

**PHARMACY & THERAPEUTICS COMMITTEE
DRUG CLASS REVIEW**

HUMAN GROWTH HORMONES

DESCRIPTION:

Pegvisomant, pegylated recombinant growth hormone injection, (*Somavert*, Pfizer)

Somatrem, recombinant growth hormone injection with methionine, (*Protropin*, Genentech)

Somatropin, recombinant growth hormone injection, (*Genotropin*, Pharmacia; *Humatrope*, Lilly; *Norditropin*, Novo Nordisk; *Nutropin*, *Nutropin AQ*, Genentech; *Saizen*, Serono; *Serostim*, Serono; *Zorbtive*, Serono). A long acting formulation of Somatropin is also available (*Nutropin Depot*, Genentech).

** This review does not include human insulin-like growth factors (*Mecasermin*, *Increlex*; *Mecasermin Rinfabate*, *Iplex*).

INTRODUCTION: ¹⁻⁷

Growth failure causes include Turner syndrome, growth hormone deficiency (GHD), Prader-Willi syndrome (PWS), and idiopathic short stature (ISS). Shortened height in patients with Turner syndrome is usually due to a genetic disorder and does not occur due to growth hormone deficiency. In PWS, there is a reduction in growth hormone secretion, but this may not explain fully the short stature. Obesity, hypotonia, and delayed motor skill acquisition are other characteristics of PWS. Short stature associated with chronic renal failure is common due to nutritional, metabolic, and endocrine changes as well as medications which may be given due to possible transplantation (steroids and immunosuppressants). Idiopathic short stature is growth failure due to unknown reasons and occurs when all other diagnosis for small height are excluded. The patient must have had normal birth weight and height, be proportional in stature, be -2 or less standard deviations below average height for age, and have a growth hormone stimulation peak of 10 $\mu\text{g/l}$ or greater.

For 50 years, human growth hormone has been the treatment for short stature. Initially, the hormone was derived from pituitary glands of human cadavers. However, the risk of Creutzfeldt-Jakob disease, as well as development of new technology led to the development of recombinant human growth hormone. Growth hormone has been used for a variety of indications, including short bowel syndrome (SBS) caused by removal of substantial amount of intestine and

resulting in malabsorption of nutrients, electrolytes and fluids with diarrhea and dependence on parenteral nutrition. Growth hormone is thought to expedite the weaning of parenteral nutrition as well as stimulate protein synthesis and amino acid transport, increase insulin-like growth factor 1 (IGF-1), enhance nutrient transport and fluid and electrolyte absorption, and lengthen mucosal adaptive surface area.

Growth hormone has also been used to treat acromegaly, a rare disorder of hypersecretion of growth hormone many times caused by pituitary adenomas. Diagnosis occurs most commonly in adults around the age of 40. Overproduction of growth hormone leads to increase in insulin-like growth factor 1 (IGF-1) by the liver and other tissues. IGF-1 causes such symptoms as soft tissue swelling, joint disorders, enlargements of hands, feet, and jaw, visceral overgrowth, as well as diseases such as arthritis, diabetes, colon cancer, increased death from cardiovascular events (i.e. hypertension, cardiac hypertrophy), and sleep apnea. Until recently, therapies for acromegaly have included transsphenoidal surgery (initial treatment of choice), radiotherapy, and medical. Medications include octreotide, a synthetically manufactured injection similar to a naturally occurring inhibitory peptide made by the hypothalamus (somatostatin), which inhibits the secretion of growth hormone by attaching to receptors on the adenomas. This therapy is effective in 50-70% of patients. Dopamine agonists (i.e. bromocriptine) have also been shown to be effective in 10% of patients.

INDICATIONS: ⁸⁻⁹

Medication	FDA Approved Indication
Somatropin	<i>In Adults and Children:</i> <ul style="list-style-type: none"> • Turner Syndrome • Growth hormone deficiency • Prader-Willi Syndrome • Short stature in children small for gestational age • Short stature associated with chronic renal insufficiency • Non-growth hormone deficient idiopathic short stature (<i>Humatrope</i>, only) • Short bowel syndrome in patients receiving specialized nutritional support (<i>Zorbtive</i> only) • AIDS related cachexia (<i>Serostim</i> only)
Somatrem	<i>In Adults and Children:</i> <ul style="list-style-type: none"> • Turner Syndrome • Growth hormone deficiency • Prader-Willi Syndrome • Short stature in children small for gestational age

Medication	FDA Approved Indication
	<ul style="list-style-type: none"> • Short stature associated with chronic renal insufficiency
Pegvisomant	Acromegaly in patients in which surgery or other therapies are either contraindicated or have provided insufficient response

CONTRAINDICATION, PRECAUTION/WARNINGS: ⁸⁻⁹

Medication	Contraindication	Precaution/Warnings	Pregnancy Category
Somatropin	<ul style="list-style-type: none"> • Acute critical illness due to complications following open-heart or abdominal surgery, multiple accidental trauma • Acute respiratory failure • Active neoplasia • Sensitivity to benzyl alcohol (somatropin injection is reconstituted with bacteriostatic water containing benzyl alcohol) • Known hypersensitivity to growth hormone • Closed epiphyses in pediatric patients • Proliferative or pre-proliferative diabetic retinopathy • In Prader-Willi syndrome who are severely obese or who have severe respiratory impairment 	<ul style="list-style-type: none"> • Active or family history of diabetes mellitus or glucose intolerance • Concomitant glucocorticoid therapy • Hypopituitarism • History of intracranial lesions • Antibody development to protein • Scoliosis • Prolonged treatment in adults • Split capital epiphyses occurs more frequently with endocrine disorders or with rapid growth • Newborns • Age greater than 65 years 	C
Somatrem	<ul style="list-style-type: none"> • Acute critical illness due to complications following open-heart or abdominal surgery, multiple accidental trauma • Acute respiratory failure • Active neoplasia • Sensitivity to benzyl alcohol (somatropin 	<ul style="list-style-type: none"> • Active or family history of diabetes mellitus • Endocrine disorders • Geriatric use • History of intracranial lesions • Scoliosis • Patients undergoing rapid growth 	C

Medication	Contraindication	Precaution/Warnings	Pregnancy Category
	injection is reconstituted with bacteriostatic water containing benzyl alcohol) <ul style="list-style-type: none"> • Known hypersensitivity to growth hormone • Closed epiphyses in pediatric patients 		
Pegvisomant	<ul style="list-style-type: none"> • Hypersensitivity to latex • Hypersensitivity to pegvisomant 	<ul style="list-style-type: none"> • Diabetes mellitus • Geriatric use • Hepatic impairment (baseline aminotransferase activity 3 times upper limit) • Pediatric usage • Functional growth hormone deficiency • Renal impairment • Growth hormone secreting tumors 	B

PHARMACOLOGY: 2, 7-10

Somatropin is recombinant growth hormone produced by *Escherichia coli* (Genotropin, Humatrope, Norditropin, Nutropin) or mammalian cell line (Saizen, Zorbitive, Serostim). It is a biosynthetic formulation identical to human growth hormone with a single 191 amino acid chain and 2 disulfide linkages between amino acids 53 and 165 and between 182 and 189. Somatrem is also a recombinant growth hormone similar to somatropin with 1 additional amino acid – a methionine. Both recombinant growth hormones bind to growth hormone receptors and directly affect the following: antagonism of peripheral actions of insulin and increasing insulin secretion, stimulation of insulin-like growth factors (IGFs) in the liver and other tissues, stimulation of triglyceride hydrolysis, and stimulation of hepatic glucose output, retention of sodium and potassium, and induction of positive calcium balance. IGF-1 mediates growth hormone action by chondrogenesis, skeletal growth, and growth of soft tissue. IGF-2 has insulin like activity. Both IGFs stimulate amino acid transport as well as DNA, RNA, and protein synthesis.

Pegvisomant is a genetically engineered protein using *Escherichia coli* and recombinant DNA technology. It has 191 amino acids similar to growth hormone with 9 amino acid substitutions. The final product is conjugated to polyethylene glycol (pegylated). Pegvisomant binds to growth hormone receptors and

prevents the binding of endogenous growth hormone. This reduces IGF-1 production.

PHARMACOKINETICS: ⁷⁻⁹

Medication	Time to Peak Concentration (IM, SC)	Metabolism	Elimination Half-Life	Excretion
Somatropin	2-6 hours; Bioavailability: 70-90%	Metabolized by liver, kidney, and other tissues	3-5 hours	Total Body Clearance
Pegvisomant	33-77 hours	Not available	6 days	Total Body Clearance

Peak IGF-1 concentration occurs 20 hours after somatropin use. Therefore, its induction and clearance are slower and the effects of somatropin may be longer than its plasma half-life.

RECENT CLINICAL STUDIES¹¹⁻²⁵:

Somatropin (*Humatrope*) for Idiopathic Short Stature

Citation	Study Design	Method	Outcomes
Leschek EW, Rose SR, Yanovski JA. J Clin Endocrinol Metab. July 2004; 89(7):3140-3148.	Randomized, double blind, placebo controlled, study	Sixty-eight pediatric patients (ages 9-16 years) were randomized to receive growth hormone (n=37) or placebo (n=31). The growth hormone dose was 0.22mg/kg/week subcutaneously divided 3 times weekly and placebo was dosed similarly. Patients were evaluated every 6 months for the following: height, Tanner pubertal stage, bone age, and fasting blood sample (for blood count, chemistry panel, insulin, hemoglobin A1c, and IGF-I). The study was discontinued on an individual basis when the growth rate decreased to less than 1.5 cm/year. A final evaluation was performed 1 year after discontinuation of medication.	Adult height measurements were available for 33 of the 68 randomized patients who were treated for an average of 4.4 years. Mean height velocity was greatest in the growth hormone treated group (p<0.01) during the first 2 years. Primary efficacy analysis showed that the growth hormone group, where all 68 patient results were analyzed, reached a significantly higher adult height than the placebo group. Bone growth was similar for growth hormone and placebo groups. IGF-I plasma concentrations at 12, 24, and 36 hours after injection increased significantly (p<0.04) compared to placebo. Fasting glucose measured at 12, 36, and 60 hours (after 6 months of therapy) after injection was significantly higher in the growth hormone group (p=0.001). However, when 2-3 days measured after injection, fasting glucose, fasting serum plasma, and hemoglobin A1c did not show any changes.
Finkelstein BS, Imperiale TF, Speroff T. Arch Pediatr Adolesc Med. Mar 2002; 156:230-240.	Meta-analysis	Systematic review of 10 controlled and 28 uncontrolled trials from MEDLINE search from 1985-2000 on growth hormone use in pediatric patients with idiopathic short stature. Six of 10 controlled trials were randomized. Growth velocity, height standard deviation (SD) scores (number of SDs from mean height for	In the controlled studies, short term therapy (1 year) showed a greater growth velocity with growth hormone over placebo (a difference of 2.86cm/ year, pooled estimate). In addition, the height of growth hormone treated groups in all studies also exceeded the placebo group by 0.60 SD. Four controlled studies had data on adult height, with average duration of therapy of 5.3 years. Growth hormone

Citation	Study Design	Method	Outcomes
		age and sex) and adult heights were assessed.	increased adult height by 0.84 SD above the placebo group (growth hormone, -1.51 SD from normal adult height versus -2.29 SD for placebo group). For uncontrolled trials, growth hormone increased growth velocity by 2.26cm/year over a 1-year period, pooled estimate. Height SD scores for the growth hormone group increased by 0.53 SD over placebo. For comparison of adult height, the average duration of therapy was 4.7 years. The studies showed 0.56-0.63 SD between predicted and actual height after growth hormone.
Kemp SF, Kuntze J, Attie KM. J Clin Endocrinol Metab. September 2005; 90(9):5247-5253.	Observational study of National Cooperative Growth Study (NCGS) - a North American, multicenter, postmarketing surveillance study, which monitors use, safety and effectiveness of growth hormone.	A total of 8018 patients were divided into 3 cohorts – cohort 1 (n=2520) with average age of 10 years, cohort 2 (n=283) with age less than 5 years, and cohort 3 (n=940) with pubertal age as staged by Tanner staging system. Each cohort was given an average dose of 0.30mg/kg growth hormone subcutaneously (SC) every week. For efficacy evaluation, growth rate, height SD scores (SDS), and with or without bone age delay was evaluated yearly for 7 years.	The number of patients enrolled decreased over the 7 years, with n=1446 for year 2 and n=235 for cohort 1 as an example. The growth rate in cohorts 1 and 2 was the highest in the first year at 8.6cm/year. The growth rate slowly increased thereafter for the remainder of the 7 years, to 5.6 cm/year in year 7. Patients in cohort 3 also had a similar growth rate the first year, at 8.9cm/year. However, the growth velocity had slowed to 3.5cm/year by year 5, mainly due to advanced puberty and epiphyseal closure. The mean height SD score increased from -3.0 at baseline to -1.2 for cohorts 1 and 2. Cohort 3 had similar height gain in SD score from -2.8 at baseline to -1.5 by year 4. No difference was found for growth velocity and height SD score between bone age delay and those with normal bone age.

Somatropin for Growth Hormone Deficiency, Turner's Syndrome, Prader-Willi Syndrome, and Short Stature due to Chronic Renal Failure

Citation	Study Design	Method	Outcomes
Attanasio AF, Shavrikova E, Blum WF. J Clin Endocrinol Metab.	Prospective, multi-national, randomized, controlled trial	149 pediatric patients with growth hormone deficiency having completed growth hormone therapy to reach final height were randomized to pediatric dose (n=58) of 25mcg/ kg per day, adult dose (n=59) of 12.5mcg/kg per day, or placebo (n=32) over 2 years. The purpose of the study was to show that continued growth hormone after final height would aid in obtaining adult body composition. Lean body mass and fat mass were monitored at baseline, 12 months, and 24 months. Lipid panel, serum IGF-I, and IGFBP-3 were monitored at baseline and every 6 months.	Height SD score was higher (at 0.15 SD) in both therapy groups over the placebo group (p<0.003). Similarly, both treatment groups significantly increased lean body mass over placebo (5.2 kg vs. 1 kg, p<0.001). Also, the fat mass decreased significantly over the study period between placebo and the 2 treatment groups (1.5 kg vs. -1.3, p<0.029); no difference occurred between the 2 doses. Females had significantly higher serum IGF-1 levels than the control group (p<0.001) at the end of 2 years; and this effect was dose dependant as well, with the higher dose contributing to the serum plasma IGF-1 level reaching the normal level while the lower dose did not (p=0.008). Overall, males had a similar trend towards reaching a normal IGF-1 level for both doses, which was significant over the placebo group. Total cholesterol and LDL/HDL ratio increased significantly over 2 years in the control group (p=0.009 and p=0.039, respectively). For those patients treated with either dose of growth hormone, there was no change in cholesterol level over the 2 years, but there was no treatment effect. There was a significant decrease in LDL/HDL ratio between the treatment groups and placebo over the 2 years (p=0.05).
Mauras N, Pescovitz OH, Allada V. J Clin Endocrinol Metab. July 2005;	Multicenter, randomized, double blinded, placebo controlled trial	Fifty-eight growth hormone deficient adolescents in transition to adulthood treated with growth hormone for a minimum of 3 years were recruited.	The growth hormone group had a significantly smaller change in body fat compared to the placebo (2.4% vs. 6%, p<0.022) at 12 months. Similar significant changes occurred

Citation	Study Design	Method	Outcomes
90(7):3946-3955.		<p>The patients were tested with growth hormone provocation to determine growth hormone deficiency during a 1 month washout period and then randomized to receive either 0.14mg/kg weekly of growth hormone (n=25), placebo (n=15). The control patients (n=18) did not qualify as having growth deficiency. They were monitored every 2 months for the first 4 months and then every 4 months thereafter for 2 years. The primary endpoints monitored included changes in body composition, bone mineral density and safety. Secondary endpoints included effects of growth hormone on plasma lipids, IGF-I concentration, carbohydrate metabolism, cardiac function, exercise tolerance, and quality of life.</p>	<p>with lean body mass, where the placebo group had a greater decrease compared to the growth hormone group (p=0.025). However, no differences were seen at 24 months. Also, no differences were noted for changes in weight and body mass index at any time points. IGF-I plasma concentration declined less in the growth hormone group (from 403 to 326ng/ml at 24 months) than in the placebo group (427 to 141ng/ml), p<0.03. The significance was even greater at the 12 month endpoint, p<0.003. No differences occurred between the groups with regards to whole body mass density, which decreased over the 2 years in all 3 groups. No difference occurred for lipid and carbohydrate metabolism between the growth hormone and placebo groups. Doppler echocardiography evaluated left ventricular systolic function, which did not change over the 24 month period between the growth hormone and placebo groups. The growth hormone group showed a greater reduction in exercise tolerance compared to placebo group at 12 months (p=0.036); however, no significant changes were seen by the end of the study. The major adverse events reported were headache, sinusitis, nausea, and nasopharyngitis.</p>
Silverman BL, Blethen SL, Reiter EO. J Pediatr Endocrinol Metabol. 2002; 15 (2):715-722.	Long-term randomized extension study of 2 multicenter, open-label, parallel-group clinical trials	Fifty-five (55) pediatric patients with growth hormone deficiency who had completed a 6-month study of efficacy and safety of long acting Nutropin Depot were randomized to continue for an additional 24 months and receive either 1.5mg/kg SC once	The 0.75mg/kg and 1.5mg/kg groups had significant growth rates (8.2 cm and 8.3 cm, respectively) over baseline (prestudy) growth rates (4.6 cm and 5.6 cm, respectively), p<0.001, at 12 months. A similar significantly higher growth rate was sustained over 12-24 months (6.9 cm and 7.2 cm, respectively).

Citation	Study Design	Method	Outcomes
		monthly (n=20) or 0.75mg/kg SC twice monthly (n=30). Primary endpoint was growth rate at 12 and 24 months of treatment. Secondary endpoints were standardized height and bone age at 12 and 24 months.	Height SD changed significantly from baseline at -3.2 to -2.2 at 24 months for the 0.75mg/kg group and -2.9 to -1.9 for the 1.5mg/kg group, p<0.0001. Bone age was delayed by 1.3 years in comparison to chronological age at baseline. Bone age advanced by 1 year after the first year of therapy and by 2.1 years at 24 months.
The Canadian Growth Hormone Advisory Committee. J Clin Endocrinol Metab. June 2005; 90(6):3360-3366.	Randomized, controlled	One hundred fifty-four adolescent females (ages 7-13 years) with Turner's Syndrome were randomized to receive either 0.30mg/kg growth hormone or placebo (n=78). Only 61 growth hormone subjects and 43 placebo patients completed the study. Completion of the trial was noted when the patient's annual height velocity was less than 2 cm per year and the bone age was greater than 14 years. Mean height and adverse events were monitored.	At completion of study, mean height was 147.5 cm for the growth hormone group versus 141.0 cm for the placebo group (p<0.001). Fifty-nine subjects (40 growth hormone, 19 placebo) also had 1 year follow-up measurements of 149 cm for the growth hormone group, 142.2 cm for the placebo group (p<0.001). Otitis media, ear disorder, joint disorder, respiratory disorder, and sinusitis were the main adverse effects reported.
Carrel AL, Myers SE, Whitman BY. J Clin Endocrinol Metab. 2002 April; 87(4): 1581-1585.	Controlled, randomized trial.	Forty-six (46) children with Prader-Willi Syndrome receiving Nutropin 1mg/m ² /day for 12-24 months in a previous trial were asked to continue for an additional 24 months to study the effects of growth hormone long-term therapy on Prader-Willi syndrome. The patients were randomized to receive either 0.3mg/m ² /day (0.063mg/kg weekly) (n=14), 1mg/m ² /day (0.2mg/kg weekly) (n=18), or 1.5mg/m ² /day (0.3mg/kg weekly)(n=14). Measurements included: height every 6 months, anthropometric	Mean growth rates were similar for the 2 lower dosages (4.4 cm/year for both the 0.3mg/m ² /day and 1.0mg/m ² per day) while the 1.5mg/m ² /day had a significantly higher mean growth rate (5.9 cm/year; p<0.05). Lean body mass also increased significantly and was dose dependant (30.1 kg, 35.1 kg, and 34.9 kg for 0.3mg, 1.0mg, and 1.5mg, respectively) (p<0.001). Mean body fat percentage declined significantly with increasing dose (49%, 43.1%, and 39.1% in the 0.3mg, 1.0mg, and 1.5mg doses, respectively) (p<0.001). Bone mineral density was 0.94 g/cm ² at baseline and rose to 1.03 g/cm ² after 24 months in all 3 dosage

Citation	Study Design	Method	Outcomes
		measurements (of head, face, body proportions, hands, and feet) every 6 months, and total and regional percent body fat, lean body mass, and bone mineral density at baseline and at 24 months.	regimens ($p < 0.001$).
Haffner D, Schaefer F, Nissel R. N Engl J Med. 28 September 2000;343 (13): 923-930.	Multicenter trial	Thirty-eight prepubertal children with short stature and chronic renal failure who had reached their prepubertal height with the aid of growth hormone therapy were assigned to receive 0.33mg/kg weekly in daily divided doses of Genotropin . They were followed until they reached their final adult height (an average of 8 years). They were compared to 50 children with chronic renal failure without any growth retardation who did not receive any growth hormone. Anthropometric measurements (i.e. height at baseline, total prepubertal height, total pubertal height, final adult height (in cm and standard-deviation score) were taken every 3-6 months. Hand radiographs were performed every 12 months. Bone age also was determined.	The prepubertal height velocity was significantly higher for the growth hormone group (16.6-18.6 cm) over baseline, the control group (9.1-9.9 cm), and a normal comparison group of children. However, the height velocity during the pubertal growth spurt was not significant between the growth hormone (7.8-8.8 cm) and control groups (6.7-7.6 cm) or normal children (6.5-7.8 cm). However, the chronic renal failure children (both growth hormone and controls) had their onset of pubertal growth spurt delayed by about 2.5 years and a shorter duration of the growth spurt by about 1.6 years when compared to normal children ($p < 0.001$). Total pubertal height gain was similar in both chronic renal failure groups, which were 65% of the normal children. The final adult height standard-deviation score was also significantly closer to adult height in the growth hormone group (-1.3 to -1.7 SD) compared to the control group (-2.1 SD), $p < 0.001$. Prepubertal bone age increased significantly over the control group. However, the bone age was only significantly higher for boys during puberty.

Somatropin for use in HIV-related Lipodystrophy and HIV-related Weight Loss and Wasting

Citation	Study Design	Method	Results
<p>Moyle GJ, Daar ES, Gertner JM. J Acquir Immune Defic Syndr. 1 Apr 2004; 35 (4): 367-375.</p>	<p>Randomized, double-blind, placebo-controlled, multicenter trial.</p>	<p>Efficacy of recombinant growth hormone on weight loss or low body mass index in HIV positive adults (median age 41 years) was assessed. 555 HIV patients (85% receiving highly active antiretroviral therapy regimen) were randomized to receive placebo (n=199), Serostim 0.1mg/kg (to maximum 6mg) daily (n=166), or Serostim 0.1mg/kg (to maximum 6mg) every other day (n=190) over a 12 week period. Patients were asked to continue with the study for an additional 36 weeks. Safety, efficacy, and tolerability of the growth hormone for treatment of weight loss and HIV wasting was studied. Work output (via cycle ergometry), body weight, lean body mass, and fat mass were monitored (via bioelectric impedance spectroscopy and DXA).</p>	<p>Median work output increased in both daily and alternate daily dosing groups (2.4 kJ and 2.6 kJ, respectively). The median work output difference between the daily dosing group and placebo (2.9 kJ) was significant at $p < 0.0001$. Body weight increased by 2.9 kg and 2.2 kg, respectively, for the daily and alternated dosing groups; the median difference in body weight between the daily dosing and placebo and alternate dosing and placebo were 2.2 kg and 1.5 kg, respectively ($p < 0.0001$). Lean body mass also increased by 5.2 kg (daily dosing) and 3.3 kg (alternate daily dosing), significant over placebo ($p < 0.0001$).</p>
<p>Kotler DP, Muurahainen N, Grunfeld C. J Acquir Immune Defic Syndr. 1 March 2004; 35:239-252.</p>	<p>Double-blind, placebo-controlled multicenter trial.</p>	<p>This study was designed to investigate the use of the recombinant growth hormone, Serostim, for 24 weeks for the treatment of abnormal adipose tissue accumulation and dyslipidemia in adult patients (mean age 44 years) infected with HIV. Two hundred forty-five patients were initially assigned to receive placebo (n=81), 4mg SC daily dosing Serostim (n=82), or 4mg SC alternate daily dosing Serostim (n=82)</p>	<p>At 12 weeks, abdominal adipose tissue decreased by 8.6% in the daily dosing group, which was significant compared to the placebo group ($p < 0.001$). The alternate daily dosing group had abdominal adipose tissue decreased by 4.2%. There were significant ($p < 0.001$) decreases in total body fat (18.6%) for the daily dosing group, 10.1% for the</p>

Citation	Study Design	Method	Results
		<p>for 12 weeks. After 12 weeks, the placebo group was reassigned to receive daily dosing of Serostim and the daily dosing group was reassigned to receive placebo (n=33) or alternate day dosing (n=34). The alternate daily dosing group continued the same therapy for an additional 12 weeks. Primary endpoints using CT scan and DXA scan were done at baseline, weeks 12 and 24 to measure abdominal SC adipose tissue; trunk, limb, and total body fat; and lean body mass. Weight, height, and anthropometric parameters (hip circumference, dorsocervical fat pad) were performed at baseline, weeks 2, 4, 12, 14, 18, and 24. Secondary endpoint of serum lipid profile measurement was performed at baseline, week 12 and week 24 after a 12 hour overnight fast.</p>	<p>alternate dosing group) and truncal fat (23.1%, daily dosing group; 13.4%, alternate dosing group) were noted when compared with the placebo group. At 24 weeks, the group which started at daily dosing and then switched to alternate dosing showed significant reductions in truncal fat, total fat and abdominal fat tissue compared to those patients who switched to placebo (p<0.05). The reductions were not significantly greater when compared to the group that continued with alternate daily dosing throughout the 24 weeks. All treatment groups had a significant decrease over baseline in the adipose tissue (p<0.03), but the decline was not as significant for the group that went from daily dosing to placebo. Similar, significant decreases were seen between the daily dosing group and baseline with regards to total cholesterol (4.5%), LDL (6.0%), and non-HDL cholesterol (7.5%), while HDL cholesterol increased (11.4%)(p<0.05). These differences were also significant when compared to placebo (p<0.05). Similarly, decreases occurred in total cholesterol (4.3%) and non-HDL cholesterol (6.2%), while the HDL increased</p>

Citation	Study Design	Method	Results
			(7.7%) with alternate daily dosing, all significant when compared to baseline ($p < 0.01$). Only the total cholesterol and non-HDL cholesterol decreases were significant compared to placebo ($p < 0.004$). Similar, but non-significant changes in lipid profile were seen after 24 weeks.

Somatropin (*Zorbitive*) for Short Bowel Syndrome receiving nutritional support

Citation	Study Design	Methods	Outcomes
Byrne TA, Wilmore DW, Iyer K. Ann Surg. November 2005; 242 (5):655-661.	Prospective, randomized, placebo-controlled, double-blind	Forty-one patients were randomized to 30gm oral glutamine with SC growth hormone placebo (n=9), oral glutamine placebo and SC growth hormone at 0.1mg/kg/day (n=16), or 30gm oral glutamine with 0.1mg/kg/day growth hormone (n=16). The patients were on parenteral nutrition (PN) and had less than one-third of their small intestine remaining. There was an initial 2 week baseline period, then a 4 week treatment period, and a 12 week follow-up period. Primary endpoint was parenteral volume change at the end of the treatment period versus baseline. Secondary endpoints included caloric need from PN and frequency of administration. A final evaluation was carried out at week 18 to determine durability of therapy. Safety was also evaluated. Appropriately individualized diets rich in protein and	There was a significant decrease in volume, caloric need, and frequency of infusion of parenteral nutrition from baseline to end of 6 weeks in all 3 treatment groups, $p < 0.02$. The glutamine with growth hormone group had a significant ($p < 0.001$) reduction over glutamine alone in parenteral nutrition volume (7.7 l vs. 3.8 l), calories (5751 vs. 2633), and frequency of infusion (4 vs. 2). There was a statistical reduction ($p < 0.008$) between glutamine with growth hormone group and glutamine alone group at the end of the 18 week follow-up period in terms of requiring volume, calories, and frequency of parenteral nutrition.

Citation	Study Design	Methods	Outcomes
		complex carbohydrates and moderately low in fats were provided.	
Seguy D, Kouroche V, Nathalie K. Gastroenterology. 2003; 124(2): 293-302.	Randomized, double-blind, placebo controlled, crossover study	Twelve adult parenteral nutrition dependent patients with small bowel syndrome (average small bowel length 48 cm) were included to receive somatropin 0.5mg/kg/day SC and placebo, each over a 3 week period with a 1 week washout between the regimens. Intestinal absorption of energy, nitrogen, carbohydrates, fat, body weight, lean body mass, D-xylose absorption, IGF-1 and IGF binding protein 3 levels were monitored.	Growth hormone significantly increased intestinal absorption of energy (15% vs. 5%, p< 0.002), nitrogen (14% vs. 6%, p<0.04) and carbohydrate absorption (10% vs. 4%, p<0.04). Body weight (p<0.003), lean body mass (p<0.006), D-xylose absorption (p<0.02) and IGF-I levels (p<0.002) also increased. Fat absorption increased, but not significantly (12% vs. 8%). Body weight gain was sustained in patients receiving the growth hormone in the first 3 week period. The authors feel that the effects of growth hormone may be transient.

Pegvisomant for Acromegaly

Citation	Study Design	Method	Outcomes
Trainer PJ, Drake WM, Laurence MB. N Engl J Med. 20 April 2000; 342(16):1171-1177.	Randomized, double-blind, placebo controlled	One hundred eleven patients were randomized to either placebo (n=31) or 1 of 3 daily SC doses of pegvisomant ; 10mg (n=26), 15mg (n=26), or 20mg (n=28). No patient was allowed on somatostatin therapy. Clinical and laboratory findings were performed at baseline and weeks 2, 4, 8, and 12. The following items were monitored: physical exam/history taking; questionnaire for patient for evaluation of acromegaly (signs and symptoms of soft tissue swelling, arthralgia, headache, excessive perspiration, and fatigue); fasting serum growth hormone level; fasting serum level of insulin-like	Serum IGF-I concentration decreased significantly between baseline and at 12 weeks for placebo (by 4%) and pegvisomant 10mg (by 26.7%), 15mg (by 50.1%), and 20mg (by 62.5%). The decrease was significantly different between pegvisomant and placebo (p<0.001) as well as between the higher doses and the 10mg dose (p<0.001). Similar results were found for free serum IGF-I and IGF binding protein 3, with the authors noting significant (p < 0.05) lowering in all 3 categories for the 3 doses of pegvisomant compared to placebo. The serum growth hormone levels increased correspondingly to declines in IGF-I in a dose-dependant fashion over the 12 week period and was significant

Citation	Study Design	Method	Outcomes
		<p>growth factor I (IGF-I) and its binding protein 3 (IGFBP-3); ring size of fourth digit of right hand.</p>	<p>($p < 0.001$) compared to placebo, which actually declined. (10mg – 2.7ng/ml; 15mg -9.2ng/ml; 20mg – 14.4ng/ml). The total score of all signs and symptoms of acromegaly also declined significantly for all 3 doses ($p = 0.02$ for 10mg, $p = 0.004$ for 15mg, $p < 0.001$ for 20mg) while it increased for the placebo group. At the 20mg dose, pegvisomant showed the most significant decline in individual signs and symptoms ($p < 0.001$ decline in swelling, excessive perspiration, and fatigue). Ring size decreased significantly ($p < 0.001$) as well over 12 week with placebo (by 0.1 size), 10mg (by 0.8 size), 15mg (by 1.9 size), and 20mg (by 2.5 size).</p>
<p>Jorgenson JOL, Feldt-Rasmussen U, Frystyk J. J Clin Endocrinol Metab. October 2005; 90 (10): 5627-5631.</p>	<p>Open-labeled, crossover</p>	<p>Eleven patients underwent a fixed treatment algorithm of 5 different therapies. They entered on somatostatin 30mg intramuscularly (IM) every 2-4 weeks; this therapy was discontinued for 2 months (no treatment); pegvisomant 10mg daily was given for 6 weeks; then pegvisomant 15mg daily was given for 6 weeks; and finally, pegvisomant 15 mg daily and somatostatin 30 mg IM every 4 weeks combined for 12 weeks. At 1 point in each of the 5 therapies, a fasting serum IGF-I and free IGR-I, endogenous serum growth hormone level, and IGF-I bioactivity were assessed.</p>	<p>There was a significant decrease in serum IGF-I between no treatment group (562 $\mu\text{g/l}$) and combination therapy (194 $\mu\text{g/l}$), $p < 0.001$. Serum IGF-I levels declined steadily in the pegvisomant 10mg (376 $\mu\text{g/l}$) and 15mg (269 $\mu\text{g/l}$) as well. The serum IGF-1 also significantly declined between the somatostatin group (458 $\mu\text{g/l}$) and the combination group, $p < 0.05$. Free serum IGF-I levels also decreased significantly, $p < 0.05$. Endogenous serum growth hormone levels also were significantly higher in the pegvisomant 15mg group (19.7 $\mu\text{g/l}$) and lowest with the somatostatin group (5.1 $\mu\text{g/l}$), $p < 0.05$. The no treatment, pegvisomant 10mg, and combination groups had the following results, respectively: 8.9, 14.6, and 11.8 $\mu\text{g/l}$, with $p < 0.01$ between the somatostatin no treatment groups and the combination therapy. Serum IGF-I bioactivity decreased significantly with pegvisomant 15mg and combination therapies</p>

Citation	Study Design	Method	Outcomes
			(p<0.001).

ADVERSE EVENTS:^{-9, 11-27}

	Endocrine	Cardiovascular	Dermatological	Other
Somatropin	Hypoglycemia, Hypothyroidism (0.7%), Hyperglycemia (3.5%)/ Glucose Intolerance	Edema (13%-55%), Hypertension (4.7-7.7%), Fluid retention, Tachycardia, Chest Pain	Rash, Increased Sweating (with Zorbitive); Pruritis; Pain and Local Reactions at Injection Site,	Pancreatitis; Leukemia; Flu-like Symptoms (15%); Pain (5-10%); Rhinitis (8.3%); Dizziness (5%), Otitis media (8%), Scoliosis (3%); Colonic Neoplasia, Cranial Tumors, Skin Cancers
Somatrem	Hypoglycemia, Hypothyroidism			Leukemia, Pancreatitis
Pegvisomant		Chest Pain	Local Reactions at Injection Site	Anti-hormone Antibodies (17%); Hepatic Aminotranferase Increase; Nausea, Diarrhea; Flu-like Symptoms

Various studies have also shown that 10-66% of patients receiving somatropin and 20-88% patients receiving somatrem for over 6 months will develop anti-growth hormone antibodies. However, in the majority of patients these antibodies do not interfere with the effect of growth hormone (i.e. neutralization). Decrease in growth occurred only in a small percentage (0.4-5%) of patients receiving either somatropin or somatrem who produce high titers of growth hormone antibodies with a large binding capacity.

DRUG INTERACTIONS:⁹

Precipitant Drug	Object Drug	Description
Corticosteroids	Somatrem, Somatropin	Retards bone growth, thereby decreasing effect of growth hormone
Somatropin	Antidiabetic Medications	Decreases effectiveness of Hypoglycemic Agents
Somatropin	Corticosteroids, Testosterone, Estrogen, Cyclosporine, certain anticonvulsants	Increase cytochrome-mediated metabolism of these medications
Opoids	Pegvisomant	Causes increased dosage of object medication (mechanism unknown)

DOSAGES: ^{2, 8-9}

For pegvisomant, the loading dose is 40mg SC under physician supervision. The starting dose is 10mg SC daily. Dosage is adjusted by 5mg every 4-6 weeks based on serum IGF-1 levels. Maximum maintenance dose is 30mg SC daily. Manufacturer recommends not initiating in patients with a baseline aminotranferase activity 3 times the upper limit. Periodic liver function tests should be monitored.

Dosages for FDA Approved Use of Somatropin and Somatrem*

Drug	Growth Hormone Deficiency	Turner's Syndrome	Idiopathic Short Stature	Short Bowel Syndrome in Patients Receiving Parenteral Nutrition	Long Term Replacement for Adults with Growth Hormone Deficiency	AIDS-associated cachexia
Somatrem	0.3mg/kg weekly SC or IM divided in daily doses	0.37mg/kg SC weekly divided 3 times weekly or daily			Adults: 0.07mg/kg IV daily	
Zorbtive				Adults & Elderly: 0.1mg/kg SC daily for 4 weeks		
Serostim						Adults: > 55 kg 6mg SC qhs; 45-55 kg 5mg SC qhs; 35-45 kg 4mg SC qhs; < 35 kg 0.1mg SC qhs
Saizen	0.06mg/kg SC 3 times weekly					
Nutropin Depot	1.5mg/kg SC on the same day of month or 0.75mg/kg twice a month on the same day					

Drug	Growth Hormone Deficiency	Turner's Syndrome	Idiopathic Short Stature	Short Bowel Syndrome in Patients Receiving Parenteral Nutrition	Long Term Replacement for Adults with Growth Hormone Deficiency	AIDS-associated cachexia
Nutropin, Nutropin AQ	0.3mg/kg/week SC divided in daily doses	0.375mg/kg SC weekly divided 3 times weekly or daily	0.3mg/kg weekly SC divided in daily doses			
Norditropin	0.024-0.034mg/kg/dose 6 to 7 times per week					
Humatrope	0.18mg/kg weekly SC or IM divided 3 times weekly, 6 times daily, or daily	0.375mg/kg SC weekly divided 3 times weekly or daily	0.37mg/kg SC weekly divided 6-7 times weekly			
Genotropin	0.16-0.24mg/kg/week SC divided in 6-7 doses					

* All doses for children unless otherwise noted

COST COMPARISON:

Drug/Availability	Usual Weekly Dose	Weekly Cost
Genotropin, Vial for injection (5.8mg, 13.8mg) Powder for injection (0.2mg/ml to 2mg/ml)	<i>Children: 4.8-7.2mg weekly Adult: 2.4-4.8mg weekly</i>	<i>Children: \$289.39 - \$694.53 (vial); \$276.80- 347.25 (powder for injection) Adult: \$289.39 (vials); \$138.80-\$276.80 (powder for injection)</i>
Humatrope Vial for injection	<i>Children: 5.4 –11.25mg weekly</i>	<i>Children: \$620.84 - \$931.26</i>
Norditropin Prefilled cartridges/pens (5mg/1.5ml, 10mg/1.5ml, 15mg/1.5ml)	<i>Children: 5.0 – 7.1mg weekly</i>	<i>Children: \$310.46 – \$620.90</i>
Nutropin Starter Kit (10mg, 5mg)	<i>Children: 9-11.25mg weekly</i>	<i>Children: \$10.00 for starter kit</i>
Nutropin AQ Prefilled cartridge (5mg/ml)	<i>Children: 9-11.25mg weekly</i>	<i>Children: \$1241.68</i>
Nutropin Depot	<i>Children: 45mg monthly or 22.5mg twice monthly</i>	Not Available
Saizen Vial for injection (5mg, 8.8mg)	<i>Children: 5.4mg weekly</i>	<i>Children: \$451.10</i>
Serostim Vials for injection (4mg, 5mg, 6mg)	<i>Adults: 24.5-42mg weekly</i>	<i>Adult: \$1008-1764</i>

Drug/Availability	Usual Weekly Dose	Weekly Cost
Genotropin, Vial for injection (5.8mg, 13.8mg) Powder for injection (0.2mg/ml to 2mg/ml)	<i>Children: 4.8-7.2mg weekly Adult: 2.4-4.8mg weekly</i>	<i>Children: \$289.39 - \$694.53 (vial); \$276.80- 347.25 (powder for injection) Adult: \$289.39 (vials); \$138.80-\$276.80 (powder for injection)</i>
Somatrem Vial for injection (10mg)	<i>Children: 9-11.25mg weekly Adults: 29.4mg weekly</i>	<i>Children: \$528.74 Adult: \$1586.22</i>
Zorbitive Vial for injection (8.8mg)	<i>Adults: 42mg weekly</i>	Not Available
Pegvisomant Vial for injection (10mg, 15mg, 20mg)	<i>Adults: 30mg SC daily</i>	<i>Adults: \$1890</i>

* For average child weight of 30 kg and adult weight of 60 kg

CONCLUSION:

The use of growth hormone products in children and adults has increased in recent years. No direct comparative trials between the marketed products have been described. The most recent approvals for growth hormone by the FDA have been for long-term use in children with idiopathic, non-growth hormone deficient short stature (*Humatrope*) and patients with short bowel syndrome dependant on parenteral nutrition (*Zorbitive*). Growth hormone has shown in short term trials to decrease the length of parenteral nutrition needed, body weight, lean body mass, and percent body fat; but studies vary on its effects on other measures such as intestinal fluid and nutrient absorption. Initiation of growth hormone in short bowel syndrome seems to be more effective if started after the patient's gut has had time to adapt after surgery and he or she is well nourished; hence, initiation of therapy is recommended after about 3-6 months to several years after small bowel resection. However, most authors of the various studies agree that growth hormone is expensive and requires daily or at minimum 3 times weekly injections, which could be a negative, especially for certain indications such as short bowel syndrome.

Pegvisomant has shown to be effective in treating acromegaly; however, more comparative studies against somatostatin and bromocriptine need to be carried out. The manufacturer recommends periodically monitoring of liver function. Cost of indefinite treatment and long-term effects of endogenous growth hormone are not known. All marketed recombinant human growth hormone products are available via normal pharmacy drug distribution systems.

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