



PHARMACY PRIOR AUTHORIZATION Clinical Guideline - Growth Hormone

**Genotropin®, Humatrope®, Norditropin®, Nutropin®, Omnitrope®,
Saizen®, Serostim®, Tev-Tropin®, Valtropin®, Zorbtive® (somatropin),**

FDA Indications

Growth Failure due to:

Drug	Peds GHD*	Adult GHD*	Peds Prader-Willi Syndrome	Peds SGA [§] (>2 yrs old)	Short-Stature Associated with Turner Syndrome	Peds Idiopathic Short Stature (NOT MEDICALLY NECESSARY FOR THIS INDICATION) [#]	Peds SHOX deficiency	Peds CRI	Noonan Syndrome
Genotropin	X	X	X	X	X	X			
Humatrope	X	X		X	X	X	X		
Norditropin	X	X		X	X				X
Nutropin, Nutropin AQ, Nutropin AQ NuSpin	X	X			X	X		X	
Omnitrope	X	X							
Saizen	X	X							
Tev-Tropin	X		X						
Valtropin	X	X			X				

GHD=growth hormone deficiency; CRI=chronic renal insufficiency; SGA=small gestational age; SHOX= short stature homeobox-containing gene

*GHD=growth hormone deficiency of either childhood- or adult-onset.

[§]Growth failure in children born small for gestational age who fail to manifest catch-up growth by 2-4 years of age.

^{||} Growth failure associated with chronic renal insufficiency up to the time of renal transplantation

[#]Idiopathic short stature = short stature due to unknown cause. Although FDA-approved for this use, it is not due to GHD, so not considered medically necessary. Considered cosmetic and therefore, NOT covered by Medicaid plans.

[◆]Patients are not GH deficient; therefore, they cannot be expected to respond adequately to exogenous GH treatment

Serostim

- Wasting or cachexia associated with HIV

Zorbtive

- Short-bowel syndrome in adult patients receiving specialized nutritional support

Dosage Forms

Injection; numerous dosage strengths and formulations available. Refer to product information for additional details.

Dosage

Dosage guidelines vary by product and indication; refer to product information for additional details.

- Dosage adjustments do not appear to be needed for hepatic or renal dysfunction

Pediatric patients: Growth hormone responsive conditions:

- **Somatropin** – Administer subcutaneously daily or 6 times per week.
 - **GHD:** 0.3 mg/kg/week; 0.7mg/kg/week during pubertal growth spurt
 - **Prader-Willi Syndrome:** 0.24 mg/kg/week
 - **Small for gestational age (SGA) with failure to catch-up by 2-4 years of age:** 0.48 mg/kg/week
 - **Turner’s Syndrome:** 0.05 mg/kg/day
 - **SHOX Deficiency:** 0.35mg/kg/week
 - **Chronic Renal Insufficiency (CRI):** 0.35 mg/kg/week
 - **Noonan Syndrome:** up to 0.066 mg/kg/day
 - **Pediatric patients transitioning to adults with confirmed persistent GHD:** the starting dose of GH in transition patients should be approximately 50% of the dose between the pediatric doses required for growth and the adult dose (usual dose is 0.4-0.8 mg/day subcutaneously). Titrate every 4-6 weeks.

Adult patients: Growth hormone Deficiency

- **Somatropin** – Administer subcutaneously daily.
 - Starting dose:
 - Age <30 years: 0.4-0.5 mg/day (may be higher for patients transitioning from pediatric treatment)
 - Age 30-60 years: 0.2-0.3 mg/day
 - Age >60 years: 0.1-0.2 mg/day
 - Use lower GH doses (0.1-0.2 mg/day) in all patients with diabetes or who are susceptible to glucose intolerance.

Adult patients: Wasting or cachexia associated with HIV:

- **Serostim**
 - Adults > 55 kg: 6 mg SC once daily at bedtime.
 - Adults 45—55 kg: 5 mg SC once daily at bedtime.
 - Adults 35—45 kg: 4 mg SC once daily at bedtime.
 - Adults < 35 kg: 0.1 mg/kg SC once daily at bedtime.

Adults and the elderly for the treatment of short bowel syndrome:

- **Zorbtive** - 0.1 mg/kg SC once daily for 4 weeks. Do not exceed a maximum of 8 mg/day.

Authorization Guidelines

Prior authorization personnel will review the request for prior authorization and apply the clinical guidelines to assess the medical necessity of the request for a prescription for growth hormone agents. If the guidelines are met, the reviewer will prior authorize the prescription. If the guidelines are not met, the prior authorization request will be referred to a physician reviewer for a medical necessity determination. Such a request for prior authorization will be approved when, in the professional judgment of the physician reviewer, the services are medically necessary to meet the medical needs of the recipient.

For patients who meet all of the following:

Medical records to support medication will be administered in provider’s office. Self-administered injectables are available through the Delaware Medicaid pharmacy benefit. Members should be directed to Delaware retail pharmacies with prescriptions to obtain these drugs.

- Not used for idiopathic short stature (use is not medically necessary)
- No evidence of diabetic retinopathy (proliferative and non proliferative) per medical records
- No evidence of active malignant conditions per medical records

- No evidence of acute critical illness per medical records
- No hypersensitivity to any of the product components.
- No hypersensitivity to benzyl alcohol (Nutropin, Omnitrope, Saizen, Serostim, Tev-Tropin, Zorbitive diluent only)
- No sensitivity to glycerin or M-cresol (Humatrope diluent)
- Not used for growth promotion in pediatric patients with epiphyseal closure (linear growth can no longer occur. i.e., bone age > 14 yrs old). The potential for achieving additional growth after Tanner 4-5 (full maturity) is small as this correlates with epiphyseal closure.
- **Prescribed by a specialist based on the condition treated (e.g., endocrinologist (for adults) or pediatric endocrinologist (for children), HIV specialist) for the following conditions:**

Growth Hormone Deficiency (GHD):

Neonates/Infants:

- Random GH level < 20 ng/ml (by RIA test).
- Abnormal IGFBP-3 (in infants)
- Other causes have been ruled out or treated (hypothyroidism, metabolic disorders)

Pediatrics:

Diagnosis	Required documentation
GHD	<ul style="list-style-type: none"> • Recent (within the last 3 months) height and weight and pretreatment growth velocity (Note: most patients will have short stature: height < 5th percentile for age and sex) • Other factors contributing to growth failure have been ruled out, or are being treated (e.g., hypothyroidism – normal TSH, T4) • Fasting Growth Hormone Stimulation test with arginine, clonidine, glucagon, insulin or levodopa: Peak < 10 ng/ml (by RIA), or Peak < 5 ng/ml (by IRMA), or based on individual lab reference range, if provided • 1 agent with peak level required if cause is known: <ul style="list-style-type: none"> ○ <u>Structural or developmental abnormalities:</u> anencephaly, pituitary aplasia ○ <u>Genetic disorders:</u> e.g., <i>PROP1</i> and <i>PIT1</i> mutations, septo-optic dysplasia ○ <u>Acquired causes:</u> e.g., craniopharyngeomas*, cranial irradiation, brain surgery, head trauma, CNS infections • 2 agents with peak levels required if cause is unknown (idiopathic).
Turner Syndrome (TS), Prader-Willi Syndrome, SHOX deficiency, or Noonan Syndrome	<ul style="list-style-type: none"> • Documentation to support the diagnosis (e.g., Turner Syndrome confirmed by karyotype studies) • Recent (within the last 3 months) <ul style="list-style-type: none"> ➢ height < 5th percentile of the normal growth curve for age and sex, ➢ weight, and ➢ pretreatment growth velocity
Chronic Renal Insufficiency (CRI)	<ul style="list-style-type: none"> • Documentation to support the diagnosis of CRI prior to renal transplant • Documentation to support correction of existing metabolic abnormalities • Recent height and weight (within the last 3 months) and pretreatment growth velocity (Note: patients may not have short stature)
Small for Gestational Age (SGA) with failure to catch-up by 2-4 years of age (depending on agent)	<ul style="list-style-type: none"> • At least 2 years of age • Documented <ul style="list-style-type: none"> ➢ Birth weight or length < 3rd percentile for gestational age, or ➢ Birth weight < 2500 grams at a gestational age of more than 37 weeks

used)	<ul style="list-style-type: none"> • Recent (within the last 3 months) <ul style="list-style-type: none"> ➤ height <5th percentile of the normal growth curve for age, ➤ weight, and ➤ pretreatment growth velocity
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* If GHD is attributed to an intracranial tumor, absence of tumor growth or recurrence should be documented for 6-12 months before initiation of GH.

Adults

Diagnosis	Required Documentation	Required Tests
Adult GHD of Childhood-onset (idiopathic)	<ul style="list-style-type: none"> • Documentation to support the diagnosis of idiopathic childhood-onset GHD • Documentation that growth hormone was not taken for 1-3 months before repeat GH stimulation test and IGF-1 were drawn 	<ul style="list-style-type: none"> • Baseline serum IGF-1 • Growth hormone stimulation test: <ul style="list-style-type: none"> ➤ <u>Insulin Tolerance Test (ITT)</u> is considered the Gold Standard – peak ≤ 5ng/ml (by RIA) or <2.5 ng/ml by IRMA), or based on individual lab reference range, if provided (1/2 of maximum normal value) ➤ <u>Arginine</u> peak ≤ 0.4ng/ml. <p>Note: Levodopa and clonidine tests are not recommended</p>
Adult GHD of Childhood-onset with known cause	<p>Documentation to support the diagnosis of childhood-onset GHD due to a known cause:</p> <ul style="list-style-type: none"> • <u>Irreversible hypothalamic-pituitary structural lesions:</u> e.g., anencephaly, pituitary aplasia • <u>Genetic disorders:</u> <i>PROP1</i> and <i>PIT1</i> mutations, septo-optic dysplasia • <u>Acquired causes:</u> pituitary tumors*, craniopharyngeomas, cranial irradiation, brain surgery, head trauma, CNS infections <p>Note: For conditions other than GHD, such as Turner Syndrome, there is no proven benefit to continuing GH treatment into adulthood once final height is achieved.</p>	Baseline serum IGF-1
Adult-onset GHD	<p>Documentation to support the diagnosis of GHD acquired as an adult due to a known cause: Surgery, cranial irradiation, Panhypopituitarism (at least 3 pituitary hormone deficiencies)</p>	Recent serum IGF-1 <84ng/ml
	<p>Traumatic brain injury and aneurysmal subarachnoid hemorrhage: GHD may be transient; therefore, GH stimulation testing should be performed at least 12 months after the event</p>	<ul style="list-style-type: none"> • Baseline serum IGF-1 • Growth hormone stimulation test: <ul style="list-style-type: none"> ➤ <u>Insulin Tolerance Test (ITT)</u> is considered the Gold Standard – peak ≤ 5ng/ml (by RIA) or <2.5 ng/ml by IRMA), or based on

		<p>individual lab reference range, if provided (1/2 of maximum normal value)</p> <ul style="list-style-type: none"> ➤ <u>Arginine</u> peak ≤ 0.4ng/ml. <p>Note: Levodopa and clonidine tests are not recommended</p>
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Adult HIV Wasting/cachexia (Serostim):

- **Height, weight, IBW, usual weight**
- **Progressive weight loss** below IBW (or usual body weight if usual weight <IBW) over the last year
- **Dietary consult and dietary modifications** over the past 3 months with documented adequate caloric intake
- **Metabolic panel** to r/o volume depletion- look for a BUN/creatinine ratio of < 20:1
- **Failure** of megestrol and Marinol® (dronabinol), testosterone

Short Bowel Syndrome (SBS) (Zorbitive®):

- Age >18 years of age
- Patient is receiving specialized nutrition (i.e., TPN, PPN)

Prior Authorization Requirements

Initial Approval

Pediatric Growth Failure Indications: 6 months (document baseline information)

Adult GHD: 6 months (document baseline IGF-I, GH test results, dose)

Adults with wasting due to HIV: 3 months (document height, weight, IBW, usual weight)

Adults with SBS: one four-week course of therapy

Renewal

Pediatric Indications:

Continue 6 month renewals if:

- Final height has not been achieved
- No evidence of epiphyseal closure, so linear growth is possible
- Growth velocity is >5cm/year on current dose, or growth velocity is <5cm/year but dose has been increased.
Note: Growth velocity will typically decrease as final height is approached (growth velocity <2 cm/year).
- Review of the pharmacy claims history supports compliance

Adults with GHD

Reauthorize for 1 year if:

- Dose has been adjusted to target serum IGF-1 at the middle for the age-and sex-appropriate reference range quoted by the laboratory used

Reauthorize for 6 months if:

- IGF-I is low but dose is being increased

Adults with wasting due to HIV

Reauthorize for 12 weeks (maximum 48 weeks total)

- Documentation supports clinical response and weight gain

Adults with SBS

None (one four-week course of therapy is allowed per year)

Additional Information

There is no evidence that one GH product is more advantageous over the other, apart from differences in pen devices, dose increments and decrements, and whether or not the product requires refrigeration.

Somatropin Precautions:

• Untreated hypothyroidism:

- Patients with untreated hypothyroidism will have an inadequate response to somatropin therapy.
- Changes in thyroid hormone plasma levels may develop during somatropin therapy because patients with Turner's syndrome have an inherent risk of developing autoimmune thyroid disease.
- Periodic thyroid function tests should be performed and treatment with thyroid hormone initiated when indicated.

• Increased intracranial pressure:

- Somatropin therapy has been reported to cause increased intracranial pressure with papilledema, visual changes, headache, and nausea and/or vomiting.
- Symptoms usually occurred within the first eight weeks of somatropin therapy. Resolution of symptoms occurred after discontinuation of somatropin therapy or after a reduction in the hormone dose. Funduscopic examination is recommended at the initiation and periodically during the course of somatropin therapy.
- Patients with chronic renal insufficiency, Prader-Willi syndrome, and Turner's syndrome may be at increased risk for developing intracranial hypertension.

Pregnancy:

- Category B: Genotropin, Omnitrope, Serostim, Saizen, Valtropin, Zorbtive, Somavert
- Category C: Humatrope, Norditropin, Nutropin, Tev-Tropin, Increlex
- Category X: Egrifta

Growth Charts and Growth calculators

- CDC Boys 5th percentile cut-off: <http://www.cdc.gov/nchs/data/nhanes/growthcharts/set1clinical/cj411021.pdf>
- CDC Girls 5th percentile cut-off: <http://www.cdc.gov/nchs/data/nhanes/growthcharts/set1clinical/cj411022.pdf>
- CDC Boys 3rd percentile cut-off: <http://www.cdc.gov/nchs/data/nhanes/growthcharts/set2clinical/cj411071.pdf>
- CDC Girls 3rd percentile cut-off: <http://www.cdc.gov/nchs/data/nhanes/growthcharts/set2clinical/cj411072.pdf>
- Nutropin Growth Percentile Chart calculator: <http://www.nutropin.com/tools-resources/evaluation/growth-percentile.jsp>
- Height Percentile calculator: <http://www.disabled-world.com/calculators-charts/child-gpc.php>

Diagnostic tests

Dynamic endocrine tests (stimulation tests): growth hormone levels are measured in response to stimuli. Multiple samples are taken over 60 or 120 minutes

- Insulin Tolerance Test (ITT) – Considered the “Gold Standard”. Measures GH response to hypoglycemia (blood sugar <40 mg/dl)
- Arginine- safer, but less established diagnostic value compared to ITT
- Clonidine – much less discriminatory than ITT. May cause drowsiness. Causes a fall in blood pressure
- Glucagon – less effective, less discriminatory than ITT. May cause nausea and vomiting
- Levodopa – safer, but less effective. May cause hypotension, nausea, vomiting

GH Test Results

- Growth Hormone test results by RIA [by radioimmunoassay (polyclonal antibody)]

- neonate <20ng/ml
 - pediatric <10ng/ml
 - adult <5ng/ml
- Growth Hormone test results by IRMA [immunoradiometric assay (monoclonal antibody)] will be 1/2 of the value
 - **Note: The RIA and IRMA values above may not apply. Laboratories are now reporting their own reference ranges. Results should be evaluated using individual laboratory reference ranges, if provided**

Other Measures of GHD

- **IGF-1:** Low IGF-I levels are not specific enough to be used alone (can be caused by poor nutrition, liver disease, poorly controlled diabetes, and inadequately treated hypothyroidism) - need to follow up with a stimulation test
- **IGF binding protein-3 (IGFBP-3)** offers no advantage over IGF-I
- **Bone age** estimated from the left wrist and hand can be included, but on its own is not specific enough to support diagnosis of GHD

Adult GHD is a recognized clinical syndrome associated with abnormal body composition, reduced physical performance, altered lipid metabolism, decreased bone mass, increased insulin resistance, and reduced QOL

GH effects in adults:

- Increases bone density (prevent osteoporosis)
- Increases lean tissue, decreases adipose tissue
- Bolsters cardiac contractility
- Improves mood and motivation
- Enhances exercise capacity
- Modulates lipoprotein metabolism

References

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5. American Association of Clinical Endocrinologists. American Association of Clinical Endocrinologists medical guidelines for clinical practice for growth hormone use in growth-hormone-deficient adults and transition Patients – 2009 Update. Endocr Pract 2009;15 (Suppl 2):1-27. Accessed at <http://alt.aace.com/pub/pdf/guidelines/GrowthHormoneGuidelines.pdf> on 4/18/11
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