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Growth Hormone Prior Authorization Criteria

Program may be implemented with the following options
 option 1) Prior authorization through preferred product
 option 2) Step therapy through preferred product
 option 3) Prior authorization for all products
 (no product preference)

For BlueCross BlueShield of Illinois, BlueCross BlueShield of New Mexico, BlueCross BlueShield of Oklahoma, and BlueCross BlueShield of Texas, Option 1 (prior authorization through preferred growth hormone product Omnitrope) will apply.

Brand	Generic	Dosage form
Genotropin [®]	somatropin	injection
Humatrope [®]	somatropin	injection
Norditropin [®]	somatropin	injection
Nutropin [®]	somatropin	injection
Nutropin [®] AQ	somatropin	injection
Omnitrope [™]	somatropin	injection
Saizen [®]	somatropin	injection
Serostim [®]	somatropin	injection
Tev-Tropin [™]	somatropin	injection
Zorbtive [™]	somatropin	injection

SUMMARY OF STEP THERAPY CRITERIA

When option 2 (step therapy through the *preferred* growth hormone product Omnitrope) is implemented, the criteria for initial and renewal approval of any *nonpreferred* growth hormone agent are 1 or 2 or 3:

1. Patient's medication history indicates trial and failure of the *preferred* GH agent Omnitrope **OR**
2. Patient has an allergy to, contraindication to, or intolerance of the *preferred* GH agent Omnitrope **OR**
3. The prescriber has submitted (and pharmacist has reviewed) evidence in support of use of the *nonpreferred* GH agent for the intended diagnosis

SUMMARY OF PRIOR AUTHORIZATION CRITERIA

The following tables summarize the prior authorization (PA) criteria for growth hormone (GH) for option 1 and option 3. It is the intent of the Growth Hormone Prior Authorization Criteria to ensure patients who are prescribed GH therapy are appropriately selected for treatment. When option 1 (prior authorization through preferred GH product Omnitrope) is implemented, the preferred GH product Omnitrope will be approved unless documentation of need for another product is received (with the exception that Zorbtive brand will be approved for therapy of short bowel syndrome).

Table 1. Summary – Children (<18 years of age), Initial Evaluation

Diagnosis	Requirements	Decision
Turner's Syndrome	Diagnosis only	12 months
Prader-Will Syndrome	Diagnosis only	12 months
AIDS wasting or cachexia	Diagnosis (unexplained weight loss >10% of baseline) AND Patient is being treated with antiviral agents	12 months
3 rd degree burns	Diagnosis AND Duration limited to acute hospitalization and for up to one year after the burn	12 months
Short bowel syndrome	Diagnosis AND Patient is receiving specialized nutritional support, which may include dietary adjustments, enteral feedings, parenteral nutrition, fluid and micronutrient supplements	4 weeks (Zorbtive only)
Chronic Renal Insufficiency	Patient height more than 2 SD below the mean (less than the 3 rd percentile) compared to normal children of same age AND Patient is NOT post-transplant	12 months
Growth Hormone Deficiency	Documented destructive pituitary lesion or GHD as a result of treatment (irradiation, surgery) or trauma OR ALL of the next 3 below Short stature as defined by height more than 2 SD below the mean (<3 rd percentile) for age and sex AND Growth velocity is <5 cm/year .AND Bone age is ≥ 2 years behind chronological age AND The patient has failed at least 2 GH stimulation tests (peak GH value of < 10 ng/ml after stimulation)	12 months
SGA (small for gestational age); Constitutional growth delay; Partial GH deficiency; Neurosecretory GH dysfunction; Non-GH-deficient short stature; Corticosteroid-induced growth failure; Wound healing in burn patients if not 3 rd degree burns Precocious puberty, with GnRH analogues; Short stature due to Down's or Noonan's syndrome; Obesity; Cystic fibrosis; Juvenile idiopathic or juvenile chronic arthritis	none	Deny – not medically necessary OR considered experimental/ investigational

GH=growth hormone, GHD=growth hormone deficiency, SD=standard deviation

Table 2. Summary – Children (<18 years of age), Renewal Evaluation

Requirements	Decision
Patient has had the diagnosis of GHD, <u>AIDS wasting</u> , <u>chronic renal insufficiency</u> , <u>Turner 's syndrome</u> , short bowel syndrome, or Prader-Willi syndrome established with a past evaluation AND Patient is <18 years of age	12 months

GH=growth hormone, GHD=growth hormone deficiency, SD=standard deviation

Table 3. Summary – Adults (>18 years of age), Initial Evaluation

Diagnosis	Requirements	Decision
Pituitary Disease Hypothalamic disease Cranial surgery Cranial radiation therapy Head trauma Medical history of childhood GHD	Patient has evidence of pituitary disease – may include documented destructive pituitary lesion, GHD as a result of treatment (irradiation, surgery) or trauma, or history of childhood GHD AND Patient has failed two GH stimulation tests (peak GH value of < 5 ng/ml after stimulation) AND The patient has clinical features associated with GH deficiency (e.g., increased abdominal fat mass, decreased lean body mass, decreased muscle mass and strength, decreased exercise capacity, impaired sense of well-being)	12 months
AIDS wasting or cachexia	Diagnosis (unexplained weight loss >10% of baseline) AND Patient is being treated with antiviral agents	12 months
3 rd degree burns	Diagnosis	12 months
Short bowel syndrome	Diagnosis AND Patient is receiving specialized nutritional support, which may include dietary adjustments, enteral feedings, parenteral nutrition, fluid and micronutrient supplements	4 weeks (Zorbtive only)
Therapy to counter aging effects; Anabolic therapy to enhance body mass or strength; Anabolic therapy to counteract catabolic illness (not HIV); Wound healing in burn patients if not 3 rd degree burns; Altered body habitus from anti-retroviral therapy in HIV; Obesity; Cystic fibrosis; Idiopathic dilated cardiomyopathy	none	Deny – not medically necessary OR considered experimental/ investigational

GH=growth hormone, GHD=growth hormone deficiency, SD=standard deviation

Table 4. Summary – Adults (>18 years of age), Renewal Evaluation

Requirements	Decision
The patient has improved since last approval of therapy (e.g., improved body composition, cardiovascular health, body mineral density, serum cholesterol, physical strength, quality of life)	12 months

GH=growth hormone, GHD=growth hormone deficiency, SD=standard deviation

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL

Option 1: (Prior Authorization through preferred GH agent, Omnitrope) *Growth Hormone use in Children*

Initial Evaluation

1. Is the patient a child <18 years of age?
If yes, continue to 2. If no, refer to the growth hormone criteria for adults.
2. Has the patient been diagnosed with
 - a. Turner Syndrome
 - b. Prader-Willi Syndrome
 - c. AIDS wasting or cachexia
 - d. Chronic renal insufficiency
 - e. Burns
 - f. Short bowel syndrome
 - g. Growth Hormone Deficiency
 - h. OtherIf a or b, continue to 13. If c, continue to 3. If d, continue to 4.
If e, continue to 6. If f, continue to 7. If g, continue to 8. If h Other, deny.
3. Is the patient being treated with antiviral therapy for HIV/AIDS?
If yes, continue to 13. If no, deny.
4. Is the patient's height more than two standard deviations below the mean (< 3rd percentile) compared to normal children of the same age?
If yes, continue to 5. If no, deny.
5. Is patient post-transplant?
If yes, deny. If no, continue to 13.
6. Does patient have 3rd degree burns?
If yes, continue to 13. If no, deny.
7. Is the patient receiving specialized nutritional support?
If yes, approve Zorbitive for 4 weeks. If no, deny.
8. Does patient have a documented destructive pituitary lesion or GHD as a result of treatment (irradiation, surgery) or trauma?
If yes continue to 12. If no, continue to 9.
9. Does the patient have short stature as defined by height more than 2 SD below the mean (< 3rd percentile) for age and sex?
If yes, continue to 10. If no, deny.
10. Does the patient have a growth velocity <5 cm/year?
If yes, continue to 11. If no, deny.
11. Does the patient have a bone age ≥ 2 years behind chronological age?
If yes, continue to 12. If no, deny.
12. Has the patient failed at least two growth hormone (GH) stimulation tests? (A failure is generally defined as a peak serum growth hormone value of less than 10 ng/ml after GH stimulation)
If yes, continue to 13. If no, deny.
13. Is the request for the preferred GH agent, Omnitrope?
If yes, approve for 12 months. If no, continue to 14.

14. Does the patient have a history of a trial and failure of, or contraindication to, intolerance of, or allergy to the preferred GH agent, Omnitrope?
If yes, approve for 12 months. If no, continue to 15.
15. Has the prescriber submitted documentation supporting therapy with a nonpreferred GH product?
If yes, pharmacist must review and may approve for 12 months based on review of information provided.
If no, deny.

Growth Hormone use in Children

Renewal Evaluation

1. Is the patient a child <18 years of age?
If yes, continue to 2. If no, refer to criteria for adults.
2. Has the patient been treated with at least six months of growth hormone (GH) therapy?
If yes, continue to 3. If no, refer to initial criteria for use in children.
3. Has the diagnosis of GHD, AIDS wasting, chronic renal insufficiency, Turner 's syndrome, or Prader-Willi syndrome been established with a past evaluation?
If yes, continue to 4. If no, deny
4. Is the request for the preferred GH agent, Omnitrope?
If yes, approve for 12 months. If no, continue to 5.
5. Does the patient have a history of a trial and failure of, or contraindication to, intolerance of, or allergy to the preferred GH agent, Omnitrope?
If yes, approve for 12 months. If no, continue to 6.
6. Has the prescriber submitted documentation supporting therapy with a nonpreferred GH product?
If yes, pharmacist must review and may approve for 12 months based on review of information provided.
If no, deny.

Growth Hormone use in Adults

Initial Evaluation

1. Is the patient an adult, age ≥ 18 years of age?
If yes, continue to 2. If no, refer to criteria for children.
2. Has the patient been diagnosed with AIDS wasting or cachexia?
If yes, continue to 3. If no, continue to 4.
3. Is the patient being treated with antiviral therapy for HIV/AIDS?
If yes, continue to 10. If no, deny.
4. Does the patient have 3rd degree burns?
If yes, continue to 10. If no, continue to 5.
5. Does the patient have short bowel syndrome?
If yes, continue to 6. If no, continue to 7.
6. Is the patient receiving specialized nutritional support?
If yes, approve Zorbtive for 4 weeks. If no, deny.
7. Does the patient have evidence of pituitary disease, hypothalamic disease, cranial surgery, cranial radiation therapy, head trauma, or a medical history of childhood GHD?
If yes, continue to 8. If no, deny.

8. Has the patient failed two growth hormone (GH) stimulation tests? (A failure is generally defined as a maximum peak of less than 5 ng/ml)
If yes, continue to 9. If no, deny.
9. Does the patient have clinical features associated with growth hormone deficiency (e.g., increased fat mass with abdominal preponderance, decreased lean body mass, decreased muscle mass and strength, decreased exercise capacity, impaired sense of well-being)?
If yes, continue to 10. If no, deny.
10. Is the request for the preferred GH agent, Omnitrope?
If yes, approve for 12 months. If no, continue to 11.
11. Does the patient have a history of a trial and failure of, or contraindication to, intolerance of, or allergy to the preferred GH agent, Omnitrope?
If yes, approve for 12 months. If no, continue to 12.
12. Has the prescriber submitted documentation supporting therapy with a nonpreferred GH product?
If yes, pharmacist must review and may approve for 12 months based on review of information provided.
If no, deny.

Growth Hormone use in Adults

Renewal Evaluation

1. Is the patient an adult, age ≥ 18 years of age?
If yes, continue to 2. If no, refer to criteria for children.
2. Has the patient been treated for at least six months with Growth Hormone (GH) therapy?
If yes, continue to 3. If no, refer to the initial criteria for use in adults.
3. Has the patient improved (from the start of therapy) in any of the following areas: body composition, cardiovascular health, bone mineral density, serum cholesterol, physical strength, or quality of life?
If yes, continue to 4. If no, deny.
4. Is the request for the preferred GH agent, Omnitrope?
If yes, approve for 12 months. If no, continue to 5.
5. Does the patient have a history of a trial and failure of, or contraindication to, intolerance of, or allergy to the preferred GH agent, Omnitrope?
If yes, approve for 12 months. If no, continue to 6.
6. Has the prescriber submitted documentation supporting therapy with a nonpreferred GH product?
If yes, pharmacist must review and may approve for 12 months based on review of information provided. If no, deny.

Option 2 (Step Therapy through preferred GH agent, Omnitrope)

Initial and Renewal Evaluation

1. Does the patient's medication history indicate previous use of the preferred GH agent, Omnitrope?
If yes, approve for 12 months. If no, continue to 2.
2. Does the patient have an allergy, contraindication, or intolerance to the preferred GH agent, Omnitrope?
If yes, approve for 12 months. If no, continue to 3.
3. Has the prescriber provided evidence in support of the use of the requested nonpreferred GH product for the treatment of the intended diagnosis?
If yes, pharmacist must review and may approve for 12 months based on information provided.
If no, deny.

Option 3 Prior Authorization (all products-no product preference)

Growth Hormone use in Children

Initial Evaluation

1. Is the patient a child <18 years of age?
If yes, continue to 2. If no, refer to the growth hormone criteria for adults.
2. Has the patient been diagnosed with
 - a. Turner Syndrome
 - b. Prader-Willi Syndrome
 - c. AIDS wasting or cachexia
 - d. Chronic renal insufficiency
 - e. Burns
 - f. Short bowel syndrome
 - g. Growth Hormone Deficiency
 - h. Other
If a or b, approve for 12 months. If c, continue to 3. If d, continue to 4. If e, continue to 6. If f, continue to 7. If g, continue to 8. If h Other, deny.
3. Is the patient being treated with antiviral therapy for HIV/AIDS?
If yes, approve for 12 months. If no, deny.
4. Is the patient's height more than two standard deviations below the mean (< 3rd percentile) compared to normal children of the same age?
If yes, continue to 5. If no, deny.
5. Is patient post-transplant?
If yes, deny. If no, approve for 12 months.
6. Does patient have 3rd degree burns?
If yes, approve for 12 months. If no, deny.
7. Is the patient receiving specialized nutritional support?
If yes, approve Zorbtive for 4 weeks. If no, deny.
8. Does patient have a documented destructive pituitary lesion or GHD as a result of treatment (irradiation, surgery) or trauma?
If yes continue to 12. If no, continue to 9.
9. Does the patient have short stature as defined by height more than 2 SD below the mean (< 3rd percentile) for age and sex?
If yes, continue to 10. If no, deny.

10. Does the patient have a growth velocity <5 cm/year?
If yes, continue to 11. If no, deny.
11. Does the patient have a bone age ≥ 2 years behind chronological age?
If yes, continue to 12. If no, deny.
12. Has the patient failed at least two growth hormone (GH) stimulation tests? (A failure is generally defined as a peak serum growth hormone value of less than 10 ng/ml after GH stimulation)
If yes, approve for 12 months. If no, deny.

Growth Hormone use in Children

Renewal Evaluation

1. Is the patient a child <18 years of age?
If yes, continue to 2. If no, refer to criteria for adults.
2. Has the patient been treated with at least six months of growth hormone (GH) therapy?
If yes, continue to 3. If no, refer to initial criteria for use in children.
3. Has the diagnosis of GHD, AIDS wasting, chronic renal insufficiency, Turner 's syndrome, or Prader-Willi syndrome been established with a past evaluation?
If yes, approve for 12 months. If no, deny

Growth Hormone use in Adults

Initial Evaluation

1. Is the patient an adult, age ≥ 18 years of age?
If yes, continue to 2. If no, refer to criteria for children.
2. Has the patient been diagnosed with AIDS wasting or cachexia?
If yes, continue to 3. If no, continue to 4.
3. Is the patient being treated with antiviral therapy for HIV/AIDS?
If yes, approve for 12 months. If no, deny.
4. Does the patient have 3rd degree burns?
If yes, approve for 12 months. If no, continue to 5.
5. Does the patient have short bowel syndrome?
If yes, continue to 6. If no, continue to 7.
6. Is the patient receiving specialized nutritional support?
If yes, approve Zorbitive for 4 weeks. If no, deny.
7. Does the patient have evidence of pituitary disease, hypothalamic disease, cranial surgery, cranial radiation therapy, head trauma, or a medical history of childhood GHD?
If yes, continue to 8. If no, deny.
8. Has the patient failed two growth hormone (GH) stimulation tests? (A failure is generally defined as a maximum peak of less than 5 ng/ml)
If yes, continue to 9. If no, deny.
9. Does the patient have clinical features associated with growth hormone deficiency (e.g., increased fat mass with abdominal preponderance, decreased lean body mass, decreased muscle mass and strength, decreased exercise capacity, impaired sense of well-being)?
If yes, approve for 12 months. If no, deny.

Growth Hormone use in Adults

Renewal Evaluation

1. Is the patient an adult, age ≥ 18 years of age?
If yes, continue to 2. If no, refer to criteria for children.
2. Has the patient been treated for at least six months with Growth Hormone (GH) therapy?
If yes, continue to 3. If no, refer to the initial criteria for use in adults.
3. Has the patient improved (from the start of therapy) in any of the following areas: body composition, cardiovascular health, bone mineral density, serum cholesterol, physical strength, or quality of life?
If yes, approve for 12 months. If no, deny.

RATIONALE FOR PRIOR AUTHORIZATION AND STEP THERAPY

The intent of the prior authorization (PA) criteria for growth hormone agents is to ensure that patients are appropriately selected and treated according to parameters defined in product labeling and/or clinical evidence and/or guidelines, and when criteria are met, to approve for use of the more cost-effective, preferred agent, Omnitrope (option 1). The PA criteria may also be applied to all human growth hormone (GH) agents without product preference (option 3) or as step therapy, encouraging the use of the preferred agent before nonpreferred products (option 2)

Growth Hormone (GH) has been used for the treatment of childhood GH deficiency (GHD) for over 40 years.¹¹ Originally GH was obtained from cadaver pituitaries and was available in only limited quantities. Biosynthetic GH is now available in unlimited supply. Consequently, use in children and adults has increased.¹¹ FDA-approved indications include the treatment of GHD in children and adults with a history of hypothalamic pituitary disease, short stature associated with chronic renal insufficiency before renal transplantation, short stature in patients with Turner Syndrome (TS), Prader-Willi Syndrome (PWS), or Noonan's Syndrome (NS), for the treatment of short stature or growth failure in children with SHOX (short stature homeobox-containing gene) deficiency, for infants born small for gestational age (SGA) who have not caught up in height, and for children with idiopathic short stature, also termed non-growth hormone-deficient short stature (NGHDSS).¹⁻⁸ The FDA has approved Serostim for the treatment of human immunodeficiency virus (HIV)-associated wasting in adults and Zorbtive for patients with Short Bowel Syndrome (SBS) receiving specialized nutritional support.^{9,10} The unlimited supply and the demonstrated benefits of GH for a variety of indications have resulted in use of the hormone in other conditions for which safety and efficacy have not been established.¹¹

All of the products included as targets and the prerequisite preferred agent, Omnitrope, are somatotropins manufactured by recombinant DNA technology and all have an amino acid sequence identical to that of human pituitary-derived GH. Although direct comparisons between different GH products have not been published and some differences exist in recommended doses, all GH products are generally considered to be equally efficacious. Information from guidelines and systematic reviews and meta analyses do not cite any particular GH product as preferred (see Formulary Chapter 4.9 G: Growth Hormones and Somatomedins).⁴⁰

Step Therapy Electronic Edit [applies to option 2 only]

The electronic step edit for the human growth hormone agents will allow automatic payment of the preferred agent, Omnitrope, and will allow automatic payment of other human growth hormone agents if claims history for the patient indicates a claim for the preferred agent or for the same product in the previous 90 days. The system searches for a claim with a days supply that begins or ends in the past 90 days. For claims with a 30 day supply the system would be able to identify a claim processed for payment between 1 and 120 days prior to the new claim. For claims that are dispensed as an extended days supply (90 days), the system would identify a claim processed between 1 and 180 days. Claims for nonpreferred agents, not meeting the preferred agent edit, would be reviewed through a manual prior authorization process.

PRIOR AUTHORIZATION FOR APPROVAL

Option 1 (Prior Authorization through preferred agent)

There are multiple preparations of GH available. There have been no observable differences in results obtained among the different preparations when administered according to approved doses and regimens.¹² The Prior Authorization (PA) Criteria for Growth Hormone will not differentiate between agents. The PA criteria will approve the use of GH in children for the indications of TS, PWS, SBS, chronic renal insufficiency, AIDS-wasting or cachexia, and GHD, if criteria are met. In adults, GH will be approved for treatment of GHD, SBS, and AIDS-wasting or cachexia. GH will be approved for promotion of wound healing in patients with 3rd degree burns. GH will not be approved for the indications of SGA or NGHDSS or for non-FDA approved indications. Children with short stature with normal GH levels do not exhibit adverse clinical consequences. It is currently not known if, and how, a gain in height relates to change in quality of life.¹³ Data demonstrating improved quality of life or better psychological health have not been collected in well-controlled studies.¹³ However, for children with GHD, failure to reach target height has detrimental consequences in terms of skeletal health and body composition.¹⁴ The manual PA process will allow for use of *nonpreferred* GH agents if the patient has a history of allergy, contraindication, intolerance, or trial and failure of the *preferred* agent Omnitrope, or the prescriber may submit other evidence or documentation in support of the requested agent for the intended diagnosis.

Growth Hormone Use in Children

The diagnosis of TS and PWS can be assigned based on results of genetic testing.¹² Females with TS either have a single X chromosome or display chromosomal mosaicism. Clinically, patients with TS may present with a number of physical abnormalities including growth failure, gonadal dysgenesis, abnormalities of internal organs, or square appearance, and cognitive difficulties, although overall intelligence in TS patients is usually normal.¹⁵ Short stature is the most common feature in TS and is almost always present, even if no other clinical features are apparent. Patients with TS experience mild intrauterine growth retardation, slow growth during infancy, delayed onset of the childhood component of growth, and growth failure in childhood and adolescence. Neither provocative testing nor documentation of clinical features will be required for approval of GH treatment for TS.

Short stature is also a major manifestation of PWS.¹² In mid-childhood, the height of fifty percent of these patients is below the third percentile (more than two SD below the mean) and final height is below the third percentile in most patients.¹⁵ The cause of short stature in PWS is uncertain, but may be the result of GH axis abnormalities. Children with PWS have a body composition similar to that of children with GHD; reduced lean body mass and increased fat mass.¹⁵ Neither provocative testing nor documentation of clinical features will be required for approval of GH treatment for PWS. All other indications for GH treatment in childhood require the assignment of severe short stature (a height more than two standard deviations below the population mean) along with other clinical information, birth data, or auxology, depending on the diagnosis, supporting the need for GH treatment.¹²

Chronic renal insufficiency (CRF) is often associated with marked growth retardation and it is not uncommon for children with this diagnosis to be more than two standard deviations below the mean for height.¹⁶ Growth delay may result from physiological abnormalities such as acidosis, secondary hyperparathyroidism, malnutrition, or zinc deficiency.¹² Existing metabolic abnormalities should be corrected, if possible, before GH therapy is initiated. A Cochrane review that included fifteen randomized controlled trials (629 children) evaluating the effect of GH for children with chronic renal insufficiency concluded that GH is effective in increasing the height standard deviation score at one year and the height velocity at six and twelve months.¹⁷ One year of treatment with 28 IU/m²/week of GH resulted in 3.80 cm/year increase in height velocity above that of untreated patients. The trial durations were too short to determine if continuing treatment results in an increase in final height.¹⁷

To qualify for GH therapy, the criteria will require patients with a diagnosis of CRF to exhibit a height more than two standard deviations below the mean for age and gender (severe short stature).¹² In patients with CRF undergoing transplantation, GH therapy is discontinued at the time of transplant.²⁴

Diagnosis of GHD in children is difficult to make and involves a combination of processes evaluating clinical and auxological information along with biochemical and radiological testing.¹⁶ Evaluation of a child

for GHD is not recommended until other causes of growth failure, such as hypothyroidism, chronic systemic disease, Turner Syndrome, or skeletal disorder, have been considered and excluded.^{11,18} Medical history or clinical presentation that may indicate that GHD may be present include hypoglycemia, prolonged jaundice, or microphallus, occurring in a newborn or traumatic delivery, cranial irradiation, head trauma or central nervous system infection, an affected family member, and craniofacial midline abnormalities.^{11,18} Short stature may be the only apparent feature present in children with GHD.¹⁸

The standard method of assessing GH secretion is to measure the serum GH response to insulin or other stimuli such as arginine, clonidine, glucagon, or levodopa.^{11,18} A peak serum GH concentration of less than 10 ng/ml is considered abnormal.¹⁸ When used in conjunction with a designation of short stature, delayed bone age, poor growth velocity, or a predicted height substantially below the mean parental height, a GH level of less than 10 ng/ml in response to stimulation is a reasonable definition of GHD.¹⁶

Several problems exist with GH stimulation testing.¹⁹ The GH level used to define deficiency is an arbitrary cutoff point, there are limited data available evaluating children with normal height velocity for comparison, and the tests have poor reproducibility. When investigating GH status in children, it is customary to consider the results of two tests, assuming that a child with normal GH levels may fail any single GH provocative test.²⁰

The PA Criteria for use of GH in children with GHD will require two GH stimulation tests reporting concentrations of GH less than 10 ng/ml and the designation of short stature (less than two SD below the mean or less than 3rd percentile for age and gender), and a growth velocity <5 cm/year.²⁴ Criteria will also require bone age as determined by standard x-ray techniques to be ≥ 2 years behind chronological age.²⁴ Criteria will allow use of GH in a child with GHD as a result of a destructive lesion of the pituitary or as a result of treatment (e.g. ablative pituitary irradiation, usually provided because of a tumor or surgery) when the child has two GH stimulation tests with results <10 ng/ml.²⁴

Approvals for GH will be for twelve months. Treatment is usually continued until growth velocity is less than 2 cm/year, final height is reached (typically 5th percentile of adult height), or epiphyseal closure is complete.^{11,24} Renewal for GH will be approved for twelve months as long as the child is <18 years of age.²⁴

Growth Hormone Use in Adults

In GHD children poor growth is the predominant clinical symptom whereas in adults with GHD there is no single symptom or sign that is specific to the diagnosis.²⁰ GHD in adults is associated with increased fat mass, particularly distributed in the truncal region, reduced lean mass, decreased bone mass, and an adverse cardiovascular risk factor profile.¹¹ Over ninety percent of adults with GHD have pituitary disease with known causes, including pituitary tumor, pituitary surgical damage, hypothalamic disease, irradiation, trauma, and reconfirmed childhood GHD. A few patients with GHD may have other kinds of pituitary-hypothalamic disease (e.g., Sheehan's syndrome, autoimmune hypophysitis, or hypophysitis associated with other inflammatory conditions, such as sarcoidosis).¹⁰ Adults selected for GH therapy should have an easily recognized cause, clear-cut clinical features of adult GHD, and laboratory evidence of GHD.¹¹

A stimulation test is needed to confirm the diagnosis of GHD in adults. Numerous tests are available; none perfectly predict GHD.¹¹ Complicating the issue is a lack of universal agreement on cutoff points for GH levels. Most experts suggest a peak value of less than 5 nanograms per milliliter after stimulation as an indication of GHD.¹¹ The insulin tolerance test (ITT) is currently considered the gold standard of the tests available and is preferred.^{11,24} The ITT is contraindicated in patients with a history of seizures or coronary artery disease.¹ Other pharmacological stimuli include arginine, levodopa, and glucagon. A test using arginine and the hypothalamic releasing hormone for GH (GHRH) has been used and is considered a more accurate predictor of GHD than arginine alone or levodopa alone.¹⁰ Regardless of the stimulation test and GH assay used, 5 ng/ml is the cutoff point for all provocative tests.^{11,24} There are too many variables to consider in the various GH assays to specify different cutoff points for different assays. Cutoff values do not vary with patient age.¹¹

The PA criteria for GH in adults will require confirmation of GH deficiency with two GH stimulation tests reporting a GH level less than 5 ng/ml for those patients suspected of GHD due to pituitary disease, pituitary hypothalamic disease, trauma, radiation, or a medical history of childhood GHD.

The goal of GH replacement in adults is to minimize the symptoms of GHD (e.g., fatigue, poor endurance, and poor sense of well-being), improve the quality of life, and achieve a serum insulin-like growth factor (IGF-1) concentration in the normal range for age and sex.¹⁰ The major endpoints of treatment are to improve blood lipid levels, improve the patient's waist-to-hip ratio, improve body composition, improve quality of life, and reduce cardiovascular risk factors.¹¹ For renewal of GH for an additional twelve months, there must be evidence of improvement of symptoms.

Growth Hormone Use in Children and Adults

HIV-associated Cachexia

HIV-associated wasting or cachexia, is a metabolic disorder characterized by abnormalities in intermediary metabolism that may cause weight loss, inappropriate decreases in lean body mass (LBM), and paradoxical preservation of body fat.⁸ Depletion of LBM leads to muscle weakness, organ failure, and death.⁸ Nutritional intervention for HIV-associated wasting results in the conversion of supplemental calories predominantly to body fat.⁸ The Center for Disease Control (CDC) defines AIDS wasting syndrome as involuntary weight loss of greater than 10% of body weight, plus either chronic diarrhea (at least two loose stools per day for greater than or equal to 30 days), or chronic weakness and documented fever (for greater than or equal to 30 days, intermittent or constant).⁴¹ Treatment with Serostim has demonstrated significant increases in lean body mass (LBM) and decreases in fat mass with increases in body weight due to gains in LBM.^{8,21} There is evidence suggesting that GH clearances are similar in adults and children, but no pharmacokinetic studies have been conducted in children with HIV.⁸ The PA criteria for GH will approve use of GH for any patient with the diagnosis of HIV-associated wasting (a greater than 10% of baseline weight loss that cannot be explained by a concurrent illness other than HIV infection) who is simultaneously being treated with antiviral agents.²⁴

Short Bowel Syndrome

Short Bowel Syndrome (SBS) is a result of extensive surgical resection of the bowel resulting in various degrees of malabsorption depending on the area and site of resection and persistence of damage to the remaining bowel.²⁵ Patients with SBS may be permanently dependent upon parental nutrition (PN). Consequences of long-term use include risk of infection, hepatic complications, and repeated hospitalizations. Patients receiving PN have a reduced quality of life compared with patients with anatomical or functional short bowel not receiving PN.

In clinical studies, the administration of GH has been shown to enhance the transmucosal transport of water, electrolytes, and nutrients.¹⁰ Intestinal mucosa contain receptors for GH and for insulin-like growth factor-1 (IGF-1), which mediates many of the cellular actions of GH. The action of GH on the gut may be direct or mediated through the local or systemic production of IGF-1.¹⁰

Patients considered for GH treatment should be well nourished to maximize mucosal absorptive function and diet and medications optimized before initiation of treatment and subsequent weaning of PN.²⁷ Appropriate patients should have intestinal failure and be dependent on PN but must also be able to ingest an adequate amount of enteral nutrients and fluids. Even if patients cannot be completely weaned, a reduction in PN use may improve quality of life and reduce costs and risks associated with PN use.²⁷ Patients with remnant colon are more likely to be weaned than those without, although treatment with GH has been shown to be beneficial for patients without a colon also.²⁷ There is currently insufficient evidence to determine the optimal timing of initiating GH treatment after the onset of SBS.²⁷

The FDA approval for Zorbtive was based on the results of a randomized, controlled, phase III clinical trial in which patients dependent on intravenous parenteral nutrition who received Zorbtive (either with or without glutamine) over a four-week period had significantly greater reductions in the weekly total volume of intravenous parenteral nutrition required for nutritional support. However, the effects beyond four weeks were not evaluated nor were the treatment location (inpatient vs. outpatient) identified.^{10,24} Zorbtive is produced from a mammalian cell line and may differ slightly in structure from the GH products produced from *Escherichia coli*.²⁷

Third-Degree Burns

Mortality was studied in a controlled trial of 54 adult burn patients who survived the first seven post-burn days. Those patients showing difficulty with wound healing were treated with GH and compared to those healing at the expected rate with standard therapy. Mortality of the GH treated patients was 11% compared to 37% in those not receiving GH (p=0.027). Infection rates were similar in both groups. In a randomized, double-blind, placebo-controlled trial of 40 severely burned children, the length of hospital stay was reduced from a mean of 0.8 days per % total body surface area (TBSA) burned for the placebo group to 0.54 days per % TBSA for the GH treatment group (p<0.05). For the average 60% TBSA-burned patient, this approximates a length of stay reduction from 46 to 32 days. Singh et al studied two groups of patients (n=22) with comparable third-degree burns; those who received GH had improved wound healing and lower mortality (8% vs. 44%). Demling et al. found significantly improved weight retention and wound healing time with GH or oxandrolone compared to standard treatment in 36 adults with severe burns. Ramirez et al. retrospectively studied 263 pediatric burn patients. Those treated with GH had no increase in mortality from matched patients who did not receive GH. However, a randomized, controlled trial in 56 children with more than 40% total body surface area burns found no benefit of GH alone compared to or in combination with propranolol. Another placebo-controlled trial found no benefit to GH with regard to length of hospitalization in 24 adult patients with severe burns.^{24,26-36,39}

Children with severe burns show significant growth delays for up to three years after injury. GH treatment in 72 severely burned children for one year after discharge from intensive care resulted insignificantly increased height in a placebo-controlled, randomized, double-blind trial. Aili Low et al. found that GH treatment in severely burned children during hospitalization resulted in significantly greater height velocity during the first two years after burn compared to untreated children.^{24,37-39}

Option 2 (Step Therapy through preferred)

Patients who do not meet the electronic step edit may be approved for nonpreferred agents through the manual PA process. Individual requests are reviewed and may be approved if the prescriber has indicated allergy, contraindication, or intolerance to the preferred agent or the prescriber may submit evidence in support of therapy with the nonpreferred agent for the intended diagnosis for the patient.

Option 3 (Prior Authorization for all products-no product preference)

Manual prior authorization for this option applies the option 1 criteria without requiring approval of the preferred agent. When criteria are met, approval will be for the requested GH agent.

FDA APPROVED INDICATIONS¹⁻¹⁰

The following information is taken from individual drug prescribing information and is provided here as background information only. Not all FDA-approved indications may be considered medically necessary. All criteria are found in the above section "Prior Authorization (PA) Criteria for Approval."

Table 5. FDA-approved Indications for Growth Hormone Agents¹⁻¹⁰

	GHD IN CHILDREN	GHD IN ADULTS	CRI	PWS	TS	SGA	NGHDSS	SHOX	HIV	NS	SHORT BOWEL SYNDROME
Genotropin	✓	✓		✓	✓	✓	✓				
Humatrope	✓	✓			✓	✓	✓	✓			
Norditropin	✓	✓	✓		✓	✓				✓	
Nutropin	✓	✓	✓		✓		✓				
Nutropin AQ	✓	✓	✓		✓		✓				
Omnitrope	✓	✓									
Saizen	✓	✓									
Serostim									✓		
Tev-Tropin	✓										
Zorbtive											✓

GHD=growth hormone deficiency, CRI=Chronic Renal Insufficiency, PWS=Prader-Willi Syndrome, TS=Turner Syndrome, SGA=small for gestational age, NGHDSS=non growth hormone deficiency short stature, SHOX=short stature homeobox-containing gene deficiency, HIV=human immunodeficiency virus, NS=Noonan Syndrome

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