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Medication Policy Manual

Policy No: dru015

Topic: Growth Hormone

Date of Origin: January 1996

- Accretropin[®], somatropin
- Genotropin[®], somatropin
- Humatrope[®], somatropin
- Norditropin[®], somatropin
- Nutropin[®], somatropin
- Nutropin AQ[®], somatropin
- Omnitrope[®], somatropin
- Saizen[®], somatropin
- Serostim[®], somatropin
- Serostim LQ[®], somatropin
- Tev-Tropin[®], somatropin
- Zorbtive[®], somatropin

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Next Review Date: July 2010

IMPORTANT REMINDER

This Medical Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medical policy is to provide a guide to coverage. Medical Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Human growth hormone, also known as somatotropin, is produced in the anterior lobe of the pituitary gland. This hormone plays an important role in growth, metabolism, and maintenance of body fat, muscle and bone.

Policy/Criteria

- I.** Most contracts require prior authorization approval of human growth hormone prior to coverage. Nutropin, Nutropin AQ, or Saizen may be considered medically necessary when one of the following criteria (A or B) are met.

Non-Preferred human growth hormone products may be considered medically necessary when either of the following criteria (A or B) are met AND when a preferred growth hormone product was not tolerated (see Appendix 2).

- A.** Initial authorization criteria for children

- 1.** For all indications, growth hormone must be prescribed by a pediatric endocrinologist, pediatric nephrologist or trauma/burn surgeon.

AND

- 2.** When the corresponding marked criteria in Table 1 are met for one of the following conditions:
 - a.** Growth hormone deficiency (GHD).
 - b.** Prader-Willi Syndrome (PWS) with documented biochemical growth hormone deficiency (GHD).
 - c.** Turner's Syndrome.
 - d.** Noonan's Syndrome
 - e.** Chronic renal insufficiency (CRI).
 - f.** Pediatric burn patients.

Table 1 Initial Authorization in Pediatrics	Growth Hormone Deficiency	Pediatrics: (not GHD related)		
		Turner's & Nonnans's Syndrome	CRI	Pediatric Burn
Approval Criteria	GHD			
<p>1. Documented Biochemical Growth Hormone Deficiency (A or B or C or D or E)</p> <p>A. Two growth hormone (GH) stimulation tests below 10 ng/ml (microgram/L).</p> <p>OR</p> <p>B. At least one GH stimulation test level less than 15 ng/ml, AND IGF-1 and IGF-BP3 levels below normal for bone age and sex.</p> <p>OR</p> <p>C. One GH stimulation test below 10 ng/ml (microgram/L) is sufficient for children with defined CNS pathology, history of irradiation or genetic conditions associated with GHD.</p> <p>OR</p> <p>D. GH stimulation tests, IGF-1 or IGF-BP3 levels are not needed for GHD if multiple pituitary hormone deficiencies exist (at least two other in addition to GHD).</p> <p>OR</p> <p>E. GH stimulation tests, IGF-1 or IGF-BP3 levels are not needed for congenital GHD (low GH levels detected during acute episode of hypoglycemia).</p>	X			
<p>2. Open Growth Plates</p> <p>An initial bone age; demonstration of open growth plates.</p>	X	X	X	
<p>3. Short Stature / Growth failure - (Subnormal Growth Rate)¹ (A or B or C)</p> <p>A. Height is less than the minimum percentile specified for age/sex.</p> <p>OR</p> <p>B. When height is below the minimum percentile for age/sex and untreated growth velocity with a minimum of 1 year of growth data is below the 25th percentile.</p> <p>OR</p> <p>C. If GHD criteria under 1E are met, growth failure/short stature is not needed.</p>	X	X	X	
	Height below the 3 rd percentile	Height below the 10 th percentile		
	Height below the 5 th percentile Growth velocity is below 25 th percentile for age/sex		Height below the 5 th percentile Growth velocity is below 25 th percentile for age/sex	
<p>4. Requires weekly dialysis or chronic renal insufficiency defined as glomerular filtration rate (GFR)* < 75 ml/min / 1.73 m². *(See Schwartz formula to calculate GFR in Appendix 1)</p>			X GFR* less than 75 ml/min / 1.73 m ²	
<p>5. Burns over at least 40% of total body surface area.</p>				X

B. Initial authorization criteria for adults (1 or 2)

1. The diagnosis of growth hormone deficiency with panhypopituitarism when one of the following criteria (a or b) is met:

a. Two pituitary hormone deficiencies (other than growth hormone) requiring hormone replacement, such as TSH, ACTH, Gonadotropins, and ADH, **and** both of the following in i and ii.

i. At least one known cause for pituitary disease or a condition affecting pituitary function, including pituitary tumor, surgical damage, hypothalamic disease, irradiation, trauma, or infiltrative diseases (histoplasmosis, Sheehan syndrome, autoimmune hypophysitis, or sarcoidosis) is documented.

AND

ii. ONE provocative stimulation less than 5 ng/ml.

The insulin tolerance test is the preferred testing method, but other secretagogues, such as arginine, GHRH, clonidine and L dopa are acceptable.

OR

b. Three pituitary hormone deficiencies (other than growth hormone) requiring hormone replacement **AND** an IGF-1 level below 80 ng/ml.

OR

2. The diagnosis of Short Bowel Syndrome when all of the following criteria in a, b, and c are met:

a. Ability to ingest solid food.

AND

b. Dependent on parenteral nutrition at least five days per week to provide at least 3,000 calories per week.

AND

c. Chart notes to indicate dietary needs and goals have been addressed.

II. Administration and Authorization Period:

A. Regence considers subcutaneously administered growth hormone to be a self-administered medication.

- B. When prior authorization is approved, growth hormone therapy (as preferred growth hormone products Nutropin, Nutropin AQ, or Saizen) may be authorized for the period defined in Table 2.

Table 2	
Indication:	Authorization Period
Pediatric GHD, Turner's & Noonan's Syndrome, CRI, PWS,	Growth hormone may be authorized for a period of up to 12 months, or until maximum bone age* is met, whichever is shorter. *(In males up to 16 ^{0/12} years of age; in females, up to 14 ^{0/12} years of age)
Pediatric Burn	Growth hormone may be authorized for a period of up to 12 months. No further authorization shall be given.
Adult GHD	Growth hormone may be authorized for a period of up to 12 months.
Short Bowel Syndrome	Growth hormone may be authorized for a period of up to 4 weeks. No further authorization shall be given.

- C. Authorization shall be reviewed at least every 12 months to confirm that current medical necessity criteria for the following conditions in Table 3 are met:

Table 3	Continued Authorization Criteria		
Indication:	Growth Velocity	Bone age	Requires weekly dialysis-or CRI *
Pediatric GHD, Turner's Syndrome, Noonan's Syndrome, PWS	greater than 2.5 cm/year	Males: not to exceed 16 ^{0/12} years of age, obtain annually when chronologic age reaches 15. Females: not to exceed 14 ^{0/12} years of age, obtain annually when chronologic age reaches 13.	N/A
CRI (chronic renal insufficiency)	greater than 2.5 cm/year	Males: not to exceed 16 ^{0/12} years of age, obtain annually when chronologic age reaches 15. Females: not to exceed 14 ^{0/12} years of age, obtain annually when chronologic age reaches 13.	* glomerular filtration rate (GFR) less than 75 ml/min / 1.73 m ² . (See Schwartz formula to calculate GFR in Appendix 1)
Pediatric Burn	No further authorization shall be given.		
Adult GHD	No criteria needed for continued authorization.		
Short Bowel Syndrome	No further authorization shall be given.		

III. Growth hormone therapy is considered not medically necessary for the following conditions:

- A.** AIDS wasting
- B.** Idiopathic short stature
- C.** Short for gestational age/Intrauterine growth retardation

IV. Growth hormone therapy is considered investigational for all other indications, including, but not limited to:

- A.** Bloom syndrome
- B.** Chronic hepatitis B

- C. Combination treatment with mecasermin (Increlex).
- D. Constitutional growth delay
- E. Corticosteroid induced growth failure
- F. Crohn's disease
- G. Cystic fibrosis
- H. Diabetes
- I. Down syndrome
- J. Fanconi's syndrome
- K. Geriatric patients
- L. Juvenile Rheumatic Disease
- M. Patients with acute or chronic catabolic illness
- N. Prader-Willi Syndrome without documented biochemical growth hormone deficiency

Position Statement

Product Comparisons

- Growth hormone products are equally safe and effective, although they differ in how the medication is prepared and injected. ^[1-4, 73-78]
 - * All synthetic growth hormone products are considered therapeutically equivalent to endogenous growth hormone.
 - * Efficacy and safety are considered similar and the available products are considered interchangeable.
 - * No clinical trials have been conducted to evaluate the comparative efficacy or safety of available synthetic growth hormone products.
- Among the available growth hormone products, Nutropin, Nutropin AQ and Saizen cover the needs of most patients.

Policy Considerations

- This policy is based on the underlying premise that growth hormone may be considered medically necessary as a replacement for growth hormone deficiency.
- Growth hormone treatment is not medically necessary when used for treatment of short stature in the absence of a growth hormone deficiency or for the majority of other conditions in which growth hormone has not been shown to provide clinical benefits or improvements in functional impairment or long-term health outcomes.

Growth hormone Therapy in Children

CONDITIONS ASSOCIATED WITH GROWTH HORMONE DEFICIENCY

- Many clinical trials using growth hormone support its efficacy to stimulate linear growth and improve body composition in children with conditions of underlying growth hormone deficiency (GHD, PWS).^[1-4, 6-8, 22-23, 33, 35]
- Growth hormone stimulation tests are needed to rule out other causes of short stature that may not be considered medically necessary under this policy.

CONDITIONS NOT ASSOCIATED WITH GROWTH HORMONE DEFICIENCY

Prader Willi Syndrome

- Prader Willi syndrome is a genetic disorder characterized by obesity, hypotonia, feeding difficulties, developmental delay, short stature, and hypogonadism.^[85-88]
- Not all children with PWS have biochemical growth hormone deficiency (GHD). Unless patients with genetically confirmed Prader-Willi syndrome also have documented growth hormone deficiency, somatropin is not indicated.^[4,67,77]
- Growth hormone therapy in children with PWS and documented biochemical GHD has been shown to increase final height and improve body composition.

In children with PWS but without documented biochemical growth hormone deficiency (GHD) there is unreliable data that growth hormone therapy improves health outcomes.

- Growth hormone therapy may lead to short term improvement in neuromuscular function. However, the data re unreliable due to insufficient numbers of subjects and small treatment effect size.^[86]
- The long term effects on health outcomes and final height increases are unclear.

There is not consensus among experts in the treatment of children with PWS. The uncertain effectiveness of growth hormone therapy needs to be weighed against the risk of sudden death in PWS children who received growth hormone therapy.

Turner's & Noonan's Syndrome

- Short stature is almost universal in Turner's syndrome. Poor growth is evident *in utero* and further decelerates during childhood and at adolescence.^[35]
- Clinical trials reporting final adult height show children with Turner's syndrome treated with growth hormone achieved for final heights of approximately 146.0 cm – 147.5 cm (58.4 – 59.0 inches) compared to an untreated control group who achieved final height of 141.0 cm - 142.1cm (56.4 – 56.8 inches).^[4, 67, 71]

- The clinical significance of mean increases in adult height (i.e., 6.5 cm = 2.6 inches) reported in clinical trials is not known.
- Noonan syndrome is a genetic disorder that causes abnormal development of multiple parts of the body. The disease occurs in approximately 1 in 1,000 to 2,500 children.
- Defects in the KRAS and PTPN11 genes cause Noonan syndrome. About half of those affected by Noonan syndrome have a PTPN11 mutation. Persons with a defect in the KRAS gene have a severe or atypical form of Noonan syndrome. Problems with these genes cause certain proteins involved in growth and development to become overactive.
- Not all patients with Noonan syndrome have short stature; some will achieve a normal adult height without treatment.^[77]
- Children who had baseline cardiac disease judged to be significant enough to potentially affect growth were excluded from the study; therefore the safety of Norditropin® in children with Noonan syndrome and significant cardiac disease is not known.^[77]

Patients obtained a final adult height gain from baseline of 1.5 and 1.6 SDS estimated according to the national and the Noonan reference, respectively. A height gain of 1.5 SDS (national) corresponds to a mean height gain of 9.9 cm in boys and 9.1 cm in girls at 18 years of age.^[77]

Chronic Renal Insufficiency

- Growth retardation from chronic renal insufficiency has been attributed to growth-inhibiting metabolic derangements (such as acidosis, secondary hyperparathyroidism, and under nutrition).^[35]
- Data supports improved linear growth in children with chronic renal insufficiency until renal transplantation is possible.^[1, 2, 4, 32]
- Growth hormone treatment is considered after metabolic derangements are minimized and until renal transplantation is possible to improve renal function.^[35]

Pediatric Burn Patients

- Severely burned children ($\geq 40\%$ total body surface area) who received human growth hormone for 12 months after hospital discharge showed improved body composition and function requiring fewer reconstructive procedures when compared with placebo.^[84]
- Persistent benefits post 12 month of administration, increases in height, bone density, and IGF-1 levels. There were no early closure of plates, and no apparent adverse drug events 12 months after cessation of therapy. (These children were followed for 24 months post injury.) There is no evidence to support more than 12 months total of therapy.^[84]

Achondroplasia

- Achondroplasia is skeletal dysplasia with extreme, disproportionate short stature caused by a fibroblast growth factor receptor mutation. Average adult height 6 to 7 standard deviation (SD) below average. ^[81]
- Growth Hormone therapy in children with achondroplasia improves relative height during 4 years of therapy without having an adverse effect on trunk leg disproportion. Whether a gain in height of approximately 1.5 SD is worth 5 years of daily injection is debatable. ^[81]

Rheumatic disease, corticosteroid induced growth retardation

- Growth hormone therapy has been investigated in the treatment of corticosteroid induced growth failure in children with rheumatic disease is not conclusive to establish overall clinical benefits or safety. ^[83]

Idiopathic Short Stature

- Idiopathic short stature (ISS) is used to define children who are very short compared with others in their age cohort for unknown or hereditary reasons. By definition, children with ISS do not have a disease.
- Children with ISS are a heterogeneous group whose short stature cannot be explained by an underlying pathology and who have: 1) normal size for gestational age at birth; 2) normal body proportions; 3) no evidence of endocrine deficiency; 4) no evidence of chronic organic disease, no psychiatric disease or severe emotional disturbance, and normal food intake; and 5) growth velocity throughout the growth process may be slow or "normal". ^[63]
- There are no documented functional impairments associated with ISS.
- Growth hormone is used to overcome short stature in these children to achieve gains in their final adult height. ^[37, 63, 67-69]
- There are no well-designed trials to support that gains in adult height from growth hormone treatment significantly improve functional status or long-term health outcomes for these children.
- Clinical trials are limited to endpoint measurements showing growth hormone treatment in children with ISS have greater increases in final adult height over placebo; however, gains in adult height often varied in among studies because of differences in patient baseline characteristics, growth hormone doses used, and length of treatment. ^[37, 63, 67-69]
- High dose growth hormone treatment has been associated with a higher rate of bone maturation and an early onset of puberty with the paradoxical effect of shortening the growth period and premature closure of the epiphyses, which may not be followed by gain in final height. ^[63]
- While some growth hormone treated children with ISS are taller than non-treated individuals and above their predicted adult height, there is some existing evidence to suggest that these children remain relatively short when compared with peers of normal stature. ^[63, 67]

Short for Gestational Age/Intrauterine Growth Retardation

- Short for gestational age (SGA) with intrauterine growth retardation (IUGR) may or may not be associated with a growth hormone deficiency and occurs from a pathophysiologic process in utero that adversely affects fetal growth. ^[35]
- Children born SGA are defined as having birth weight of 2,500 grams at a gestational age of 40 weeks or birth weight and/or length below the 3rd percentile for gestational age. ^[35]
- Most children, including those with Russell-Silver variant of IUGR, usually achieve catch-up growth in length during the first 6 to 12 months of life; however, approximately 10% of children born SGA do not exhibit catch up growth by age two, defined as height below -2 SD. ^[65-66] If such children have not caught up by two years of age, they are unlikely to do so in the future.
- The need to use supraphysiologic doses of growth hormone to promote growth suggests children with SGA/IUGR may have partial growth hormone resistance. ^[35]
- Clinical trials show that growth hormone treatment results in a significant height gains compared to pre-treatment predictions and final adult height that is closer to their mid-parental target height. ^[9-11, 60-64]
- As with ISS, there is inadequate data to support gains in final adult height in children with SGA/IUGR with growth hormone therapy make a substantial clinical difference in functional status or long-term outcomes.

Growth hormone Therapy in Adults

ADULT GROWTH HORMONE DEFICIENCY

- The metabolic improvements and long-term benefit with continuation of GH treatment in GH-deficient adolescents transitioning to adulthood remains uncertain. ^[70]
- Life expectancy is significantly decreased in hypopituitary patients with adult growth hormone deficiency (AGHD). Cardiovascular disease is a common cause of death in such patients. ^[13-17, 31]
- Growth hormone in adults with AGHD has been shown to improve cardiovascular risk factors by decreasing visceral fat, increasing lean body mass, decreasing insulin resistance, and improving lipid profiles. ^[18, 25-30]
- Although long-term outcomes data are not yet available, growth hormone therapy may be considered of most benefit in patients with pan-hypopituitarism, for whom epidemiologic studies ^[13-17, 31] demonstrate increased cardiovascular mortality.
- Continuation of GH treatment in GH-deficient adolescents transitioning to adulthood.

ACUTE AND CHRONIC CATABOLIC ILLNESSES

- High doses of growth hormone in critically ill patients with wasting are associated with increased morbidity and mortality (44% in the growth hormone treated patients vs. 18% in placebo patients). ^[34]

- Clinical trials using growth hormone therapy to increase lean body mass in AIDS-wasting patients has been limited to 12 weeks of therapy. There are no data to support direct improvements in long-term outcomes, such as reduction in hospitalizations, decreased TPN utilization, and increased survival. [24, 39, 40]

SHORT BOWEL SYNDROME (SBS)

- According to the American Gastroenterological Association, [1] SBS is a disorder clinically defined by malabsorption, diarrhea, fluid and electrolyte disturbances, and malnutrition. The final common etiologic factor in all causes of SBS is the functional or anatomic loss of extensive segments of small, resulting in severely compromised absorptive capacity.
- Four open label studies [49, 57-59] suggest that short-term (1-4 weeks) use of growth hormone in TPN-dependent patients with SBS.
 - * These studies show that addition of growth hormone in TPN-dependent SBS patients may improve intestinal absorption of nutrients, [49,58] increase lean body mass, [57] and hasten weaning from TPN. [59]
 - * There is no evidence that shows that benefits are maintained beyond four weeks of treatment. [59]
- Although previously reported randomized controlled trials did not show short-term clinical benefit in using growth hormone (1-4 weeks) in patients with SBS, [52-56] they demonstrate the physiologic effects. This literature focused on the physiologic effects of growth hormone and failed to demonstrate clinical benefit.
- Growth hormone for patients with short bowel syndrome should be limited to patients receiving specialized nutritional support in conjunction with optimal management of short bowel syndrome. Specialized nutritional support may consist of a high carbohydrate, low fat diet adjusted for individual patient requirements. Optimal management may include dietary adjustments, enteral feedings, parenteral nutrition, fluid and micronutrient requirements. [82]
- One randomized, placebo controlled, double blind clinical trial demonstrated that 4 weeks of growth hormone treatment decreased parenteral nutrition needs from 5- 6 times to per week to 1-2 times per week and maintained this decrease over 90 days post growth hormone administration. [82]
 - * Normalized nutritional state and diet are key to achieving the adaptive response to growth hormone. [82]

OTHER OFF-LABEL CONDITIONS

- Preliminary studies using growth hormone in other medical conditions (including, but not limited to, cystic fibrosis, Down Syndrome, Noonan syndrome, glucocorticoid-dependent inflammatory bowel disease, and Crohn's disease) are not conclusive to establish overall clinical benefits or safety. [12,35,49-51,79]

- One study describes improvements of clinical symptoms with combined use of growth hormone and lactulose in the treatment and prevention of multiple organ dysfunction in patients with severe chronic hepatitis B. However, study design problems, lack of study details, and efficacy measures that were poorly defined, make this study of uncertain usefulness.^[72]
- Diabetes: A small randomized clinical trial performed in obese, type 2 diabetic patients with poor glycemic control treated with growth hormone showed a decrease in visceral fat. Growth Hormone therapy failed to influence fasting glucose or HbA_{1C}.^[80]

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Cross References

- Human Growth Hormone, BlueCross BlueShield Association Medical Policy, #5.01.06, Issue 4/2006.
- Self Administered Injectables dru110

Codes	Number	Description
CPT	90772	Injection (intramuscular or subcutaneous), therapeutic
HCPCS	J2941	Somatropin 1mg

Appendix 1: Calculation of GFR (ml/min/1.73m²) utilizing the Schwartz formula ^[36]

For weight < 10kg; GFR = 0.45 x height (cm) divided by Serum Cr (mg/dL)

For weight >= 10kg and <= 70kg; GFR = 0.55 x height (cm) divided by Serum Cr (mg/dL)

For weight > 70kg; GFR = [1.55 x age (years) + 0.5 x height (cm)] divided by Serum Cr (mg/dL)

Appendix 2: Preferred/Non-Preferred Growth Hormone Products

Preferred Products

Nutropin
 Nutropin AQ
 Saizen

Non-Preferred Products

Accretropin
 Genotropin
 Humatrope
 Norditropin
 Omnitrope
 Serostim
 Serostim LQ
 Tev-Tropin
 Zorbtive