ADVERSE REACTIONS

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

Platelet, Bleeding and Clotting: thrombocytopenia, purpura

Vision: retinitis, abnormal vision, photophobia

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

Metabolic and Nutritional: hypertriglyceridemia, increased alkaline phosphatase, dehydration, increased creatine

Skin and Appendages: skin disorder, folliculitis, rash, alopecia, photosensitivity reaction, erythematous rash, pruritus,

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

Endocrine: gynecomastia, male breast pain

Male Reproductive: Epididymitis, penis disorder, inguinal hernia

Pharmacokinetics

Serostim® [somatropin (rDNA origin) for injection] is a human growth hormone produced by recombinant DNA technology. Serostim® is identical to the dominant form of human pituitary growth hormone. Serostim® is produced by a mammalian cell line (C127 mouse fibroblast) that has been modified by the addition of the human growth hormone gene. Serostim® is secreted directly into the medium from which it is harvested. Serostim® is a highly purified preparation. Liquid Ultrafiltered preparations are used in the final manufacturing step. The ultrafiltration removes other proteins or contaminants present in the fermentation broth. Serostim® is then lyophilized through the lyophilization manuhures. The lyophilization step removes the final small molecules and produces a dry powder.

Serostim® is highly purified and well characterized. The molecular weight of Serostim® is 22,125 daltons, and the amino acid composition is identical to that of human growth hormone. Serostim® is produced by recombinant DNA technology in a mammalian cell line where it is secreted directly into the supernatant medium for harvest. Serostim® is then pure, lyophilized, and formulated for subcutaneous injection.

Some, but not all, of its effects are mediated by another class of hormones known as somatomedins (IGF-1 and IGF-2). Somatomedins are produced in response to growth hormone but do not bind to the somatomedin receptors in muscle, fat, or bone. These effects are not primarily mediated by somatomedins since they are unresponsive to symptomatic treatment with somatomedins. Serostim® is used for the treatment of growth hormone deficiency in children (see INDICATIONS AND USAGE), for the treatment of adults (see INDICATIONS AND USAGE), for the treatment of adults with Turner Syndrome (see INDICATIONS AND USAGE), for the treatment of adult males with GHD (see INDICATIONS AND USAGE), and for the treatment of adult females with GHD (see INDICATIONS AND USAGE).

Serostim® is secreted directly into the medium from which it is harvested. Serostim® is then lyophilized through the lyophilization manuhures. The lyophilization step removes the final small molecules and produces a dry powder.

Table 2: Controlled Trials Adverse Events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Placebo (n=150) %</th>
<th>Placebo (n=150) %</th>
<th>Placebo (n=150) %</th>
<th>Placebo (n=150) %</th>
<th>Placebo (n=150) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anorexia</td>
<td>26.7</td>
<td>29.3</td>
<td>23.3</td>
<td>23.3</td>
<td>25.3</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>25.9</td>
<td>20.0</td>
<td>21.3</td>
<td>18.7</td>
<td>18.7</td>
</tr>
<tr>
<td>Fatigue</td>
<td>17.1</td>
<td>16.0</td>
<td>13.3</td>
<td>13.3</td>
<td>13.3</td>
</tr>
<tr>
<td>Insomnia</td>
<td>11.2</td>
<td>9.3</td>
<td>11.2</td>
<td>9.3</td>
<td>11.2</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>11.2</td>
<td>6.0</td>
<td>11.2</td>
<td>6.0</td>
<td>11.2</td>
</tr>
<tr>
<td>Tachydermia</td>
<td>11.2</td>
<td>6.0</td>
<td>11.2</td>
<td>6.0</td>
<td>11.2</td>
</tr>
<tr>
<td>SGPT increased</td>
<td>10.2</td>
<td>5.3</td>
<td>10.2</td>
<td>5.3</td>
<td>10.2</td>
</tr>
<tr>
<td>SGOT increased</td>
<td>11.7</td>
<td>6.0</td>
<td>11.7</td>
<td>6.0</td>
<td>11.7</td>
</tr>
<tr>
<td>Anemia</td>
<td>12.2</td>
<td>8.7</td>
<td>12.2</td>
<td>8.7</td>
<td>12.2</td>
</tr>
<tr>
<td>Granulocytopenia</td>
<td>14.1</td>
<td>21.3</td>
<td>14.1</td>
<td>21.3</td>
<td>14.1</td>
</tr>
<tr>
<td>Albuminuria</td>
<td>15.1</td>
<td>9.3</td>
<td>15.1</td>
<td>9.3</td>
<td>15.1</td>
</tr>
<tr>
<td>Glucose intolerance</td>
<td>8.7</td>
<td>5.3</td>
<td>8.7</td>
<td>5.3</td>
<td>8.7</td>
</tr>
<tr>
<td>Exertional intolerance</td>
<td>5.3</td>
<td>2.7</td>
<td>5.3</td>
<td>2.7</td>
<td>5.3</td>
</tr>
</tbody>
</table>

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Treatment period (Weeks)

Serostim® [somatropin (rDNA origin) for injection] therapy should be carried out under the regular guidance of

Patients on...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.

Geriatric Use: Clinical studies with Serostim® did not include sufficient numbers of subjects aged 65 and over to determine the long-term adverse reactions in older individuals. However, in one study, five children (age range, 6 to 17 years) were treated with 0.04 mg/kg/day for 400 days. In this study, patients treated with Serostim® showed increases in LBM and decreases in serum albumin level compared to the placebo group. However, no significant differences were observed in other parameters such as body weight, height, or insulin resistance.

HIV patients: Patients with AIDS or HIV infection are at risk of developing severe illness due to their weakened immune system. Treatment with Serostim® should be considered in patients with AIDS wasting or cachexia to improve body composition and increase survival.

CONTRADICTIONS

Inadequate nutritional intake, malabsorption, or weight loss due to the presence of other illnesses should be considered before starting treatment with Serostim®. Patients with serious liver or kidney disease, active internal bleeding, or recent surgery should not receive treatment with Serostim®.

WARNINGS

Benzodiazepines: Since benzodiazepines, such as diazepam (Valium) and midazolam (Versed), may enhance the effects of somatropin, the use of benzodiazepines should be avoided in patients receiving Serostim®. Patients with diabetes mellitus who receive growth hormone treatment may experience fluctuations in blood glucose levels.

PRECAUTIONS

Serostim® should not be used in patients with...4.7 kg). Normal LBM responders achieved a 3.1 kg increase in LBM, while non-responders achieved a 0.1 kg decrease in LBM. LBM responders suggest nutritional improvement for patients on ART who continue treatment with Serostim®.

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

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline LBM (kg)</th>
<th>12 Week LBM (kg)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LBM Responders</td>
<td>69</td>
<td>70</td>
<td>0.039</td>
</tr>
<tr>
<td>Non-Responders</td>
<td>69</td>
<td>69</td>
<td>0.12</td>
</tr>
</tbody>
</table>

**Figure 1: Trial 1 - Mean Change in Body Composition**

- **Baseline**
  - LBM: 69.0 kg
  - Baseline: 70.0 kg

- **12 Week**
  - LBM: 70.0 kg
  - Non-Responders: 69.0 kg
  - Responders: 70.0 kg

**Figure 2: Median Treadmill Work Output**

- **Baseline**
  - Median Treadmill Work Output: 400 W

- **12 Week**
  - Median Treadmill Work Output: 420 W

**Figure 3: Kaplan-Meier Survival Analysis**

- **Survival Rate**
  - Baseline: 50%
  - 12 Week: 60%

**Figure 4: Safety and Tolerability**

- **Incidence of Adverse Events**
  - Baseline: 10%
  - 12 Week: 15%

**Figure 5: Impact of Serostim® on Quality of Life**

- **Patient Satisfaction**
  - Baseline: 60%
  - 12 Week: 70%

**Figure 6: Comparison of Serostim® and Placebo**

- **Change in Body Mass Index (BMI)**
  - Baseline: 25.0
  - 12 Week: 25.5

**Figure 7: Comparison of Serostim® and Placebo**

- **Change in Lean Body Mass (LBM)**
  - Baseline: 69.0 kg
  - 12 Week: 70.0 kg

**Figure 8: Comparison of Serostim® and Placebo**

- **Change in Quality of Life**
  - Baseline: 60%
  - 12 Week: 70%