Therapeutic Class Overview
Growth Hormone

INTRODUCTION

- Growth hormone (GH) affects many of the metabolic processes carried out by somatic cells, most notably increasing body mass. Overall growth is stimulated by GH therapy; however, the effects are not evenly distributed among protein, lipid and carbohydrate compartments. Specifically, body protein content and bone mass increase, total body fat content decreases and there is an increase in plasma and liver lipid content due to the mobilization of free fatty acids from peripheral fat stores. Another physiological effect of GH is stimulation of cartilage growth (Molitch et al, 2011).
- Growth hormone deficiency (GHD) in pediatric patients is a clinical diagnosis that is confirmed by biochemical testing. A patient's growth patterns are compared to the established norms. The clinical manifestations of GHD will vary depending on whether a patient has complete or partial deficiency. In complete deficiency, pediatric patients will present with early severe growth failure, delayed bone age, central disposition of body fat and very low serum concentrations of GH, insulin-like growth factor 1 (IGF-1) and IGF binding protein-3. These patients are also more prone to hypoglycemia, prolonged jaundice, microphallus in males and giant cell hepatitis. GHD in pediatric patients with partial deficiency may be more difficult to diagnose, as these manifestations may not be as obvious (Molitch et al, 2011).
- Once a diagnosis of GHD is confirmed in pediatric patients, GH therapy should be initiated and continued until cessation of linear growth. Therapy should be initiated as soon as possible as evidence demonstrates that growth response is more robust when GH therapy is started at a younger age (Molitch et al, 2011).
- Several preparations of GH are currently available for use in pediatric patients. Recombinant GH preparations, administered by subcutaneous (SC) injection, are currently the most widely utilized. Due to the variability in individual response to therapy, after initial dosing, the dose of GH is adjusted based on growth response and IGF-1 level. While not universally supported, the therapeutic goal of therapy is to achieve a level of IGF-1 that is slightly higher than average, because growth velocity is typically greatest at these levels. A patient's growth velocity, as compared to a similar population, should also be monitored to determine if the growth response is adequate (Molitch et al, 2011).
- Possible explanations for an inadequate response to GH therapy include poor adherence, incorrect diagnosis of GHD, subtherapeutic dose of GH, or concurrent mild GH insensitivity. In pediatric patients, GH therapy is typically continued at least until linear growth is nearly complete (e.g., decreased to less than 2.5 centimeters per year). At this point, retesting for GHD should occur to determine if GH therapy should be continued into adulthood (Molitch et al, 2011).
- The majority of pediatric patients with idiopathic, isolated GHD in their childhood will have normal GH secretion during late adolescence and young adulthood. In contrast, pediatric patients with genetic GHD, multiple pituitary hormone deficiencies, and/or those with structural defects in the hypothalamic-pituitary region rarely recover the ability to secrete GH as an adult. Therefore, retesting may not be required (Molitch et al, 2011).
- GHD may also occur in adult patients. Fifteen to 20 percent of adult-onset GHD represents the continuation of childhood-onset GHD into maturity; the remainder is adult-onset acquired from damage to the pituitary gland or hypothalamus. GHD is associated with increased metabolic syndrome, increased cardiovascular morbidity and mortality rates, reduced lean body mass, increased abdominal adiposity, early atherosclerosis, dyslipidemia, coagulation abnormalities, insulin resistance, decreased bone mineral density, and a decreased quality of life (Mathioudakis and Salvatori, 2008). The role of GH therapy in adults is not as clear as it is in pediatric patients in whom therapy is required for normal growth. There is evidence to demonstrate that when used in adult patients with GHD, GH therapy increases muscle mass and decreases body fat. Evidence of other potential beneficial effects of GH therapy in adults is not as well established and includes improvement in bone mineral density, sense of well-being, muscle strength and lipid profile. GH therapy can be considered in adult patients with severe clinical manifestations and unequivocal evidence of GHD due to organic disease of childhood-onset or adult-onset (Molitch et al, 2011).
- All of the GH preparations contain somatropin, otherwise known as recombinant human GH. The various preparations are Food and Drug Administration (FDA)-approved for use in a variety of pediatric conditions associated with a failure in growth, including chronic kidney disease (CKD), Turner syndrome, being born small for gestational age, Prader-Willi syndrome, mutations in the Short Stature Homeobox gene, and Noonan syndrome, as well as for idiopathic short stature.

- The majority of preparations are also indicated for the treatment of GHD in adults. Of note, SEROSTIM® is FDA-approved solely for the treatment of human immunodeficiency virus-associated wasting or cachexia in adults. In addition, ZORBTIVE® is approved for the treatment of short bowel syndrome in patients receiving specialized nutritional support. Specific FDA-approved indications for the various GH preparations are outlined in Table 2. All of the available GH preparations are available for SC injection and there are currently no generics available within the class.
- Growth hormone preparations are available in various formulations, and several delivery devices are available. The dosing device may be a factor in patient adherence with the prescribed regimen.
- Medispan Class: Growth Hormones

Table 1. Medications Included Within Class Review

Drug	Manufacturer	FDA Approval Date	Generic Availability
GENOTROPIN®	Pharmacia & Upjohn	08/24/1995	-
HUMATROPE®	Eli Lilly	03/08/1987	-
NORDITROPIN®	Novo Nordisk	06/20/2000	-
NUTROPIN AQ®	Genentech	12/29/1995	-
OMNITROPE®	Sandoz	05/30/2006	-
SAIZEN®	EMD Serono	10/08/1996	-
SEROSTIM	EMD Serono	08/23/1996	-
ZOMACTON™*	Ferring Pharmaceuticals	01/04/2002	-
ZORBTIVE	EMD Serono	12/01/2003	-

*In March 2015, Ferring Pharmaceuticals received approval for changing the name of their product TEV-TROPIN to ZOMACTON (PR Newswire, 2015).

(Drugs@FDA, 2017; Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, 2017)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	GENOTROPIN	HUMATROPE	NORDITROPIN	NUTROPIN AQ	OMNITROPE	SAIZEN	SEROSTIM	ZOMACTON	ZORBTIVE
Growth failure associated with chronic renal insufficiency before renal transplant				✔					
Growth failure associated with Noonan syndrome			✔						
Growth failure associated with Prader-Willi syndrome	✔				✔				
Growth failure associated with short-stature homeobox-containing gene deficiency		✔							
Growth failure associated with Turner syndrome	✔	✔	✔	✔	✔				
Growth failure in children born small for gestational age	✔	✔	✔		✔				
Growth hormone deficiency	✔	✔	✔	✔	✔	✔		✔	
Idiopathic short stature	✔	✔		✔	✔				
Human immunodeficiency virus-associated wasting or cachexia							✔		
Treatment of short bowel syndrome in patients receiving nutritional support									✔

(Prescribing information: GENOTROPIN, 2016; HUMATROPE, 2016; NORDITROPIN, 2016; NUTROPIN AQ, 2016; OMNITROPE, 2016; SAIZEN, 2017; SEROSTIM, 2016; ZOMACTON, 2016; ZORBTIVE, 2016)

Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- There are limited head-to-head clinical trials comparing different GH preparations to one another.
- Clinical trials to support the use of GH for the treatment of growth failure associated with chronic renal insufficiency before renal transplant and Noonan syndrome in pediatric patients are limited (Fine et al, 1995; Noordam et al, 2001; Santos et al, 2010; Vimalachandra et al, 2006). For the treatment of growth failure associated with chronic renal insufficiency, a Cochrane Review of 15 randomized controlled trials demonstrated that after one year of treatment with GH (28 international units/m^2/week), height velocity increased 3.8 cm/year more than no treatment. The duration of the trials was not long enough to determine if continuing treatment with GH resulted in an increase in final adult height (Vimalachandra et al, 2006). In addition, a randomized controlled trial evaluating GH in patients with Noonan syndrome found a positive effect of GH on linear growth. Specifically, there was a significantly greater change in height standard deviation score and bone maturation was accelerated with GH compared to no treatment. In this trial, data also suggests that once treatment with GH is discontinued, "catch-down" (artificially stimulated growth declines once GH is discontinued) growth can occur (Noordam et al, 2001).
- Clinical trials consistently demonstrate the significant benefits of GH in pediatric patients with Prader-Willi syndrome in accelerating growth and in improving body composition. Benefits were also observed in improving bone mineral density, lipid profiles, energy expenditure, strength and agility, and pulmonary function (Carrel et al, 1999; Carrel et al, 2004; Festen et al, 2008; Lindgren et al, 1997; Lindgren et al, 1998; Lindgren et al, 1999; Myers et al, 1999; Myers et al, 2007). Data from one trial suggests that growth velocity declines dramatically once treatment is discontinued (Lindgren et al, 1997).
- HUMATROPE demonstrated efficacy in increasing first-year height velocity in patients with Short Stature Homeobox-containing gene deficiency when compared to no treatment (P<0.0001) (Blum et al, 2007).
- Several clinical trials consistently demonstrate that GH significantly increases the growth rate of pediatric patients with Turner syndrome. Overall, various dose ranging trials did not consistently demonstrate a superior weight-based GH dosing regimen over another; all doses of GH were beneficial. In addition, data suggest that increases in height are greatest during the first year of therapy (Baxter et al, 2007; Bertrand et al, 1996; Massa et al, 1995; Nienhuis et al, 1993; Sas et al, 1999a; Takano et al, 1989a; Takano et al, 1989b; Takano et al, 1989c; Takano et al, 1993; Takano, 1995; van Pareren et al, 2003; van Teunenbroek et al, 1996). A Cochrane Review of four randomized controlled trials demonstrated that GH (0.3 to 0.375 mg/kg/week) increased short-term growth in patients with Turner syndrome by approximately three centimeters during the first year of treatment. Despite the increase, the final height achieved was still below the normal range (Baxter et al, 2007).
- For the treatment of growth failure in pediatric patients born small for gestational age, clinical trials again consistently demonstrate the significant benefits of GH on increasing growth rates (Arends et al, 2003; Bannink et al, 2010; Boguszewski et al, 1998; Bozzola et al, 2004; Chatelain et al, 1994; de Zegher et al, 1996; de Zegher et al, 2005; De Schepper et al, 2008; Jung et al, 2009; Maiorana et al, 2009; Sas et al, 1999b). Data from individual clinical trials and three meta-analyses demonstrate that response to GH therapy is dose-dependent, and higher doses of GH result in additional gain (de Zegher et al, 1996; de Zegher et al, 2005).
- Treatment with GH has been shown to increase height velocity in both prepubertal and pubertal pediatric patients with GHD (Coelho et al, 2008; Cohen et al, 2002; de Muinck Keizer-Schrama et al, 1992; Kristrom et al, 2009; MacGillivray et al, 1996; Mauras et al, 2000; Romer et al, 2009; Sas et al, 2010; Shih et al, 1994; Wilson et al, 1985). Two head-to-head trials have demonstrated no differences in safety and efficacy with different GH preparations for the treatment of pediatric GHD. One of the trials compared three GH preparations (GENOTROPIN, HUMATROPE and SAIZEN), while the second evaluated two preparations (GENOTROPIN and OMNITROPE) (Romer et al, 2009; Shih et al, 1994).
- In pediatric patients with idiopathic short stature, somatropin has been shown to increase first-year growth velocity and final height (Albertsson-Wikland et al, 2008; Bryant et al, 2007; Finkelstein et al, 2002; Hopwood et al 1993; Kristrom et al, 2009; van Gool et al, 2010; Wit et al, 2005). Additionally, once daily compared to three times weekly dosing and higher compared to lower dosing demonstrated a greater increase in growth velocity (Bryant et al, 2007; Finkelstein et al, 2002).
- Several placebo-controlled, randomized trials have demonstrated the efficacy of GH in improving body composition and lipid profiles in adult patients with GHD (Abrahamsen et al, 2002; Abrahamsen et al, 2004; Arwert et al, 2005; Arwert et al, 2006; Attanasio et al, 2004; Attanasio et al, 2005; Beauregard et al, 2008; Bell et al, 2004; Burman et al,

1997; Chihara et al, 2004; Chihara et al, 2005; Chihara et al, 2006; Chihara et al, 2008a; Chihara et al, 2008b; Chipman et al,1997; Colao et al, 2005; Conway et al, 2009; Cuneo et al, 1993; Davidson et al, 2004; Drake et al, 2003; Eden et al, 1993; Elgzyri et al, 2004; Falleti et al, 2006; Gilchrist et al, 2002; Gomez et al, 2000; Hoffman et al, 2004a; Hoffman et al, 2004b; Holmes et al, 1995; Hwu et al, 1997; Janssen et al, 1998; Kehely et al, 2002; Leese et al, 1998; Maison et al, 2003; Mauras et al, 2005; McGauley et al, 1990; Newman et al, 2011; Nolte et al, 1997; Rahim et al, 1998; Rosenfalck et al, 1999; Rubeck et al, 2009; Russell-Jones et al, 1994; Sesmilo et al, 2000; Shalet et al, 2003; Sneppen et al, 2002; Snyder et al, 2007; Underwood et al, 2003; Vahl et al, 2000; Verhelst et al, 1997; Weaver et al, 1995; Webster et al, 1997; Widdowson et al, 2010; Yuen et al, 2005). Furthermore, results from meta-analyses and randomized controlled trials have demonstrated that treatment with GH was associated with improved cardiac function and bone mineral density (Barake et al, 2014; Davidson et al, 2004; Maison et al, 2003). However, there are currently conflicting data with regard to the effect of GH on cognitive function, quality of life and exercise capacity (Arwert et al, 2005; Falleti et al, 2006; Rubeck et al, 2009; Widdowson, 2010).

- In patients with human immunodeficiency virus-associated wasting, SEROSTIM has been shown to increase body weight, lean body mass and work output. However, effects on quality of life were variable (Moyle et al, 2004; Schambelan et al, 1996).
- A meta-analysis assessing the safety and efficacy of GH with or without glutamine supplementation for adult patients with short bowel syndrome was conducted. Five studies were included in the review. Human GH with or without glutamine appears to provide benefit in terms of increased weight (median [MD] 1.66 kg; 95% confidence interval [CI], 0.69 to 2.63; P=0.0008), lean body mass (MD 1.93 kg; 95% CI, 0.97 to 2.9; P=0.0001), energy absorption (MD 4.42 Kcal; 95% CI, 0.26 to 8.58; P=0.04) and nitrogen absorption (MD 44.85 g; 95% CI, 0.2 to 9.49; P=0.04) for patients with short bowel syndrome. One randomized controlled trial focused on parenteral nutrition (PN) requirements and demonstrated decreased PN volume and calories and number of infusions in patients who received GH with or without glutamine supplementation. Only patients who received GH with glutamine maintained statistically significant PN reductions at three-month follow-up. The results suggest a positive effect of GH on weight gain and energy absorption. After cessation of therapy, however, the effects return to baseline in the majority of the trials (Wales et al, 2010).
- For pediatric patients, treatment guidelines recommend the use of GH therapy with somatropin as a treatment option for children with growth failure associated with any of the following: GHD, Noonan syndrome, Turner syndrome, Prader-Willi syndrome, chronic renal insufficiency, born small for gestational age with subsequent growth failure at four years of age or later, and short stature homeobox-containing gene deficiency (Bondy et al, 2007; Cohen et al, 2008; Deal et al, 2013; Goldstone et al, 2008; Grimberg et al, 2016; National Kidney Foundation, 2009). Guidelines do not prefer one GH agent over another. Choice of preparation should be individualized based on potential advantages and disadvantages of therapy, therapeutic need and the likelihood of adherence. If more than one preparation is suitable for a particular patient, the least costly one should be utilized.
- For adult patients, treatment guidelines recommend the use of GH therapy for the approved indications of the preparations in patients with clinical features suggestive of adult GHD and biochemically proven evidence of adult GHD (Cook et al, 2009). Therapy should be individualized independent of body weight. The dose of GH should be low initially and gradually increased to the minimally effective dose that normalizes IGF-1 levels without side effects (Cook et al, 2009; Molitch et al, 2011). The 2009 American Association of Clinical Endocrinologists Guidelines indicate that no evidence exists to support any specific growth hormone product over another (Cook et al, 2009).

SAFETY SUMMARY

- Contraindications: Active malignancy, diabetic retinopathy, hypersensitivity to the agent or any of its excipients, acute respiratory failure, treatment of patients with acute critical illness, and do not use for growth promotion in patients with closed epiphyses.
- Key Warnings/Precautions:
    - Somatropin may increase progression or recurrence of intracranial neoplasms particularly meningiomas in patients treated with radiation to the head for their first neoplasm.
    - Undiagnosed or untreated hypothyroidism may impair optimal response to somatropin.
    - Somatropin may decrease insulin sensitivity, and previously undiagnosed diabetes mellitus may be unmasked during treatment.
    - Slipped capital femoral epiphyses and scoliosis can occur in pediatric patients.
    - Fluid retention has been associated with somatropin in adult patients.
    - Increases in serum levels of inorganic phosphorous, alkaline phosphatase, parathyroid hormone and insulin-like growth factor-1 may occur.
    - Tissue atrophy may occur when somatropin is administered SC at the same site over a long period of time.
    - Somatropin may reduce serum cortisol levels or unmask central hypoadrenalism in patients at risk for pituitary hormone deficiency.
- Adverse Drug Events: Nerve, muscle, or joint pain, edema, carpal tunnel syndrome, numbness and tingling of the skin, high cholesterol levels, and injection site reactions.
- Drug Interactions: Estrogens, glucocorticoids, and insulin or other hypoglycemic agents.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Dosage Form: Strength	Usual Recommended Dose	Administration Considerations
GENOTROPIN	Cartridge, powder for reconstitution: 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; preservative-free	Adult Growth hormone deficiency: Initial (non-weight based), 0.15 to 0.3 mg SC daily, then increase every one to two months by increments of 0.1 to 0.2 mg/day, based on the clinical response and serum IGF-1 concentrations; initial (weight-based), not more than 0.04 mg/kg/week SC divided into six or seven doses, then increase every four to eight weeks to not more than 0.08 mg/kg/week based on the clinical response, adverse effects and serum IGF-I concentrations Pediatric Growth failure associated with Prader-Willi syndrome: 0.24 mg/kg/week SC divided into six or seven doses Growth failure associated with Turner syndrome: 0.33 mg/kg/week SC divided into six or seven doses Growth failure in children born small for gestational age: up to 0.48 mg/kg/week SC divided into six or seven doses Growth hormone deficiency: 0.16 to 0.24 mg/kg/week SC divided into six or seven doses	Give in the thigh, buttocks, or abdomen; the site of SC injections should be rotated daily to help prevent lipoatrophy.

Drug	Dosage Form: Strength	Usual Recommended Dose	Administration Considerations
		Idiopathic short stature: up to 0.47 mg/kg/week SC divided into six or seven doses	
HUMATROPE	Cartridge, powder for reconstitution: 6 mg, 12 mg, 24 mg Vial, powder for reconstitution: 5 mg	Adult Growth hormone deficiency: Initial (non-weight based), 0.15 to 0.3 mg SC daily, then adjust every one to two months by increments of 0.1 to 0.2 mg/day, based on the clinical response and serum IGF-1 concentrations; initial (weight-based), not more than 0.006 mg/kg SC daily, then adjust based on the clinical response, adverse effects and serum IGF-I concentrations; maximum, 0.0125 mg/kg/day Pediatric Growth failure associated with short-stature homeobox-containing gene deficiency: 0.05 mg/kg SC daily (0.35 mg/kg/week) Growth failure associated with Turner syndrome: up to 0.054 mg/kg SC daily (0.375 mg/kg/week) Growth failure in children born small for gestational age: up to 0.067 mg/kg SC daily (0.47 mg/kg/week) Growth hormone deficiency: 0.026 to 0.043 mg/kg SC daily (0.18 to 0.3 mg/kg/week) Idiopathic short stature: up to 0.053 mg/kg SC daily (0.37 mg/kg/week)	Administer only by SC injection with regular rotation of injection sites to avoid lipoatrophy.
NORDITROPIN	Prefilled pen (NORDITROPIN FLEXPRO®): 5 mg/1.5 mL 10 mg/1.5 mL 15 mg/1.5 mL 30 mg/3 mL	Adult Growth hormone deficiency: Initial (non-weight based), 0.15 to 0.3 mg SC daily, then adjust every one to two months by increments of 0.1 to 0.2 mg/day, based on the clinical response and serum IGF-1 concentrations; initial (weight-based), not more than 0.004 mg/kg SC daily, then adjust after six weeks based on the clinical response, adverse effects and serum IGF-I concentrations; maximum, 0.016 mg/kg/day Pediatric Growth failure associated with Noonan syndrome: up to 0.066 mg/kg SC daily Growth failure associated with Turner syndrome: up to 0.067 mg/kg SC daily Growth failure in children born small for gestational age: up to 0.067 mg/kg SC daily	Rotate injection site to avoid lipoatrophy.

Drug	Dosage Form: Strength	Usual Recommended Dose	Administration Considerations
		Growth hormone deficiency: 0.024 to 0.034 mg/kg SC daily, six to seven times a week	
NUTROPIN AQ	Prefilled cartridge (NUTROPIN AQ NUSPIN®): 5 mg/2 mL 10 mg/2 mL 20 mg/2 mL	Adult Growth hormone deficiency: Initial (non-weight based), 0.15 to 0.3 mg SC daily, then adjust every one to two months by increments of 0.1 to 0.2 mg/day, based on the clinical response and serum IGF-1 concentrations; initial (weight-based), 0.006 mg/kg SC daily, then adjust based on the clinical response, adverse effects and serum IGF-I concentrations; maximum, 0.025 mg/kg/day in patients ≤35 years old and 0.0125 mg/kg/day in patients >35 years old Pediatric Growth failure associated with chronic renal insufficiency before renal transplant: up to 0.35 mg/kg/week SC divided into daily doses, continue up to the time of renal transplantation Growth failure associated with Turner syndrome: up to 0.375 mg/kg/week SC divided into three to seven doses Growth hormone deficiency: up to 0.3 mg/kg/week SC divided into daily doses; up to 0.7 mg/kg/week divided daily may be used in pubertal patients Idiopathic short stature: up to 0.3 mg/kg/week SC divided into daily doses	Inject in the thigh, upper arm, abdomen, or buttock. Always rotate to avoid lipoatrophy.
OMNITROPE	Prefilled cartridge: 5 mg/1.5 mL 10 mg/1.5 mL Vial, powder for reconstitution: 5.8 mg	Adult Growth hormone deficiency: Initial (non-weight based), 0.15 to 0.3 mg SC daily, then adjust every one to two months by increments of 0.1 to 0.2 mg/day, based on the clinical response and serum IGF-1 concentrations; initial (weight-based), 0.04 mg/kg/week SC divided into daily doses, then adjust every four to eight weeks based on the clinical response, adverse effects and serum IGF-I concentrations; maximum, 0.08 mg/kg/week Pediatric Growth failure associated with Prader-Willi syndrome: 0.24 mg/kg/week SC divided into six or seven doses Growth failure associated with Turner syndrome: 0.33 mg/kg/week SC divided into six to seven doses	Dose should be given daily by SC injection (administered preferably in the evening). Administer in the thigh, buttocks, or abdomen. Always rotate injection sites to prevent lipoatrophy.

Drug	Dosage Form: Strength	Usual Recommended Dose	Administration Considerations
		Growth failure in children born small for gestational age: up to 0.48 mg/kg/week SC divided into six or seven doses Growth hormone deficiency: 0.16 to 0.24 mg/kg/week SC divided into six or seven doses Idiopathic short stature: 0.47 mg/kg/week SC divided into six or seven doses	
SAIZEN	Cartridge, powder for reconstitution: 8.8 mg (click.easy) Vial, powder for reconstitution: 5 mg (15 IU) 8.8 mg (26.4 IU)	Adult Growth hormone deficiency: Initial (non-weight based), 0.15 to 0.3 mg SC daily, then adjust every one to two months by increments of 0.1 to 0.2 mg/day, based on the clinical response and serum IGF-1 concentrations; initial (weight-based), 0.005 mg/kg SC daily, then adjust after four weeks based on the clinical response, adverse effects and serum IGF-I concentrations; maximum, 0.01 mg/kg/day after four weeks depending on patient's tolerance Pediatric Growth hormone deficiency: 0.18 mg/kg/week SC or IM divided into three, six or seven doses	
SEROSTIM	Vial, powder for reconstitution: 4 mg (12 IU) Vial, powder for reconstitution (preservative-free): 5 mg (15 IU) 6 mg (18 IU)	Adults Human immunodeficiency virus-associated wasting or cachexia: SC at bedtime with the following weight-based dosage: body weight <35 kg, 0.1 mg/kg/day; 35 to 45 kg, 4 mg/day; 45 to 55 kg, 5 mg/day; >55 kg, 6 mg/day; maximum, 6 mg/day	Injection sites include the thigh, upper arm, abdomen, or buttocks and should be rotated to avoid local irritation.
ZOMACTON	Vial, powder for reconstitution: 5 mg, 10 mg	Pediatric Growth hormone deficiency: 0.1 mg/kg SC three times a week	
ZORBTIVE	Vial, powder for reconstitution: 8.8 mg	SBS: 0.1 mg/kg SC daily to a maximum of 8 mg daily	Administration for more than 4 weeks has not been adequately studied. Treat moderate fluid retention and arthralgias symptomatically or reduce dose by 50%. Discontinue for up to 5 days for severe toxicities. Upon resolution of symptoms, resume at

Drug	Dosage Form: Strength	Usual Recommended Dose	Administration Considerations
			50% of original dose. Permanently discontinue if severe toxicity recurs or does not disappear within 5 days. Injection sites should be rotated.

SPECIAL POPULATIONS

The precautions for use of somatropin in selected special populations are common for all formulations and are listed below in Table 4.

Table 4. Special Populations

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy* and Nursing
somatropin	Safety and efficacy in patients aged 65 years and older have not been established for somatropin. Elderly patients may be more sensitive to the actions of somatropin. A lower starting dose and smaller dose increments should be considered.	Safety and efficacy have not been established for ZORBTIVE and SEROSTIM.	Patients with chronic renal failure tend to have decreased somatropin clearance compared to those with normal renal function. However, no formal studies have been conducted in patients with renal insufficiency.	A reduction in somatropin clearance has been noted in patients with hepatic dysfunction as compared with normal controls. However, no studies have been conducted in patients with hepatic impairment. The clinical significance of this decrease is unknown.	Pregnancy Category B: GENOTROPIN, OMNITROPE, SAIZEN, SEROSTIM, and ZORBTIVE Pregnancy Category C: HUMATROPE, NUTROPIN AQ, NORDITROPIN, and ZOMACTON Unknown whether excreted in breast milk; use with caution.

*Pregnancy Category B = No evidence of risk in humans, but there remains a remote possibility. Animal reproduction studies have failed to demonstrate a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women.
Pregnancy Category C = Risk cannot be ruled out. Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

CONCLUSION

- The safety and efficacy of GH therapy in pediatric patients with failure to grow is well established. Once a diagnosis of GHD is confirmed, GH therapy should be initiated immediately and continued at least until linear growth is nearly complete (e.g., decreased to less than 2.5 cm/year). Available GH preparations are indicated for use in a variety of pediatric conditions associated with a failure in growth, chronic kidney disease, Turner syndrome, being born small for gestational age, Prader-Willi syndrome, mutations in the Short Stature Homeobox gene and Noonan syndrome, as well as for idiopathic short stature.
- The role of GH therapy in adult patients with GHD is less clear. There is evidence to demonstrate that when used in adult patients with GHD, GH therapy increases muscle mass and decreases body fat. Evidence of other potential

beneficial effects of GH therapy in adults are not as well established, including improvement in bone mineral density, sense of well-being, muscle strength and lipid profile (Molitch et al, 2011).

- There are several GH preparations currently available, which all contain somatropin (recombinant human growth hormone). The various preparations are equally biopotent and have the same natural sequence structure (Molitch et al, 2011). They vary primarily in the formulations and devices. All of the available GH preparations are available for SC injection and there are currently no generics available within the class.
- Adverse reactions that may be observed with GH therapy include fluid retention, hypoglycemia, hyperglycemia, hypothyroidism, hypertriglyceridemia, abnormal bone growth, carpal tunnel syndrome, and joint pain. Adverse effects seen with GH use in adults differ from those in children, particularly the incidence of peripheral edema and related side effects.
- Several delivery devices are available for administration of growth hormones. The dose frequency and dosing devices may be a factor in patient adherence with the prescribed regimen.
- For pediatric patients, treatment guidelines recommend the use of GH therapy with somatropin as a treatment option for children with growth failure associated with any of the following: GHD, Turner syndrome, Prader-Willi syndrome, chronic renal insufficiency, born small for gestational age with subsequent growth failure at four years of age or later, and short stature homeobox-containing gene deficiency (Bondy et al, 2007; Cohen et al, 2008; Deal et al, 2013; Goldstone et al, 2008; Grimberg et al, 2016; National Kidney Foundation, 2009). Guidelines do not prefer one GH agent over another. Choice of preparation should be individualized based on potential advantages and disadvantages of therapy, therapeutic need and the likelihood of adherence. If more than one preparation is suitable for a particular patient, the least costly one should be utilized.
- For adult patients, treatment guidelines recommend the use of GH therapy for the approved indications of the preparations in patients with clinical features suggestive of adult GHD and biochemically proven evidence of adult GHD (Cook et al, 2009). Therapy should be individualized independent of body weight. The dose of GH should be low initially and gradually increased to the minimally effective dose that normalizes IGF-1 levels without side effects (Cook et al, 2009; Molitch et al, 2011). The 2009 American Association of Clinical Endocrinologists Guidelines state that no evidence exists to support any specific growth hormone product over another.

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