**Growth Hormones (GH)**

**UTILIZATION MANAGEMENT CRITERIA**

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<th>DRUG CLASS</th>
<th>Synthetic recombinant Growth Hormone (Somatropin)</th>
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**BRAND NAMES:**
- Genotropin®
- Humatrope®, HumatroPen®
- Norditropin® Nordiflex®, Norditropin Flexpro®
- Nutropin®, Nutropin AQ®, Nutropin AQ Nuspin™
- Omnitrope®
- Saizen®
- Serostim®
- Zomacton®
- Zorbitive®

**FDA-APPROVED INDICATIONS**
- Growth failure associated with chronic kidney disease (CKD)
- Growth failure associated with Noonan syndrome
- Growth failure associated with Prader-Willi syndrome
- Growth failure associated with Turner syndrome
- Growth failure in children
  - For children born small for gestational age (SGA) who fail to manifest catch-up growth by 2 years of age
  - For the treatment of children with short stature born SGA with no catch-up growth by 2 to 4 years of age
- Growth hormone deficiency in adults
  - For the replacement of endogenous growth hormone in adults with growth hormone deficiency (GHD) who meet either of the following 2 criteria:
    - Adult-onset: Patients who have GHD, either alone or associated with multiple hormone deficiencies (hypopituitarism), as a result of pituitary disease, hypothalamic disease, surgery, radiation, or trauma.
    - Childhood-onset: Patients who were GHD during childhood as a result of congenital, genetic, acquired, or idiopathic causes. In general, confirmation of the diagnosis of adult GHD in both groups usually requires an appropriate growth hormone stimulation test. However, confirmatory testing may not be required in patients with congenital/genetic GHD or multiple pituitary hormone deficiencies caused by organic disease.
- Idiopathic short stature
- Short bowel syndrome
- Short stature homeobox–containing gene deficiency
- Wasting or cachexia associated with HIV (Serostim): For the treatment of patients with HIV with wasting or cachexia to increase lean body mass (LBM) and body weight, and improve physical endurance. Concomitant antiretroviral therapy is necessary.

**COVERAGE AUTHORIZATION CRITERIA:**

A. Requests for products other than Omnitrope will be approved if the patient has tried Omnitrope and had an inadequate response to this product or could not tolerate it as long as the below criteria are met; **AND**

B. **In children** (under age 18) with open epiphyses, Growth Hormone (GH) therapy may be considered medically necessary and is eligible for coverage for the following conditions:

1. **Initial Coverage**
   a. Children who have growth failure due to inadequate secretion of GH, as documented by failure of at least one GH stimulation test (e.g., L-dopa, clonidine, glucagon, propranolol, arginine, or insulin challenge test). **Medical record documentation required; AND**
   b. Documented serial height/length and weight records showing linear growth failure, and who are persistently under the 3rd percentile (i.e., > 1.88 SD below mean for age and sex) in height. **Medical record documentation required.**
   Please note: Documentation of significant growth deceleration is sufficient for children with history of relevant CNS pathology or history of brain irradiation; **OR** Neonates with hypoglycemia and GH deficiency (one abnormal GH test is sufficient for hypoglycemic neonates in whom GH deficiency is suspected); **OR**
   c. Other diagnoses for which use of growth hormone may be covered. **Medical record documentation required.**
      i. Female children with Turner Syndrome who are under the 5th percentile in height; **OR**
      ii. Children with SHOX (short stature homeobox-containing gene) deficiency who are persistently under the 3rd percentile (i.e., > 1.88 SD below mean for age and sex) in height; **OR**
      iii. Children with growth failure due to Prader-Willi Syndrome (PWS) or Noonan Syndrome; **OR**
      iv. Children with severe burns (3rd degree) who have been treated with GH during their hospitalization may be eligible for coverage for up to 1 year after burn to prevent observed growth delays. Treatment can be covered for no more than one year after discharge from hospital. There is no evidence of benefit for treatment beyond one year. (See also D.3 below.); **OR**
      v. Children who were born small for gestational age (SGA) or with intrauterine growth retardation (IUGR) in whom the birth weight and/or length were more than 2 standard deviations (SD) below the mean for the gestational age, and fail to show catch-up growth by age 2 (defined as a height velocity below 1 SD score, adjusted for age). For children with IUGR or who are SGA who have been previously treated with GH, coverage may be continued if the criteria under 2.a-e below are met and the medical records indicate that the child met the criteria above at the time of initiation of GH therapy; **OR**
vi. Children with **chronic kidney disease (CKD)** (defined as GFR of < 75 ml/min/1.73m²) resulting in short stature (i.e., persistently under 3rd percentile in height). GH therapy should be discontinued at the time of kidney transplant. GH therapy may be resumed one year following kidney transplant if catch up growth has not occurred; OR

vii. A 6 month trial of GH may be considered medically necessary in children who do not fail a growth hormone (GH) stimulation test but are identified to have biochemical abnormalities in the growth hormone metabolic pathway and meet the following criteria:

1. Persistently below the 1.2 percentile in height, (2.25 SD below the mean for age & sex or > 2 SD below the mid-parental height percentile); **AND**
2. Growth velocity < 25th percentile for bone age; **AND**
3. Bone age > 2 SD below the mean for age; **AND**
4. Low serum insulin-like growth factor 1 (IGF-1, also called Somatomedin C) **AND/OR** insulin-like growth factor binding protein 3 (IGFBP3).

***Children whose height is >3.0 SD below age-matched mean and whose IGF-1 levels are also >3 SD below mean may be diagnosed with primary IGF-1 deficiency. See policy, Treatment for Severe Primary IGF-1 Deficiency; OR***

2. **Continued pediatric GH therapy is considered** medically necessary, and will be covered if *(Medical record documentation required for all of the below)*:

   a. The member has a prior approval for this medication from Blue Cross NC; **AND**
   b. Increase in growth velocity over pre-treatment level is >50 percent; **AND**
   c. Annual growth velocity in response to therapy is calculated to be > 4.5 cm/year in a pre-pubertal child or > 2.5 cm/yr in a post-pubertal child; **AND**
   d. Expected final adult (estimated mid-parental) height has not been achieved; **AND**
   e. Epiphyses have not closed. Epiphyseal closure is defined as a bone age of 16 years in a male or 14 years in a female on wrist films. **Note:** Wrist films for bone age must be obtained annually for renewal submission for girls > 10 years old and boys > 12 years old.

C. **In adults**, GH therapy may be considered medically necessary and is eligible for coverage for the following conditions:

1. **Initial Coverage:**

   a. Childhood onset symptomatic GH deficiency, where persistent GH deficiency is documented by at least one failed GH stimulation test performed at least 3 months after the cessation of prior GH therapy. *(Medical record documentation required; OR)*
   
   b. Adult onset symptomatic GH deficiency associated with low GH levels (documented by failure of at least two GH stimulation tests). **Please Note:** 24-hour continuous measurements of GH, serum levels of IGF-1, or serum levels of IGFBP-3 are considered inadequate to document GH deficiency. *(Medical record documentation required; OR)*
   
   c. Adult onset symptomatic GH deficiency associated with multiple hormone deficiencies (i.e., panhypopituitarism), as a result of pituitary disease,
hypothalamic disease, surgery radiation therapy, or trauma. The diagnosis of panhypopituitarism is established when either one of the two following criteria (a. or b.) are met:

i. At least 2 additional hormone deficiencies (other than GH) requiring hormone replacement therapy are documented (e.g., TSH, ACTH, ADH or gonadotropin hormones) as well as failure of at least 1 GH stimulation test. **Medical record documentation required; OR**

ii. Three pituitary hormone deficiencies (other than GH) requiring hormone replacement therapy (where clinically appropriate) are documented AND a low IGF-1 level (below 80 ng/ml) is documented in lieu of GH stimulation testing. **Medical record documentation required; AND**

2. **Continued adult GH therapy** is considered medically necessary, and will be covered if:

   a. The member has a prior approval for this medication from Blue Cross NC; **AND**

   b. There is continued clinical benefit in member's symptoms or signs **Medical record documentation required.**

D. **Other conditions** in which GH therapy may be considered medically necessary and are eligible for coverage include the following **(Medical record documentation required for all of the below):**

1. HIV cachexia or "wasting syndrome," defined by unintentional weight loss of at least 10% of baseline weight, or BMI < 20 kg/m2, not attributable to other causes (such as AIDS-associated diarrhea, infection, malignancy or depression), when optimal antiviral therapy has been instituted. Therapy is continued until this definition is no longer met; **OR**

2. Short Bowel Syndrome (SBS), defined as the inability to maintain adequate nutritional status without parenteral (intravenous) supplementation required at least 5 days/week for a total of at least 3,000 calories/week, due to surgical or functional loss of small bowel. **Medical record documentation required; AND**

   a. Continued coverage for Short Bowel Syndrome will be approved on a quarterly basis (every 3 months) when continued benefit is documented by a sustained decrease in IV nutritional requirements and sustained weight; **OR**

3. Promotion of wound healing in children or adults with 3rd degree burns

E. For members on formularies which exclude a medication named in this criteria (**Non-formulary Medication**), formulary exception requests that satisfy the clinical criteria above may be considered for approval (see Non-formulary Exception criteria for details).

**Criteria for GH NOT being covered:**

A. The use of GH for short stature in patients with no proven GH deficiency (e.g., idiopathic short stature without evidence of biologic impairment of the growth hormone pituitary axis) is not covered. It is considered cosmetic.

B. **Investigational conditions.** The use of GH therapy is considered investigational and is not covered for certain conditions, including but not limited to:

   1. Constitutional delay (defined as lower than expected height percentiles compared with their target height percentiles and delayed skeletal maturation when growth velocities and rates of bone age advancement are normal)

   2. Therapy for geriatric patients, defined as age > 65
3. Anabolic therapy provided to counteract acute or chronic catabolic illness due to surgery outcomes, trauma (except for children with severe burns or for promotion of wound healing in children or adults with third degree burns), cancer, chronic hemodialysis (except as specified above for chronic renal insufficiency), or chronic infectious disease producing catabolic (protein wasting) changes in both adult and pediatric patients (except for the specific covered indication of AIDS wasting under "Coverage Authorization Criteria").
4. Anabolic therapy provided to enhance body mass or strength for professional, recreational or social reasons
5. Glucocorticoid-induced growth failure
6. Short stature after renal transplantation
7. Short stature due to Bloom or Down Syndrome
8. Treatment of altered body habitus (e.g., buffalo hump) associated with antiviral therapy in HIV infected patients
9. Precocious puberty
10. Obesity
11. Cystic fibrosis
12. Idiopathic dilated cardiomyopathy
13. Infertility
14. Juvenile rheumatoid (or idiopathic chronic) arthritis
15. Chronic hepatitis
16. Diabetes

CONTRAINDICATIONS:
- Acute Critical Illness
- Children or adults with active malignancies or other tumors
- Children with Prader-Willi Syndrome who are severely obese or have severe respiratory impairment—reports of sudden death
- Active Malignancy
- Active Proliferative or Severe Non-Proliferative Diabetic Retinopathy
- Children with closed epiphyses
- Known hypersensitivity to somatropin or excipients

WARNINGS AND PRECAUTIONS:
- Acute Critical Illness: Potential benefit of treatment continuation should be weighed against the potential risk
- Neoplasm: Monitor patients with preexisting tumors for progression or recurrence. Increased risk of a second neoplasm in childhood cancer survivors treated with somatropin—in particular meningiomas in patients treated with radiation to the head for their first neoplasm
- Impaired Glucose Tolerance and Diabetes Mellitus: May be unmasked. Periodically monitor glucose levels in all patients. Doses of concurrent antihyperglycemic drugs in diabetics may require adjustment
- Intracranial Hypertension: Exclude preexisting papilledema. May develop and is usually reversible after discontinuation or dose reduction
- Fluid Retention (i.e., edema, arthralgia, carpal tunnel syndrome, especially in adults): May occur frequently. Reduce dose as necessary
- Hypopituitarism: Closely monitor other hormone replacement therapies
- Hypothyroidism: May first become evident or worsen
- Slipped Capital Femoral Epiphysis: May develop. Evaluate children with the onset of a limp or hip/knee pain
- Progression of Preexisting Scoliosis: May develop
- Otitis Media and Cardiovascular Disorders in Turner syndrome: Patients with Turner syndrome should be evaluated for otitis media and other ear disorders and monitored for cardiovascular disorders
- Pancreatitis: Consider pancreatitis in patients with persistent severe abdominal pain, especially children
- Adverse events and death associated with benzyl alcohol: Formulations containing benzyl alcohol should not be used in premature babies or neonates. Consider the combined daily metabolic load of benzyl alcohol from all sources

REFERENCES:


POLICY IMPLEMENTATION/UPDATE INFORMATION
January 2018: Added additional medical record documentation requirements

January 2017: Reviewed for ASO Net Results and Essential formularies; non-formulary verbiage added.

June 2015: Historical revision

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