

Targeted Class Review: Growth Hormones for Adults

Date of Review: April 2023

End Date of Literature Search: 12/02/2022

Current Status of PDL Class:
See **Appendix 1**.

Purpose for Class Review:

A comprehensive review of growth hormone therapy in adults has not previously been completed for Pharmacy and Therapeutics (P and T) Committee assessment. This drug class update examines comparative evidence for safety and efficacy of various growth hormone preparations in the management of adult growth hormone deficiency and other FDA-approved indications in adults.

Plain Language Summary:

- Hormones are important chemicals that carry messages throughout the body through the blood to organs, muscles, and other tissues. Growth hormone (GH) is natural hormone released by a gland in the brain that helps children grow, helps adults maintain a normal body structure, and plays a role to support the body's ability to build up and break down substances needed to keep children and adults healthy. People who do not naturally make enough growth hormone due to a medical condition may be diagnosed with growth hormone deficiency (GHD). Growth hormone may be used as a medicine in people that do not make enough in their own body naturally. Growth hormone medication is approved by the Food and Drug Administration to treat specific medical conditions that affect a person's ability to grow and develop. Growth hormone medication should be prescribed by a doctor with special training for treating children and adults with a medical condition that would benefit from growth hormone treatment.
- Other medical conditions besides GHD have been treated with GH. The purpose of this document is to review the medical evidence that supports the possible benefits and harms of GH therapy in adults who may need GH therapy to treat their medical condition.
- In adults with GHD, there is conflicting evidence that shows GH therapy benefits the heart, increases bone strength, improves fitness level, or leads to a better quality of life (QoL) over a long period of time compared to no treatment.
- In adults with short bowel syndrome who need a special diet, there may be some benefit compared to placebo that GH treatment may lower body fat, improve their amount of muscle tissue, and help them get better nutrition.
- In patients with Prader-Willi syndrome or HIV associated wasting/cachexia, there was not enough evidence available to decide whether GH therapy improves long-term health outcomes.
- A guideline published by the National Institute for Health and Care Excellence (NICE) for Human growth hormone (somatropin) in adults with GHD continues to recommend that:
 - GH medicine should only be used for patients with severe GHD, if needed to improve their quality of life, and if they are already receiving other hormone treatments.

- After starting a patient on GH medicine, wait 9 months then decide if the patient should continue. Doctors should not stop treatment if it is still helping improve the patient's quality of life.
- If a patient was treated for GHD as a child and then is finished growing, only continue GH medicine if needed to treat severe GHD, to improve their quality of life, and if they are already receiving other hormone treatments.
- Patients who start to lose GH in early adulthood, after they are done growing but before the age of 25 years, should be given GH treatment until their adult bone mass has peaked.⁴
- Only a doctor with special training should start a patient on GH medicine for GHD. Therapy may be continued by the patient's regular doctor only when there has been a discussion with the prescriber who first started the patient on the medicine.
- There is not enough evidence to recommend the use of one type of GH medicine over another.
- The Drug Use Research and Management (DURM) group recommends no changes to our current policy for the use of growth hormone medicine.

Research Questions:

1. What is the comparative evidence assessing efficacy of growth hormone agents for the treatment of adults with growth hormone deficiency, HIV-associated cachexia, short bowel syndrome, or Prader Willi syndrome?
2. What is the comparative evidence assessing long term safety and harms of growth hormone agents for the treatment of adults with growth hormone deficiency, HIV-associated cachexia, short bowel syndrome, or Prader-Willi syndrome?
3. Are there any subgroups (based on age, ethnicity, comorbidities, disease duration or severity) that would particularly benefit or be harmed by growth hormone agents for the treatment of adults with growth hormone deficiency, HIV-associated cachexia, short bowel syndrome, or Prader-Willi syndrome?

Conclusions:

- There are 2 systematic reviews and one high quality clinical practice guideline included in this review.
- There is insufficient comparative evidence based on one systematic review to assess whether GH therapy for adult GHD results in long-term improvements in glucose metabolic parameters, cardiovascular disease risk factors, body composition, bone structure, or health-related quality of life.¹
- A Cochrane review found low quality evidence for patients with short bowel syndrome who were dependent upon parenteral nutritional support that GH treatment resulted in a statistically significant increase in lean body mass (LBM) compared to placebo either with or without glutamine (Mean difference (MD) 1.93 kg; 95% Confidence Interval (CI) 0.97 to 2.90; P = 0.0001; 3 studies).² The clinical relevance of this magnitude of change is unknown.
- The Health Evidence Review Commission (HERC) has allowed limited appropriate use of GH for adults.³ There was insufficient evidence to draw conclusions on the impact of GH therapy on significant adverse events in adults with growth hormone deficiency, HIV-associated cachexia, short bowel syndrome, or Prader Willi syndrome.
- A guideline published by the National Institute for Health and Care Excellence (NICE) for administration of human growth hormone (somatropin) in adults with GHD continues to recommend the following:⁴
 - Initiate GH treatment only if severe GHD, impaired QoL, or already receiving treatment for any other pituitary hormone deficiencies.⁴
 - Re-assess GH treatment 9 months after initiation and discontinue if there is an insufficient improvement in QoL.⁴
 - Patients who develop GH deficiency in early adulthood, after linear growth is completed but before the age of 25 years, should be given GH treatment until adult peak bone mass has been achieved.
 - After adult peak bone mass has been achieved, the decision to continue GH treatment should be based on initiation criteria (severe GHD, impaired QoL, or already receiving treatment for any other pituitary hormone deficiencies).

- Initiate GH treatment for GHD only by a qualified specialist (e.g. endocrinologist) and continue in primary care only with an agreed upon shared-care protocol.⁴
- There is insufficient evidence to recommend the use of a specific formulation of GH in preference to another.
- Additional comparative studies evaluating the effectiveness and safety of GH therapy in the adult Medicaid population are needed.

Recommendations:

- No changes to the preferred drug list (PDL) are recommended based on the review of current evidence.
- After evaluation of costs in executive session, no PDL changes were recommended.

Summary of Prior Reviews and Current Policy

In December 2022, prior authorization (PA) criteria for the growth hormone class was updated to align fee-for-service PA criteria with new Health Evidence Review Commission (HERC) guidance for use of human growth hormones (HGH) and their FDA-approved indications.³ HGH is supplied in several formulations for the treatment of a limited number of pediatric and adult conditions (see **Appendix 1** for representative agents). HERC recently updated its guidance to allow limited coverage of HGH for adults and allow individualized review for HGH needs for children.³

Background:

Growth hormone, or somatotropin, is a polypeptide hormone released from somatotroph cells in the anterior pituitary that is commonly associated with linear growth during childhood and adolescence.^{5,6,7} Metabolic processes throughout adult life are augmented by GH including the reduction of glucose utilization in peripheral tissues and stimulation of lipolysis.^{5,6,7} Growth hormone triggers protein synthesis in a wide range of bodily tissues to increase muscle mass and stimulate bone formation.^{5,6,7,8}

Adult Growth Hormone Deficiency (AGHD) is rare clinical syndrome that is a result of diminished GH production or tissue unresponsiveness to GH.⁹ About 20% of AGHD cases may be a continuation of a childhood GH deficiency, but AGHD may also be adult-acquired.^{8,9} Patients with AGHD may present with non-specific signs and symptoms such as hypertension, fatigue and decreased muscle strength, difficulty with concentration and memory, metabolic abnormalities (e.g. glucose intolerance, elevated triglycerides, increased visceral fat, impaired lipid metabolism, etc.), depression, and sleep impairment.^{8,9} Some patients may show little to no symptoms.⁹ Since many signs and symptoms of adult GHD are clinically similar to the typical adult aging process, individuals with AGHD may be unaware of this deficiency unless tested. Some of the more common clinical features of AGHD are listed in **Table 1**.

Table 1: Common Clinical Features of Adult Growth Hormone Deficiency⁹

Reported Symptoms
-Depression and fatigue, sleep and memory impairment, anxiety
-Increased fat mass; decreased LBM muscle strength
-Decreased exercise performance and cardiac capacity
-Dry skin
-Osteopenia or osteoporosis with increased risk of fracture
-Low serum HDL (mainly females), high serum TGs, impaired glucose tolerance

Abbreviations: HDL=high-density lipoprotein; HTN=hypertension; LBM=lean body mass; TGs=triglycerides

There are 6,000 new cases of adult GHD diagnosed in the United States annually with a prevalence estimated around 1:100,000.^{9,10} Roughly 15% to 20% of the adult GHD cases are continued from a childhood onset of GHD.⁸⁻¹² GH mutations may result in multiple pituitary hormone deficiencies or can cause isolated dysfunction. Various congenital abnormalities of AGHD may be linked to genetic mutations in transcription factors (e.g., HESX-1, LHX3/4, PIT-1, PITX-2, PROP-1), defects in the growth hormone-releasing hormone (GHRH) receptor gene, or even flaws in the GH gene itself.¹¹ Although adult-onset GHD cases are more common in those between 45 years of age and older, it may be acquired at any time in adulthood as a result of damage to the hypothalamic-pituitary axis via tumors (and their treatment), traumatic brain injury (TBI), or even infection.^{5-7,12,13} Studies have reported that GHD affects men more frequently than women (19 cases vs 14.2 cases per million, respectively) and the disparity appears to increase with age.^{9,13} GHD may be isolated or can manifest along with multiple hormone deficiencies.^{6,9,13} There are no known mechanisms to prevent or screen for GHD.

The anterior pituitary secretes GH in short bursts at different periods throughout the night and daily following meals, after exercise, and during stress.⁵⁻⁷ Although hypothalamic GHRH stimulates the production and release of GH, its synthesis is also regulated by other peripheral hormones such as glucocorticoids, thyroid hormone, and estrogen.¹⁴ GH secretion tends to gradually increase in childhood and peak at puberty, then steadily decline throughout adulthood.^{13,14} Obesity and hypothyroidism tend to suppress GH secretion.¹⁵ The GH receptor may be found in numerous body organs and tissues such as the liver, muscle fat, kidneys and cartilage.¹⁵ When the GH receptor is activated in the liver and peripheral tissues, Insulin Growth Factor (IGF)-1 is produced which promotes anabolic effects.¹⁵ Given that GH is secreted in a pulsatile manner with oversight of complex biofeedback regulatory mechanisms, random sampling of GH levels is often of little benefit to diagnose AGHD and may even lead to false positives.⁵⁻⁷ Since low serum IGF-1 levels tend to correlate with deficient GH secretion, IGF-1 measurements may have some utility in confirmation of AGHD.¹³⁻¹⁷ However, because IGF-1 levels are often normal in adult GHD and lower levels are observed during weight loss and in liver disease, the utility of IGF-1 as a stand-alone AGHD diagnostic tool is not recommended and additional testing is typically required.¹³⁻¹⁷

For a definitive AGHD diagnosis, clinicians utilize provocative tests.^{13-15,18} Provocative tests are typically warranted for patients with a high GHD probability (e.g. childhood onset GHD, post irradiation hypothalamic-pituitary disease, TBI, etc.) and are based on a maximal GH response to a stimulation test.^{13-15,18} Two of the more common AGHD diagnostic tests are the insulin tolerance test (ITT) or a glucagon stimulation test.^{13-15,18} The ITT is the most frequently employed test and requires a GH response of <3-5mcg/L for a GHD diagnosis.^{13-15,18} However, the ITT may be cumbersome to perform, and its use is contraindicated in patients with coronary artery disease (CAD), those with seizure risk, and the elderly because it induces hypoglycemia.^{13-15,18} A stimulation test with glucagon is an appropriate alternative to the ITT stimulation test.^{13-15,18} The growth hormone-releasing hormone (GHRH)-arginine test may also be used to diagnose adult GHD but there has been limited use in the United States due to reduced availability and manufacturing challenges.¹⁵ An alternative AGHD diagnostic agent, macimorelin, is a synthetic Ghrelin receptor agonist that stimulates GH release in the pituitary and hypothalamus and has been recently approved for use in the United States.^{19,20} Provocative testing for GHD may be unnecessary in adult patients who had childhood onset GHD with evidence of structural pituitary disease plus multiple hormone deficiencies since these conditions are not reversible.^{5,6,13} In these individuals, clinical signs and symptoms of GHD with a low IGF-1 measurement are enough for a GHD diagnosis.¹³ Imaging may identify the existence of tumors or structural defects. Before deciding whether GH replacement should be continued for an adult patient, many organizations recommend retesting with provocative tests after the completion of linear growth since roughly half the adult patients have normal GH levels and may not need additional therapy.^{17,18,21,22}

Characteristics of the more common GH stimulation tests used in the United States are listed in **Table 2**.

Table 2: Provocative Tests for Adult Growth Hormone Deficiency Diagnosis¹⁸

Test	Procedure	Interpretation of GHD	Safety/adverse effects	Comments	Diagnostic performance
ITT	IV insulin 0.05-0.15 U/kg. Record neuroglycopenic symptoms. Blood sampling: fasting, and 20, 30, 40, and 60 min after hypoglycemia is achieved.	GH < 3-5 mg/L at every time point after hypoglycemia is achieved.	Unpleasant neuroglycopenic symptoms. Contraindications: epilepsy, cardiovascular disease, pregnancy, age >65 years. Delayed hypoglycemia may occur.	-Adequate hypoglycemia required for validation of test. -Can simultaneously assess HPA axis -Close medical supervision required. -Poor reproducibility.	PPV 93%, sensitivity 96%, and specificity 92%.
Glucagon	1 mg (1.5 mg if >90 kg) IM Measure GH every 30 min over 4 h.	GH ≤ 3 mg/L at every time point.	Nausea, vomiting, headaches, delayed hypoglycemia, diaphoresis and abdominal cramps.	-Questionable diagnostic accuracy in subjects with high BMIs and glucose intolerance. -Requires lower BMI-dependent GH cut-points to achieve optimal specificity.	Sensitivity and specificity 100% in lean subjects.
Macimorelin	8-hour fast required; administer 0.5 mg/kg oral solution; measure at 30, 45, 60, and 90 min time points after administration.	Maximally stimulated serum GH level <2.8 ng/mL (30, 45, 60 and 90 min time points) following administration confirms the presence of adult GHD	Dysgeusia, dizziness, headache, fatigue, nausea, hunger	-Avoid concomitant use with medications known to cause QTc-interval prolongation. -Safety and diagnostic performance not established for BMI of > 40 kg/m ² . -High cost	Using a GH cutoff of 2.8 ng/mL for the macimorelin test, the sensitivity was 87% and specificity was 96%.

Abbreviations: BMI=body mass index; GH=growth hormone; h=hours; HPA=hypothalamic-pituitary-adrenal; IM=intramuscular; ITT=insulin tolerance test; IV=intravenous; kg= kilogram; L=liter; mg=milligram; min=minute; ml=milliliter; ng=nanogram; PPV=positive predictive value; U=unit.

GH replacement therapy for AGHD patients has been recommended to improve various clinical outcomes but clear evidence of benefit from high quality studies is limited in the adult population.¹³⁻¹⁵ Nonetheless, GH treatment may be a viable option for adult GHD patients with significant clinical indicators and overt evidence of GHD from pituitary removal (or destruction) or panhypopituitarism since birth.¹³⁻¹⁵ Some common goals of GHD treatment in adulthood are to improve the patient’s metabolic and cardiovascular risk profile, body composition, bone structure, and quality of life.²² A variety of studies have investigated the effects of GH treatment on surrogate cardiovascular markers such as serum lipoprotein profiles (e.g. LDL reduction, HDL improvement) but results have been

mixed and inconsistent.²³ For example, significant increases in lean body mass and reductions in body fat content have been observed with GH replacement therapy, but no effects on BMI were observed.^{24,25} Growth hormone therapy may be associated with favorable changes in myocardial structure and function but these data are reported from mostly small, open label studies.²⁶⁻²⁸ While there is limited evidence that GH replacement may increase markers of bone mineral density after 6 months, the effects do not appear to persist beyond 18 months of treatment.^{25,29} There is no published data to confirm an association between GH therapy and pituitary tumor regrowth, but due to a concern that increased IGF-1 levels may increase risk of malignancy, GH therapy is contraindicated in patients with active malignancy or severe diabetic retinopathy.^{13,22,30,31} There are a number of studies and guidelines that have explored patient psychological well-being and quality of life as an important outcome measure of GHD therapy and some studies have reported a benefit.³²⁻³⁴ In a subpopulation of females with GHD and prior acromegaly, GH therapy was reported to result in QoL improvements in areas such as socialization and self-confidence after 6 months based on select questionnaires.³² The mechanism of beneficial effect on QoL attributed to GH replacement remains elusive and no standardized QoL assessment tool has been identified.³² It does not appear that GHD has any relationship with mortality nor does GHD replacement therapy have any evidence of benefit on mortality rate.³⁵

Growth hormone replacement therapy has been utilized to treat other conditions in adults, some of which are FDA-approved (see **Table 3**). Short bowel syndrome (SBS) is a disorder caused by reduced functional surface area of the intestine that leads to decreased absorption of nutrients, fluids, and electrolytes.^{36,37} SBS symptom severity is dependent upon the extent damage or loss of intestinal surface area and compensatory ability of the remaining bowel.³⁸ Growth hormone has been shown to influence intestinal growth, function, and result in other trophic changes.^{36,37} Studies with GH therapy plus the amino acid glutamine have shown mixed success for nutrient absorption, weight gain, and for reducing parenteral nutritional needs in the treatment of SBS in adults.^{2,39} Likewise, GH therapy has been used to stimulate weight gain and work output in cachexia or wasting caused by AIDS.^{15,40} There is research to suggest that GH therapy induces a positive nitrogen balance with decreased fat and increased muscle mass.¹⁵ However, when GH is administered concomitantly with protease inhibitor therapy, the risk of diabetes is increased in this population, which may be a concern.¹⁵ The treatment of SBS and cachexia or wasting associated with AIDS are both FDA-approved indications of GH therapy.^{41,42}

Table 3: FDA-approved Uses of Recombinant Growth Hormone for Adults

Condition	Etiology/Pathology	Clinical Manifestations	GH Function	Approved GH Preparations
GHD ^{5,9,43-50}	Impaired production of GH from congenital malformations/genetic defects or acquired causes (e.g. trauma, infection, malignancy)	Early growth failure at 6-12 months with decreased growth velocity until 3 years of age, delayed bone age, jaundice, central obesity, craniofacial abnormalities, hypoglycemia, hypothyroidism, defective primary or secondary sexual development	Decreased visceral fat, increased muscle mass, and increased exercise capacity	Genotropin™ Humatrope™ Norditropin™ Nutropin AQ™ Omnitrope™ Saizen™ Zomacton™
HIV Associated Cachexia ^{40,41}	Altered metabolism and malabsorption due to HIV infection	Weight loss, anorexia, muscle atrophy, fatigue and weakness	To increase lean body mass, body weight and improve physical endurance	Serostim™

Short Bowel Syndrome ^{37,42}	Reduction of functional intestinal surface area from intestinal resection or tissue damage leads to malabsorption of nutrients, fluid, and/or electrolytes.	Diarrhea, dehydration, electrolyte abnormalities, weight loss, confusion and apathy	To increase weight, lean/fat-free body mass, and nutritional absorption	Zorbitive™
Abbreviations: CKD = chronic kidney disease; FDA = Food and Drug Administration; GFR = glomerular filtration rate; GHD = growth hormone deficiency; HIV = human immunodeficiency virus; PWS= Prader-Willi syndrome; rGH = recombinant growth hormone; SHOX = Short stature homeobox-containing gene				

Growth hormone replacement therapy has also been used to treat children with PWS as they transition to adulthood.⁵¹ Clinical features of PWS resemble that of patients with GHD, such as short stature, increased body fat, and decreased muscle mass and strength.⁵¹ Some studies have reported a positive effect of GH therapy on body composition and quality of life in adult patients with PWS, but due to methodological limitations of the included studies, the true effects are unknown.⁵¹ Most studies of adults with PWS have been small, observational studies of short duration with much heterogeneity.⁵¹ Evidence of benefit in other key areas such as BMD, BMI, and fasting glucose levels has been inconclusive.³ The long-term benefits or harms of GH therapy in adult patients with PWS are unknown.⁵¹

GH replacement in adults is individualized according to age, gender, and even estrogen levels.⁵² The endocrinologist may consider patient age, severity, and comorbidities when dosing of GH replacement therapy, but age-based dosing with titration tends to be favored compared to weight-based regimens due to less frequency of adverse effects.⁵² Patients on oral estrogen therapy may require higher doses of GH replacement while those on testosterone replacement may need a lower GH dose due to testosterone’s potentiation of GH action.²² There is no suggested limit to the duration of GH therapy if objective benefits are observed in areas such as bone mineral density and body composition, or subjective improvements in quality of life.²² However, guidelines suggest that if after 1 year of GH treatment no benefits are observed in key outcome measures, therapy discontinuation may be considered.^{13,22} A 6-month follow up appointment is recommended for patients that discontinue GH therapy to reassess if a restart of therapy is warranted.^{13,22} Standard GH dosing protocols are listed in **Table 4**.

Table 4: Standard Growth Hormone Replacement Dosing Recommendations²²

Age or Comorbidities/Conditions	Dosing*
<ul style="list-style-type: none"> • <30 years • Women on oral estrogen therapy 	0.4 to 0.5 mg/day (or higher for patients transitioning from pediatric treatment)
30 to 60 years	0.2 to 0.3 mg/day
<ul style="list-style-type: none"> • >60 years • Diabetes mellitus or prediabetes • Obesity • Previous gestational diabetes 	0.1 to 0.2 mg/day
Patients transitioning from childhood to adulthood GH deficiency	Resume GH doses at 50% of the dose last used in childhood

*=see prescribing information of individual agents for FDA-approved dosing and adjustments

There are several GH replacement agents available in the United States. GH preparations are generally supplied as subcutaneous solutions either in a prefilled pen/cartridge or in a vial, as powder for reconstitution. Clinical practice guidelines do not distinguish among the various preparations of GH as there is limited evidence of differences in clinical outcomes from one brand to another.^{13,22} Each formulation may have a different strength, administration device, and/or storage requirement.^{16,41-50} Dosing frequency may also vary among different products and conditions.^{41-50,53} The choice of preparation may be individualized based on therapeutic needs, patient response, and adherence.⁴¹⁻⁵⁰ A drug information summary is available in **Appendix 2**, which includes pharmacology and pharmacokinetic characteristics of these drugs, contraindications, warnings and precautions, including any Black Boxed Warnings and Risk Evaluation Mitigation Strategies.

There were approximately 10 fee-for-service Oregon Health Plan Fee-for-Service (OHP-FFS) patients who received growth hormones in quarter 3 of 2022. Approximately 72% of the paid claims were for Norditropin Flexpro, 11% for Omnitrope, 11% for Genotropin, and 6% for Humatrope. Growth hormones currently represent a relatively small proportion of overall health care claims and costs to the Oregon Health Authority (OHA).

Methods:

A Medline literature search for new systematic reviews and RCTs assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:

CADTH Rapid Response Report - Human Growth Hormone Treatment for Adult Growth Hormone Deficiency: A Review of the Clinical Effectiveness, Safety, Cost-Effectiveness, and Guidelines¹

A 2015 CADTH review evaluated the evidence for efficacy and safety of human growth hormone for adult GHD.¹ Literature was evaluated from 2007 through 2015.¹ The intervention in the RCTs was GH replacement therapy as compared to placebo.¹ No other relevant health technology assessments, meta-analyses, or randomized controlled trials (RCTs) were identified since the previous review.¹ Clinical outcomes included CVD risk factors, metabolic parameters, anthropometry, bone parameters, cognitive function, quality of life (QoL) and adverse events. All studies reviewed included patients with severe GHD who were 25 years of age or older.¹ Quality of the included systematic review (SR) was assessed using the Assessing the Methodological Quality of Systematic Reviews (AMSTAR) tool.¹

One systematic review met inclusion criteria and consisted of 11 studies (N=534) 2 of which were RCTs (N=62)], in patients 60 years of age or older.¹ The RCTs had a duration of 6 and 12 months.¹ One RCT found no differences in cognition, Hemoglobin (Hb)A1c, insulin, or serum glucose with GH therapy compared to placebo.¹ One RCT reported a decrease in total cholesterol, Low-density Lipoprotein (LDL), and LDL/HDL ratio and an increase in resting heart rate with GH therapy compared to placebo.¹ However, the included studies did not quantify results or discuss statistical significance of all findings in the conclusion.¹ Adverse events reported with GH therapy use were cerebrovascular events, neoplasms, fluid retention, arthralgia, peripheral edema, and headache.¹ One RCT observed no differences in adverse events between placebo and GH therapy groups.¹ No evidence was identified to support clinical effectiveness of GH therapy for direct health impacts in

GHD patients.¹ Therefore, it was determined that evidence was insufficient to determine the safety of GHR therapy or to formulate any meaningful outcome conclusions.¹

Wales, et al – Human growth hormone and glutamine for patients with short bowel syndrome²

A 2010 Cochrane systematic review and meta-analysis evaluated the role of GH treatment for patients with short bowel syndrome.² Five randomized controlled trials were included (n=79) with durations from 3 to 18 weeks.² Comparisons were between GH therapy and placebo in mostly adult patients diagnosed with short bowel syndrome and dependent on parenteral nutrition support.² In 4 of the studies, ages ranged from 18-75 years, while 1 study included 8 patients with a mean age of 12.9 years.² There were 34 males and 45 females included.² The primary outcome of interest was change in body weight (kg) while secondary outcomes included change in lean body mass, energy absorption, nitrogen absorption, fat absorption, carbohydrate absorption, serum IGF-1, parenteral nutrition (PN) requirements (volume/calories used or frequency of administration), and adverse events.²

The risk of bias was low for all of the 5 included studies.² Pooled estimates calculated for 3 studies found GH treatment by the end of therapy resulted in a statistically significant increase in LBM compared to placebo either with or without glutamine (MD 1.93 kg; 95% CI 0.97 to 2.90; P = 0.0001).² The meta-analysis of 3 trials found by the end of therapy that GH treatment resulted in a statistically significant increases in energy absorption (MD 4.42 Kcal; 95% CI 0.26 to 8.58; P = 0.04), nitrogen absorption (MD 44.85 g; 95% CI 0.20 to 9.49; P = 0.04), and fat absorption (MD 5.02 g; 95% CI 0.21 to 9.82; P = 0.04).² There is no minimum clinically important difference published for these outcomes so the clinical relevance of this magnitude of change is unknown.² For those who received GH therapy, glutamine and diet manipulation, there was a statistically significant reduction in weekly PN volume (~2 L), calories (~1400), and number of infusions (~1) required compared to GH and glutamine placebo (p<0.001). The reported reduction in PN requirements appeared to be maintained at 3 months (P<0.005).² There were no statistically significant changes reported in carbohydrate absorption or serum IGF-1 in the pooled analysis.² The most frequently reported adverse events were peripheral edema (44/57 [77%]), arthralgia (2/120 [10%]), and carpal tunnel syndrome (16/49[32%]).² Due to the small number of patients enrolled, the limited duration of the studies, and the short-lived effect of GH therapy, it is unclear whether GH therapy has long-term benefit in this population as any observed improvements were short-term and did not continue after therapy ceased.² The evidence was insufficient to recommend routine use of GH or glutamine in short bowel syndrome.²

After review, 15 systematic reviews were excluded due to poor quality (e.g., network meta-analyses), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

Guidelines:

High Quality Guidelines:

National Institute of Health Care Excellence (NICE) – Human growth hormone (somatropin) in adults with growth hormone deficiency⁴

NICE published guidance for the use of human growth hormone (somatropin) in adults with growth hormone deficiency.⁴ Originally published in 2003, NICE reviewed the evidence again in 2014 and did not find any new information that affected the recommendations.⁴ The assessment identified 17 published RCTs that evaluated the effects of GH including QoL in roughly 900 adult patients with GH deficiency.⁴ Twenty-three different assessment scales were used, within a variety of trial designs.⁴ The duration of the studies was typically 6 months and the number of participants ranged from 6 to 173.⁴ Most studies included both adult- and childhood-onset GH deficiency.⁴ Highlights of NICE treatment recommendations for patients with GHD are summarized as follows:

- Initiate GH treatment only if severe GHD, impaired QoL, or already receiving treatment for any other pituitary hormone deficiencies.⁴

- Re-assess GH treatment 9 months after initiation and discontinue if there is an insufficient improvement in QoL.⁴
- Patients who develop GH deficiency in early adulthood, after linear growth is completed but before the age of 25 years, should be given GH treatment until adult peak bone mass has been achieved.⁴
- After adult peak bone mass has been achieved, the decision to continue GH treatment should be based on initiation criteria (severe GHD, impaired QoL, or already receiving treatment for any other pituitary hormone deficiencies).⁴
- Initiate GH treatment for GHD only by a qualified specialist and continue in primary care only with an agreed upon shared-care protocol.⁴

Strengths and limitations of the evidence were not provided.

Additional Guidelines for Clinical Context:

American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) Guidelines for Management of Growth Hormone Deficiency in Adults and Patients Transitioning from Pediatric to Adult Care²²

A 2019 practice guideline on the management of growth hormone deficiency in adults and patients transitioning from pediatric to adult care was released by American Association of Clinical Endocrinologists and American College of Endocrinology.²² The guideline used a clinical practice guideline algorithm and checklist process detailed in a previous publication, but no comprehensive search strategy was recorded.²² The authors, including the Task Force Chair, revealed numerous conflicts of interest with various manufacturers and no systematic methods were detailed in the evidence search strategies. Therefore, the results are included solely for clinical context purposes.²²

Recommendations were assigned a grade (A=very strong; B=strong; C=not strong; D=primarily based on expert opinion) with a numerical value based on best level of evidence (LOE): 1=strong [e.g. RCTs and meta-analysis of only RCTs], 2=intermediate [e.g. non-randomized or observational studies], 3=weak [e.g. case reports and economic studies], or 4=no evidence [e.g. theory or opinion].²² The strongest recommendations in clinically important areas based on evidence from RCTs or meta-analysis of only RCTs may be summarized as follows:

Childhood-Onset GHD (CO-GHD) versus Adult-onset GHD (AO-GHD)

- Clinicians should recognize etiology of GHD as CO-GHD occurs during the developmental years and adults with CO-GHD may have had a longer duration of being GH-deficient than their AO-GHD counterparts (Grade A; LOE 1).

Continuing GH Replacement Therapy

- Adults with childhood-onset GHD caused by structural pituitary abnormalities or brain tumors should be followed up closely during transition due to more risk markers than those with adult-onset GHD (Grade A; LOE 1).²²
- Resume GH replacement therapy in patients with confirmed persistent GHD (e.g. determined by GH-stimulation testing, or in those with multiple pituitary hormone deficiencies and structural pituitary abnormalities or brain tumors and/or genetic mutations) during transition period after final height achieved due to evidence of long-term improvement in body composition, bone health, quality of life, and lipid metabolism in adulthood (Grade A; LOE 1).²²

Adult GHD Testing

- GH-stimulation test(s) is recommended during transition for patients with idiopathic isolated GHD and serum IGF-1 SDS <0, when longitudinal growth is complete, and at least 1 month after discontinuation of pediatric GH therapy (Grade A; LOE 1).²²

- The insulin tolerance test (ITT) remains the gold-standard test to establish the diagnosis of adult GHD using a peak GH cut-point of 5 mg/L. The ITT is increasingly used less frequently in the U.S. because of safety concerns, laboriousness, potential to cause severe hypoglycemia, and contraindicated in certain patients, such as elderly patients and those with seizure disorders and cardiovascular or cerebrovascular disease. The glucagon-stimulation test (GST) could be considered as an alternative test (Grade B; LOE 1).²²

Monitoring GH Replacement Therapy

- Individualize GH therapy dosing independent of body weight, starting with a low dose, and gradually up-titrating the dose to normalize serum IGF-1 levels with the primary aim of minimizing the induction of side effects (Grade A; LOE 1).²²
- Initiate GH therapy using low GH dosages (0.1 to 0.2 mg/day) in GH-deficient patients with concurrent DM, obesity, older age, and previous gestational DM to avoid impairment of glucose metabolism. Higher GH therapy starting doses (0.3 to 0.4 mg/day) are advised in nondiabetic young adults <30 years of age and women on oral estrogen therapy (Grade A; LOE 1).²²
- After starting on GH therapy, it is recommended to follow patients at 1- to 2-month intervals initially, increasing the GH dose in increments of 0.1 to 0.2 mg/day based on the clinical response, serum IGF-1 levels, side effects, and individual considerations. Once maintenance doses are achieved, follow-up at approximately 6- to 12-month intervals. Shorter follow-up time intervals and smaller dose increments can be implemented especially for the elderly, and those with other comorbidities, such as DM (Grade A; LOE 1).²²
- Monitor for interactions of GH with glucocorticoid and/or thyroid hormones. Dose adjustments for these agents may be required especially upon GH therapy initiation; less frequent monitoring may be undertaken once stable doses established unless symptoms develop, or radiotherapy administered (Grade B; LOE 1).²²

GH Replacement Side Effects

- Reduce dose or stop therapy to manage fluid retention; use lower doses in obese and older patients who are more susceptible to side effects (Grade A; LOE 1).²²
- Avoid use of high doses of GH therapy to minimize side-effects and target serum IGF-1 levels within the age-adjusted laboratory reference range (IGF-1 SDS between -2 and + 2) (Grade A; LOE 1).²²

Long-term Safety of GH Therapy

- If DM develops during GH therapy, or if GH therapy is considered in patients with concurrent DM, use of low-dose GH therapy, and addition and/or adjustments in antidiabetic medications are suggested. If DM worsens, it is reasonable to initiate or increase the doses of antidiabetic therapy or discontinue GH therapy and optimize treatment of DM first before considering resuming GH therapy in these patients (Grade B; LOE 1).²²

GH Therapy for Sports and Anti-Aging

- Drug testing of GH abuse via urine sampling not accurate or reliable, and 24-hour blood sampling not practical nor feasible in sports setting (Grade A; LOE 1).²²
- In the U.S., off-label distribution or marketing of GH for the enhancement of athletic performance or to treat aging or aging-related conditions is illegal and punishable by imprisonment. Under no circumstances should GH be prescribed for sports or for “anti-aging” purposes (Grade A; LOE 1).²²

Hormonal Replacement in Hypopituitarism in Adults: An Endocrine Society Clinical Practice Guideline⁵⁴

The Endocrine Society created practice guidelines for hormonal replacement in hypopituitarism. The guidelines were developed through a Clinical Guidelines Subcommittee Task Force.⁵⁴ Strength of recommendations were either strong (1) or weak (2), while quality of evidence graded on a 4-point scale as high- (4+), moderate- (3+), low- (2+) or very low-quality (1+).⁵⁴ Details regarding the search strategy or the criteria for the evidence selection was not described.⁵⁴ Multiple

authors including the Task Force Chair had significant conflicts of interest and it was not disclosed whether the views or interests of the funding body influenced the final recommendations.⁵⁴ Therefore, the guidelines will be used for clinical context only. In GHD therapy, there following were strong recommendations with at least moderate quality evidence:

- In patients with suspected GH deficiency (GHD), we recommend GH stimulation testing. Single GH measurements are not helpful. (Strong recommendation; moderate quality evidence)⁵⁴
- Offer GH replacement to those patients with proven GHD and no contraindications. We recommend a starting dose of 0.2– 0.4 mg/d for patients younger than 60 years and 0.1– 0.2 mg/d for patients older than 60 years. (Strong recommendation; moderate quality evidence)⁵⁴

Endocrine Society 2011 – Evaluation and Treatment of Adult GHD¹³

The Endocrine Society published practice guidelines developed from a Clinical Guidelines Subcommittee Task Force for guidance on the evaluation and treatment of adult GHD.¹³ The Task Force used the GRADE system to describe the strength of recommendations and the quality of evidence.¹³ Strength of recommendations were denoted as strong (1) or weak (2), while quality of evidence was graded on a 4-point scale which ranged from high quality (4+) to very low quality (1+).¹³ Details regarding the search strategy or the criteria for the evidence selection was not described. Multiple authors including the Task Force Chair had significant conflicts of interest and it was not disclosed whether the views or interests of the funding body influenced the final recommendations.¹³ Therefore, the guidelines will be used for clinical context only.

Table 6: Endocrine Society Clinical Recommendations for Evaluation and Treatment of Adult GHD (modified)¹³

Recommendation	Strength	Quality of Evidence
GHD Definition in Adults		
Patients with childhood-onset GHD who are candidates for GH therapy after reaching adult height should be retested for GHD (unless deficiencies from known mutations or structural pituitary lesions/damage)	Strong	High
Adult patients with structural hypothalamic/pituitary disease, surgery or irradiation in these areas, head trauma, or evidence of other pituitary hormone deficiencies be considered for evaluation for acquired GHD	Strong	High
Use two GH stimulation tests before making the diagnosis of idiopathic GHD	Weak	Very low
GHD Diagnosis		
Insulin tolerance test (ITT) and the GHRH-arginine test have sufficient sensitivity and specificity to establish the diagnosis of GHD. However, GHRH-arginine test may be misleading in those with clearly hypothalamic causes of suspected GHD	Strong	High
Use glucagon stimulation test to diagnose GHD when GHRH test not available and ITT is either contraindicated or not practical	Weak	Low
A low IGF-I level at least 1 month off GH therapy is sufficient documentation of persistent GHD without additional provocative testing	Strong	Moderate
A normal IGF-I level does not exclude the diagnosis of GHD but makes provocative testing mandatory to make the diagnosis of GHD	Strong	High
A low IGF-I level, in the absence of catabolic conditions, is strong evidence for significant GHD and may be useful in identifying patients who may benefit from treatment and therefore require GH stimulation testing	Strong	Low
Deficiencies in three or more pituitary axes strongly suggests the presence of GHD, and in this context, provocative testing is optional	Strong	Moderate

GHD Consequences and GH Treatment Benefits		
GH therapy of GH-deficient adults offers significant clinical benefits in body composition and exercise capacity	Strong	Moderate
GH therapy of GH-deficient adults offers significant clinical benefits in skeletal integrity	Weak	Low
After documentation of persistent GHD, GH therapy should be continued after completion of adult height to obtain full skeletal/muscle maturation during the transition period	Strong	Low
GH therapy of GH-deficient adults improves several cardiovascular surrogate outcomes (e.g. lipoprotein metabolism) but tends to increase insulin resistance	Weak	Low
GH has not yet been shown to improve mortality	Weak	Very Low
GH therapy of GH-deficient adults improves the quality of life of most patients	Weak	Low
Side Effects and Risks Associated with GH Therapy		
GH treatment is contraindicated in the presence of an active malignancy	Strong	Very Low
GH treatment in patients with diabetes mellitus may require adjustments in antidiabetic medications	Strong	Moderate
Thyroid and adrenal function should be monitored during GH therapy of adults with GHD	Weak	Low
Treatment Regimens		
GH dosing regimens should be individualized rather than weight-based; start with low doses titrate to clinical response, side effects, and IGF-I levels	Strong	High
GH dosing should take gender, estrogen status, and age into consideration	Strong	High
During GH treatment, patients should be monitored at 1- to 2-month intervals during dose titration and semiannually thereafter with a clinical assessment and an evaluation for adverse effects, IGF-I levels, and other parameters of GH response	Weak	Low

After review, 2 additional guidelines were excluded due to poor quality.^{55,56}

Randomized Controlled Trials:

A total of 1775 citations were manually reviewed from the initial literature search. After further review, all citations were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), or outcome studied (eg, non-clinical).

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Appendix 1: Current Preferred Drug List

Generic	Brand	Form	PDL
somatropin	GENOTROPIN	CARTRIDGE	Y
somatropin	GENOTROPIN	SYRINGE	Y
somatropin	NORDITROPIN FLEXP	PEN INJCTR	Y
somatropin	NUTROPIN AQ NUSPIN	PEN INJCTR	N
somatropin	HUMATROPE	CARTRIDGE	N
somatropin	HUMATROPE	VIAL	N
somatropin	NORDITROPIN	CARTRIDGE	N
somatropin	OMNITROPE	CARTRIDGE	N
somatropin	OMNITROPE	VIAL	N
somatropin	SAIZEN	VIAL	N
somatropin	SAIZEN-SAIKENPREP	CARTRIDGE	N
somatropin	SEROSTIM	VIAL	N
somatropin	ZOMACTON	VIAL	N
somatropin	ZORBTIVE	VIAL	N
lonapegsomatropin-tcgd	SKYTROFA	CARTRIDGE	N

Appendix 2: Clinical Pharmacology and Pharmacokinetics. ^{41-49,53}

Somatotropin Mechanism of Action: Polypeptide hormone produced through recombinant DNA technology that promotes skeletal, visceral and general body growth, stimulates protein anabolism, and affects fat and mineral metabolism.						
Formulation (manufacturer)	Absorption	Metabolism/ Excretion	Half life (hours)	C-max	AUC	Vd
Genotropin ^{®43} (Pfizer, Inc)	80%	Catabolism in both liver and kidneys; 0.3 L/hr/kg	3	17.4 (± 9.2) ng/mL to 23.0 (± 9.4) ng/mL	Not reported	1.3 L/kg
Norditropin ^{®45} (Novo Nordisk, Inc.)	N/A	Liver and kidneys; N/A	7-10	17.1 (±10.0) ng/mL to 13.8 (±5.8) ng/mL	Not reported	43.9 L
Nutropin AQ ^{® 46} (Genentech, Inc.)	81%	Liver and kidneys; 116–174 mL/hr/kg	2.1 ± 0.43	71.1 µg/L	677 µg•hr/L	50 mL/kg
Humatrop ^{®44} (Lilly USA, LLC.)	75%	Liver and kidneys; 0.18 L/hr/kg	3.8	63.3 ng/mL	Not reported	0.96 L/kg
Omnitrop ^{®47} (Sandoz, Inc.)	N/A	Liver and kidneys; 0.14 L/hr•kg	2.5-2.8	72-74 mcg/L	Not reported	Not reported
Zomacton ^{®49} (Ferring Pharmaceuticals, Inc.)	70%	Liver and kidneys; 0.133 L/min (intravenous)	2.3	38.1 ng/mL	Not reported	53.3 L
Saizen ^{®48} (EMD Serono, Inc.)	70 to 90%	Liver and kidneys; 14.6 ± 2.8 L/hr	2	Not reported	Not reported	12.0 ± 1.08 L
Serostim ^{®41} (EMD Serono, Inc.)	70 to 90%	Liver and kidneys; 0.0015 ± 0.0037 L/h	4.28 ± 2.15	Not reported	Not reported	12.0 ± 1.08 L
Zorbtive ^{®42} (EMD Serono, Inc.)	70 to 90%	Liver (minor); Primarily kidney; 0.0015 ± 0.0037 L/h.	4	Not reported	Not reported	12.0 ± 1L

Drug Safety Warnings/Precaution: ^{41-49,53}

- Growth hormone deficiency due to intracranial lesion
- Diabetes (may cause insulin resistance)
- Pituitary hormone deficiency or hypoadrenalism
- Thyroid dysfunction
- Fluid retention: Fluid retention may occur in adults; manifestations generally transient and dose dependent.
- Hypersensitivity: Serious systemic hypersensitivity reactions, including anaphylactic reactions and angioedema, have been reported.

- Intracranial hypertension: Intracranial hypertension with headache, nausea, papilledema, visual changes, and/or vomiting has been reported; symptoms usually occur within the first 8 weeks of therapy and signs and symptoms of intracranial hypertension may rapidly resolve after discontinuation or reduction of dose. Fundoscopic examination prior to initiation of therapy and periodically thereafter is recommended. Patients with Turner syndrome, chronic renal impairment and Prader-Willi syndrome may be at increased risk for intracranial hypertension.
- Lipoatrophy: Lipoatrophy has been reported at injection sites when used at the same site for a prolonged period. Ensure proper injection technique and rotate injection sites.
- Neoplasm: Increased risk of malignancy progression in patients with active malignancy; preexisting malignancy should be inactive and treatment complete prior to initiating therapy. Patients with HIV and pediatric patients with short stature (genetic cause) have increased baseline risk of developing malignancies; consider risk/benefits prior to initiation of therapy and monitor these patients carefully. Rule out pituitary tumor (or other brain tumors) prior to initiation of treatment because growth hormone deficiency may be an early sign of the presence of these tumors.
- Pancreatitis: Has been rarely reported; incidence in children with Turner syndrome may be greater than adults.
- Slipped capital femoral epiphyses: Patients with endocrine disorders (including growth hormone deficiency and Turner syndrome) or in patients undergoing rapid growth may develop slipped capital femoral epiphyses more frequently; evaluate any child with new onset of limp or with complaints of hip/knee pain.

Use in Specific Populations:^{41-49,53}

- Elderly: Patients with advanced age may be more sensitive to the actions of somatropin; consider lower starting doses and smaller dose increments.
- Pediatric:
 - Failure to increase growth rate, especially during the first year of therapy, indicates need for close assessment of adherence and evaluation for other causes of growth failure, such as hypothyroidism, undernutrition, advanced bone age, and antibodies to recombinant human growth hormone.
 - Childhood cancer survivors may have increased risk of intracranial tumor development
- Renal transplant recipients: use of Nutropin AQ is not indicated in patients with functioning renal allografts.
- Effects in Pregnancy/Lactation: Safety not established
- Adrenal insufficiency: Patients who have or are at risk for pituitary hormone deficiency(ies) may be at risk for reduced serum cortisol levels and/or unmasking of central (secondary) adrenal insufficiency with somatropin therapy; patients with previously diagnosed adrenal insufficiency may require increased glucocorticoid doses. Excessive glucocorticoid therapy may inhibit the growth-promoting effects of somatropin in children.
- Chronic kidney disease: Slipped capital femoral epiphysis or avascular necrosis of the femoral head may be seen in children with advanced renal osteodystrophy. Obtain x-rays of the hip prior to initiating somatropin in chronic kidney disease patients; be alert to the development of a limp or complaints of hip or knee pain.
- Hypothyroidism: Patients who have or are at risk for pituitary hormone deficiency(ies) may be at risk for central (secondary) hypothyroidism; patients with Turner syndrome have an increased risk of developing autoimmune thyroid disease and primary hypothyroidism. Untreated/undiagnosed hypothyroidism may decrease response to somatropin therapy, particularly the growth response in children.
- Prader-Willi syndrome: Sudden death has been reported in pediatric patients with Prader-Willi syndrome following the use of growth hormone. The reported fatalities occurred in patients with one or more risk factors, including severe obesity, history of upper airway obstruction or sleep apnea, respiratory impairment, or unidentified respiratory infection; male patients may be at greater risk. Treatment interruption recommended for patients who show signs of upper airway obstruction, including the onset of, or increased, snoring and/or new-onset sleep apnea. Unless patients with Prader-Willi syndrome also have a diagnosis of growth hormone deficiency, use is not indicated for the long-term treatment of pediatric patients who have growth failure due to Prader-Willi syndrome.

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- Scoliosis: Progression of scoliosis may occur in children experiencing rapid growth.
 - Turner syndrome: Patients with Turner syndrome are at increased risk for otitis media and other ear/hearing disorders, autoimmune thyroid disease, primary hypothyroidism, and cardiovascular disorders (eg, hypertension, aortic aneurysm/dissection, stroke).

Drug Interactions:^{41-49,53}

- Antidiabetic Agents: Hyperglycemia-Associated Agents may diminish the therapeutic effect of Antidiabetic Agents.
- Corticosteroids (Systemic – prednisone, cortisone, etc): May diminish the therapeutic effect of Growth Hormone Analogs and Growth Hormone Analogs may decrease serum concentrations of the active metabolite(s) of Corticosteroids.
- Estrogen Derivatives: May diminish the therapeutic effect of Growth Hormone Analogs. Management: Initiate somapacitan at 2 mg once weekly in patients receiving oral estrogens. Monitor for reduced efficacy of growth hormone analogs; increased doses may be required.
- Macimorelin: Products that affect Growth Hormone may diminish the diagnostic effect of Macimorelin.
- Thyroid Products: Somatropin may diminish the therapeutic effect of Thyroid Products

Boxed Warnings:

There are no known boxed warnings for somatropin products.

Risk Evaluation Mitigation Strategy (REMS) Programs:

There are no known REMS programs for somatropin products.

Contraindications:^{41-49,53}

- Hypersensitivity to somatropin or any component of the formulation
- Growth promotion in pediatric patients with closed epiphyses
- Acute critical illness due to increased complications/mortality following open heart or abdominal surgery
- Multiple accidental trauma, or acute respiratory failure
- Active neoplasia
- Diabetic retinopathy
- Pediatric patients with Prader-Willi syndrome
 - who have severe obesity or severe respiratory impairment (Genotropin, Humatrope, Norditropin, Nutropin AQ, Omnitrope, Saizen, Zomacton)
 - who have a history of upper airway obstruction or sleep apnea (Genotropin, Humatrope, Norditropin, Nutropin AQ, Omnitrope, Zomacton)

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) ALL 1946 to December 2, 2022

1 somapacitan.mp. /23

2 somatropin.mp. /310

3 somatotropin.mp. /8265

4 humatrope.mp. /29

5 nutropin.mp. /26

6 serostim.mp. /39

7 zomacton.mp. /6

8 saizen.mp. /39

9 norditropin.mp. /97

10 zorbtive.mp. /3

11 genotropin.mp. /123

12 omnitrope.mp. /56

13 human growth hormone.mp. or Human Growth Hormone/ 20417

14 growth hormone.mp. or Growth Hormone/ 77150

15 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14/ 77869

16 limit 15 to (english language and full text and humans and (clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or guideline or meta analysis or practice guideline or randomized controlled trial or "systematic review")) /3038

17 Adults.mp. or Adult/ 5755856

18 16 and 17 /1775

Appendix 4: Key Inclusion Criteria

Population	Adults with GHD, SBS, HIV Associated Wasting or Cachexia, or Prader-Willi Syndrome
Intervention	Growth hormone
Comparator	Placebo or active treatment
Outcomes	Mortality, metabolic and cardiovascular risk, body composition, bone structure, and quality of life
Timing	NA
Setting	Outpatient

Growth Hormones

Goal(s):

- Restrict use of growth hormone (GH) in adults for where there is medical evidence of effectiveness and safety and supported by expert guidelines.

NOTE: Treatment with GH in children and adolescents (for any indication) are evaluated for medical appropriateness and medical necessity on a case-by-case basis.

Length of Authorization:

- Up to 12 months

Requires PA:

- All GH products require prior authorization for OHP coverage. Treatment is not included for use in antiaging therapy or to enhance athletic ability or for body building.

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Table 1. Pediatric and Adults FDA Approved Indications for Growth Hormone

	somatropin									Lonapeg-somatropin
	Genotropin	Norditropin	Nutropin AQ	Humatrope	Omnitrope	Saizen	Serostim	Zorbtive	Zomacton	Skytrofa
Pediatric Indications										
GHD	X	X	X	X	X	X			X	X
Prader-Willi Syndrome	X	X			X					
Noonan Syndrome		X								
Turner Syndrome	X	X	X	X	X				X	

Idiopathic Short Stature	X	X	X	X	X				X	
SHOX Deficiency				X					X	
Growth Failure Secondary to CKD			X							
Small for Gestational Age	X	X		X	X				X	
HIV Associated Cachexia							X			
Adult Indications										
GHD	X	X	X	X	X	X			X	
HIV Associated Cachexia							X			
SBS								X		

Abbreviations: CKD = chronic kidney disease; FDA = Food and Drug Administration; GHD = growth hormone deficiency; HIV = human immunodeficiency virus; SBS = short bowel syndrome; SHOX = Short stature homeobox-containing gene

Initial Approval Criteria		
1. What is the diagnosis being treated?	Record ICD10 code	
2. Is the diagnosis promotion of growth delay in a child with 3 rd degree burns?	Yes: Document and send to DHS Medical Director for review and pending approval	No: Go to #3

Initial Approval Criteria

<p>3. Is the request for one of the conditions listed below?</p> <p>For children and adolescents age 17 and younger</p> <ul style="list-style-type: none"> • Growth hormone deficiency (GHD) • Prader-Willi syndrome • Noonan syndrome • Turner syndrome • Idiopathic Short Stature • Growth Failure secondary to chronic kidney disease (CKD) • Small for gestational age • Short stature homeobox-containing (SHOX) gene deficiency • HIV Associated Cachexia <p>For adults age 18 years and older</p> <ul style="list-style-type: none"> • Growth hormone deficiency (GHD) • HIV Associated Cachexia • Short Bowel Syndrome (SBS) 	<p>Yes: Go to #4</p>	<p>No: For current age \geq 21 years: Pass to RPh. Deny; medical appropriateness</p> <p>For current age $<$ 21 years: Go to #5.</p>
<p>4. Has the provider documented goals of therapy and objective baseline assessment (e.g., quality of life, exercise capacity, height, body composition improvements, etc)?</p> <p>Note: these same assessments should be evaluated for continuation of treatment.</p>	<p>Yes: Go to #6</p>	<p>No: Pass to RPh. Deny; medical appropriateness</p>
<p>5. Is there documentation that the condition is of sufficient severity that it impacts the patient's health (e.g., quality of life, function, growth, development, ability to participate in school, perform activities of daily living, etc)?</p>	<p>Yes: Go to #11</p>	<p>No: Pass to RPh. Deny; medical appropriateness</p>

Initial Approval Criteria		
6. Is this a request for initiation of growth hormone therapy?	Yes: Go to #7	No: Go to Renewal Criteria
7. Is the agent being prescribed by, or in consultation with, an appropriate specialist (e.g., an endocrinologist for adults or a pediatric endocrinologist or pediatric nephrologist for children/adolescents)?	Yes: Go to #8	No: Pass to RPh. Deny; medical appropriateness
8. Is the request for a pediatric patient with Prader-Willi syndrome who also has: <ul style="list-style-type: none"> • Severe obesity? Or • A history of upper airway obstruction or sleep apnea? Or • Severe respiratory impairment? <p>Note: Recombinant somatropin is contraindicated in these patients due to the risk of sudden death.</p>	Yes: Pass to RPh. Deny; medical appropriateness	No: Go to #9
9. Is the request for treatment of hypopituitarism (E23.0)?	Yes: Go to #10	No: Go to #11

Initial Approval Criteria

<p>10. Is the growth hormone deficiency confirmed by a negative response to a growth hormone stimulation test (eg, serum GH levels of <5 ng/ml on stimulation testing with either glucagon or insulin)?</p> <p><u>OR</u></p> <p>Is there evidence that the patient had the pituitary removed/destroyed or has had panhypopituitarism since birth?</p>	<p>Yes: Go to #11</p>	<p>No: Pass to RPh. Deny; medical appropriateness</p>
<p>11. Is the request for a preferred product OR has the patient failed to have benefit with, or have contraindications or intolerance to, at least 2 preferred products?</p> <p>Message: Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics Committee.</p>	<p>Yes: Approve for up to 12 months</p>	<p>No: Go to #12</p>
<p>12. Will the prescriber change to a preferred product that is medically appropriate for the condition?</p> <p><u>Message:</u></p> <ul style="list-style-type: none"> Preferred products are reviewed for comparative effectiveness and safety by the Oregon Pharmacy and Therapeutics (P&T) Committee. 	<p>Yes: Inform prescriber of covered alternatives in class and approve for up to 12 months.</p>	<p>No: Go to #13</p>
<p>13. Is the request for lonapegsomatropin?</p>	<p>Yes: Go to #14</p>	<p>No: Approve for up to 6 months</p>
<p>14. Is the request for a pediatric patient 1 year or older with a body weight ≥ 11.5 kg?</p>	<p>Yes: Approve for up to 6 months</p>	<p>No: Pass to RPh. Deny; medical appropriateness.</p>

Renewal Criteria

1. Document approximate date of initiation of therapy and diagnosis (if not already done).		
2. Was treatment with this agent initiated in a patient prior to reaching adulthood (<18 years of age) to improve growth velocity or height?	Yes: Go to #3	No: Go to #5
3. Is growth velocity 2 cm or more per year?	Yes: Go to #6	No: Go to #4
4. Is there documentation that benefits of therapy continue to outweigh risks? When main goal of therapy is growth promotion in children to normalize final adult height, current guidelines recommend discontinuation of treatment once growth velocity is less than 2-2.5 cm per year. Risks, benefits, and goals of therapy should be reassessed in patients whose epiphyses are closed.	Yes: Go to #5	No: Pass to RPh. Deny; medical appropriateness.
5. Is there documentation of improvement from baseline as assessed by the prescribing provider?	Yes: Go to #6	No: Pass to RPh. Deny; medical appropriateness.
6. Is the product requested preferred?	Yes: Approve for up to 12 months	No: Go to #7
7. Will the prescriber consider a change to a preferred product? <u>Message:</u> <ul style="list-style-type: none"> Preferred products are reviewed for comparative effectiveness and safety by the Oregon Pharmacy and Therapeutics (P&T) Committee. 	Yes: Inform prescriber of covered alternatives in class and approve for up to 12 months	No: Approve for up to 6 months

P&T Review: [4/23 \(DE\)](#); 12/22;12/21; 6/21;11/18; 9/17; 9/16; 9/15; 9/14; 9/10; 5/10; 9/08; 2/06; 11/03; 9/03
 Implementation: 1/1/19; 10/13/16; 1/1/11, 7/1/10, 4/15/09, 10/1/03, 9/1/06; 10/1/03