Growth Hormone
Therapeutic Class Review (TCR)

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FDA-APPROVED INDICATIONS

Drug	Manufacturer	FDA-Approved Indications				
		GHD (Pediatric/ Adult)	Turner Syndrome	SGA*	ISS	Other
Genotropin®[1]	Pfizer	X	X	X	X	PWS
Humatrope®[2]	Eli Lilly	X	X	X	X	SHOX*
Norditropin®[3]	Novo Nordisk	X	X	X	X	Noonan Syndrome, PWS
Nutropin AQ® NuSpin®[4]	Genentech	X	X	--	X	CRI
Omnitrope®[5]	Sandoz	X	X	X	X	PWS
Saizen®[6]	EMD Serono	X	--	--	--	--
Serostim®[7]	EMD Serono	--	--	--	--	HIV wasting or cachexia to increase lean body mass and weight, and improve physical endurance
Zomacton™[8]	Ferring	X	X	X	X	SHOX*
Zorbtive®[9]	EMD Serono	--	--	--	--	SBS

CRI = chronic renal insufficiency; GHD = growth hormone deficiency; HIV = Human Immunodeficiency Virus; ISS = idiopathic short stature; PWS = Prader-Willi syndrome; SBS = short bowel syndrome; SGA = small for gestational age; SHOX = short stature homeobox gene

* SHOX – indicated in patients with no catch-up growth by 2 to 4 years of age

OVERVIEW

Human growth hormone (hGH, somatropin) 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. Short stature and growth deceleration are common pediatric concerns, and 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.[10]

Growth hormone deficiency (GHD) results from inadequate production of growth hormone (GH) and can produce various medical conditions dependent on age. GHD can be congenital or acquired in childhood or adult life, in addition to being partial or complete. In infancy and childhood, growth failure may be the major effect. Adults with GHD may have diminished lean body mass, poor bone density, and a number of physical and psychological manifestations. GHD is usually permanent and may be an isolated deficiency or occur in association with deficiencies of other pituitary hormones. Between 40% to 50% of childhood cancer survivors develop an endocrine disorder during their lifetime, with some developing decades following cancer treatment.[11]

In most cases, the diagnosis of GHD should be based on results from 2 provocative tests as recommended by the Pediatric Endocrine Society (PES).[12] The 2019 AACE Growth Hormone Task Force does not advocate use of one product over another, but they do recommend using individualized dose

adjustments to improve effectiveness and minimize side effects.[13] The 2019 Growth Hormone Research Society Guidelines advise assessing the somatropin dose every 6 to 12 months, with dose adjustments based on the change in SDS and height velocity.[14]

Prader-Willi syndrome (PWS) is a genetic disorder in which several genes on chromosome 15 are missing or unexpressed on the paternal chromosome.[15] PWS is characterized by hyperphagia and food preoccupations, as well as small stature and mental retardation. The major manifestations of PWS are neurobehavioral and endocrine abnormalities, hypothalamic obesity, hypotonia, short stature, developmental delay, and aspects of hypothalamic endocrine dysfunction and pubertal delay or absence. In some cases, the impaired GH secretion (which can persist into adulthood) may be the result of hypothalamic dysfunction. Daily growth hormone injections support linear growth, increase muscle mass, and may lessen food preoccupation and weight gain in patients with PWS.

Children with chronic renal insufficiency (CRI) may have difficulty attaining a normal height and weight for several reasons, including malnutrition, renal osteodystrophy, electrolyte, calcium and vitamin D imbalances, inadequate use of protein by the body, and abnormalities in the growth hormone (GH)-insulin-like growth factor (IGF)-1 axis. In CRI, GH levels may be normal or elevated; however, patients may exhibit insensitivity to the action of GH. In addition, levels of free IGF-1 may be reduced, thereby decreasing its bioavailability. These GH/IGF-1 axis disturbances can be overcome by the administration of supraphysiological doses of exogenous GH.[16,17]

Babies born small for gestational age (SGA) have birth weights that fall below the tenth percentile for that gestational age. Typically, intrauterine growth retardation is the causative factor. Although the majority of these children catch up in height to normal range during the first 2 years of life, approximately 10% of SGA children fail to exhibit catch-up growth by age 2 years. Growth hormone levels in these children may be low or within normal range. Decreased growth may be due to insensitivity to growth hormone as well as low IGF-1 levels. It is thought that administering exogenous GH may overcome GH insensitivity. If left untreated, these children are likely to remain below expected height throughout adolescence and adulthood.[18,19]

Short stature homeobox gene (SHOX) is a gene on the X and Y chromosomes that controls the formation of many body structures, including the growth and maturation of bones in the arms and legs. Patients with SHOX deficiency (gene mutation or present in only 1 copy) may present with a broad phenotypic spectrum ranging from isolated short stature with no distinguishing clinical features to short stature with moderate to severe skeletal dysplasia. Approximately 1% to 4% of patients with clinical features consistent with idiopathic short stature may test positive for SHOX deficiency.[20]

In Turner syndrome (TS), female sexual characteristics are present but are underdeveloped due to several chromosomal abnormalities. At least 95% of all patients with TS have short stature. The etiology of the growth retardation may be due to haploinsufficiency of the SHOX gene, not GHD. However, subnormal levels of GH and IGF-1 have been reported, and it has been postulated that a diminished sensitivity for growth factors might explain the short stature.[21] Short stature in patients with TS is characterized by mild intrauterine growth retardation, slow growth during infancy, delayed onset of the childhood component of growth, and growth failure during childhood and adolescence. These factors lead to a diminished final height which can be positively affected by growth hormone therapy.

Idiopathic short stature (ISS) is defined by the Growth Hormone Research Society as a condition in which the height of an individual is more than a 2 standard deviation score (SDS) below the corresponding mean height for a given age, sex, and population group without evidence of systemic, endocrine, nutritional, or chromosomal abnormalities.[22] The PES defines ISS as height standard deviation score ≤ -2.25 with a predicted adult height less than the normal range (63 inches in men; 59 inches in women).[23] Specifically, children with ISS have normal birth weight and are GH sufficient. The PES recommends against routine use of GH in children with height standard deviation ≤ -2.25 since response to therapy varies. The PES advises that GH therapy decision should be based on physical and psychological effects and risks versus benefits. Treatment benefit should be reassessed after 12 months of optimally-dosed therapy.[24]

Patients with human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) may experience cachexia: loss of weight, muscle atrophy, fatigue, weakness, and anorexia.[25] Human growth hormone therapy allows the body to use fat for energy, thereby preserving lean body mass.[26] Serostim is indicated for the treatment of HIV patients with wasting or cachexia to increase lean body mass and body weight and to improve physical endurance.

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.[27] Intestinal mucosa contains receptors for growth hormone and for IGF-1, which is known to mediate many of the cellular actions of growth hormone. In human clinical studies, the administration of growth hormone enhanced the transmucosal transport of water, electrolytes, and nutrients. Zorbtive is indicated for the treatment of SBS in patients receiving specialized nutritional support.[28]

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. Short stature is present in as many as 80% of patients. Growth hormone has been used successfully to correct short stature associated with the disorder.[29]

PHARMACOLOGY[30,31,32,33,34,35,36,37,38]

Somatropin is a polypeptide hormone of recombinant DNA origin. The amino acid sequence of somatropin is identical to that of hGH of pituitary origin. Growth-promoting effects of growth hormone are due to anabolic peptide formation mediated by insulin-like growth factors. The peptides, specifically IGF-1, act as direct stimulators of cell proliferation and growth. Skeletal and organ growth, the number and size of muscle cells, red blood cell mass, chondroitin and collagen synthesis, lipid mobilization, connective tissue, and the metabolism of minerals, proteins, carbohydrates, and lipids are all positively impacted by growth hormone. Somatropin also decreases fat mass and promotes increased lean body mass.

PHARMACOKINETICS[39,40,41,42,43,44,45,46,47]

Growth hormone is administered by IM or SC injection. The absolute bioavailability after a SC injection of somatropin ranges between 61% and 100%. Peak plasma concentrations of somatropin are reached 3 to 7 hours following administration. Approximately 10% to 30% 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. 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 2 to 10 hours. Because of the slow induction and clearance of IGF-1, the effects of somatropin last much longer than its elimination half-life. Somatropin is metabolized by the liver, kidney, and other tissues; little excretion occurs via the urine.

CONTRAINDICATIONS/WARNINGS[48,49,50,51,52,53,54,55,56]

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, multiple accidental trauma, or acute respiratory failure; PWS with severe obesity and a history of upper airway obstruction or sleep apnea, or severe respiratory impairment; and active proliferative or severe non-proliferative diabetic retinopathy. Patients with a known hypersensitivity to the drug or diluent should not use the product. Genotropin 5 mg and 12 mg and Zomacton 10 mg contain the preservative m-cresol and should not be used in patients with a known hypersensitivity. There are post-marketing reports of serious hypersensitivity reactions including anaphylactic reactions and angioedema with somatropin products.

Treatment with growth hormone may decrease insulin sensitivity, especially at higher doses in susceptible patients. Growth hormone therapy has been associated with cases of new-onset impaired glucose intolerance, impaired fasting glucose, new-onset type 2 diabetes mellitus, and exacerbation of preexisting diabetes mellitus. All patients, especially patients with type 1 or 2 diabetes, impaired glucose tolerance, and those at high risk for developing diabetes mellitus should be monitored closely for hyperglycemia during growth hormone therapy. Alterations in antidiabetic medication therapy may be needed for some patients as a result.

Undiagnosed or untreated hypothyroidism may prevent an optimal response to growth hormone therapy, particularly in children, and monitoring is warranted. Patients with hypothyroidism or hypopituitarism should have periodic laboratory tests and their hormonal replacement therapy monitored when taking somatropin therapy.

Intracranial hypertension with visual changes, headache, nausea, vomiting, and papilledema has been reported in a small number of patients treated with growth hormone. Symptoms usually occurred within the first 8 weeks after the initiation of therapy and resolved after stopping growth hormone therapy or reducing the dose. Prior to beginning growth hormone therapy a screening for pre-existing papilledema should be performed and routine checks thereafter are warranted. If papilledema occurs the somatropin therapy should be stopped and, if intracranial hypertension is diagnosed, therapy can be restarted at a lower dose after the signs and symptoms have resolved. Patients with Turner syndrome and PWS may be at an increased risk for developing intracranial hypertension.

Fluid retention during somatropin replacement therapy in adults may frequently occur. Clinical signs are usually transient and dose dependent. Fluid retention can be manifested by edema, arthralgia, myalgia, and nerve compression syndromes, such as carpal tunnel syndrome and paraesthesias. Carpal tunnel syndrome specifically may occur during treatment with Genotropin, Serostim, or Zorbtive. If the symptoms of carpal tunnel syndrome do not resolve with decreased dosing, growth hormone therapy should be discontinued.

An increased risk of a second neoplasm has been reported in childhood cancer survivors who were treated with radiation to the brain/head for their first neoplasm who also developed subsequent growth hormone deficiency and were treated with somatropin. The most common intracranial tumors that develop in these patients are meningiomas. Patients who have a history of growth hormone deficiency secondary to an intracranial neoplasm should be monitored for progression or reappearance of tumors. Children with rare genetic causes of short stature have an increased risk of developing neoplasms; therefore, prescribers should consider the risk to benefit when starting somatropin therapy and monitor patients closely. Since HIV patients are more susceptible to malignancies prescribers should consider the benefits and risks of somatropin therapy. Patients should also be monitored for malignant skin lesions.

Preexisting malignancies should be inactive prior to starting somatropin therapy and should be stopped if there is evidence of recurrent activity. Pituitary tumors should be ruled out prior to starting therapy and therapy should be stopped if an intracranial tumor is present.

Slipped capital femoral epiphyses may occur more often in patients with endocrine disorders or in patients undergoing quick growth. Children should be monitored for onset of a limp or complaints of hip or knee pain during growth hormone therapy.

Progression of scoliosis can occur in patients who experience rapid growth but somatropin is not associated with increasing the incidence of scoliosis. Patients should be monitored for progression of the disease.

Bone age should be monitored during somatropin therapy in pubertal patients and/or patients receiving concomitant thyroid hormone therapy as epiphyseal maturation may progress quickly.

Cases of pancreatitis have been reported rarely in children and adults receiving somatropin treatment. However, some evidence supports a greater risk of developing pancreatitis in children compared with adults. Published literature indicates that girls who have Turner syndrome may be at greater risk than other children treated with somatropin. Pancreatitis should be considered in any somatropin-treated patient who develops abdominal pain especially when the patient is a child.

Patients with Turner syndrome should be closely monitored for otitis media, other ear disorders, and cardiovascular complications since they are at an increased risk of an adverse event.

Fatalities have been reported with the use of growth hormone for pediatric patients with PWS having 1 or more of the following risk factors: severe obesity, history of respiratory impairment or sleep apnea, severe respiratory impairment, or an unidentified respiratory infection. Patients with PWS should be examined for upper airway obstruction and sleep apnea before starting somatropin therapy and routine monitoring should occur thereafter. If signs and symptoms of upper airway obstruction or sleep apnea occur somatropin therapy should be interrupted or discontinued. All PWS patients treated with somatropin should have their weight controlled and be monitored for signs and symptoms of respiratory infection and be treated aggressively if 1 occurs. Male patients with 1 or more of the aforementioned risk factors may be at greater risk of complications than females. Somatropin is contraindicated in these patients.

Caution is advised when using growth hormone products as they may contain benzyl alcohol which has been associated with serious adverse events and death in pediatric patients. Symptoms include

neurological deterioration, seizures, intracranial hemorrhage, hematologic abnormalities, skin breakdown, hepatic and renal failure, and cardiovascular collapse. Practitioners administering these with other medications containing benzyl alcohol should consider the combined daily load of benzyl alcohol. When products are used in newborns, if appropriate, the medication should be reconstituted with sterile normal saline for injection; only 1 dose per vial should be used and the unused portion should be discarded.

Patients take somatropin therapy over a long period of time and should rotate injection sites to minimize local adverse reactions such as tissue atrophy. Local or systemic allergic reactions may occur at the somatropin injection sites.

Children using somatropin for the treatment of growth failure secondary to chronic kidney disease should be monitored for renal osteodystrophy.

In some in vitro experimental systems, somatropin has been shown to potentiate HIV replication. However, when antiretroviral agents (didanosine, lamivudine, zidovudine) were added there was no increase in viral production. In controlled clinical trials, no significant increases in viral burden occurred that were associated with somatropin. Due to the potential increase of virus replication it is recommended that HIV patients remain on antiretroviral medications throughout Serostim therapy.

In 2010 and 2011, the FDA reviewed the results of the French Sante Adult GH Enfant Study (SAGhE). The study found persons with idiopathic growth hormone deficiency and idiopathic or gestational short stature, who were treated with long-term recombinant human growth hormone during childhood, were at a small increased risk for death compared to individuals in the general French population.[57, 58] In the study, there was a 30% increased risk for death in patients using recombinant human growth hormone therapy compared with the general French population. The risk of death was increased when doses of recombinant growth hormone that are higher than what is normally prescribed for pediatric growth hormone deficiency were used. In 2011, the FDA determined the evidence from the study was inconclusive due to the study having design weaknesses which limited the interpretability of the study and the study's data sources lacked evidence to support a link between recombinant human growth hormone and an increased risk of death. The FDA has recommended that prescribers and patients continue to prescribe and use recombinant human growth hormone according to the labeled recommendations. The FDA expected to have additional data from the study in 2012; however, to date, no updates have been published by the FDA.

DRUG INTERACTIONS[59,60,61,62,63,64,65,66,67]

Previously undiagnosed central hypoadrenalism may be discovered as a result of growth hormone therapy and glucocorticoid replacement may be needed. 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, cyclosporine).

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

Patients who require treatment for diabetes should be monitored closely and adjustments to medications may be warranted.

ADVERSE EFFECTS[68,69,70,71,72,73,74,75,76]

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. However, current evidence does not support the conclusion that growth hormone therapy is the causative agent for this potential secondary malignancy. New onsets and reoccurrence of benign and cancerous neoplasms have also been reported.

Metabolic complications may be seen occasionally during growth hormone therapy; hyperglycemia, hypoglycemia, hypothyroidism, hypertriglyceridemia, 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 42% of patients treated with growth hormone as compared to 8% of placebo-treated patients. 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, the conditions improved when growth hormone was discontinued while in others the glucose intolerance persisted. Some patients may require initiation or adjustment of antidiabetic treatment.

Pancreatitis, gastroenteritis, abdominal pain, nausea, and incidences of hyperlipidemia have also been reported in pediatric and adult patients.

Central nervous symptoms are common when using somatropin and include sensory changes, fatigue, weakness, headache, pain, arthralgia, paresthesia, hypoesthesia, myalgia, skeletal pain, muscle pain, altered mood, and pain and stiffness of the extremities. These adverse events have been more commonly associated with 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.

In patients treated with growth hormone for Turner syndrome, there is a statistically increased incidence of otitis media (43%), other ear disorders (18%), and surgical procedures (45%) as compared to placebo ($p \leq 0.05$). Other adverse reactions reported in patients with Turner syndrome included respiratory illness, joint pain, and urinary tract infections.

In patients treated with growth hormone for Prader-Willi syndrome, there were reports of edema, arthralgia, aggressiveness, benign intracranial hypertension, hair loss, myalgia, and headache.

Respiratory conditions such as upper respiratory infection, cough, respiratory disorder, pharyngitis, bronchitis, laryngitis, tonsillitis, nasopharyngitis, and rhinitis have been reported primarily in pediatric patients.

Infrequent reports of injection site reactions (e.g. pain or burning associated with the injection, fibrosis, rash, nodules, pigmentation, inflammation, or bleeding), headache, lipoatrophy, hematuria, mild hyperglycemia, and hypothyroidism have been reported. Injection site discomfort has been

reported and is more common in pediatric patients after switching from another somatropin product to Nutropin AQ.

Flu-like symptoms have been reported in adults and children.

Other adverse events, such as hypertension, hematoma, carpal tunnel syndrome, chest pain, hip pain, arthralgia, arthrosis, myalgia, depression, antibody formation, gynecomastia (in pediatrics), and insomnia have also been reported.

SPECIAL POPULATIONS[77,78,79,80,81,82,83,84,85]

Pregnancy

Humatrope, Nutropin AQ, NuSpin, and Norditropin are Pregnancy Category C. Previously assigned Pregnancy Category C, the labeling for Zomacton has been updated to comply with the Pregnancy and Lactation Labeling Rule (PLLR) and states that while the fetus is unlikely to be exposed to the benzyl alcohol contained in the Zomacton 5 mg diluent, the vial should be reconstituted with 0.9% sodium chloride injection and unused portion should be discarded; or the Zomacton 10 mg benzyl alcohol-free formulation should be used during pregnancy. Genotropin, Omnitrope, Saizen, Serostim, and Zorbtive are Pregnancy Category B.

Hepatic Function Impairment

A reduction in recombinant human growth hormone (rhGH) clearance has been noted in patients with severe liver dysfunction. The clinical significance of this decrease is unknown.

Renal Function Impairment

Patients with chronic renal failure may experience decreased somatropin clearance compared to patients with normal renal function.

DOSAGES[86,87,88,89,90,91,92,93,94]

Drug	Dosage Forms	Dosage
Genotropin	Two chamber cartridge (for use with Pen or Mixer): 5 mg, 12 mg contains preservative MiniQuick® syringe device: 0.2 mg, 0.4 mg, 0.6 mg, 0.8 mg, 1 mg, 1.2 mg, 1.4 mg, 1.6 mg, 1.8 mg, 2 mg (SD) contains no preservative	Weekly doses should be divided into 6 or 7 SC injections given in the thigh, buttocks, or abdomen and must not be injected intravenously ▪ GHD (ped): 0.16 to 0.24 mg/kg/week ▪ GHD (adult): – weight-based dosing: not more than 0.04 mg/kg/week to start; may increase to maximum of 0.08 mg/kg/week at 4 to 8 week intervals – non-weight-based dosing: 0.15 to 0.3 mg/day to start; may increase every 1 to 2 months by increments of 0.1 to 0.2 mg/day ▪ ISS: up to 0.47 mg/kg/week ▪ PWS: 0.24 mg/kg/week ▪ SGA: up to 0.48 mg/kg/week ▪ TS: 0.33 mg/kg/week

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

Dosages (continued)

Drug	Dosage Forms	Dosage
Humatrope	Vials (with diluent): 5 mg (MD) Cartridge kits (with prefilled diluent syringes): 6 mg, 12 mg, 24 mg (MD)	Weekly doses should be divided into 6 or 7 SC injections given in the upper arm, thigh, buttocks, or abdomen ▪ GHD (ped): 0.18 to 0.3 mg/kg/week ▪ GHD (adult): – weight-based dosing: not more than 0.006 mg/kg/day to start; may increase to maximum of 0.0125 mg/kg/day – non-weight-based dosing: 0.15 to 0.3 mg/day to start; may increase every 1 to 2 months by increments of 0.1 to 0.2 mg/day ▪ ISS: up to 0.37 mg/kg/week ▪ SGA: up to 0.47 mg/kg/week ▪ SHOX: 0.35 mg/kg/week ▪ TS: up to 0.375 mg/kg/week
Norditropin	FlexPro® prefilled pens: 5 mg, 10 mg, 15 mg, 30 mg (MD)	Weekly doses should be divided into 6 or 7 SC injections given in the upper arm, thigh, buttocks, or abdomen ▪ GHD (ped): 0.17 to 0.24 mg/kg/week ▪ GHD (adult): – weight-based dosing: (not recommended for obese patients) not more than 0.004 mg/kg/day to start; may increase to maximum of 0.016 mg/kg/day – non-weight-based dosing: 0.15 to 0.3 mg/day to start; may increase every 1 to 2 months by increments of 0.1 to 0.2 mg/day ▪ ISS: up to 0.47 mg/kg/week ▪ Noonan Syndrome: up to 0.46 mg/kg/week • PWS: 0.24 mg/kg/week ▪ SGA: up to 0.47 mg/kg/week ▪ TS: up to 0.47 mg/kg/week
Nutropin AQ NuSpin	Pens: 5 mg, 10 mg, 20 mg (MD)	Weekly doses should be divided into 7 SC injections given in the upper arm, thigh, buttocks, or abdomen ▪ GHD (ped): prepubertal: up to 0.3 mg/kg/week ▪ GHD (ped): pubertal: up to 0.7 mg/kg/week ▪ GHD (adult): – weight-based dosing: not more than 0.006 mg/kg/day to start; may increase to maximum of 0.025 mg/kg/day in patients ≤ 35 years old and 0.0125 mg/kg daily in patients > years old – non-weight-based dosing: 0.15 to 0.3 mg/day to start; may increase every 1 to 2 months by increments of 0.1 to 0.2 mg/day ▪ CRI: up to 0.35 mg/kg/week ▪ ISS: up to 0.3 mg/kg/week ▪ TS: up to 0.375 mg/kg/week divided into equal doses given 3 to 7 times per week

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

Dosages (continued)

Drug	Dosage Forms	Dosage
Omnitrope	Vials: 5.8 mg (MD) Cartridge: 5 mg/1.5 mL, 10 mg/1.5 mL (MD)	Weekly doses should be divided into 6 or 7 SC injections given in the thigh, buttocks, or abdomen ▪ GHD (ped): 0.16 to 0.24 mg/kg ▪ GHD (adult): – weight-based dosing: not more than 0.04 mg/kg/week to start, may increase every 1 to 2 months to maximum of 0.08 mg/kg/week – non-weight-based dosing: 0.15 to 0.3 mg/day to start; may increase every 1 to 2 months by increments of 0.1 to 0.2 mg/day ▪ ISS: up to 0.47 mg/kg/week ▪ PWS: 0.24 mg/kg/week ▪ SGA: up to 0.48 mg/kg/week ▪ TS: 0.33 mg/kg/week
Saizen	Vials (with diluent): 5 mg, 8.8 mg (MD) Click.easy® cartridge: 8.8 mg (MD) Saizenprep reconstitution device: 8.8 mg vial with 1 cartridge 1.51 mL diluent sterile water for injection	Weekly doses should be divided into 3 alternate days, 6 days, or 7 SC daily injections given in the upper arm, thigh, buttocks, or abdomen ▪ GHD (ped): 0.18 mg/kg/week ▪ GHD (adult): – weight-based dosing: not more than 0.005 mg/kg/day to start, may increase to maximum of 0.01 mg/kg/day after 4 weeks – non-weight-based dosing: 0.15 to 0.3 mg/day to start; may increase every 1 to 2 months by increments of 0.1 to 0.2 mg/day
Serostim	Vials (with diluent): 5 mg, 6 mg (SD) Vials (with diluent): 4 mg (MD)	HIV/AIDS wasting or cachexia: 0.1 mg/kg SC daily at bedtime (up to a total dose of 6 mg) or 0.1 mg/ks every other day
Zomacton	Vials (with diluent): 5 mg, 10 mg (MD)	Weekly doses should be divided into 3, 6, or 7 SC injections given in the upper arm, thigh, buttocks, or abdomen ▪ GHD (ped): 0.18 to 0.3 mg/kg/week ▪ GHD (adult): – weight-based dosing (not recommended for obese patients): start at 0.006 mg/kg/day to start; may increase to maximum of 0.0125 mg/kg/day – non-weight-based dosing: 0.15 to 0.3 mg/day to start; may increase every 1 to 2 months by increments of 0.1 to 0.2 mg/day ▪ TS: Up to 0.375 mg/kg/week ▪ ISS: Up to 0.37 mg/kg/week ▪ SHOX: 0.35 mg/kg/week ▪ SGA: Up to 0.47 mg/kg/week
Zorbtive	Vials (with diluent): 8.8 mg (MD)	▪ SBS: 0.1 mg/kg/day SC, maximum of 8 mg daily; administration for > 4 weeks has not been adequately studied; Zorbtive is not indicated for patients < 18 years of age or in adults > 65 years of age

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

Adults for GHD

Alternatively, taking into account further literature, a starting dose of approximately 0.2 mg/day (range, 0.15 to 0.3 mg/day) may be used without considering the patient's body weight. This dose can be increased gradually every 1 to 2 months by increments of approximately 0.1 to 0.2 mg/day, according to individual patient requirements based on serum IGF-1 concentrations and clinical response. During therapy, the dose should be decreased, if required, by the occurrence of adverse events and/or serum IGF-1 levels above the age- and gender-specific normal range. Maintenance dosages vary considerably between patients.

Since older patients are more likely to experience adverse effects of somatropin compared to younger individuals, a lower starting dose and smaller dose increments should be considered. In addition, obese individuals are more likely to experience adverse effects when treated with a weight-based regimen. Estrogen-replete women may need higher doses than men in order to reach the defined treatment goals and administration of oral estrogen may increase the dose requirements in women.

Adults who were treated with somatropin for growth hormone deficiency in childhood and whose epiphyses are closed should be reevaluated before continuation of growth hormone at the reduced dose level. Per current therapy standards, confirmation of the diagnosis of adult growth hormone deficiency in both groups involves growth hormone provocative tests except when patients have multiple other pituitary hormone deficiencies due to organic disease or when patients have congenital/genetic growth hormone deficiency.

Pediatrics

Response to somatropin therapy in pediatric patients tends to decrease over time. The need for close assessment of compliance and evaluation for other causes of growth failure, such as hypothyroidism, undernutrition, advanced bone age, and antibodies to recombinant human GH (rhGH) may be needed in pediatric patients who have growth failure especially during the first year of therapy.

Treatment for short stature should be discontinued when the epiphyses are fused.

According to the prescribing information for Humatrope, Norditropin, and Zomacton for patients with SGA, literature has recommended initial treatment with larger doses of somatropin (e.g., 0.067 mg/kg/day), especially in very short children (e.g., height standard deviation score [HSDS] < -3), and/or older/early pubertal children, and that a reduction in dosage (e.g., gradually towards 0.033 mg/kg/day) should be considered if substantial catch-up growth is observed during the first few years of therapy. However, in younger SGA children (e.g., approximately < 4 years), who generally respond well with less severe short stature (e.g., baseline HSDS values between -2 and -3), consideration should be given to initiating treatment at a lower dose (e.g., 0.033 mg/kg/day), and titrating the dose as needed over time. In all children, clinicians should closely monitor growth response, and adjust the rhGH dose as needed.

Formulation

Differences in the products with respect to dosages and some adverse effects are a reflection of the various dosage forms and product packaging. These differences should be considered when evaluating the products.

Vials

All products requiring reconstitution are supplied in kits containing a vial of active drug as lyophilized powder along with a vial of diluent. Reconstitution is a major cause of patient dissatisfaction. Solutions are easier for the majority of patients to use as no reconstitution is required and reduced levels of pain associated with injection.[95]

If sensitivity of the diluent for Humatrope occurs the medication may be reconstituted with bacteriostatic water for injection or sterile water for injection. Humatrope vials should be refrigerated and used within 14 days after reconstitution with bacteriostatic water or diluent. If reconstituted with sterile water, refrigerate and discard within 24 hours. If sensitivity to the Saizen or Zorbtive diluent (bacteriostatic water for injection) occurs, reconstitute the vial with sterile water for injection and use immediately; unused solution should be discarded.

After reconstitution, the contents of Omnitrope vials must be refrigerated and used within 3 weeks.

Before reconstitution, Saizen vials should be stored at room temperature. Once reconstituted, the medication should be stored under refrigeration for up to 14 days. If sensitivity to the Saizen diluent (bacteriostatic water for injection) occurs, reconstitute the vial with sterile water for injection and use immediately; unused solution should be discarded.

Serostim vials and diluent should be stored at room temperature prior to first use. For single-use vials (5mg, 6 mg vials) the reconstituted solution should be used immediately and any unused portion should be discarded; reconstituted solution in the multi-use (4 mg) vials should be stored under refrigeration for up to 14 days.

Zomacton requires refrigeration before and after reconstituting. Once reconstituted, the 5 mg product is stable for up to 14 days when reconstituted with bacteriostatic sodium chloride. The 10 mg product is stable for up to 28 days when reconstituted with 1 ml of bacteriostatic water for injection containing metacresol (preservative).

Zorbtive is available in vials; each vial (8.8 mg) is reconstituted in 1 to 2 mL of bacteriostatic water producing a concentration of 8.8 mg or 4.4 mg, respectively. Before reconstitution, the medication can be stored at room temperature. The reconstituted 8.8 mg may be refrigerated for up to 14 days. If sensitivity to the Zorbtive diluent occurs, reconstitute the vial with sterile water for injection and use immediately; unused solution should be discarded.

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 allows for internal reconstitution. The MiniQuick is a single-use, disposable syringe that already houses a 2-chamber cartridge in which the drug powder and diluent are mixed. The MiniQuick can be stored in the refrigerator or at room temperature (≤ 77°F) for up to 3 months; however, after reconstitution it can only be refrigerated for 24 hours. Cartridges are added to the pen and mixer devices. Both use internal reconstitution; the cartridges can be refrigerated before and after reconstitution for 28 days and can be reused. Somatropin cartridges must be used with their corresponding color-coded delivery systems.

Humatrope cartridges are 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. When changing cartridge size/strength patients must get a new pen to match the new cartridge size/strength; they are not interchangeable. The pen device can be used for up to 3 years after first use. The cartridges should not be used if the patient is allergic to metacresol or glycerin. Only the diluent that is supplied with the cartridges should be used.

Norditropin is supplied as a prefilled pen (FlexPro). Reconstitution is not necessary; the drug is already in solution. Norditropin pens must be refrigerated prior to initial use. After the initial injection, the pen may be either stored in the refrigerator and used within 4 weeks or stored for up to 3 weeks at room temperature. The FlexPro PenMate® is a device for patients using the FlexPro pens who prefer hidden needles. The PenMate, provided through NordiCare®, conceals the needle so patients cannot see it being injected into their skin.

Nutropin AQ NuSpin is available as a Nuspin injection device (multi-dose; dial-a-dose). Nutropin AQ NuSpin injection must always be refrigerated, before initial use and for 28 days afterward.

Omnitrope® Pen 5 and Omnitrope® Pen 10 use a cartridge containing drug already in solution. The cartridge is loaded into the pen, where it remains until empty. Omnitrope cartridges should be refrigerated prior to the initial use, as well. Following the first use, the cartridge and pen can be refrigerated for up to 28 days.

Needle-free devices for SC administration of Saizen (cool.click®2) and for Serostim (SeroJet®) are available. The cool.click 2 is designed to be used with Saizen and Serostim vials. The click.easy device is an internal reconstitution mechanism; the resulting solution is administered with the easypod® which hides the injection 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, and the time and date of the last dose. The entire device can be stored in the refrigerator and cartridges may be stored for up to 21 days. With Serostim, reconstitution of the growth hormone solution is still done through a manual process prior to drawing it into the administration device. Reconstituted Saizen and multi-use Serostim vials must be refrigerated until used with the remainder discarded after 14 days. Single-use Serostim should be used immediately after reconstitution and any remaining drug should be discarded. Serostim and Saizen can both be stored at room temperature prior to initial use.

Zomacton's ZOMA-Jet® provides a needle-free alternative by delivering the medication via a rapid-pulse fluid stream when using the 5 mg and 10 mg products. The dose must be drawn from the vial into the device, through an adaptor, before administration.[96]

All injection devices have dial-a-dose capabilities. Zorbtive is not currently available with administration devices. Evaluation of patient preferences, with possible increases in compliance, may place added value on one delivery system over another.

CLINICAL TRIALS

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved 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% 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 and/or 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.

Most growth hormone products are given 6 or 7 times weekly. Saizen and Zomacton can be dosed in pediatric patients as few as 3 times per week, as can Nutropin AQ NuSpin when treating Turner syndrome. Dose frequency, injection site discomfort, and dosing devices may be a factor in patient compliance with the prescribed regimen.

Other than slight pharmaceutical differences, no pharmacologic difference among the agents exists in terms of safety and efficacy.

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