOCRINE		
Gynaecomastia	2.4	0.7
Breast Pain Male	1.5	0.0

* statistically significant difference, $p<0.05$

The table above displays all adverse events reported in clinical studies, regardless of causality assessment and severity. Among the adverse events, several can be considered as adverse reactions to SEROSTIM, either by analyzing the difference in frequency as compared to placebo, or by evaluating their plausibility in relationship to the known mechanism of action of SEROSTIM. Carpal tunnel syndrome, peripheral neuropathies and hyperglycaemia were more frequent than in the placebo group and are known effects of somatropin (see WARNINGS AND PRECAUTIONS).

Less Common Clinical Trial Adverse Drug Reactions

Adverse events which occurred in less than 1% of study participants receiving SEROSTIM 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.

Body as a Whole – General :	Syncope, chest pain substernal, hypovolaemia
Gastro-intestinal System :	abdomen enlarged, eructation, haemorrhoids, melaena, oesophageal ulceration, duodenitis, enanthema, gastric ulcer, gastro-intestinal disorder, haemorrhage rectum, haemorrhoids thrombosed, hiccup, intestinal obstruction, peptic ulcer, periodontal destruction, stomatitis aphthous, tooth disorder
Musculo-skeletal System :	bursitis
Central & Peripheral Nervous System :	cerebral atrophy, migraine, gait abnormal, neuritis cranial, sensory disturbance, dysphonia, hyperkinesias, hyperreflexia, vertigo
Respiratory System:	chest x-ray abnormal, hypoxia, pneumothorax, respiratory insufficiency
White Cell and Reticuloendothelial System Disorders :	leukocytosis
Skin and Appendages :	skin dry, eczema, rash maculo-papular, hypertrichosis, psoriasis
Psychiatric :	agitation, confusion, concentration impaired, libido decreased, libido increased, neurosis
Metabolic and Nutritional :	Hypoglycaemia, hyperkalaemia, hypophosphataemia, serum iron decreased, diabetes mellitus, hyperglobulinaemia, hypocalcaemia, hyponatraemia, oedema pharynx, serum iron increased
Resistance Mechanism Disorders :	toxoplasmosis
Urinary System :	dysuria, nephropathy toxic, renal calculus, urine abnormal, polyuria,

	renal cyst
Liver and Biliary System :	cholecystitis, hepatitis cholestatic, hepatosplenomegaly, jaundice
Red Blood Cell :	splenomegaly
Heart Rate and Rhythm :	bradycardia, qt prolonged, palpitation
Vision :	conjunctivitis, conjunctival discolouration, glaucoma, miosis, retinal oedema
Platelet, Bleeding & Clotting :	prothrombin increased
Cardiovascular, General :	hypotension postural, cardiomegaly, cyanosis
Application Site :	otitis externa
Neoplasms :	lymphoma malignant
Reproductive, Male :	Prostatic disorder, genital eruption male, orchitis
Hearing and Vestibular	tinnitus
Endocrine:	adrenal hypercorticism, hypothyroidism
Vascular (extracardiac) :	peripheral ischaemia, atherosclerosis, flushing, purpura, telangiectasis

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.

Abnormal Hematologic and Clinical Chemistry Findings

Adverse Event	**SEROSTIM (n=205) %**	**Placebo (n=150) %**
Leukopenia*	15.1	24.7
Albuminuria	15.1	9.3
Granulocytopenia	14.1	21.3
Lymphadenopathy	14.1	16.0
Anemia	12.2	8.7
SGOT increased	11.7	6.0
Tachycardia	11.2	6.0
Hyperglycemia	10.2	6.0
SGPT increased	10.2	5.3
Phosphatase alkaline increased	7.3	4.7
Creatinine Phosphokinase increased	2.0	0.7
LDH increased	2.0	0.7
Amylase increased	1.5	2.0

*statistically significant difference, $p < 0.05$

Post-Market Adverse Drug Reactions

During post-marketing surveillance, the following adverse reactions have been reported. The indicated frequency is an estimate based on reporting rates.

Reactions reported at frequency >1% :

Body as a Whole – General Disorders:
Oedema (mainly peripheral)
Carpal tunnel syndrome
Musculo-skeletal Disorders:
Arthralgia, myalgia
Central & Peripheral Nervous System Disorders:

Paresthesia, hypoesthesia
Metabolism Disorders:
Increase in blood glucose levels
Endocrine Disorders:
Gynecomastia
Heart Rate and Rhythm Disorders:
Tachycardia

Reactions reported at frequency <1%:

Central & Peripheral Nervous System Disorders:
Idiopathic intracranial hypertension has been reported with somatropin in children
Diabetes - During postmarketing surveillance, cases of new onset glucose intolerance, diabetes mellitus and exacerbation of pre-existing diabetes mellitus have been reported in patients receiving SEROSTIM. Some patients developed diabetic ketoacidosis. In some patients, these conditions improved when SEROSTIM was discontinued while in others the glucose intolerance persisted.
Neoplasms:
Some cases of malignancies (mainly lymphoma) have been reported in post-marketing surveillance (see WARNINGS AND PRECAUTIONS).

Reactions reported with frequency unknown:

Gastrointestinal disorders:
Pancreatitis
Immune system disorders:
Localized and generalized hypersensitivity reactions

DRUG INTERACTIONS

During clinical trials in which all patients received concomitant anti-retroviral therapy there were no detectable increases in plasma viral load following SEROSTIM (somatropin for injection) therapy, as measured by quantitative HIV-RNA analysis. Patients with AIDS wasting considered for treatment with SEROSTIM should also receive concomitant approved anti-retroviral therapy.

No formal interaction studies have been performed in patients treated with SEROSTIM. Published in vitro data indicate that growth hormone treatment may increase cytochrome P 450 3A4 mediated antipyrine clearance in man. Caution is recommended when administering SEROSTIM with compounds that are metabolized by the CP450 or CY3A4 liver enzymes (e.g corticosteroids, sex steroids, anticonvulsants, cyclosporine and others.

Concomitant glucocorticoid treatment may inhibit the human growth hormone. If glucocorticoid replacement therapy is required, glucocorticoid dosage and compliance should be monitored carefully to avoid either adrenal insufficiency or inhibition of growth promoting effects. In patients treated with somatropin, previously undiagnosed secondary hypoadrenalism may be unmasked requiring glucocorticoid replacement therapy. In addition patients treated with glucocorticoid replacement therapy for previously diagnosed hypoadrenalism may require an increase in their maintenance or stress doses.

Growth hormone therapy may affect the metabolism of glucocorticoids, by inhibiting the microsomal enzyme 11β-hydroxysteroid dehydrogenase type 1 (11βHSD-1) which is required

for the conversion of cortisone to its active metabolite, cortisol, in hepatic and adipose tissue. Individuals with untreated GH deficiency have relative increases in 11βHSD-1 and serum cortisol. Introduction of Growth hormone therapy may result in inhibition of 11βHSD-1 and reduced serum cortisol concentrations. In consequence, previously undiagnosed central (secondary) hypoadrenalism may be unmasked and glucocorticoid replacement may be required in patients treated with Growth Hormones.

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. However, the maximum recommended weekly dose should not be exceeded.

Interactions with food, herbal products and laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations
Before initiating a patient on SEROSTIM (somatropin for injection) therapy, please review completely the CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS sections. The patient's medical history for hypersensitivity reactions should be carefully evaluated prior to performing the injection.

SEROSTIM treatment should be carried out under regular guidance of a physician experienced in the diagnosis and management of HIV and wasting.

SEROSTIM dosage should be individualized for each patient according to body weight.

Recommended Dose and Dosage Adjustment
SEROSTIM 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 should be administered at a dose of 0.1 mg/kg subcutaneously daily at bedtime.

Missed Dose
For patients who miss a dose, it is not recommended to double the next dose. The patients should be reminded to contact the physician monitoring their treatment.

Administration

Administer subcutaneously daily at bedtime. Dose reductions for side effects felt to be related to treatment with SEROSTIM, which are unresponsive to symptomatic treatment, may be effected by reducing the number of doses given per week. In controlled trials, dose reductions were accomplished by reducing the frequency of dosing to five or three times a week.

Injection sites should be rotated.

SEROSTIM once reconstituted should be administered using sterile, disposable syringes and needles. The syringe used should be of appropriately small volume to ensure accurate dose withdrawal. The calculated dose should be withdrawn for subcutaneous administration.

Reconstitution:
See Part III CONSUMER INFORMATION/Proper use of this Medication for reconstitution instructions.

Once the appropriate dose for a patient has been determined, reconstitute each vial of SEROSTIM with the diluent supplied.

Once SEROSTIM is reconstituted with the diluent supplied (Sterile Water for Injection, USP), the reconstituted solution should be used immediately (within 3 hours). Although not recommended, it may be stored for up to 24 hours at 2-8 °C. As there is no preservative in this reconstituted solution, any unused solution should be discarded once the dose is given.

OVERDOSAGE

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

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTIONS AND CLINICAL PHARMACOLOGY

Mechanism of Action

HIV-associated wasting is a metabolic disorder characterized by specific 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. LBM depletion results in muscle weakness, organ failure, immune deficiency, general inanition and death. Unlike nutritional intervention for HIV-associated wasting, in which supplemental calories are converted predominantly to body fat which is essentially inert in day-to-day metabolic balance, the anabolic and anti-catabolic effects of somatropin treatment resulted in a prompt and sustained increase in LBM and a decrease in body fat with a significant increase in body weight due to the dominant effect of LBM gain.

Pharmacodynamics

Effects on Protein, Lipid, and Carbohydrate Metabolism: A one-week study in 6 patients with HIV-associated wasting has shown that treatment with somatropin 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 somatropin resulted in the retention of phosphorous, potassium, nitrogen, and sodium. The ratio of retained potassium and nitrogen during somatropin therapy was consistent with retention of these elements in lean tissue. In clinical studies (12 weeks), somatropin significantly increased lean body mass. There was also a proportionate increase in intracellular and extracellular fluid during somatropin 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 somatropin-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 somatropin after subcutaneous administration of a formulation not equivalent to the marketed formulation was determined to be 70-90%. The t½ (Mean ± SD) after subcutaneous administration is significantly longer than that seen after intravenous administration to normal male volunteers, down-regulated with somatostatin (3.94 ± 3.44 hrs. vs. 0.58 ± 0.08 hrs.), indicating that the subcutaneous absorption of the clinically tested formulation of the compound is slow and rate-limiting.

Distribution: The steady-state volume of distribution (Mean ± SD) following IV administration of somatropin in healthy volunteers is 12.0 ± 1.08 L.

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

Elimination: The t½ (Mean ± SD) in nine patients with AIDS-related wasting with an average weight of 56.7 ± 6.8 kg, given a fixed dose of 6.0 mg r-hGH subcutaneously was 4.28 ± 2.15 hrs. The renal clearance of r-hGH after subcutaneous administration in nine patients with AIDS-related wasting was 0.0015 ± 0.0037 L/h. No significant accumulation of r-hGH appears to occur after 6 weeks of dosing as indicated.

Summary of SEROSTIM Pharmacokinetics Parameters in healthy volunteers

Parameters		C_{max} (mIU/mL)	AUC_{last} (mIU/mL)	AUC (mIU/mL)	AUC extrapolated (%)	t_{max} (h) median values
SEROSTIM	Mean (Min-max)	146	1090	1150	4.37	3.05

		(92 – 244)	(706–1440)	(867–1490)	(0.9–12.2)	(2.00–6.00)

1 mg = approx. 3 IU

Special Populations and Conditions

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 (somatropin for injection) in normal volunteers or patients infected with HIV.

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.

STORAGE AND STABILITY

Storage Recommendations:
Store SEROSTIM (somatropin for injection) lyophilized product at or below 25 °C. Do not use SEROSTIM after the expiry date shown on the label.

Diluents for Reconstitution:
The recommended diluent for reconstitution is:

Sterile Water for Injection, USP

Incompatibility:
SEROSTIM should not be mixed with other drugs.

Preparation of Solution:
To prevent possible contamination of the vial, wipe the rubber stopper with an antiseptic solution before puncturing it with the needle.

To reconstitute SEROSTIM, inject 1 mL of diluent into the vial of SEROSTIM, aiming the liquid against the vial wall. Swirl the vial with a GENTLE rotary motion until the contents are dissolved completely. DO NOT SHAKE. Because SEROSTIM is a protein, shaking can result in a cloudy solution; however, this opalescence does not indicate any decrease in potency.

Parenteral drug products should be inspected visually prior to administration. Do not inject if the reconstituted product contains particulate matter or is discoloured.

Stability and Storage of Solution:
When reconstituted with the diluent provided (Sterile Water for Injection,USP), the reconstituted solution should be used immediately (within 3 hours). Although not recommended, it may be stored for up to 24 hours at 2-8 °C. As there is no preservative in this reconstituted solution, any unused solution should be discarded once the dose is given.

SPECIAL HANDLING INSTRUCTIONS

The SEROSTIM (somatropin for injection) solution should not be administered if it contains particles or is not clear.

Any unused product or waste material should be disposed of in accordance with local requirements.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms and Composition

SEROSTIM (somatropin for injection) is available as a sterile, non-pyrogenic, lyophilized powder.

Each vial contains 5 mg somatropin, 1.2 mg phosphoric acid, 0.7 mg sodium hydroxide, 34.2 mg sucrose; sodium hydroxide and/or phosphoric acid for pH adjustment to pH 7.5 ± 0.1.

Packaging

The following vial size is available:
Cartons containing 1 vial of 5 mg somatropin for injection together with diluent (Sterile Water for Injection, USP).
Cartons containing 7 vials of 5 mg somatropin for injection together with diluent (Sterile Water for Injection, USP).

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Somatropin for injection

Chemical name: recombinant human Growth Hormone for Injection (r-hGH)

Molecular Formula: $C_{990}\ H_{1528}\ N_{262}\ O_{300}\ S_7$

Structural Formula:

-PHE-PRO-THR-ILE-PRO-LEU-SER-ARG-LEU-PHE-ASP
-ASN-ALA-MET-LEU-ARG-ALA-HIS-ARG-LEU-HIS-GLN-LEU-ALA
-PHE-ASP-THR-TYR-GLN-GLU-PHE-GLU-GLU-ALA-TYR-ILE-PRO
-LYS-GLU-GLN-LYS-TYR-SER-PHE-LEU-GLN-ASN-PRO-GLN-THR
-SER-LEU-CYS-PHE-SER-GLU-SER-ILE-PRO-THR-PRO-SER-ASN
-ARG-GLU-GLU-THR-GLN-GLN-LYS-SER-ASN-LEU-GLU-LEU-LEU
-ARG-ILE-SER-LEU-LEU-LEU-ILE-GLN-SER-TRP-LEU-GLU-PRO
-VAL-GLN-PHE-LEU-ARG-SER-VAL-PHE-ALA-ASN-SER-LEU-VAL
-TYR-GLY-ALA-SER-ASP-SER-ASN-VAL-TYR-ASP-LEU-LEU-LYS
-ASP-LEU-GLU-GLU-GLY-ILE-GLN-THR-LEU-MET-GLY-ARG-LEU
-GLU-ASP-GLY-SER-PRO-ARG-THR-GLY-GLN-ILE-PHE-LYS-GLN
-THR-TYR-SER-LYS-PHE-ASP-THR-ASN-SER-HIS-ASN-ASP-ASP
-ALA-LEU-LEU-LYS-ASN-TYR-GLY-LEU-LEU-TYR-CYS-PHE-ARG
-LYS-ASP-MET-ASP-LYS-VAL-GLU-THR-PHE-LEU-ARG-ILE-VAL
-GLN-CYS-ARG-SER-VAL-GLU-GLY-SER-CYS-GLY-PHE .

Molecular Weight: 22, 125 daltons

Description of Drug Substance:

Somatropin is a polypeptide hormone consisting of 191 amino acid residues and its structure is identical to that of growth hormone extracted from human pituitary glands. A large loop is formed by a disulfide bond between Cys^{53} and Cys^{165}. A second, smaller loop is formed by a disulfide bond near the carboxyl-terminal between Cys^{182} and Cys^{189}. The solution is a slightly opalescent liquid.

Biological Activity: The biological activity of growth hormone is approximately 3.0 international units/1mg

CLINICAL TRIALS

The clinical efficacy of SEROSTIM (somatropin for injection) was assessed in a short term metabolic study and two placebo-controlled Phase III clinical trials.

Study demographics and trial design

Table 1 - Summary of patient demographics for clinical trials

Study #	Trial design	Dosage, route of administration and duration	Total number of study subjects (n=number)	Mean age (Range) in Years	Gender
GF 4795	Open, parallel group, controlled (volunteers and HIV^+)	0.1 mg/kg/day s.c. once daily for 7 days	12 HIV negative (n=6) HIV^+ (n=6)	HIV–negative subjects: 31.8 (25-41) HIV^+ subjects: 35.8 (28-44)	Male (12)
GF 5341	Randomized, double-blind, placebo-controlled, in HIV^+ subjects	0.1 mg/kg/day s.c. once daily for 12 weeks	178 GH (n=90) Placebo (n=88)	39.2 (26-70) GH group 39.1 (27-73) Placebo group	Male (172) and Female (6)
GF5511	Open-label long-term extension. Continuation treatment after Serono protocol GF5341	0.1 mg/kg/day s.c. once daily	136 GH-GH (n=66) PL-GH (n=70)	39.67 (26-70) GH- GH group 39.29 (27-72) Placebo- GH group	Male (134) and Female (2)
GF 7033	Randomized, double-blind, placebo-controlled, in HIV^+ subjects	6 mg/day s.c. once daily for 12 weeks	177 GH (n=115) Placebo (n=62)	38.2 (24-69) GH group 37.5 (25-64) Placebo group	Male (173) and Female (4)

Study results

Narrative summary of study results

Metabolic data were obtained on HIV^+ men (with an average weight loss of 19%) and healthy HIV^- volunteers (with a normal weight for height) who were treated with SEROSTIM for 7 days while consuming a constant metabolic diet. Resting energy expenditure was paradoxically increased in the HIV^+ individuals at baseline. The rate of resting energy expenditure increased

during SEROSTIM treatment in both groups 136 (32.4) ± 2 (0.5) kJ (Cal)/kg LBM.day and 123 (29.3) ± 2 (0.2) kJ (Cal)/kg LBM.day (in HIV positive and HIV negative subjects, respectively). SEROSTIM therapy led to a prompt and sustained increase in body weight in HIV^+ and HIV^- individuals. Cumulative weight gain averaged 2.6 kg (4.5 ± 0.8%) in HIV positive subjects, and 2.3 kg (3.4 ± 0.5 %) among HIV negative subjects, respectively after 7 days. Urinary nitrogen excretion decreased in both groups while stool nitrogen was unchanged, indicating a positive nitrogen balance and retention of ingested protein. A decrease in blood urea nitrogen and the measured ratio of retained potassium to nitrogen were consistent with incorporation of dietary protein into lean tissue. Protein oxidation decreased, whereas lipid oxidation increased significantly. Thus short-term SEROSTIM treatment exerted an anti-catabolic, protein-sparing effect with significantly decreased protein oxidation and significantly increased lipid oxidation.

Table 2 - GF 4795 – Change in percent body weight, resting energy expenditure and urinary nitrogen excretion from baseline

Mean ± SEM	Body weight [a] (Δ vs baseline, %)		Resting Energy Expenditure[b] (Δ kcal/d vs baseline)		Urinary N Excretion [c] (Δ g/d vs baseline)	
Study day	HIV positive	HIV negative	HIV positive	HIV negative	HIV positive	HIV negative
0	-0.1± 0.1	-0.1± 0.3	7.0± 11.0	-29.0± 8.0	-0.10± 0.40	-0.18± 0.38
7	4.5± 0.8	3.4± 0.5	190.0± 32.0	185.0± 24.0	-5.56± 0.57	-4.24± 0.66

(a) Change in body weight is expressed as the mean (± SEM) of the differences (%) of that day's weight, compared to the average weight measured during the Baseline period*.
(b) Mean (± SEM) of differences between daily REE and average Baseline REE*
(c) Mean(± SEM) of differences between daily urinary nitrogen excretion and average Baseline urinary nitrogen excretion*
*Baseline values equaled of the average value for inpatient days –6, -5,-4,-3, -2, and -1

The clinical efficacy of SEROSTIM was assessed in two placebo-controlled clinical trials (GF 5341 and GF 7033). Of the 205 AIDS subjects exposed to HIV, only 5 were women. All study subjects received concomitant anti-HIV therapy. A multicenter, double-blind, placebo-controlled study compared SEROSTIM, at an average daily dose of 6 mg (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), the mean weight increase in the SEROSTIM treated group was 1.6 kg (3.5 lb). Mean differences in lean body mass change between the SEROSTIM-treated group and the placebo-treated group was 3.1 kg (6.82 lb) as measured by DEXA. Mean increase in weight and lean body mass 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). Patients in the SEROSTIM group also had significant gains in strength and endurance, as evidenced by a 13% greater maximal work output on treadmill testing, as well as significant improvement in overall quality of life. Increases in lean body mass were also correlated with a decrease in the rate of new AIDS-associated diagnoses.

Table 3 - GF 5341 – Body weight at baseline and Endpoint and change in body weight at Endpoint by treatment group (ITT population)

Variable	Visit	Treatment group	N	Mean	SD	Median	Range	p-value [(a)]
Body Weight (kg)	Baseline	r-hGH Placebo	88 83	61.67 61.49	7.92 7.44	61.36 62.27	(40.30-83.18) (41.36-77.27)	
	Endpoint[(b)]	r-hGH Placebo	88 83	62.75 61.58	9.45 7.93	63.64 61.36	(38.64-90.45) (40.91-80.91)	
Change in weight (kg)	Endpoint[(b)]	r-hGH Placebo	88 83	1.08 0.09	3.97 2.92	1.82 0.00	(-12.27-9.09) (-7.00-9.09)	0.009*

(a) p-values are from Wilcoxon Rank Sum
(b) Endpoint is equal to the latest post-baseline weight measurement
* Statistically significant at the 0.05 level

Table 4 - GF 5341 – Summary statistics and change from baseline for body weight (Evaluable population)

Variable	Visit	Treatment group	N	Mean	SD	Range	p-value [(a)]
Body Weight (kg)	Baseline	r-hGH Placebo	69 71	61.73 61.99	7.01 7.27	(40.30-82.27) (47.27-77.27)	
	Week 12	r-hGH Placebo	69 71	63.37 62.11	8.62 7.81	(40.60-90.45) (46.36-80.91)	
Change in weight (kg)	Week 12	r-hGH Placebo	69 71	1.63 0.12	3.71 3.11	(-5.91-9.09) (-7.00-9.09)	0.011*

(a) p-values for significance of treatment group differences are from an analysis of variance model with group and site as the factors
* Statistically significant at the 0.05 level

Patients completing 12 weeks of treatment were eligible to receive open-label SEROSTIM therapy. There were 48 GH-GH subjects and 53 PL-GH subjects who had body weight measurements obtained at baseline and at Month 3. 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 mean weight change during 12-weeks of open label treatment with SEROSTIM and LBM change were not significant. There was a significantly lower occurrence rate of new AIDS-defining diagnoses during open-label therapy for the group who had received SEROSTIM in the three previous months.

Table 5 - GF 5511 – Body weight at baseline and Month 3 and change in body weight at Month 3 (by enrollment group)

Variable	Visit	Enrollment group	N	Mean	SD	Median	Range	p-value [(a)]
Weight (kg)	Baseline	GH-GH PL-GH	48 53	64.30 62.39	7.02 7.96	64.62 62.27	(48.18, 78.90) (46.36, 79.55)	
	Month 3	GH-GH PL-GH	48 53	64.02 63.26	7.45 8.70	64.77 64.55	(47.27, 79.50) (39.55, 80.91)	
Change in	Month 3	GH-GH	48	-0.27	3.20	-0.15	(-11.36, 10.00)	0.700

weight (kg)		PL-GH	53	0.87	3.27	1.36	(-9.09, 6.36)	0.012*

(a) p-values are from the Wilcoxon Signed Rank Test
* Statistically significant at the 0.05 level

Figure 1: Studies GF5341 and 5511: Changes in Body Composition (mean±SEM)

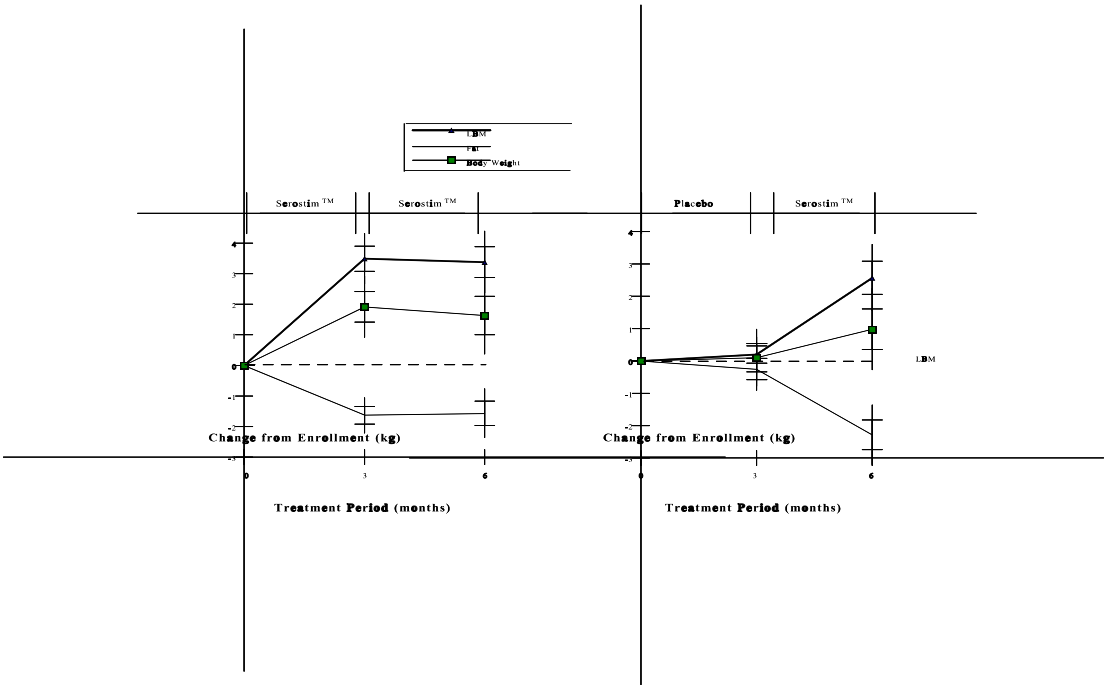
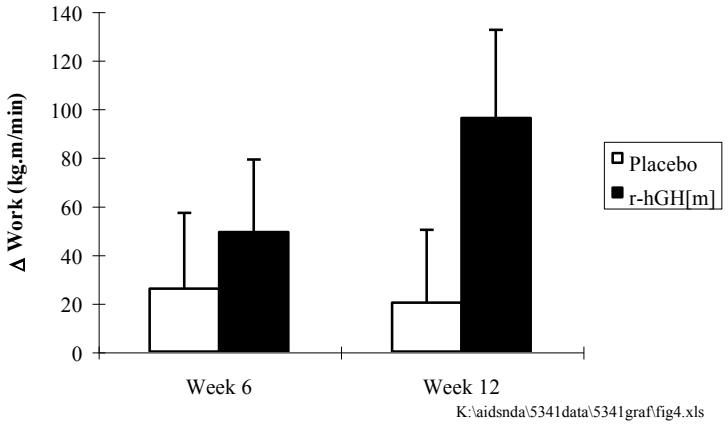


Figure 2: Study GF 5341: Treadmill Analysis Placebo versus r-hGH[m] (Evaluable Population)



* p = 0.039, Wilcoxon Rank Sum Test p-value for treatment difference.

A second multicenter, double-blind, placebo-controlled study comparing SEROSTIM, 6 mg/day administered subcutaneously vs. placebo, in AIDS patients with wasting enrolled 177 patients

who were randomized in a 2:1 ratio, to receive SEROSTIM or placebo. In the 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 drop-out was concurrent medical events including opportunistic infections.

Combined Clinical Results

When results of the two major Phase III clinical trials (GF5341 and GF7033) were combined, the group receiving SEROSTIM had a significantly greater improvement in overall quality of life compared to the placebo group, using two different instruments, the HIV-PARSE questionnaire, and the Well-Being scale. There was also a significant increase in the absolute neutrophil count in the group receiving SEROSTIM compared to placebo. The table below summarizes the key 3-month efficacy results of the two placebo-controlled studies combined.

Table 6: Summary of Three Month Efficacy Results from Placebo-Controlled Clinical Trials (Change from Baseline)

	SEROSTIM		**Placebo**	
	n	Results	n	Results
Lean Body Mass (kg)	69	+3.0*	69	-0.1
LBM Responders¥	69	70%*	69	12%
Absolute neutrophil count (cells/cm^2)	194	+290*	143	-170
Overall Quality of Life				
Well-Being questionnaire (score)	69	6.6*	44	5.7
PARSE (% responders)	138	61%*	114	45%
Treadmill work (kg ,m/min)	63	98.62*	60	20.07

¥ Major LBM response defined as >4% increase of LBM

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

TOXICOLOGY

A series of toxicology studies including acute, subacute, subchronic and long-term studies were conducted with somatropin. The animal species used for these studies included mice, rats and monkeys.

Single Dose Studies

Six acute toxicity studies were conducted in mice, rats and monkeys.

	Route of		

Species	Administration	Dose	Observations
Rats and mice	Subcutaneous	40 IU/kg (approx. 13.3 mg/kg)	Mortality, Clinical Signs, Behaviour Body Weight, Toxic Effects
Rats and mice	Intravenous	40 IU/kg (approx. 13.3 mg/kg)	
Rats	Subcutaneous and Oral	250 IU/kg (approx. 83.33 mg/kg)	
Rats	Oral	5, 10, 20, 40 IU/kg (approx. 1.67, 3.33, 6.67, 13.3 mg/kg)	
Monkeys	Subcutaneous	5, 10, 20 IU/kg (approx. 1.67, 3.33, 6.67 mg/kg)	
Mice	Oral	5, 10, 20, 40 IU/kg (approx. 1.67, 3.33, 6.67, 13.3 mg/kg)	

Animals were sacrificed and gross pathology examinations showed no abnormal finding, except for a vacuole in hepatocytes and a hyaline droplet in renal epithelium in one female monkey of the 20 IU/kg dose group.

Long-Term Studies

Six long-term studies by the subcutaneous route of administration were conducted with somatropin: 2 four-week subacute toxicity studies (one in rats and the other in monkeys), two thirteen-week studies (one in rats and one in monkeys) and 2 fifty-two-week studies (rats and monkeys).

Four-Week Studies		
	RATS (4 week study)	**MONKEYS (4 week study)**
# Animals	15/sex/group	3-5/sex/group
Dosage	Daily injections of 0, 0.2, 1.0, 5.0 and 10.0 IU/kg (approximately 0, 0.067, 0.33, 1.6 and 3.33 mg/kg) in bacteriostatic saline	Daily injections of 0, 0.2, 1.0 and 5.0 IU/kg (approximately 0, 0.067, 0.33 and 1.6 mg/kg) of somatropin or 0.2 and 5 IU/kg Asellacrin (pituitary-derived hGH) in 0.9% NaCl
Observations	Clinical signs, mortality, behaviour, ophthalmoscopic examinations, body weight, food consumption (rats) laboratory analyses and post-mortem examinations	
Results	The drug was well tolerated up to 10 IU/kg (approximately 3.33 mg/kg). Small number of slight hematological, biochemical and morphological changes, most notably in 5 and 10 IU/kg (approximately 1.6 and 3.33 mg/kg) groups. These were for the most part reversible, and none appeared detrimental to the health of the animals. Local tolerability was satisfactory.	The drug was well tolerated up to 5 IU/kg (approximately 1.6 mg/kg). None of the observations appeared to be treatment-related and no clearly identifiable antibodies to hGH were observed.

Thirteen-week Studies		
	RATS (13 week study)	**MONKEYS (13 week study)**

# of Animals	15/sex/group	3/sex/group
Dosage	Daily injections of 0, 0.2, 1.0 and 10 IU/kg (approximately 0, 0.067, 0.33 and 3.33 mg/kg) of somatropin, or 0.2 and 10 IU/kg Asellacrin (pituitary-derived hGH) in 0.9% NaCl	Daily injections of 0, 0.2, 1 and 5.0 IU/kg (approximately 0.067, 0.33 and 1.67 mg//kg) in 0.9% NaCl
Observations	Clinical signs, mortality, behaviour, ophthalmoscopic examinations, body weight, food consumption, laboratory analyses, anti-hGH antibodies (monkeys) and post-mortem examinations.	
Results	No overt signs of toxicity, a number of slight changes were observed due mainly to the biological activity of a heterologous hormone administered for a prolonged period of time.	Slightly higher values of GOT, GPT, γ-GTP and LAP found in males of the 5 IU (approx. 1.67 mg) group (but without any underlying histological change in liver) were the only findings. No antibodies to hGH were detected.

Fifty-two-week Studies		
	RATS (52 week study)	**MONKEYS (52 week study)**
# of Animals	20-30/sex/group	4/sex/group
Dose	Daily injections of 0, 0.2, 0.6 and 1.8 IU/kg (approximately 0, 0.067, 0.2 and 0.6 mg/kg) in 0.9% NaCl	Daily injections of 0, 0.2, 0.6 and 1.8 IU/kg (approximately 0, 0.067, 0.2 and 0.6 mg/kg) in 0.9% NaCl
Observations	Clinical signs, mortality, behaviour, ophthalmoscopic examinations, body weight, food consumption (rat), laboratory analyses, anti-hGH antibodies and post-mortem examinations	
Results	No treatment-related deaths. Ten rats died from incidental causes or spontaneous incidental pathology. No treatment-related clinical signs. No clinical changes at the injection site. Body weight and food consumption unaffected. No treatment-related eye abnormalities were seen. Minor increase in mean serum glucose levels in top-dose males. All rats developed high levels of antibodies to hGH by week 12, still present 8 weeks after end of study. Slight tendency towards increase of adrenal gland and spleen mean absolute weights without dose-correlation possible partial correlation with the slight increase in fasting body weight. No systemic drug-related modifications in gross pathology and histology. Some local changes due to needle trauma in treated and control rats.	No treatment-related deaths. One male (0.6 IU/kg/day [approximately 0.2 mg/kg]) died on day 245 (accidental trauma). No clinical or laboratory modifications attributable to the drug. No gross alterations at injection sites. No anti-hGH antibodies detected. Post-mortem examination showed no changes attributable to the drug. Histological examination of injection sites revealed needle trauma, with comparable frequency and severity among control and treated animals.

Other Studies

Sensitization potential

The potential of somatropin, bacteriostatic saline and metacresol for sensitization were assessed in the guinea pig maximization test. Groups of 20 male Dunkin Hartley albino guinea pigs were dosed intradermally and epicutaneously with somatropin reconstituted with bacteriostatic saline or 0.3% metacresol, with bacteriostatic saline, with 0.9% NaCl solution or with 0.3% metacresol alone. None of the animals showed a positive reaction when challenged with an occlusive skin patch. In the group treated with drug reconstituted in bacteriostatic saline, 40% and 50% of the

animals showed positive at the first and second intradermal challenges respectively. When reconstituted in metacresol, the drug caused severe anaphylaxis after intradermal challenge, due to the high dose used in the study. In the study using bacteriostatic saline as the diluent, lower doses were injected and only a moderate skin reaction due to sensitization was observed in guinea pigs. The drug appears to be a moderate sensitizer in guinea pigs, which is understandable since the human protein present in the drug is heterologous to this species but such events are not expected to occur in humans.

Irritating potential

One study investigating the ocular and dermal irritation potentials of the drug in rabbits showed no abnormalities.

Mutagenicity

A series of mutagenicity studies, consisting of Ames Test, Gene Conversion Test in S. cerevisiae, Unscheduled DNA Synthesis in Cultured HeLa Cells, Chromosome Aberration in Human Lymphocytes Cultured In Vitro and a Bone Marrow Micronucleus Test, were conducted in order to evaluate the mutagenic potential of somatropin.

Neither mutagenic nor clastogenic activity was observed with somatropin for any of the mutagenicity tests listed above.

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PART III: CONSUMER INFORMATION

[Pr]SEROSTIM® 5 mg/vial
(Somatropin for injection)

This leaflet is Part III of a three-part "Product Monograph" published when the drug is approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about SEROSTIM. Contact your health care professional if you have any questions about the drug.

ABOUT THIS MEDICATION

What is SEROSTIM used for?
SEROSTIM is indicated for the treatment of HIV wasting associated with catabolism, weight loss or cachexia.

What does SEROSTIM do?
HIV-associated wasting is a metabolic disorder characterized by specific 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. LBM depletion results in muscle weakness, organ failure, immune deficiency, general inanition and death. Unlike nutritional intervention for HIV-associated wasting, in which supplemental calories are converted predominantly to body fat which is essentially inert in day-to-day metabolic balance, the anabolic and anti-catabolic effects of SEROSTIM treatment resulted in a prompt and sustained increase in LBM and a decrease in body fat with a significant increase in body weight due to the dominant effect of LBM gain.

When should SEROSTIM not be used?
SEROSTIM should not be used in the following patient groups:

- in patients with acute critical illness due to complications following open heart or abdominal surgery, multiple accidental trauma or patients having acute respiratory failure.
- in the presence of any progression of underlying intracranial tumour. Intracranial tumour should be inactive and anti-malignancy treatment must be completed with evidence of remission prior to instituting therapy and SEROSTIM should be discontinued if there is evidence of recurrent activity. Patients should be examined frequently for progression or recurrence of the underlying disease process.
- patients who are hypersensitive to growth hormone or to any ingredient in the formulation, or component of the container.
- patients with active neoplasia (either newly diagnosed or recurrent). Any anti-tumour therapy should be completed prior to starting therapy with SEROSTIM and should be discontinued if there is evidence of recurrent tumor growth.
- patients with diabetes mellitus.
- patients with proliferative or preproliferative diabetic retinopathy.

The medicinal ingredient in SEROSTIM:
The common name of the active ingredient in SEROSTIM is somatropin.

The nonmedicinal ingredients in SEROSTIM:
Each vial of SEROSTIM contains the following non-medicinal ingredients: sucrose, phosphoric acid and sodium hydroxide.

The diluent which comes with SEROSTIM 5 mg/vial is sterile water.

What dosage forms of SEROSTIM are available?
SEROSTIM is available as a sterile, non-pyrogenic, lyophilized powder.

SEROSTIM is available in 5 mg vials each with vials of diluent (Sterile Water for Injection).

WARNINGS AND PRECAUTIONS

Before you use SEROSTIM talk to your doctor or pharmacist if:

- you are hypersensitive to somatropin or to any of the other ingredients of SEROSTIM
- you are pregnant or breastfeeding
- you have an acute critical illness due to complications following open heart or abdominal surgery, multiple accidental trauma or to patients having acute respiratory failure
- you develop hyperglycemia
- you experience increased tissue turgor (non-edematous swelling, particularly in the hands and feet) and musculoskeletal discomfort (pain, swelling and/or stiffness)
- you experience carpal tunnel syndrome

MEDICATION INTERACTIONS

During clinical trials in which all patients received anti-retroviral therapy there were no detectable increases in plasma viral load following SEROSTIM therapy. Patients with AIDS wasting considered for treatment with SEROSTIM should also receive approved anti-retroviral therapy.

No formal interaction studies have been performed in patients treated with SEROSTIM.

Interactions with food, herbal products and laboratory tests have not been established.

PROPER USE OF THIS MEDICATION

Usual dose:
SEROSTIM 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 0.1mg/kg

In patients who weigh less than 35 kg, SEROSTIM should be administered at a dose of 0.1 mg/kg subcutaneously daily at bedtime.

Treatment with the medicinal product should be initiated under the supervision of a specialised physician.

Preparing SEROSTIM for Administration
Here are the things you will need before you inject SEROSTIM:

- 3 alcohol swabs
- Cotton swab
- 3 cc syringe & 23 gauge needle for mixing
- BD insulin syringe for injection
- 1 vial of SEROSTIM
- Diluent vial (You need this sterile liquid - the diluent - to dissolve the SEROSTIM powder and make it injectable.)
- Syringe safety disposal container for used vials and needles

Always use unopened, sterile needles and syringes and keep the needles capped until needed.

TIP: Your doctor or nurse will explain how much diluent to add to the vial of SEROSTIM and how much SEROSTIM to inject.

Getting Ready to use SEROSTIM
1. Begin by choosing a clean flat surface (like a kitchen or bathroom counter).
2. Wash your hands thoroughly with soap and water. This helps prevent infection.
3. Check the expiration date of your SEROSTIM vial.

Drawing Up the Diluent
1. Carefully twist the needle cover off the long needle syringe.
2. Pull out the plunger to the amount recommended by your doctor or nurse. This brings air into the syringe.
3. Remove the flip-off cap from the diluent vial and discard. Wipe the rubber stopper of the vial with an alcohol swab.
4. Hold the vial firmly on the countertop. Put the needle into the stopper of the SEROSTIM diluent vial. Push the plunger of the syringe and inject the air into the vial.
5. Turn the vial upside down. Make sure the needle tip stays in the liquid. Pull back on the plunger until the marks on the barrel of the syringe show that the amount of the diluent suggested by your doctor or nurse has been drawn out.
6. If air bubbles appear in the syringe, gently push the plunger into the syringe to send the air into the vial. You may have to tap the syringe lightly so you can push the bubbles out. Draw up more diluent, if needed, until you have the amount your doctor has prescribed.
7. Pull out the needle from the diluent.

TIP: Be careful not to touch the uncapped needle with your fingers or let the needle touch anything.

Mixing SEROSTIM
1. Remove the flip-off cap from the SEROSTIM vial and discard. Wipe the rubber stopper of the vial with an alcohol swab.
2. With the same syringe, put the long needle into the stopper of the SEROSTIM vial. Gently place the needle tip against the vial wall. Slowly inject the diluent, aiming the stream of diluent at the glass wall of the vial. DO NOT AIM THE STREAM AT THE WHITE POWDER at the bottom of the vial.
3. Take out the needle and throw it away in the safety container.
4. Gently swirl (don't shake) the vial until the powder is completely dissolved. The SEROSTIM mixture should be clear. If it stays hazy, cloudy or has pieces floating in it after mixing, do not use it.

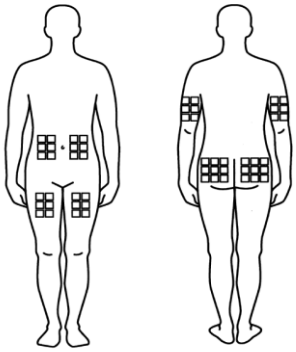
TIP: If SEROSTIM becomes cloudy after mixing, return it to your pharmacist or nurse.

Preparing SEROSTIM for Injection
1. Re-wipe the rubber stopper of the SEROSTIM vial with an alcohol swab.
2. Pick up the insulin syringe with the short needle and carefully take off the needle cover.
3. Pull out the plunger to the amount recommended by your doctor or nurse. This brings air into the syringe.
4. Slowly insert the needle straight through the center of the rubber stopper of the vial of newly mixed SEROSTIM. Gently push the plunger to inject air into the vial.
5. Turn the vial upside down with the syringe needle still in it, holding the vial in one hand. Be sure the tip of the needle is in the solution. Using your other hand, slowly pull back on the plunger until the amount of SEROSTIM prescribed is in the syringe.
6. Remove the needle from the vial.
Hold the syringe straight up and tap gently. Put the plastic needle guard back until injection time. The injection should be given as soon after filling the syringe as possible. Do not store SEROSTIM in the syringe.

TIP: Be careful not to touch the uncapped needle with your fingers - or let the needle touch anything.

Picking an Injection Site
You should pick a different site to inject each day, rotating through arms, legs and abdomen. The buttocks can be used, as well (see Injection Site Diagram). Keep track of your injection sites on a calendar. Using a site too often can lead to infection or irritation.

Injection Site Diagram



Injecting SEROSTIM
1. Clean the skin at the injection site with an alcohol swab using a circular motion.
TIP: Let the skin dry after cleaning it with alcohol. This helps reduce stinging.
2. Remove the cap from the needle and, using the hand with which you write, pick up the syringe and hold it like a pencil.
3. Pinch up a generous fold of skin and hold it while quickly inserting the needle all the way in at a 90 degree angle to the skin. With your index finger, push the plunger in to inject the medication. Take as much time as you need to inject all the solution. You may wish to count to 5.
TIP: When inserting the needle, you need very little force, but quick action.
4. As you release the skin from your grip, withdraw the needle at the same angle at which it was inserted. Place the cotton swab on the injection site and apply a gentle pressure.
5. Do not put the needle back in the needle guard. Carefully throw away the needle guard and all used needles and syringes in the safety container after a single use.
TIP: NEVER reuse a needle.

Disposal containers must be made of thick, puncture-proof plastic with a lid that fits firmly, such as an empty pop bottle. Containers may be returned to the clinic for disposal or you may wish to contact your pharmacy for further information regarding the safe disposal of used syringes.

Things to remember
1. Make injections routine - give the injection at the same time each evening before bedtime.
2. Before mixing, store vials at room temperature.
3. Vials of SEROSTIM reconstituted with the diluent provided (Sterile Water for Injection, USP) should be used immediately (within 3 hours), and any unused solution should be discarded.
4. Check the expiration date.
5. Do not use if it turns cloudy, lumpy or discoloured.
6. Make certain that the dosage is equal to the amount prescribed.
7. Rotate your injection sites each time, as discussed with your nurse.
8. If you are unsure about the mixing of the medication or if you are having difficulty with the injection procedure, contact your nurse or doctor.

Overdose
There is no known antidote to SEROSTIM or any specific treatment for SEROSTIM overdose other than withholding treatment and patient observation. In case of overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions or effects and appropriate symptomatic treatment instituted immediately.

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose
If you forget to take an injection on your usual day of the week, do not double your next injection. If you have forgotten more than one injection, contact your physician for advice on how to proceed.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The most common adverse reactions reported in the clinical trials and felt to be associated with SEROSTIM were musculoskeletal discomfort and increased tissue turgor (non-edematous 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.

Clinical adverse events which occurred during the first 12 weeks of study in at least 10% of those who received SEROSTIM during the two placebo-controlled trials are listed below by treatment group.

Adverse Event	SEROSTIM	Placebo
	n=205	n=150
	%	%
Musculoskeletal discomfort	53.7	33.3
Fever	31.2	29.3
Increased tissue	27.3	2.7
Diarrhea	25.9	20
Neuropathy	25.9	17.3
Nausea	25.9	16
Headache	19	20.7

Abdominal pain	17.1	18.7
Fatigue	17.1	16
Leukopenia	15.1	24.7
Albuminuria	15.1	9.3
Granulocytopenia	14.1	21.3
Lymphadenopathy	14.1	16
Anorexia	12.2	8.7
Anemia	12.2	9.3
Vomiting	11.7	8.7
SGOT increased	11.7	12
Insomnia	11.2	9.3
Tachycardia	11.2	6
Hyperglycemia	10.2	6
SGPT increased	10.2	5.3

This is not a complete list of side effects. If you experience any unusual symptoms or side effects, you should report them to the doctor immediately. It is also wise to discuss the possibility of side effects with the doctor before beginning treatment.

HOW TO STORE SEROSTIM

Before reconstitution (mixing)
Lyophilized product:
Store SEROSTIM lyophilized product at or below 25 °C (room temperature).

Do not use SEROSTIM after the expiry date shown on label.

After reconstitution (mixing)
Reconstituted product:
When reconstituted with the diluent provided (Sterile Water for Injection, USP), the reconstituted solution should be administered immediately (within 3 hours). Although not recommended, it may be stored for up to 24 hours at 2-8 °C. As there is no preservative in this reconstituted solution, any unused solution should be discarded once the dose is given.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to:
  Canada Vigilance Program
  Health Canada
  Postal Locator 0701D
  Ottawa, Ontario
  K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The CanadaVigilance Program does not provide medical advice

MORE INFORMATION

This document plus the full Product Monograph, prepared for health care professionals can be obtained from
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