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 vary depending on whether a patient has complete or partial deficiency. In complete deficiency, pediatric patients 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 (eg, 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 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. Approximately 15% to 20% 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 (*Reed et al 2013*). 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- or adult-onset (*Molitch et al 2011*).
- Most 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, Noonan syndrome, and 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, while 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 GH preparations are available for SC injection, and there are currently no generics available within the class.

- In 2020, the first long-acting GH derivative, somapacitan-beco (Sogroya), was FDA-approved for the treatment of GHD in adults (*FDA 2020*). Somapacitan-beco reversibly binds to circulating albumin, thus prolonging the product's half-life (*Johannsson et al 2020*). This is the first GH therapy to be administered once weekly instead of once daily for adult GHD (*FDA 2020*).
- GH 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	Generic Availability
Genotropin (somatropin)	-
Humatrope (somatropin)	-
Norditropin Flexpro (somatropin)	-
Nutropin AQ (somatropin)	-
Omnitrope (somatropin)	-
Saizen (somatropin)	-
Serostim (somatropin)	-
Sogroya (somapacitan-beco)*	-
Zomacton (somatropin)	-
Zorbtive (somatropin)	-

*Sogroya was FDA-approved on August 28, 2020 but has not yet been launched by its manufacturer.

(*Drugs@FDA 2021, Purple Book: Database of Licensed Biological Products 2021*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Genotropin	Humatrope	Norditropin Flexpro	Nutropin AQ	Omnitrope	Saizen	Serostim	Sogroya	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 failure due to GH deficiency	✔	✔	✔	✔	✔	✔			✔	
Adults with GH deficiency	✔	✔	✔	✔	✔	✔		✔	✔	
Idiopathic short stature	✔	✔	✔	✔	✔				✔	
Human immunodeficiency virus-associated wasting or cachexia							✔			

Indication	Genotropin	Humatrope	Norditropin Flexpro	Nutropin AQ	Omnitrope	Saizen	Serostim	Sogroya	Zomacton	Zorbtive
Treatment of short bowel syndrome in patients receiving specialized nutritional support										✔

(Prescribing information: *Genotropin 2019, Humatrope 2019, Norditropin Flexpro 2020, Nutropin AQ 2016, Omnitrope 2019, Saizen 2020, Serostim 2019, Sogroya 2020, Zomacton 2018, Zorbtive 2019*)

- 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.
- One phase 3, randomized controlled trial (RCT) compared weekly somapacitan-beco to placebo in adults with GHD (REAL 1) (*Johannsson et al 2020*). Daily GH therapy was also included as an active comparator. A total of 301 patients were randomized 2:1:2 to once-weekly somapacitan-beco (blinded), once-weekly placebo (blinded), or daily GH (open-label). At 34 weeks, somapacitan-beco reduced truncal fat percentage when compared to placebo (primary outcome), with an estimated difference of -1.53% (95% confidence interval [CI], -2.68 to -0.38; p = 0.0090). The between-group estimated difference for reduction in truncal fat percentage for somapacitan-beco vs daily GH therapy (secondary analysis) was 1.17% (95% CI, 0.23 to 2.11); this endpoint was not designed as a confirmatory test and no p-value was calculated. Improvements were maintained with both somapacitan-beco and daily GH throughout a 52-week open-label extension period.
- Clinical data support the use of GH for the treatment of growth failure associated with chronic renal insufficiency. A meta-analysis of 16 RCTs (N = 809) evaluating the effects of GH in children with CKD found that patients who were treated with GH had a greater increase in mean height velocity (3.88 cm) than those who received either no treatment or placebo after 1 year (*Hodson et al 2012*). A retrospective, matched control cohort study found that long-term therapy with GH (mean 4.2 years) reduced linear growth deceleration in children with CKD and improved final height (*Bizzarri et al 2018*).
- Clinical trials have demonstrated efficacy of GH for the treatment of growth failure in patients with Noonan syndrome. An RCT 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 suggest that once treatment with GH is discontinued, “catch-down” (artificially stimulated growth declines once GH is discontinued) growth can occur (*Noordam et al 2001*). In a follow-up analysis of 29 patients treated with GH for a median of 6.4 years, a total of 22 children reached an adult height in the normal range (*Noordam et al 2008*). In a study of 65 patients enrolled in the National Cooperative Growth Study (NCGS) database, it was found that treatment with GH led to gains over predicted height of 9.2 cm in females and 10.9 cm in males (*Romano et al 2009*).
- Clinical trials and a 2020 meta-analysis have demonstrated 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, Passone et al 2020*). Data from 1 trial suggested 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 have demonstrated 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 suggested 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 4 RCTs demonstrated that GH (0.3 to 0.375 mg/kg/week) increased short-term growth in patients with Turner syndrome by approximately 3 cm 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 have demonstrated 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 Schepper et al 2008, de Zegher et al 1996, de Zegher et al 2005, Jung et al 2009, Maiorana et al 2009, Sas et al 1999b*). Data from individual clinical trials and 3 meta-analyses found that response to GH therapy is dose-dependent, and higher doses of GH resulted 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, Kriström 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 demonstrated no differences in safety and efficacy with different GH preparations for the treatment of pediatric GHD. One of the trials compared 3 GH preparations (Genotropin, Humatrope, and Saizen), while the second evaluated 2 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, Deodati et al 2011, Finkelstein et al 2002, Hopwood et al 1993, Kriström et al 2009, van Gool et al 2010, Wit et al 2005*). Additionally, once daily compared to 3 times weekly dosing and higher compared to lower dosing demonstrated a greater increase in growth velocity (*Bryant et al 2007, Finkelstein et al 2002*).
- A registry study evaluated the long-term effectiveness and safety of GH in South Korean pediatric patients ≥ 2 years of age with GHD, idiopathic short stature, Turner syndrome, small for gestational age, and chronic renal failure. Interim analysis of 5-year data for 2024 patients (7324 patient-years) found that most patients showed a beneficial effect on height standard deviation score for up to 4 years, with the most prominent effect observed within 1 year of treatment initiation. The incidence of adverse events was low, and most cases of neoplasm were benign and/or unrelated to GH therapy (*Rhie et al 2019*).
- A systematic review and meta-analysis of 54 placebo-controlled, RCTs enrolling over 3400 patients found that GH therapy was associated with reduced body fat and increased lean mass in adults with GHD (*Hazem et al 2012*). Eleven of 16 trials that assessed quality of life outcomes reported positive outcomes, but a meta-analysis was not possible. Furthermore, results from meta-analyses and RCTs 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 assessed the safety and efficacy of GH with or without glutamine supplementation for adult patients with short bowel syndrome; 5 studies were included in the review. Human GH with or without glutamine appeared to provide benefit in terms of increased weight (mean difference [MD] 1.66 kg; 95% 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 RCT, which focused on parenteral nutrition (PN) requirements, demonstrated decreased PN volume, 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 3-month follow-up. The results suggested a positive effect of GH on weight gain and energy absorption. However, after cessation of therapy, the effects returned to baseline in the majority of the trials (*Wales et al 2010*).

CLINICAL GUIDELINES

- 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, GHD in childhood cancer survivors, Noonan

syndrome, Turner syndrome, Prader-Willi syndrome, chronic renal insufficiency, born small for gestational age, and short stature homeobox-containing gene deficiency (*Cohen et al 2008, Deal et al 2013, Gravholt et al 2017, Grimberg et al 2016, Ketteler et al 2018, Sklar et al 2018*). Routine use of GH in every child with idiopathic short stature is not recommended; decisions about GH therapy should take into account physical and psychological burdens as well as risks and benefits (*Grimberg et al 2016*). 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.

- Treatment guidelines recommend offering GH therapy to adult patients with proven GHD and no contraindications (*Fleseriu et al 2016*). 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 (*Fleseriu et al 2016, Yuen et al 2019).* The 2019 American Association of Clinical Endocrinologists/American College of Endocrinology guidelines, which focus on adults and patients transitioning from pediatric to adult care, state that no evidence exists to support any specific GH product over another (*Yuen et al 2019*).
- Small studies evaluating the use of GH in short bowel syndrome have yielded conflicting results; methodological differences limit definitive conclusions on the efficacy of GH. In carefully selected patients who are candidates for growth factor treatment, the glucagon-like peptide-2 analog, teduglutide, is recommended as first-line therapy (*Pironi et al 2016*).

SAFETY SUMMARY

- Contraindications to GH products include active malignancy, diabetic retinopathy, hypersensitivity to the agent or any of its excipients, acute critical illness, and use for growth promotion in children with closed epiphyses. Somatropin is also contraindicated in children with Prader-Willi syndrome who are severely obese, have severe respiratory impairment, or have a history of upper airway obstruction or sleep apnea (Genotropin, Humatrope, Norditropin Flexpro, Nutropin AQ, Omnitrope, Saizen, Zomacton).
- Key Warnings/Precautions (applicable to all GH products unless otherwise noted):
  - Therapy may contribute to increased mortality in patients with acute critical illness due to complications from open heart surgery, abdominal surgery, accidental trauma, or respiratory failure.
  - Somatropin may increase progression or recurrence of intracranial neoplasms, particularly meningiomas in patients treated with radiation to the head for their first neoplasm.
    - The Safety and Appropriateness of GH treatments in Europe (SAGhE) study, which followed almost 24,000 patients for an average of 14.8 years per patient, found that GH therapy does not increase the risk for leukemia or other cancers in patients with isolated growth failure as compared with the age-matched general population. GH was associated with a modest increase in risk for a secondary cancer in patients with a primary cancer diagnosis. In patients with other non-cancer primary diagnoses, there was a modest increase in cancer risk, primarily bone or bladder cancer (*Swerdlow et al 2017*).
  - Malignancy:
    - In childhood cancer survivors who were treated with radiation to the brain/head for their first neoplasm and were later treated with somatropin, an increased risk of a second neoplasm has been reported. Patients with a history of GHD secondary to an intracranial neoplasm who are treated with somatropin should be monitored routinely for progression or recurrence of the tumor.
    - Because children with certain rare genetic causes of short stature have an increased risk of developing malignancies, practitioners should thoroughly consider the risks and benefits of starting somatropin in these patients. If treatment with somatropin is initiated, these patients should be carefully monitored for development of neoplasms.
    - Patients on somatropin should be carefully monitored for increased growth, or potential malignant changes, of preexisting nevi.
    - Somapacitan-beco increases the risk of malignancy progression in patients with active malignancy. There is also a potential risk of new skin malignancy during treatment, including malignant changes of preexisting nevi.
  - Undiagnosed or untreated hypothyroidism may impair optimal response to therapy.
  - A decrease in insulin sensitivity and previously undiagnosed diabetes mellitus may be unmasked during treatment.
  - Intracranial hypertension and pancreatitis have been reported with therapy.
  - Slipped capital femoral epiphyses and scoliosis can occur in pediatric patients.
  - Fluid retention has been associated with treatment in adult patients.

- Increases in serum levels of inorganic phosphorous, alkaline phosphatase, parathyroid hormone and IGF-1 may occur.
- Tissue atrophy may occur when therapy is administered via SC injection at the same site over a long period of time.
- Therapy may reduce serum cortisol levels or unmask central hypoadrenalism in patients at risk for pituitary hormone deficiency.

- Adverse drug events: Arthralgia, back pain, dyspepsia, myalgia, edema, carpal tunnel syndrome, paresthesia, hyperglycemia, headaches, lipoatrophy, and injection site reactions.
- Drug Interactions: Estrogens, glucocorticoids, insulin or other hypoglycemic agents, and drugs metabolized by cytochrome P450 enzymes.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Genotropin (somatropin)	Injection	SC	Weekly dose divided into 6 or 7 injections to Daily	Injections should be rotated to help prevent lipoatrophy.
Humatrope (somatropin)	Injection	SC	Weekly dose divided into 6 or 7 injections to Daily	Injections should be rotated to help prevent lipoatrophy.
Norditropin Flexpro (somatropin)	Injection	SC	Weekly dose divided into 6 or 7 injections to Daily	Injections should be rotated to help prevent lipoatrophy.
Nutropin AQ (somatropin)	Injection	SC	Weekly dose divided into 3 to 7 injections to Daily	Injections should be rotated to help prevent lipoatrophy.
Omnitrope (somatropin)	Injection	SC	Weekly dose divided into 6 or 7 injections to Daily	Injections should be rotated to help prevent lipoatrophy.
Saizen (somatropin)	Injection	SC	Weekly dose divided into 3, 6, or 7 injections to Daily	Injections should be rotated to help prevent lipoatrophy.
Serostim (somatropin)	Injection	SC	Daily	Injections should be rotated to avoid local irritation.
Sogroya (somapacitan-beco)	Injection	SC	Once weekly	Injections should be rotated to help prevent lipoatrophy
Zomacton (somatropin)	Injection	SC	Weekly dose divided into 3, 6, or 7 injections to Daily	Injections should be rotated to help prevent lipoatrophy.
Zorbtive (somatropin)	Injection	SC	Daily	Injections should be rotated to help prevent lipoatrophy. Dosage titration is recommended for fluid retention and arthralgia/carpal tunnel syndrome.

See the current prescribing information for full details.

CONCLUSION

- The safety and efficacy of GH therapy in pediatric patients with growth failure are well established. Treatment guidelines recommend the use of somatropin as a treatment option for children with growth failure associated with any of the following: GHD, GHD in childhood cancer survivors, Turner syndrome, Prader-Willi syndrome, chronic renal insufficiency, born small for gestational age, and short stature homeobox-containing gene deficiency (*Clayton et al 2007*, *Cohen et al 2008, Deal et al 2013, Gravholt et al 2017, Grimberg et al 2016, Ketteler et al 2018, Sklar et al 2018*). Routine use of GH in every child with idiopathic short stature is not recommended; decisions about GH therapy should take into account physical and psychological burdens as well as risks and benefits (*Grimberg et al 2016*). 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.

- For adult patients, guidelines recommend offering GH therapy to those with proven GHD and no contraindications. (*Fleseriu et al 2016).* No evidence exists to support any specific GH product over another (*Yuen et al 2019*).
- There are several GH preparations currently available, most of which contain somatropin (recombinant human GH). These preparations are equally biopotent and have the same natural sequence structure (*Rogol et al 2020*).
- In addition to the somatropin products, somapacitan-beco has been approved by the FDA as a longer-acting GH derivative with once-weekly dosing for adult GHD.
- Differences between GH products such as device features, dose increments, requirement for reconstitution, and requirement for refrigeration may influence individual patient preferences. All of the available GH preparations are available for SC injection, and there are currently no generics available within the class.
- Common adverse reactions that may be observed with GH therapy include arthralgia, back pain, dyspepsia, myalgia, edema, carpal tunnel syndrome, paresthesia, hyperglycemia, headaches, lipoatrophy, and injection site reactions.

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