

Somatropin

Brand Name: Genotropin, Humatrope, Nutropin, Serostim, Norditropin, Nutropin AQ, Zorbtive

Drug Description

Somatropin (rDNA origin) is a human growth hormone produced by recombinant DNA technology. [1]

HIV/AIDS-Related Uses

Recombinant somatropin (Serostim) was approved by the FDA on August 23, 1996 for use in conjunction with the appropriate antiretroviral therapy for treatment of AIDS-associated wasting or cachexia to increase lean body mass and body weight and improve physical endurance.[2]

Somatropin is being studied in HIV infected patients to examine immunologic effects in patients who have experienced incomplete immune restoration on highly active antiretroviral therapy (HAART). There is evidence to suggest that the lack of complete immune restoration following HAART results in part from a limitation in the ability of the thymus to produce new cells. A recent study demonstrated that patients treated with recombinant human growth hormone (r-hGH) had an increase in thymus size and volume and significant increases in thymic output. It has been proposed that the new thymus-derived naive CD4 cells will recognize HIV and other antigens and will lead to demonstrable increases in CD4 and CD8 cell responses to those antigens.[3]

Non-HIV/AIDS-Related Uses

Somatropin is also indicated in adults for treatment of growth failure caused by growth hormone (GH) deficiency when both of the following criteria are present: (1) GH deficiency of adult onset, alone or with multiple hormone deficiencies (such as hypopituitarism) as a result of hypothalamic or pituitary disease, radiation therapy, surgery, or trauma; and (2) negative response to a standard growth hormone stimulation test.[4]

Somatropin is indicated in children for long-term treatment of growth failure caused by pituitary GH deficiency (pituitary dwarfism), including GH

deficiency caused by cranial irradiation, or for growth failure caused by Prader-Willi syndrome. It is also indicated for treatment of growth failure caused by chronic renal insufficiency in children and for long-term treatment of short stature associated with Turner's syndrome.[5]

Somatropin has been approved for the treatment of Short Bowel Syndrome (SBS) in patients receiving specialized nutritional support and should be used in conjunction with optimal management of SBS.[6]

Pharmacology

Growth hormone (GH) is an anterior pituitary hormone. The hormone stimulates production of insulin-like growth factor-I (IGF-I) also known as somatomedin C, which is thought to mediate most anabolic actions. IGF-I concentrations are low in children with GH deficiency but normalize in response to administration of exogenous GH. GH stimulates linear growth by affecting cartilaginous growth areas of long bones. It also stimulates growth by increasing the number and size of skeletal muscle cells, influencing the size of organs, and increasing red cell mass through erythropoietin stimulation. GH influences metabolism of carbohydrates by decreasing insulin sensitivity and possibly by affecting glucose transport; of fats by causing mobilization of fatty acids; of minerals by causing the retention of phosphorus, sodium, and potassium through promotion of cellular growth; of proteins by increasing protein synthesis, which results in nitrogen retention; and of connective tissue by stimulating synthesis of chondroitin sulfate and collagen and by increasing urinary excretion of hydroxyproline. GH therapy in adults is associated with increases in lean body mass, total body water, and physical performance and decreases in body fat and waist circumference.[7]

The absolute bioavailability of somatropin after subcutaneous (SQ) injection is approximately 80%. Somatropin distribution localizes to highly perfused organs, especially the kidneys and liver.[8] The steady state volume of distribution following

Somatropin

Pharmacology (cont.)

intravenous (IV) administration is 12.0 +/- 1.08 liters.[9] [10]

Somatropin products are in FDA Pregnancy Categories B and C. Adequate and well-controlled studies have not been done in pregnant women; however, studies in rats and rabbits administered doses of up to 31 and 62 times, respectively, the recommended human pediatric dose on a body surface area basis have not shown that somatropin causes adverse effects in the fetus. It is not known whether somatropin is distributed into human breast milk.[11]

Serum half-life after IV injection is approximately 20 to 30 minutes. After intramuscular (IM) or SQ injection, serum concentrations decline, with a half-life of approximately 3 to 5 hours. This decline reflects continued release of the hormone from the injection site. Approximate duration of action of somatropin is 12 to 48 hours.[12]

Biotransformation is primarily renal, but also hepatic. In renal cells, somatropin is cleaved into its constituent amino acids, which are returned to systemic circulation.[13] The half-life after SQ administration is significantly longer than that seen after IV administration. In nine patients with AIDS-related wasting (average weight of 56.7 +/- 6.8 kg), a fixed dose of 6.0 mg of somatropin had a half-life of 4.28 +/- 2.15 h. The renal clearance after SQ administration was 0.0015 +/- 0.0037 l/h. Significant accumulation of somatropin appears to occur after 6 weeks of dosing as indicated.[14] Somatropin is eliminated by biliary elimination, with approximately 0.1% of a dose excreted as unchanged drug.[15]

Adverse Events/Toxicity

Prolonged use of excessive doses of GH in patients who are not GH deficient may theoretically cause acromegalic features (face, hands, feet) and other problems associated with acromegaly, including organ enlargement, diabetes mellitus, atherosclerosis, hypertension, and nerve entrapment syndrome (carpal tunnel syndrome). Development

of antibodies to GH that may interfere with growth response may occur in a small number of patients.[16]

Side effects seen with the use of somatropin include: otitis media and other ear disorders in patient with Turner's syndrome; allergic reaction; intracranial hypertension; lipodystrophy; pain or swelling at the site of injection; pancreatitis; slipped capital femoral epiphysis; carpal tunnel syndrome; gynecomastia; headache; increased growth of nevi; joint or muscle pain; peripheral edema; and unusual tiredness or weakness.[17]

If weight loss continues after two weeks of GH therapy, other causes, such as opportunistic infection, should be considered.[18]

Drug and Food Interactions

In some in vitro studies, GH at concentrations of 50 to 250 ng/ml has been shown to potentiate HIV replication. However, when the antiretroviral agents didanosine, lamivudine, or zidovudine were added to the culture medium, no increase in virus production was seen. The antiretroviral activity of stavudine and zalcitabine was not shown to be affected by growth hormone in similar in vitro studies. In clinical trials, no increase in virus production was seen in patients receiving growth hormone; however, all patients concomitantly received antiretroviral agents.[19]

Depending on the dose, anabolic steroids, androgens, estrogens, and thyroid hormones may interact with somatropin. Concurrent use of excessive doses of these hormones may accelerate epiphyseal closure, although hormone supplement therapy may be necessary in patients with deficiencies of these hormones to maintain the growth response to GH.[20]

Inhibition of the growth response to GH may occur with chronic therapeutic use of corticotropin or with daily oral doses of corticosteroids, such as betamethasone, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, and triamcinolone. Concurrent use with corticotropin is not recommended; of the others,

Somatropin



Drug and Food Interactions (cont.)

hydrocortisone or cortisone is usually preferred, except in extenuating circumstances.[21]

Contraindications

There have been reports of fatalities after initiating therapy with GH in pediatric patients with Prader-Willi syndrome who had one or more of the following risk factors: severe obesity, history of upper airway obstruction or sleep apnea, or unidentified respiratory infection. Male patients with one or more of these factors may be at greater risk than females.[22]

Somatropin 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. Somatropin is contraindicated in patients with active neoplasm; any anti-tumor therapy should be completed prior to starting therapy with this hormone product. The safety of continuing GH treatment in patients receiving replacement doses for approved indications who concurrently develop these illnesses has not been established. Therefore, the potential benefit of treatment continuation with GH in patients who develop acute critical illnesses should be weighed against the potential risk.[23]

Somatropin reconstituted with bacteriostatic water for injection should not be administered to patients with known sensitivity to benzyl alcohol. Somatropin is contraindicated in any patient with a sensitivity to any component of the GH product.[24]

Risk-benefit should be considered in patients with diabetes mellitus, untreated hypothyroidism, and malignancy, including intracranial tumors actively growing within the previous 12 months.[25]

Clinical Trials

For information on clinical trials that involve Somatropin, visit the ClinicalTrials.gov web site at <http://www.clinicaltrials.gov>. In the Search box, enter: Somatropin AND HIV Infections.

Dosing Information

Mode of Delivery: Subcutaneous injection.[26]

Dosage Form: Vials containing 4, 5, or 6 mg somatropin.[27]

Storage: Prior to dilution, vials of liquid somatropin and diluent should be stored at room temperature, 15 C to 30 C (59 F to 86 F).[28]

Lyophilized somatropin powder should be stored refrigerated at 2 C to 8 C (36 F to 46 C) and protected from light and freezing.[29]

Chemistry

CAS Name: Somatotropin[30]

CAS Number: 12629-01-5[31]

Molecular formula:
C990-H1529-N263-O299-S7[32]

Molecular weight: 22124.12[33]

Stability: When somatropin is reconstituted with Sterile Water for Injection, USP, the reconstituted solution should be used immediately and any unused portion should be discarded.[34]

Some formulations of somatropin come with a diluent that contains preservative, while others do not. See the corresponding prescribing information for specific information.[35]

Other Names

Growth hormone (human)[36]

r-hGH[37]

Human growth hormone[38]

Somatropina[39]

Somatropin



Further Reading

Cominelli S, Raguso CA, Karsegard L, Hirschel B, Gaillard R, Genton L, Pichard C. Weight-losing HIV-infected patients on recombinant human growth hormone for 12 wk: a national study. *Nutrition*. 2002 Jul-Aug;18(7-8):583-6.

Engelson ES, Glesby MJ, Mendez D, Albu JB, Wang J, Heymsfield SB, Kotler DP. Effect of recombinant human growth hormone in the treatment of visceral fat accumulation in HIV infection. *J Acquir Immune Defic Syndr*. 2002 Aug 1;30(4):379-91.

Napolitano LA, Lo JC, Gotway MB, Mulligan K, Barbour JD, Schmidt D, Grant RM, Halvorsen RA, Schambelan M, McCune JM. Increased thymic mass and circulating naive CD4 T cells in HIV-1-infected adults treated with growth hormone. *AIDS*. 2002 May 24;16(8):1103-11.

Rondanelli M, Caselli D, Arico M, Maccabruni A, Magnani B, Bacchella L, De Stefano A, Maghnie M, Solerte SB, Minoli L. Insulin-like growth factor I (IGF-I) and IGF-binding protein 3 response to growth hormone is impaired in HIV-infected children. *AIDS Res Hum Retroviruses*. 2002 Mar 20;18(5):331-9.

Schwarz JM, Mulligan K, Lee J, Lo JC, Wen M, Noor MA, Grunfeld C, Schambelan M. Effects of recombinant human growth hormone on hepatic lipid and carbohydrate metabolism in HIV-infected patients with fat accumulation. *J Clin Endocrinol Metab*. 2002 Feb;87(2):942.

Tai VW, Schambelan M, Algren H, Shayevich C, Mulligan K. Effects of recombinant human growth hormone on fat distribution in patients with human immunodeficiency virus-associated wasting. *Clin Infect Dis*. 2002 Nov 15;35(10):1258-62.

Manufacturer Information

Somatropin
Serono Inc.
One Technology Place
Rockland, MA 02370
(800) 283-8088

Serostim
Serono Inc.
One Technology Place
Rockland, MA 02370
(800) 283-8088

Genotropin
Pharmacia Corporation
100 Route 206 North
Peapack, NJ 07977
(888) 768-5501

Nutropin
Genentech Inc
1 DNA Way
South San Francisco, CA 94080-4990
(800) 821-8590

Humatrope
Eli Lilly and Co
Lilly Corporate Center
Indianapolis, IN 46285
(800) 545-5979

Norditropin
Novo Nordisk
100 College Road West
Princeton, NJ 08540-7810
(800) 727-6500

Nutropin AQ
Genentech Inc
1 DNA Way
South San Francisco, CA 94080-4990
(800) 821-8590

Somatropin



Manufacturer Information (cont.)

Zorbtive
Serono Inc.
One Technology Place
Rockland, MA 02370
(800) 283-8088

For More Information

Contact your doctor or an AIDSinfo Health Information Specialist:

- Via Phone: 1-800-448-0440 Monday - Friday, 12:00 p.m. (Noon) - 5:00 p.m. ET
- Via Live Help: http://aidsinfo.nih.gov/live_help Monday - Friday, 12:00 p.m. (Noon) - 4:00 p.m. ET

References

1. Serono, Inc. - Serostim Prescribing Information, August 2003, p.1. Available at: http://www.aidswasting.com/aids/serostim/images/serostim_pi.pdf. Accessed 12/12/03.
2. USP DI - 2003; p. 1438
3. Protocol ID: ACTG A5174 - Version 2.0, p. 34-35
4. USP DI - 2003; p. 1438
5. USP DI - 2003; p. 1438
6. FDA - New and Generic Drug Approvals. Zorbtive Approved Label, p. 6. Available at http://www.fda.gov/cder/foi/label/2003/20604s026_zorbtive_lbl.pdf. Accessed 12/12/03.
7. USP DI - 2003; p. 1439
8. USP DI - 2003; p. 1439
9. USP DI - 2003; p. 1439
10. Serono, Inc. - Serostim Prescribing Information, August 2003, p.2. Available at: http://www.aidswasting.com/aids/serostim/images/serostim_pi.pdf. Accessed 12/12/03.
11. USP DI - 2003; p. 1439
12. USP DI - 2003; p. 1439
13. USP DI - 2003; p. 1439
14. Serono, Inc. - Serostim Prescribing Information, August 2003, p.2. Available at: http://www.aidswasting.com/aids/serostim/images/serostim_pi.pdf. Accessed 12/12/03.

Somatropin



15. USP DI - 2003; p. 1439
16. USP DI - 2003; p. 1440
17. USP DI - 2003; p. 1440-1441
18. USP DI - 2003; p. 1441
19. USP DI - 2003; p. 1441
20. USP DI - 2003; p. 1439
21. USP DI - 2003; p. 1439-1440
22. FDA - New and Generic Drug Approvals. Changes Being Effectuated for Genotropin. Available at http://www.fda.gov/cder/foi/applletter/2003/21597_20604slr026ltr.pdf. Accessed 12/12/03.
23. Serono, Inc. - Serostim Prescribing Information, August 2003, p. 5-6. Available at: http://www.aidswasting.com/aids/serostim/images/serostim_pi.pdf. Accessed 12/12/03.
24. FDA - New and Generic Drug Approvals. Zorbtive Approved Label, p. 6-7. Available at http://www.fda.gov/cder/foi/label/2003/20604s026_zorbtive_lbl.pdf. Accessed 12/12/03.
25. USP DI - 2003; p. 1440
26. USP DI - 2003; p. 1442
27. Serono, Inc. - Serostim Prescribing Information, August 2003, p.12. Available at http://www.aidswasting.com/aids/serostim/images/serostim_pi.pdf. Accessed 12/12/03.
28. Serono, Inc. - Serostim Prescribing Information, August 2003, p.11. Available at: http://www.aidswasting.com/aids/serostim/images/serostim_pi.pdf. Accessed 12/12/03.
29. Pfizer - Genotropin Prescribing Information, p.9. Available at: http://www.pfizer.com/download/uspi_genotropin.pdf. Accessed 12/12/03.
30. ChemIDplus. - Available at: <http://chem.sis.nlm.nih.gov/chemidplus/>. Accessed 12/12/03.
31. ChemIDplus. - Available at: <http://chem.sis.nlm.nih.gov/chemidplus/>. Accessed 12/12/03.
32. Merck Index - 2001; p. 1553
33. Merck Index - 2001; p. 1553
34. Serono, Inc. - Serostim Prescribing Information, August 2003, p. 12. Available at: http://www.aidswasting.com/aids/serostim/images/serostim_pi.pdf. Accessed 12/12/03.
35. Pfizer - Genotropin Prescribing Information, p.9. Available at: http://www.pfizer.com/download/uspi_genotropin.pdf. Accessed 12/12/03.
36. ChemIDplus. - Available at <http://chem.sis.nlm.nih.gov/chemidplus/>. Accessed 12/12/03.
37. ChemIDplus. - Available at: <http://chem.sis.nlm.nih.gov/chemidplus/>. Accessed 12/12/03.
38. ChemIDplus. - Available at: <http://chem.sis.nlm.nih.gov/chemidplus/>. Accessed 12/12/03.
39. ChemIDplus. - Available at: <http://chem.sis.nlm.nih.gov/chemidplus/>. Accessed 12/12/03.