Growth Hormone Review

04/19/2010

Copyright © 2004 - 2010 by Provider Synergies, L.L.C. All rights reserved.
Printed in the United States of America.

All rights reserved. No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopying, recording, digital scanning, or via any information storage and retrieval system without the express written consent of Provider Synergies, L.L.C.

All requests for permission should be mailed to:

Attention: Copyright Administrator
Intellectual Property Department
Provider Synergies, L.L.C.
10101 Alliance Road, Ste 201
Cincinnati, Ohio 45242

The materials contained herein represent the opinions of the collective authors and editors and should not be construed to be the official representation of any professional organization or group, any state Pharmacy and Therapeutics committee, any state Medicaid Agency, or any other clinical committee. This material is not intended to be relied upon as medical advice for specific medical cases and nothing contained herein should be relied upon by any patient, medical professional or layperson seeking information about a specific course of treatment for a specific medical condition. All readers of this material are responsible for independently obtaining medical advice and guidance from their own physician and/or other medical professional in regard to the best course of treatment for their specific medical condition. This publication, inclusive of all forms contained herein, is intended to be educational in nature and is intended to be used for informational purposes only. Send comments and suggestions to PSTCREditor@magellanhealth.com.

PROVIDER SYNERGIES L.L.C.
Together, we can do more.

FDA-Approved Indications

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

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. 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 2009 American Association of Clinical Endocrinologists Guidelines for Clinical Practice indicate that no evidence exists to support any specific growth hormone product over another.[11]

Growth hormone deficiency (GHD) results from inadequate production of growth hormone (GH) and can produce various medical conditions dependent on age. 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 can be congenital or acquired in childhood or adult life, in addition to being partial or complete. The condition is usually permanent

© 2004 – 2010 Provider Synergies, L.L.C.
All Rights Reserved.
Restricted Access – Proprietary and/or Confidential. Do not disseminate or copy without approval.

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.[12] 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 and increased 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)-I 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.[13,14]

Babies born small for gestational age (SGA) are those with birth weights that fall below the 10th 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 two years of life, approximately ten percent of SGA children fail to exhibit catch-up growth by age two 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.[15,16]

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 one 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 two to three percent of patients with clinical features consistent with idiopathic short stature may test positive for SHOX deficiency.[17]

In Turner syndrome (TS), female sexual characteristics are present but are underdeveloped due to several chromosomal abnormalities. Short stature affects at least 95 percent of all patients with TS. The etiology of the growth retardation may be due to haploinsufficiency of the SHOX gene, not GHD. However, subnormal levels of GH and IGF-I have been reported, and it has been postulated that a diminished sensitivity for growth factors might explain the short stature.[18] 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) refers to extreme short stature that does not have a diagnostic explanation. "Short stature" has been defined by the American Association of Clinical Endocrinologists and the Growth Hormone Research Society as height more than two standard deviations (SD) below the mean for age and sex. This corresponds to the shortest 2.3 percent of children. Idiopathic short stature refers to a height of more than 2.25 SD below the mean for age and

All Rights Reserved.
Restricted Access – Proprietary and/or Confidential. Do not disseminate or copy without approval.

sex, or the shortest 1.2 percent of children. Growth hormone has been shown to be effective in treating ISS.[19]

Patients with HIV/AIDS may experience cachexia: loss of weight, muscle atrophy, fatigue, weakness, and anorexia. Serostim is indicated for the treatment of HIV patients with wasting or cachexia to increase lean body mass and body weight and improve physical endurance. Human growth hormone therapy allows the body to use fat for energy, thereby preserving lean body mass.[20]

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. Intestinal mucosa contains receptors for growth hormone and for Insulin-like Growth Factor 1 (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 Short Bowel Syndrome (SBS) in patients receiving specialized nutritional support.[21]

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 percent of patients. Growth hormone has been used successfully to correct short stature associated with the disorder.[22]

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.[23] 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 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[24,25,26,27,28,29,30,31,32,33]

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.

Contraindications/Warnings[34,35,36,37,38,39,40,41,42,43]

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; and active proliferative or severe non-proliferative diabetic retinopathy.

Fatalities have been reported with the use of growth hormone for PWS in patients who have one or more of the following risk factors: severe obesity, history of respiratory impairment or sleep apnea, or unidentified respiratory infection. Somatropin is contraindicated in these patients.

All Rights Reserved.
Restricted Access – Proprietary and/or Confidential. Do not disseminate or copy without approval.

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. Growth hormone therapy has been associated with cases of new-onset impaired glucose intolerance, new-onset type 2 diabetes mellitus, and exacerbation of preexisting diabetes mellitus.

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

Intracranial hypertension has been reported in a small number of patients treated with growth hormone. Symptoms usually occurred within the first eight weeks after the initiation of therapy. Patients with Turner syndrome, chronic renal insufficiency, or Prader-Willi syndrome may be at increased risk.

Slipped capital femoral epiphyses may occur more frequently in patients with endocrine disorders or in patients undergoing rapid 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.

Carpal tunnel syndrome may occur during treatment with Serostim or Zorbtive. If the symptoms of carpal tunnel syndrome do not resolve with decreased dosing, growth hormone therapy should be discontinued.

Acute pancreatitis has been associated with growth hormone therapy.

Drug Interactions[44,45,46,47,48,49,50,51,52,53]

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[54,55,56,57,58,59,60,61,62,63]

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.

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.[64] Edema usually occurs early in therapy and is transient or responsive to dosage reduction. During post-marketing surveillance, cases of new onset glucose intolerance,

© 2004 – 2010 Provider Synergies, L.L.C.
All Rights Reserved.
Restricted Access – Proprietary and/or Confidential. Do not disseminate or copy without approval.

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.

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.

Special Populations[65,66,67,68,69,70,71,72,73,74]

Pregnancy

Humatrope, Nutropin, Nutropin AQ and Tev-Tropin are Pregnancy Category C. Genotropin, Omnitrope, Saizen, Serostim, and Zorbtive are Pregnancy Category B.

Lactation

It is not known whether growth hormone is excreted in human milk.

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.

Other

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

All Rights Reserved.
Restricted Access – Proprietary and/or Confidential. Do not disseminate or copy without approval.

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

Drug (mfr)	Dosage Forms	Dosage
Genotropin[75] (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 given as a daily subcutaneous injection; 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 ISS: 0.47 mg/kg/week 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 TS: 0.33 mg/kg/week divided and given as six or seven SC injections
Humatrope[76] (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 ISS: up to 0.37 mg/kg/wk SC divided into equal doses and given six or seven times per week SGA: up to 0.067 mg/kg/day (0.47 mg/kg/week). SHOX: 0.35 mg/kg/week SC divided and given daily TS: 0.375 mg/kg/week SC divided and given daily or on three alternate days
Norditropin[77] (Novo Nordisk)	NordiPen® cartridges: 5, 15 mg (MD) Nordiflex prefilled pens: 5, 10, 15 mg (MD)	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 increase to maximum of 0.016 mg/kg/day after six weeks Noonan Syndrome: Up to 0.066 mg/kg/day SC TS: Up to 0.067 mg/kg/day SC SGA: Up to 0.067 mg/kg/day SC
Nutropin[78] (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 ISS: 0.3 mg/kg/week SC divided into daily doses TS: 0.375 mg/kg/week SC divided into equal doses given three to seven times per week
Nutropin AQ[79] (Genentech)	Vials: 10 mg (MD) Pen cartridge: 10, 20 mg (MD)	
Omnitrope[80] (Sandoz)	Vials: 1.5 mg, 5.8 mg (MD) Cartridge: 5 mg/1.5 mL, 10 mg/1.5 mL (MD)	GHD (ped): 0.16 to 0.24 mg/kg SC per week divided into 6 to 7 doses daily SC injections GHD (adult): not more than 0.04 mg/kg/week divided into daily SC injections, dosage may be increased at four to eight week intervals and should not exceed 0.08 mg/kg/week depending on patient's tolerance
Saizen[81] (Serono)	Vials (with diluent): 5, 8.8 mg (MD), click.ease[R] 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[82] (Serono)	Vials (with diluent): 5, 6 mg (SD) Vials (with diluent): 4, 8.8 mg (MD)	HIV/AIDS wasting: 0.1 mg/kg SC daily or every other day
Tev-Tropin[83] (Gate/TEVA)	Vials (with diluent): 5 mg (MD)	GHD (ped): up to 0.1 mg/kg SC three times per week
Zorbtive[84] (Serono)	Vials (with diluent): 8.8 mg (MD)	SBS: 0.1 mg/kg/day SC, maximum of 8 mg daily. Administration for greater than four weeks has not been adequately studied.

All Rights Reserved.
Restricted Access – Proprietary and/or Confidential. Do not disseminate or copy without approval.

Dosing considerations[85,86,87,88,89,90,91]

Adults for GHD

Alternatively, taking into account recent literature, a starting dose of approximately 0.2 mg/day (range, 0.15–0.30 mg/day) may be used without consideration of body weight. This dose can be increased gradually every one to two months by increments of approximately 0.1–0.2 mg/day, according to individual patient requirements based on the clinical response and serum IGF-I concentrations. During therapy, the dose should be decreased if required by the occurrence of adverse events and/or serum IGF-I levels above the age- and gender-specific normal range. Maintenance dosages vary considerably from person to person.

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

Pediatrics

Response to somatropin therapy in pediatric patients tends to decrease with time. However, in pediatric patients, the failure to increase growth rate, particularly during the first year of therapy, indicates 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).

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

Patients with SGA - According to the prescribing information for Humatrope and Norditropin: recent literature has recommended initial treatment with larger doses of somatropin (e.g., 0.067 mg/kg/day), especially in very short children (i.e., HSDS < -3), and/or older/early pubertal children, and that a reduction in dosage (e.g., gradually towards 0.0334 mg/kg/day) should be considered if substantial catch-up growth is observed during the first few years of therapy. On the other hand, in younger SGA children (e.g., approximately < 4 years), who respond the best in general, with less severe short stature (i.e., 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 carefully monitor the growth response, and adjust the rhGH dose as necessary.

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:

© 2004 – 2010 Provider Synergies, L.L.C.
All Rights Reserved.
Restricted Access – Proprietary and/or Confidential. Do not disseminate or copy without approval.

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 is a major cause of patient dissatisfaction. Solutions are also associated with greater convenience and reduced levels of pain associated with injection.[92] 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.

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.

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-associated anxiety, the PenMate attachment hides the needle during the injection process.

Nutropin AQ is available in a pen cartridge. 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.

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. Following the first use, the cartridge and pen can be refrigerated for up to 28 days. Omnitrope cartridges should be refrigerated prior to the initial use, as well.

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 easypod®, cool.click™, and 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.

All Rights Reserved.
Restricted Access – Proprietary and/or Confidential. Do not disseminate or copy without approval.

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.[93] 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.

Tev-tropin's Tjet® provides a needle-free alternative by delivering the medication via a rapid-pulse fluid stream. This method of administration has demonstrated itself to be bioequivalent to traditional needle delivery. The dose must be still be drawn from the vial into the device, through an adaptor, before administration.[94]

All injection devices have dial-a-dose capabilities. Nutropin and Zorbtive are 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 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.

All Rights Reserved.
Restricted Access – Proprietary and/or Confidential. Do not disseminate or copy without approval.

Most 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 treating Turner syndrome. Dose frequency 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.

References

[1] Genotropin [package insert]. Kalamazoo, MI; Pharmacia and Upjohn Company; August 2009.
[2] Humatrope [package insert]. Indianapolis, IN; Eli Lilly and Company; August 2009.
[3] Norditropin [package insert]. Princeton, NJ; Novo Nordisk Pharmaceuticals, Inc.; March 2010.
[4] Nutropin [package insert]. South San Francisco, CA; Genentech, Inc.; June 2006.
[5] Nutropin AQ [package insert]. South San Francisco, CA; Genentech, Inc.; January 2008.
[6] Omnitrope [package insert]. Princeton, NJ; Sandoz, Inc.; March 2009.
[7] Saizen [package insert]. Rockland, MA; Serono, Inc.; September 2007.
[8] Serostim [package insert]. Rockland, MA; Serono, Inc; September 2007.
[9] Tev-Tropin [package insert]. Sellersville, PA; Gate Pharmaceuticals/TEVA; October 2007.
[10] Zorbtive [package insert]. Rockland, MA; Serono, Inc.; January 2009.
[11] AACE Growth Hormone Task Force. American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice for Growth Hormone Use in Growth Hormone-Deficient Adults and Transition Patients – 2009 Update. Endocrine Practice. 2009; 15(Suppl 2):1-27.
[12] Available at: http://psych.med.nyu.edu/conditions-we-treat/conditions/prader-willi-syndrome. Accessed April 19, 2010.
[13] Mahan J. Applying the Growth Failure in CKD Consensus Conference: Evaluation and treatment algorithm in children with chronic kidney disease. Growth Hormone & IGF Research. 2006; 16(Suppl 1):68-78.
[14] Baumann G. Growth hormone binding protein and free growth hormone in chronic renal failure. Pediatric Nephrology. 1996; 10(3):328-330.
[15] de Zegher F. Small as Fetus and Short as Child: From Endogenous to Exogenous Growth Hormone. Journal of Clinical Endocrinology & Metabolism. 1997; 82(7):2021-2026.
[16] Shalitin S. Children Born Small for Gestational Age: Growth Patterns, Growth Hormone Treatment and Long-Term Sequelae. IMAJ. 2003; 5:877-882.
[17] Humatrope [package insert]. Indianapolis, IN; Eli Lilly and Company; August 2009.
[18] Van Pareren Y, et al. Final Height in Girls with Turner Syndrome after Long- Term Growth Hormone Treatment in Three Dosages and Low Dose Estrogens. Journal of Clinical Endocrinology & Metabolism. 2003; 88(3):1119–1125.
[19] Available at: http://www.aace.com/pub/pdf/guidelines/hgh.pdf. Accessed April 19, 2010.
[20] Serostim [package insert]. Rockland, MA; Serono, Inc; September 2007.
[21] Zorbtive [package insert]. Rockland, MA; Serono, Inc.; January 2009.
[22] Available at: http://www.emedicine.com/ped/topic1616.htm. Accessed April 19, 2010.
[23] Genotropin [package insert]. Kalamazoo, MI; Pharmacia and Upjohn Company; August 2009.
[24] Genotropin [package insert]. Kalamazoo, MI; Pharmacia and Upjohn Company; August 2009.
[25] Humatrope [package insert]. Indianapolis, IN; Eli Lilly and Company; August 2009.
[26] Norditropin [package insert]. Princeton, NJ; Novo Nordisk Pharmaceuticals, Inc.; March 2010.
[27] Nutropin [package insert]. South San Francisco, CA; Genentech, Inc.; June 2006.
[28] Nutropin AQ [package insert]. South San Francisco, CA; Genentech, Inc.; January 2008.
[29] Saizen [package insert]. Rockland, MA; Serono, Inc.; September 2007.
[30] Serostim [package insert]. Rockland, MA; Serono, Inc; September 2007.
[31] Tev-Tropin [package insert]. Sellersville, PA; Gate Pharmaceuticals/TEVA; October 2007.
[32] Zorbtive [package insert]. Rockland, MA; Serono, Inc.; January 2009.
[33] Omnitrope [package insert]. Princeton, NJ; Sandoz, Inc.; March 2009.
[34] Genotropin [package insert]. Kalamazoo, MI; Pharmacia and Upjohn Company; August 2009.
[35] Humatrope [package insert]. Indianapolis, IN; Eli Lilly and Company; August 2009.
[36] Norditropin [package insert]. Princeton, NJ; Novo Nordisk Pharmaceuticals, Inc.; March 2010.
[37] Nutropin [package insert]. South San Francisco, CA; Genentech, Inc.; June 2006.
[38] Nutropin AQ [package insert]. South San Francisco, CA; Genentech, Inc.; January 2008.
[39] Saizen [package insert]. Rockland, MA; Serono, Inc.; September 2007.
[40] Serostim [package insert]. Rockland, MA; Serono, Inc; September 2007.
[41] Tev-Tropin [package insert]. Sellersville, PA; Gate Pharmaceuticals/TEVA; October 2007.
[42] Zorbtive [package insert]. Rockland, MA; Serono, Inc.; January 2009.
[43] Omnitrope [package insert]. Princeton, NJ; Sandoz, Inc.; March 2009.
[44] Genotropin [package insert]. Kalamazoo, MI; Pharmacia and Upjohn Company; August 2009.
[45] Humatrope [package insert]. Indianapolis, IN; Eli Lilly and Company; August 2009.
[46] Norditropin [package insert]. Princeton, NJ; Novo Nordisk Pharmaceuticals, Inc.; March 2010.
[47] Nutropin [package insert]. South San Francisco, CA; Genentech, Inc.; June 2006.
[48] Nutropin AQ [package insert]. South San Francisco, CA; Genentech, Inc.; January 2008.

All Rights Reserved.
Restricted Access – Proprietary and/or Confidential. Do not disseminate or copy without approval.

[49] Saizen [package insert]. Rockland, MA; Serono, Inc.; September 2007.
[50] Serostim [package insert]. Rockland, MA; Serono, Inc; September 2007.
[51] Tev-Tropin [package insert]. Sellersville, PA; Gate Pharmaceuticals/TEVA; October 2007.
[52] Zorbtive [package insert]. Rockland, MA; Serono, Inc.; January 2009.
[53] Omnitrope [package insert]. Princeton, NJ; Sandoz, Inc.; March 2009.
[54] Genotropin [package insert]. Kalamazoo, MI; Pharmacia and Upjohn Company; August 2009.
[55] Humatrope [package insert]. Indianapolis, IN; Eli Lilly and Company; August 2009.
[56] Norditropin [package insert]. Princeton, NJ; Novo Nordisk Pharmaceuticals, Inc.; March 2010.
[57] Nutropin [package insert]. South San Francisco, CA; Genentech, Inc.; June 2006.
[58] Nutropin AQ [package insert]. South San Francisco, CA; Genentech, Inc.; January 2008.
[59] Saizen [package insert]. Rockland, MA; Serono, Inc.; September 2007.
[60] Serostim [package insert]. Rockland, MA; Serono, Inc; September 2007.
[61] Tev-Tropin [package insert]. Sellersville, PA; Gate Pharmaceuticals/TEVA; October 2007.
[62] Zorbtive [package insert]. Rockland, MA; Serono, Inc.; January 2009.
[63] Omnitrope [package insert]. Princeton, NJ; Sandoz, Inc.; March 2009.
[64] Nutropin AQ [package insert]. South San Francisco, CA; Genentech, Inc.; January 2008.
[65] Genotropin [package insert]. Kalamazoo, MI; Pharmacia and Upjohn Company; August 2009.
[66] Humatrope [package insert]. Indianapolis, IN; Eli Lilly and Company; August 2009.
[67] Norditropin [package insert]. Princeton, NJ; Novo Nordisk Pharmaceuticals, Inc.; March 2010.
[68] Nutropin [package insert]. South San Francisco, CA; Genentech, Inc.; June 2006.
[69] Nutropin AQ [package insert]. South San Francisco, CA; Genentech, Inc.; January 2008.
[70] Saizen [package insert]. Rockland, MA; Serono, Inc.; September 2007.
[71] Serostim [package insert]. Rockland, MA; Serono, Inc; September 2007.
[72] Tev-Tropin [package insert]. Sellersville, PA; Gate Pharmaceuticals/TEVA; October 2007.
[73] Zorbtive [package insert]. Rockland, MA; Serono, Inc.; January 2009.
[74] Omnitrope [package insert]. Princeton, NJ; Sandoz, Inc.; March 2009.
[75] Genotropin [package insert]. Kalamazoo, MI; Pharmacia and Upjohn Company; August 2009.
[76] Humatrope [package insert]. Indianapolis, IN; Eli Lilly and Company; August 2009.
[77] Norditropin [package insert]. Princeton, NJ; Novo-Nordisk Pharmaceuticals Inc.; March 2010.
[78] Nutropin [package insert]. South San Francisco, CA; Genentech, Inc.; June 2006.
[79] Nutropin AQ [package insert]. South San Francisco, CA; Genentech, Inc.; January 2008.
[80] Omnitrope [package insert]. Princeton, NJ; Sandoz, Inc.; March 2009.
[81] Saizen [package insert]. Rockland, MA; Serono, Inc.; September 2007.
[82] Serostim [package insert]. Rockland, MA; Serono, Inc.;September 2007.
[83] Tev-Tropin [package insert]. Sellersville, PA; Gate Pharmaceuticals/TEVA; October 2007.
[84] Zorbtive [package insert]. Rockland, MA; Serono, Inc.; January 2009.
[85] Genotropin [package insert]. Kalamazoo, MI; Pharmacia and Upjohn Company; August 2009.
[86] Humatrope [package insert]. Indianapolis, IN; Eli Lilly and Company; August 2009.
[87] Norditropin [package insert]. Princeton, NJ; Novo-Nordisk Pharmaceuticals Inc.; March 2010
[88] Nutropin [package insert]. South San Francisco, CA; Genentech, Inc.; June 2006.
[89] Nutropin AQ [package insert]. South San Francisco, CA; Genentech, Inc.; January 2008.
[90] Omnitrope [package insert]. Princeton, NJ; Sandoz, Inc.; March 2009.
[91] Saizen [package insert]. Rockland, MA; Serono, Inc.; September 2007.
[92] Stanhope R, et al. An open-label acceptability study of Norditropin SimpleXx--a new liquid growth hormone formulation. J Pediatr Endocrinol Metab. 2001; 14:735-740.
[93] Silverstein JH, et al. Clinical Testing Results and High Patient Satisfaction with a New Needle-Free Device for Growth Hormone in Young Children. Endocrine. 2001; 15:15-17.
[94] Tjet User Manual. Sellersville, PA; Gate Pharmaceuticals/TEVA; June 2009.

All Rights Reserved.
Restricted Access – Proprietary and/or Confidential. Do not disseminate or copy without approval.