Growth Hormone Review

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Growth Hormone Review

Overview

Drug	Manufacturer	FDA-Approved Indications				
		GHD (Pediatric/ Adult)	Turner syndrome	CRI	ISS	Other
Genotropin®[1]	Pfizer	X	X			PWS, SGA
Humatrope®[2]	Lilly	X	X		X	SHOX
Norditropin®[3]	Novo Nordisk	X	X			Noonan Syndrome
Nutropin®[4]	Genentech	X	X	X	X	
Nutropin AQ®[5]	Genentech	X	X	X	X	
Omnitrope®[6]	Sandoz	X				
Saizen®[7]	Serono	X				
Serostim®[8]	Serono					HIV wasting or cachexia
Tev-Tropin™[9]	Gate/Teva	X (pediatric only)				
Zorbtive®[10]	Serono					SBS

GHD = Growth hormone deficiency
PWS = Prader-Willi Syndrome
CRI = Chronic renal insufficiency
SGA = Small for gestational age
ISS = Idiopathic short stature
SHOX = Short stature homeobox gene
SBS = Short bowel syndrome
HIV = Human Immunodeficiency virus

Human growth hormone (hGH) is a 191-amino acid polypeptide hormone secreted by the anterior pituitary gland. It has important metabolic effects including stimulation of protein synthesis and cellular uptake of amino acids. Previously, the only source of exogenous growth hormone was human cadavers. Advances in biotechnology, however, have made recombinant DNA-derived growth hormone available for general use. Exogenous growth hormone is used to treat a variety of disorders in which endogenous growth hormone is insufficient to meet the needs of the patient. The 2003 American Association of Clinical Endocrinologists Guidelines for Clinical Practice speak of growth hormone dosing in general terms and do not specify any particular products for any of the disease states.[11]

Growth hormone deficiency (GHD) is the effect of inadequate production of growth hormone. Deficiency of growth hormone produces different problems at various ages. In infancy and childhood, growth failure may be the major effect. Adults with GHD may have diminished lean body mass and poor bone density and a number of physical and psychological symptoms. GHD can be congenital or

acquired in childhood or adult life, and partial or complete. It is usually permanent, but sometimes transient, and may be an isolated deficiency or occur in association with deficiencies of other pituitary hormones.

Prader-Willi Syndrome (PWS) is a genetic disorder in which seven genes on chromosome 15 are missing or unexpressed on the paternal chromosome. PWS is characterized by hyperphagia and food preoccupations, as well as small stature and mental retardation. Daily growth hormone injections support linear growth and increased muscle mass, and may lessen food preoccupation and weight gain.

In chronic renal insufficiency (CRI), the kidneys lose the ability to regulate the amounts of nutrients, such as calcium and vitamin D, involved in the growth process. Children with CRI may have difficulty attaining a normal height and weight for several reasons, including slow bone growth, malnutrition, and problems using protein. Growth hormone treatment can correct some of these deficiencies.

Small for gestational age (SGA) babies are those whose birth weight lies below the 10th percentile for that gestational age. They have usually been the subject of intrauterine growth retardation. If the child has not caught up to the normal growth range by the age of two years, growth hormone therapy is initiated.

In Turner syndrome, female sexual characteristics are present but are underdeveloped due to several chromosomal abnormalities. Idiopathic short stature (ISS) refers to extreme short stature that does not have a diagnostic explanation. Short stature homeobox gene (SHOX) is a gene on the X chromosome and Y chromosome which is associated with short stature in humans if mutated or present in only one copy.

Patients with HIV/AIDS typically experience cachexia: loss of weight, muscle atrophy, fatigue, weakness, and anorexia. In these conditions, growth hormone improves growth and final adult height.

Short bowel syndrome (SBS) is a malabsorption disorder caused by either the surgical removal of the small intestine or the loss of its absorptive function due to various diseases. Growth hormone has been shown to enhance intestinal function, resulting in better absorption by the remaining small intestine.

The principal features of Noonan Syndrome, a congenital disorder, include heart malformation, short stature, indentation of the chest, learning disabilities, impaired blood clotting, and a certain configuration of facial features. Growth hormone is given to correct the short stature element of this disorder.

Pharmacology

Somatropin is a polypeptide hormone of recombinant DNA origin. The amino acid sequence of somatropin is identical to that of hGH of pituitary origin.[12] The growth-promoting effects of growth hormone are due to anabolic peptide formation mediated by insulin-like growth factors. These peptides, specifically IGF-I, act as a direct stimulator of cell proliferation and growth. Skeletal growth, the number and size of muscle cells, red blood cell mass, chondroitin and collagen synthesis, and lipid mobilization are all positively impacted by growth hormone.

Pharmacokinetics[13,14,15,16,17,18,19,20,21,22]

Growth hormone is administered by IM or SC injection. Peak plasma concentrations of somatropin are reached two to six hours following administration. Approximately 20 percent of the circulating somatropin is bound to growth hormone-binding protein. Peak plasma concentrations of IGF-1 occur about 20 hours after administration of somatropin. Somatropin is metabolized by the liver, kidney, and other tissues; little excretion occurs via the urine. The plasma elimination half-life is approximately 20 to 30 minutes. Because of continued release of somatropin from the injection site, serum concentrations decline with a half-life of about three to five hours. Because of the slow induction and clearance of IGF-1, the effects of somatropin last much longer than its elimination half-life.

Special Populations[23,24,25,26,27,28,29,30,31,32]

Pregnancy

All products in this review are Pregnancy Category C except for Genotropin, Omnitrope, Saizen, Serostim, and Zorbtive, which are Pregnancy Category B.

Other

There are no data at this time to suggest differences in pharmacokinetics or pharmacodynamics in other subsets of the population.

Contraindications/Warnings[33,34,35,36,37,38,39,40,41,42]

Growth hormone is contraindicated in patients with the following conditions: closed epiphyses (pediatric patients only); active malignancy; acute critical illness in response to open heart surgery, abdominal surgery or multiple accidental trauma, or acute respiratory failure; Prader-Willi syndrome in the presence of severe obesity or severe respiratory impairment; and active proliferative or severe non-proliferative diabetic retinopathy.

Treatment with growth hormone may decrease insulin sensitivity, particularly at higher doses in susceptible patients. Patients with type 1 or 2 diabetes or impaired glucose tolerance should be monitored closely for hyperglycemia during growth hormone therapy.

Undiagnosed or untreated hypothyroidism may prevent an optimal response to growth hormone therapy, particularly in children.

Patients with Turner syndrome, chronic renal insufficiency, or Prader-Willi syndrome may be at increased risk for the development of intracranial hypertension.

Drug Interactions[43,44,45,46,47,48,49,50,51,52]

Previously undiagnosed central hypoadrenalism may be discovered as a result of growth hormone therapy. In patients already diagnosed with this condition, an increase in maintenance or stress dosing of glucocorticoids may be necessary. However, excessive glucocorticoid therapy will inhibit the growth-promoting effect of growth hormone.

Growth hormone treatment may alter the clearance of compounds known to be metabolized by the CYP450 liver enzymes (e.g., corticosteroids, sex steroids, anticonvulsants, and cyclosporine).

Women using oral estrogen replacement may require larger growth hormone doses to achieve treatment goals.

Adverse Effects[53,54,55,56,57,58,59,60,61,62]

Leukemia has been reported in a small number of GHD patients treated with growth hormone. It is not known if this increased risk is related to the pathology of GHD itself, growth hormone therapy, or other associated treatments such as radiation therapy for intracranial tumors. On the basis of current evidence, however, it cannot be concluded that growth hormone therapy is responsible for this potential secondary malignancy.

Metabolic complications may be seen occasionally during growth hormone therapy; hyperglycemia, hypoglycemia, hypothyroidism, glycosuria, and fluid retention have been reported. Peripheral edema may occur, more commonly in adults than children. In adults with GHD, edema or peripheral edema was reported in 41 percent of patients treated with growth hormone as compared to 25 percent of placebo-treated patients.[63] Edema usually occurs early in therapy and is transient or responsive to dosage reduction. During post-marketing surveillance, cases of new onset glucose intolerance, diabetes mellitus, and exacerbation of pre-existing diabetes mellitus have been reported. Some patients developed diabetic ketoacidosis and diabetic coma. In some patients, these conditions improved when growth hormone was discontinued while in others the glucose intolerance persisted. Some patients may require initiation or adjustment of antidiabetic treatment.

Arthralgia, myalgia, pain and stiffness of the extremities, weakness, and headache have been commonly associated with growth hormone therapy, occurring more frequently in adults than children. In adults treated with growth hormone, the onset of muscle and joint pain most often occurs early in therapy. As with edema, the pain tends to be transient or responds to a reduction in growth hormone dose.

Seizures and exacerbation of pre-existing psoriasis has been reported infrequently with growth hormone therapy.

In patients treated with growth hormone for Turner Syndrome, there is a statistically increased incidence of otitis media, other ear disorders, and surgical procedures as compared to placebo.

Injection site reaction (pain or burning associated with injection), lipoatrophy, or nodules are associated with the administration of growth hormone.

Fatalities have been reported with the use of hGH for PWS in patients that have with one or more of the following risk factors: severe obesity, history of respiratory impairment or sleep apnea, or unidentified respiratory infection.

Dosages SD = single-dose vial, MD = multiple-dose vial, IM = intramuscular, SC = subcutaneous

Drug (mfr)	Dosage Forms	Dosage
Genotropin[64] (Pfizer)	Two chamber cartridge (for use with Pen or Mixer): 5.8, 13.8 mg (MD) Miniquick® syringe device: 0.2-2 mg in 0.2 mg increments (SD)	GHD (ped): 0.16 to 0.24 mg/kg/week divided and given as six or seven SC injections GHD (adult): no more than 0.04 mg/kg/week to start; the dose may be increased at four- to eight-week intervals according to individual patient requirements and tolerance to a maximum of 0.08 mg/kg/week. The weekly dose should be divided and given as six or seven SC injections. PWS: 0.24 mg/kg/week divided and given as six or seven SC injections SGA: 0.48 mg/kg/week divided and given as six or seven SC injections Turner syndrome: 0.33 mg/kg/week divided and given as six or seven SC injections
Humatrope[65] (Lilly)	Vials (with diluent): 5 mg (MD) Cartridge kits (with prefilled diluent syringes): 6, 12, 24 mg (MD)	GHD (ped): 0.18 mg/kg/week up to 0.3 mg/kg/week divided and given SC on three alternate days, six times per week, or daily (IM use is acceptable) GHD (adult): not more than 0.006 mg/kg/day SC to start; may be increased to maximum of 0.0125 mg/kg/day Idiopathic short stature: up to 0.37 mg/kg/wk SC divided into equal doses and given six or seven times per week SHOX: 0.35 mg/kg/week SC divided and given daily Turner syndrome: 0.375 mg/kg/week SC divided and given daily or on three alternate days
Norditropin[66] (Novo Nordisk)	NordiPen® cartridges: 5, 15 mg (MD) Nordiflex prefilled pens: 5, 10, 15 mg (MD) Vials (with diluent): 4, 8 mg (SD)	GHD (ped): 0.024-0.034 mg/kg/day given SC six or seven times per week GHD (adult): not more than 0.004 mg/kg/day SC to start; may be increased to maximum of 0.016 mg/kg/day after six weeks Noonan Syndrome: Up to 0.066 mg/kg/day SC Turner Syndrome: Up to 0.067 mg/kg/day SC
Nutropin[67] (Genentech)	Vials (with diluent): 5, 10 mg (MD)	GHD (ped) - prepubertal: up to 0.3 mg/kg/wk divided into daily SC injections GHD (ped) - pubertal: up to 0.7 mg/kg/wk divided into daily SC injections GHD (adult): not more than 0.006 mg/kg/day SC to start; may increase according to patient requirements to maximum of 0.025 mg/kg/day in patients under 35 years and 0.0125 mg/kg daily in patients over 35 years. CRI: 0.35 mg/kg/week divided into daily SC injections Idiopathic short stature: 0.3 mg/kg/week SC divided into daily doses Turner syndrome: 0.375 mg/kg/week SC divided into equal doses given three to seven times per week
Nutropin AQ[68] (Genentech)	Vials: 10 mg (MD) Pen cartridge: 10, 20 mg (MD)	
Omnitrope[69] (Sandoz)	Vials: 5.8 mg (MD)	GHD (ped): 0.16 to 0.24 mg/kg SC per week divided into daily SC injections GHD (adult): not more than 0.04 mg/kg/week divided into daily SC injections, dosage not to exceed 0.08 mg/kg/week after 4 weeks depending on patient's tolerance
Saizen[70] (Serono)	Vials (with diluent): 5, 8.8 mg (MD), Cartridge: 8.8 mg (MD)	GHD (ped): 0.06 mg/kg SC or IM three times per week GHD (adult): not more than 0.005 mg/kg/day SC to start, dosage not to exceed 0.01 mg/kg/day after 4 weeks depending on patient's tolerance
Serostim[71] (Serono)	Vials (with diluent): 5, 6 mg (SD) Vials (with diluent): 4, 8.8 mg (MD)	HIV patients: 0.1 mg/kg SC daily or every other day
Tev-Tropin[72] (Gate/TEVA)	Vials (with diluent): 5 mg (MD)	GHD (ped): up to 0.1 mg/kg SC three times per week
Zorbtive[73] (Serono)	Vials (with diluent): 8.8 mg (MD)	Short bowel syndrome: 0.1 mg/kg/day SC, maximum of 8 mg daily

Clinical Trials

Studies were identified through searches performed on PubMed and http://www.ifpma.org/clinicaltrials.html and review of information sent by manufacturers. Search strategy included the use of all brand names in this class. Randomized, comparative, controlled trials performed in the United States comparing agents within this class in an outpatient setting for the approved indications are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question and include follow-up (endpoint assessment) of at least 80 percent of participants entering the investigation. Despite some inherent bias found in all studies, including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance.

There are no studies meeting the inclusion criteria.

Summary

The currently available growth hormone replacement products are, by definition, similar in their clinical effects. The differences in FDA-approved indications reflect only that the manufacturer of a specific product has pursued approval for those particular indications. No head-to-head data are available.

The differences in these products with respect to dosages and some adverse effects are a reflection of their various dosage forms and product packaging. It is these differences that should be considered when evaluating these products:

Vials

All products requiring reconstitution are supplied in “kits” containing a vial of active drug along with a vial of diluent. Nutropin AQ and Norditropin contain a sterile solution for injection; therefore, no diluent for reconstitution is required. Reconstitution has been shown to be a major cause of patient dissatisfaction. Solutions are also associated with greater convenience and reduced levels of pain associated with injection.[74] Solutions are easier for the majority of patients to use as no reconstitution is required.

Devices

Several of the products have specific devices to facilitate use of the medication by the patient or caregiver.

Genotropin is supplied in single-use syringe devices (Miniquick, Pen) that allow for internal reconstitution. The Miniquick is a single-use, disposable syringe that already houses a cartridge for internal reconstitution. The Miniquick can only be refrigerated for 24 hours after reconstitution. Cartridges are added to the Pen and Mixer devices. Both use internal

reconstitution; the cartridges can be refrigerated after reconstitution for 28 days and can be reused.

For Humatrope, the cartridge is placed in the pen for reconstitution and subsequent injection. Humatrope cartridges must be refrigerated before reconstitution and can be reused if refrigerated for up to 28 days following reconstitution.

Norditropin can be supplied as cartridges for use with the NordiPen and as a prefilled pen (NordiFlex). Reconstitution is not necessary; the drug is already in solution. Both cartridges and pens are refrigerated prior to initial use, then may be refrigerated and used again for up to four weeks. While 15 mg cartridges and pens must be refrigerated, 5 mg cartridges and 5 and 10 mg pens may be kept at room temperature for three weeks following the initial use. For patients with needle-caused anxiety, the PenMate attachment hides the needle during the injection process.

Nutropin AQ is available in a pen cartridge and as a prefilled pen (NuSpin). As with Nutropin AQ vials, the contents are already in solution. Nutropin AQ must always be refrigerated, before initial use and for 28 days afterward.

Needle-free devices for SC administration of Saizen (cool.click™) and for Serostim (SeroJet™) are available at no extra cost. The click.easy device is an internal reconstitution mechanism; the resulting solution is administered with the cool.click or the one.click pen, which hides the injection needle. With Serostim, reconstitution of the growth hormone solution is still done through a lengthy manual process prior to drawing it into the administration device. Reconstituted Saizen and Serostim vials must be refrigerated until used with the remainder discarded after 14 days. Cartridges may be stored for up to 21 days.

In a survey of 50 diabetic children (ages four to 10 years), the cool.click device was found to be easier to use than needles and was preferred by the children over syringe-needle methods of drug administration.[75] Saizen is also available as an auto-injector pen, one.click™ and can be used with the click.easy™ vials to simplify the reconstitution procedure.

Saizen may be administered by the easypod device. This tool contains a reconstituted cartridge with an attached needle. When placed at a 90-degree angle to the injection site, the injection button will turn green when ready. When pressed, the injection button light will go off and the device will beep twice, indicating that the injection was completed. The easypod tracks the remaining drug in the cartridge and its expiration date, the daily dose to administer, the time and date of the last dose, and hides the injection needle. The entire device can be stored in the refrigerator.

All of these injection devices have dial-a-dose capabilities. Nutropin, Omnitrope, Tev-Tropin, and Zorbtive do not have administration devices available. Evaluation of patient preferences (with possible increases in compliance) may place added value on one delivery system over another.

Frequency of administration

Most of the growth hormone products are given six or seven times weekly. Humatrope, Saizen, and Tev-Tropin can be given to pediatric patients as few as three times per week, as can Nutropin when being used for Turner syndrome. This may play a factor in patient compliance with the prescribed regimen.

Other than these slight pharmaceutical differences, there is no pharmacologic difference among the agents in terms of safety and efficacy. Due to the similarity of these products, preferred drug list status should be based on cost factors with some consideration given to delivery system as it may affect patient compliance.

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