BlueCross BlueShield of Alabama

Growth Hormone Prior Authorization Criteria Program Summary

This criteria applies to Commercial, GenPlus, NetResults A series, NetResults F series, and Health Insurance Marketplace.

OBJECTIVE
The intent of the Growth Hormone Prior Authorization (PA) Criteria is to appropriately select patients for therapy according to Food and Drug Administration (FDA) approved product labeling and/or clinical guidelines and/or clinical studies. When criteria for use are met, the preferred agent, Omnitrope, may be approved for use; use of the nonpreferred growth hormone products will be evaluated if the prescriber indicates failure of, documented intolerance of, FDA labeled contraindication to, or hypersensitivity to Omnitrope.

TARGET DRUGS
Preferred Growth Hormone products
Omnitrope® (somatropin)

Nonpreferred Growth Hormone products
Genotropin® (somatropin)
Humatrope® (somatropin)
Norditropin® NordiFlex, Norditropin Flexpro (somatropin)
Nutropin AQ® (somatropin)
Nutropin AQ Nuspin® (somatropin)
Saizen® , Saizen Click.Easy (somatropin)
Serostim® (somatropin)
Tev-Tropin® (somatropin)
Zomacton® (somatropin)
Zorbtive® (somatropin)

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL
Growth Hormone (GH) products will be approved as below.

For **Children - Initial Evaluation** when following are met:
1. The patient has ONE of the following diagnoses:
    a. The patient is a neonate (≤4 months of age) with hypoglycemia in the absence of metabolic disorder
        AND
        i. The GH level is <20 ng/mL
    OR
    b. The patient has a diagnosis of Turner's Syndrome
    OR
    c. The patient has a diagnosis of Noonan Syndrome
    OR
    d. The patient has a diagnosis of Prader-Willi Syndrome
    OR
    e. The patient has a diagnosis of SHOX gene deficiency
    OR
    f. The patient has a diagnosis of short bowel syndrome (SBS) AND is receiving enteral or parenteral nutritional support or other specialized nutritional support

OR

g. The patient has a diagnosis of panhypopituitarism or has deficiencies in at least 3 or more pituitary axes AND serum IGF-1 levels below the age- and sex-appropriate reference range when off GH therapy
OR
h. The patient has a diagnosis of chronic renal insufficiency and BOTH of the following:
    i. The patient's height is more than 2 standard deviations (SD) below the mean (less than the third percentile) compared to normal children of the same age
    AND
    ii. Other etiologies for growth retardation have been ruled out
OR
i. The patient has a diagnosis of growth hormone deficiency (GHD), short stature, or other AND BOTH of the following:
    i. The patient has ONE of the following:
        1. Height more than 2 SD below the mean for age and sex
        OR
        2. Height more than 1.5 SD below the midparental height
        OR
        3. A decrease in height SD of more than 0.5 over one year in children >2 years of age
        OR
        4. Height velocity more than 2 SD below the mean over one year or more than 1.5 SD sustained over two years.
    AND
    ii. The patient has failed at least 2 GH stimulation tests (peak GH value of <10 mcg/L after stimulation)
OR
j. The patient has a diagnosis of small for gestational age (SGA) and ALL of the following:
    i. The patient is at least 2 years of age
    AND
    ii. The patient has a documented birth weight and/or length that is 2 or more standard deviations (SD) below the mean for gestational age
    AND
    iii. At 24 months of age, the patient failed to manifest catch-up growth evidenced by a height 2 or more standard deviations (SD) below the mean for age and sex

AND

2. The patient does not have any FDA labeled contraindication(s) to therapy with the requested agent
AND
3. For all agents except Omnitrope, ONE of the following:
    a. The patient has failed the preferred growth hormone product Omnitrope
    OR
    b. The patient has documented intolerance, FDA labeled contraindication, or hypersensitivity to the preferred growth hormone product Omnitrope
    OR
    c. The prescriber has submitted documentation in support of the use of the non-preferred growth hormone product, for the intended diagnosis which has been reviewed and approved by the Clinical Review pharmacist

Length of Approval: 4 weeks for SBS
12 months for other indications

For **Children – Renewal Evaluation** when BOTH of the following are met:

1. The patient has been approved for the requested GH product previously through the Prime Therapeutics PA process
   AND
2. ONE of the following:
   a. The patient has a diagnosis of short bowel syndrome (SBS) AND has shown clinical benefit from treatment with growth hormone
      OR
   b. The patient has any other diagnosis AND ALL of the following:
      i. The patient does not have closed epiphyses
         AND
      ii. The patient's height is increased or height velocity has improved since initiation or last GH approval

   AND
3. The patient is being monitored for side effects of GH
   AND
4. The patient does not have any FDA labeled contraindication(s) to therapy with the requested agent

Length of Approval: 4 weeks for SBS
12 months for other indications

For **Adults - Initial Evaluation** when ANY ONE of the following is met:

1. The patient has ONE of the following diagnoses:
   a. The patient has a diagnosis of AIDS wasting/cachexia AND ALL of the following:
      i. The patient is receiving antiretroviral therapy and GH concurrently
         AND
      ii. ONE of the following:
         1. The patient has had an unintentional weight loss of 10% or more of body weight over 12 months
            OR
         2. The patient has had an unintentional weight loss of >7.5% over 6 months
            OR
         3. The patient has a mid-upper arm circumference $<10^{th}$ percentile
            OR
         4. The patient has a body cell mass (BCM) loss ≥5% over 6 months as documented by bioelectrical impedance analysis
            OR
         5. The patient has a BCM <35% for males or <23% for females AND a BMI of <27 kg/m^2

      AND
      iii. ONE of the following:
         1. The patient's medication history indicates use of an appetite stimulant (dronabinol or megestrol)
            OR
         2. The patient has documented intolerance, FDA labeled contraindication, or hypersensitivity to an appetite stimulant (dronabinol or megestrol)

   OR
   b. The patient has a diagnosis of short bowel syndrome (SBS) AND is receiving enteral or parenteral nutritional support or other specialized nutritional support
      OR

c. The patient has a diagnosis of childhood growth hormone deficiency (GHD) with genetic or organic origin AND ONE of the following:
    i. The patient has a low IGF-1 (insulin-like growth factor-1) level without GH replacement
    OR
    ii. The patient has failed at least one growth hormone (GH) stimulation test as an adult (peak GH value of ≤5 mcg/L after stimulation)

OR

d. The patient has a diagnosis of acquired adult GHD secondary to structural lesions or trauma AND ONE of the following:
    i. The patient has a diagnosis of panhypopituitarism or is deficient in at least 3 or more pituitary hormones and the patient's IGF-1 level is low
    OR
    ii. The patient has failed at least one growth hormone (GH) stimulation test as an adult

OR

e. The patient has a diagnosis of idiopathic GHD (adult or childhood onset) AND the following:
    i. The patient has failed at least two growth hormone (GH) stimulation tests as an adult

AND

2. The patient does not have any FDA labeled contraindication(s) to therapy with the requested agent
AND
3. For all agents except Omnitrope, then ONE of the following:
    a. The patient has failed the preferred growth hormone product Omnitrope
    OR
    b. The patient has documented intolerance, FDA labeled contraindication, or hypersensitivity to the preferred growth hormone product Omnitrope
    OR
    c. The prescriber has submitted documentation in support of the use of the non-preferred growth hormone product, for the intended diagnosis which has been reviewed and approved by the Clinical Review pharmacist

Length of Approval: 4 weeks for short bowel syndrome (SBS);
12 weeks for AIDs wasting/cachexia;
12 months for other indications

For **Adults - Renewal Evaluation** when ANY ONE of the following is met:

1. The patient has been approved for the requested GH product previously through the Prime Therapeutics PA process
AND
2. ONE of the following:
    a. The patient has a diagnosis of short bowel syndrome (SBS) AND has shown clinical benefit from treatment with growth hormone
    OR
    b. The patient has a diagnosis of AIDS wasting/cachexia AND BOTH of the following:
        i. The patient continues to receive concurrent antiretroviral and GH therapy
        AND
        ii. The patient shows evidence of benefit of GH treatment (weight increase or weight stabilization)
    OR
    c. The patient has any other diagnosis AND ALL of the following:
        i. The patient's IGF-1 level has been evaluated to confirm the appropriateness of the current dose
        AND

ii. The patient has had benefits from GH therapy in any of the following response parameters; body composition, hip-to-waist ratio, cardiovascular health, bone mineral density, serum cholesterol, physical strength, or quality of life

AND

3. The patient does not have any FDA labeled contraindication(s) to therapy with the requested agent

AND

4. The patient is being monitored for adverse effects of GH

Length of Approval: 4 weeks for SBS;
12 weeks for AIDs wasting/cachexia;
12 months for other indications

Agent	**Contraindication(s)**
Genotropin, Humatrope, Norditropin, Nutropin, Nutropin AQ, Omnitrope, Saizen, Tev-Tropin, Zomacton	• Acute critical illness • 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 • Hypersensitivity to somatropin or diluents/excipients
Serostim	• Acute critical illness • Active malignancy • Diabetic retinopathy • hypersensitivity
Zorbtive	• Acute critical illness • Active neoplasia • Known hypersensitivity to growth hormone

FDA APPROVED INDICATIONS AND DOSAGE[1-8,26,29]**

Available Products	GHD* IN CHILD-REN	GHD IN ADULTS±	CKD	PWS	TS	SGA	ISS	SHOX	HIV	NS	SBS
Genotropin® (mg/kg/week)	✓ 0.16-0.24	✓ 0.04-0.08		✓ 0.24	✓ 0.33	✓ Up to 0.48	✓ Up to 0.47				
Humatrope® (mg/kg/week^)	✓ 0.18-0.3	✓ 0.006-0.0125^ mg/kg/day			✓ Up to 0.375	✓ Up to 0.47	✓ Up to 0.37	✓ 0.35			
Norditropin® (mg/kg/day)	✓ 0.024-0.034	✓ 0.004-0.016			✓ Up to 0.067	✓ Up to 0.067				✓ Up to 0.066	
Nutropin® AQ (mg/kg/week)	✓ 0.3-0.7	✓ 0.006-0.025 (<35 y.o.) or up to 0.0125 (≥35 y.o.) mg/kg/day	✓ Up to 0.35		✓ Up to 0.375		✓ Up to 0.3				
Omnitrope (mg/kg/week)	✓ 0.16-0.24	✓ 0.04-0.08		✓ 0.24	✓ 0.33	✓ Up to 0.48	✓ Up to 0.47				
Saizen® (mg/kg/week)	✓ 0.18	✓ 0.005 initial mg/kg/day May be increased to no more than 0.01 mg/kg/day after 4 weeks									
Serostim® (mg/kg/day)									✓ 0.1 (up to 6 mg daily)		
Tev-Tropin® (mg/kg 3 times/week)	✓ 0.1										
Zomacton® (mg/kg 3 times/week)	✓ 0.1										
¥Zorbtive® (SC:mg/kg/day)											✓ 0.1 (up to 8 mg daily)

* GHD-growth hormone deficiency, CKD-chronic kidney disease, PWS-Prader Willi Syndrome, TS-Turner's Syndrome, SGA-Small for Gestational Age, ISS-Idiopathic Short Stature, SHOX-SHOX deficiency, , HIV- HIV patients with wasting or cachexia, NS-Noonan Syndrome, SBS-Short Bowel Syndrome

^Max dose for Humatrope adult GHD is 0.0125 mg/kg/day (12.5 µg/kg/day);

±can also dose by *Non-weight based dosing:* A starting dose of approximately 0.2 mg/day (range, 0.15-0.30 mg/day) may be used without consideration of body weight, and increased gradually every 1-2 months by increments of approximately 0.1-0.2 mg/day.

¥ - Administration for more than 4 weeks has not been adequately studied

****Current guidelines recommend adult non-weight based dosing be initiated at 0.1 - 0.2 mg/day and gradually titrated to the minimal dose that normalizes serum IGF-1 levels.**

CLINICAL RATIONALE

The clinical manifestations of growth hormone deficiency (GHD) are variable, depending on the age of onset. Children usually present with short stature, while adults have reduced physical performance and impaired psychological well-being.[9]

Prader-Willi Syndrome (PWS) is a genetic disorder in which seven genes on chromosome 15 are missing or unexpressed on the paternal chromosome. PWS is characterized by hyperphagia and food preoccupations, as well as small stature and mental retardation.[14]

Children with chronic renal insufficiency (CRI) may have difficulty attaining a normal height and weight for several reasons, including malnutrition, renal osteodystrophy, electrolyte, calcium and vitamin D imbalances, inadequate use of protein by the body, and abnormalities in the growth hormone (GH)- insulin-like growth factor (IGF)-1 axis.[15]

Short stature homeobox gene (SHOX) is a gene on the X and Y chromosomes that controls the formation of many body structures, including the growth and maturation of bones in the arms and legs. Patients with SHOX deficiency (gene mutation or present in only one copy) may present with a broad phenotypic spectrum ranging from isolated short stature with no distinguishing clinical features to short stature with moderate to severe skeletal dysplasia.[13]

In Turner syndrome (TS), female sexual characteristics are present but are underdeveloped due to several chromosomal abnormalities. Short stature affects at least 95% of all patients with TS. Short stature in patients with TS is characterized by mild intrauterine growth retardation, slow growth during infancy, delayed onset of the childhood component of growth, and growth failure during childhood and adolescence.[16]

Idiopathic short stature (ISS) refers to extreme short stature that does not have a diagnostic explanation. "Short stature" has been defined by the American Association of Clinical Endocrinologists as height more than two standard deviations (SD) below the mean for age and sex. ISS refers to a height of more than 2.25 SD below the mean for age and sex, or the shortest 1.2% of children.[17]

Patients with HIV/AIDS may experience cachexia: loss of weight, muscle atrophy, fatigue, weakness, and anorexia. Serostim is indicated for the treatment of HIV patients with wasting or cachexia to increase lean body mass and body weight and improve physical endurance. GH therapy allows the body to use fat for energy, thereby preserving lean body mass.[2] Diagnosis of wasting may utilize any of the following elements: subjective global assessment; mid-upper arm circumference and skin–fold; guidelines proposed in 2001 delineate parameters of time, body cell mass (BCM) loss, and loss of total body mass (BMI).[23]

Short bowel syndrome (SBS) is a malabsorption disorder caused by either the surgical removal of the small intestine or the loss of its absorptive function due to various diseases. In clinical studies, the administration of GH enhanced the transmucosal transport of water, electrolytes, and nutrients. Zorbtive is indicated for the treatment of SBS in patients receiving specialized nutritional support.[4]

The principal features of Noonan Syndrome, a congenital disorder, include heart malformation, short stature, indentation of the chest, learning disabilities, impaired blood clotting, and a certain configuration of facial features. Short stature is present in as many as 80% of patients.[13]

Short stature may be the only apparent feature present in children with GHD.[20] The following features indicate a need for further investigation; severe short stature (height more than three SD below the mean), height more than 1.5 SD below the midparental height, height more than two SD below the mean and a height velocity over one year more than one SD below the mean for chronological age, or a decrease in height SD of more than 0.5 over one year in children over two years of age.[20] Patients who have GHD presenting at infancy or have acquired GHD, short stature may not yet be apparent. These patients may present with height velocities more than 2 SD below the mean over one year or more than 1.5 SD sustained over two years. [20]

The International Societies of Pediatric Endocrinology and the Growth Hormone Research Society state that the definition of short gestation age (SGA) is not straightforward; however, they recommend that SGA should be defined as a weight and/or length less than -2 SD because this will identify the majority of those in whom ongoing growth assessment is required (this definition is also mirrored in other publications).[27,29] It is believed that identification of SGA is important since these infants are at an increased risk for perinatal morbidity, associated health problems (e.g. neurodevelopmental disorders), persistent short stature, and metabolic alterations in later life. Regarding GH therapy, they state that there should be a positive response to GH treatment (height velocity SD score more than +0.5 in the first year of treatment). If there is an inadequate response, reevaluation is indicated, including consideration of compliance, GH dose, diagnosis, and the decision to discontinue treatment. In those with a positive response to GH, withdrawal of GH therapy after 2–3 yr leads to catch-down growth and is not recommended. Discontinuation of GH treatment in adolescence is recommended when the growth rate falls to less than 2 cm/yr.[27]

The Royal College of Obstetricians and Gynaecologist (2013) define SGA as an infant born with a birth weight less than the 10th percentile. Historically SGA birth has been defined using population percentiles. But, the use of percentiles customized for maternal characteristics (maternal height, weight, parity and ethnic group) as well as gestational age at delivery and infant sex, identifies small babies at higher risk of morbidity and mortality than those identified by population percentiles. With respect to the fetus, definitions of SGA birth and severe SGA vary. They defined SGA birth as an estimated fetal weight (EFW) or abdominal circumference (AC) less than the 10th percentile and severe SGA as an EFW or AC less than the 3rd percentile.[28]

Laboratory Tests for Diagnosis of GHD

Evaluation for GHD should be considered if the following conditions exist:[10-12,19]

- A child with a standing height of more than 3 standard deviation below the mean for chronological age, sex, and ethnic background
- A child with a height velocity below the fifth to tenth percentile for age, with no clear etiology
- A child with a standing height that is 2 SD to 3 SD below the mean for chronologic age, and with growth deceleration (growth velocity less than the twenty-fifth percentile) that cannot otherwise be explained
- Hypothalamic-pituitary dysfunction (e.g., microphallus, septo-optic dysplasia, intracranial tumor, history of cranial irradiation) with decelerating growth
- Deficits in other hypothalamic-pituitary hormones, either congenital or acquired
- Adults with manifestations suggestive of GHD

In newborns, a serum growth hormone level of < 20 ng/mL is highly suggestive of GHD.

Guidelines recommend that the presence of deficiencies in three or more pituitary axes (panhypopituitarism) and serum IGF-1 levels below the age- and sex-appropriate reference range when off GH therapy are deemed GHD, and do not require further stimulation testing.17,[22,24]

GH stimulation (provocative) tests play a critical role in the diagnosis of GHD. The most frequently used tests include the insulin tolerance test (ITT); arginine; growth hormone releasing hormone (GHRH), with or without arginine; levodopa (L-dopa); glucagon, with or without a beta blocker, such as propranolol; and clonidine.[10,11,19]

Most endocrinologists use a cutoff serum growth hormone concentration of more than 10 mcg/L in children and of more than 3 mcg/L (some authorities use 5 mcg/L) in adults to define normal response on provocative tests. The following are the most recent guidelines regarding stimulation testing; however, they are both outdated (2009 and 2011) and not up-to-date with current clinical practice.[10,11,17,19]

- The Growth Hormone Research Society has recommended the ITT as the standard test for the diagnosis of GHD in adults.[11]
- In an ITT, insulin is administered intravenously to produce a nadir in the plasma glucose level of less than 40 mg/dL (2.2 mmol/L); serum (or blood) glucose and serum growth hormone levels are measured at times 0, 15, 30, 60, 90, and 120 minutes after administering insulin. An experienced staff under the direct supervision of a physician should perform the test. GHD is diagnosed when the growth hormone level is less than 5 mcg/L.
- An ITT is contraindicated in patients with cardiovascular disease, cerebrovascular disease, or seizure disorders, or in patients older than 65 years.
- The GHRH-arginine test was used by many centers as an alternative to the ITT. When the GHRH-arginine test was employed, a GHD was diagnosed when the growth hormone level was < 4.1 mcg/L. However, manufacture of Geref (GHRH) was indefinitely discontinued in 2008 and unavailability of recombinant GHRH in the United States has created a need for a reliable alternative to this test. To establish the diagnosis of adult GHD in patients with child-onset GHD, the ITT is the preferred test. The glucagon test, and rarely the ARG test, are acceptable alternatives.
- In patients with a GHD of hypothalamic origin (as a result, for example, of irradiation), GHRH can give falsely normal testing. In such patients, ITT or glucagon should be used.[17]
- In patients where the ITT is not desirable and when recombinant GHRH is not available, the glucagon test is a reliable alternative, but not the levodopa and clonidine tests.[17]

Some clinicians require that these criteria occur on 2 provocative tests because of the high frequency of false-negative results for each single test.[10,19]

Treatment of Growth Hormone Deficiency

All somatotropin (GH) therapy is indicated in children with growth hormone deficiency (GHD) with an abnormal growth velocity curve, and an untreated growth velocity less than the tenth percentile for bone age and gender.[13] The American Association of Clinical Endocrinologists (AACE) and the National Institute for Health and Clinical Excellence (NICE) recommend somatropins in children with GHD, Turner's syndrome, chronic renal insufficiency, and Prader-Willi Syndrome.[17-18] The NICE 2010 updated guidelines also include the recommendation for the use of somatropins in children born small for gestational age with subsequent failure at 4 years of age or later and short stature homeobox-containing gene (SHOX) deficiency.[18] There is no differentiation between different somatropin products made in either guideline, and no specific product is recommended over another.

The American Association of Clinical Endocrinologists Medical Guidelines for GH use in GH Deficient Adults and Transition Patients-2009 Update recommendations include[17]:

- GH should only be prescribed to patients with clinical features suggestive of adult GHD and biochemically proven evidence of adult GHD.
- No data are available to suggest that GH has beneficial effects in treating aging and age-related conditions and the enhancement of sporting performance; therefore, we do not recommend the prescription of GH to patients for any reason other than the well-defined approved uses of the drug.
- For childhood GH treatment of conditions other than GHD, such as Turner's syndrome and idiopathic short stature, there is no proven benefit to continuing GH treatment in

adulthood; hence, there is no indication to retest these patients when final height is achieved.
- On restarting GH therapy, 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.
- "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; therefore, we do not recommend the use of one commercial GH preparation over another."

The Endocrine Society Clinical Practice guideline (2011) for evaluation and treatment of adult growth hormone deficiency recommends that 2 stimulation tests be performed for patients with idiopathic GHD due to the difficulty in accurately diagnosing this condition. These guidelines also advise that deficiencies in 3 or more pituitary axes is strongly suggestive of GHD and stimulation testing is optional in this situation.[22]

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