



HUMAN GROWTH HORMONE PREAUTHORIZATION AND STEP-THERAPY PROGRAM

Preauthorization Criteria for Approval

Medications and Dosage Forms Included in Criteria

Table with 3 columns: Generic Name, Brand Name, Dosage Form. Lists various Somatropin (rDNA origin) brands like Genotropin, Humatrope, Norditropin, Nutropin, etc.

FDA Approved Indications

Genotropin1

Genotropin is indicated for:

Pediatric Patients

- The treatment of pediatric patients who have growth failure due to an inadequate secretion of endogenous growth hormone.
The treatment of pediatric patients who have growth failure due to Prader-Willi syndrome (PWS).
The treatment of growth failure in children born small for gestational age (SGA) who fail to manifest catch-up growth by age 2.
The treatment of growth failure associated with Turner syndrome.
The treatment of idiopathic short stature (ISS), also called non-growth hormone-deficient short stature...

Adult Patients

- Replacement of endogenous growth hormone in adults with growth hormone deficiency who meet either of the following two criteria:
Adult Onset: Patients who have growth hormone deficiency, either alone or associated with multiple hormone deficiencies (hypopituitarism), as a result of pituitary disease, hypothalamic disease, surgery, radiation therapy, or trauma; or
Childhood Onset: Patients who were growth hormone deficient during childhood as a result of congenital, genetic, acquired, or idiopathic causes.

According to current standards, confirmation of the diagnosis of adult growth hormone deficiency in both groups involves an appropriate growth hormone provocative test with two exceptions: (1) patients with multiple other pituitary hormone deficiencies due to organic disease; and (2) patients with congenital/genetic growth hormone deficiency.

***Humatrope*²**

Humatrope is indicated for:

Pediatric Patients

- The treatment of pediatric patients who have growth failure due to an inadequate secretion of normal endogenous growth hormone.
- The treatment of short stature associated with Turner syndrome in patients whose epiphyses are not closed.
- The treatment of idiopathic short stature, also called non-growth hormone-deficient short stature, defined by height SDS ≤ -2.25 , and associated with growth rates unlikely to permit attainment of adult height in the normal range, in pediatric patients whose epiphyses are not closed and for whom diagnostic evaluation excludes other causes associated with short stature that should be observed or treated by other means.
- The treatment of short stature or growth failure in children with *SHOX* (short stature homeobox-containing gene) deficiency whose epiphyses are not closed.

Adult Patients

- The replacement of endogenous growth hormone in adults with growth hormone deficiency who meet either of the following two criteria:
 - Adult Onset: Patients who have growth hormone deficiency, either alone or associated with multiple hormone deficiencies (hypopituitarism), as a result of pituitary disease, hypothalamic disease, surgery, radiation therapy, or trauma; or
 - Childhood Onset: Patients who were growth hormone deficient during childhood as a result of congenital, genetic, acquired, or idiopathic causes.

In general, confirmation of the diagnosis of adult growth hormone deficiency in both groups usually requires an appropriate growth hormone stimulation test. However, confirmatory growth hormone stimulation testing may not be required in patients with congenital/genetic growth hormone deficiency or multiple pituitary hormone deficiencies due to organic disease.

***Norditropin*³**

Norditropin is indicated for:

Pediatric Patients

- The long-term treatment of children with growth failure due to inadequate secretion of endogenous growth hormone.
- The treatment of children with short stature associated with Noonan syndrome.
- The treatment of children with short stature associated with Turner syndrome.

Adult Patients

- The replacement of endogenous growth hormone in adults with growth hormone deficiency who meet either of the following two criteria:
 - Adult Onset: Patients who have growth hormone deficiency, either alone or associated with multiple hormone deficiencies (hypopituitarism), as a result of pituitary disease, hypothalamic disease, surgery, radiation therapy, or trauma; or
 - Childhood Onset: Patients who were growth hormone deficient during childhood as a result of congenital, genetic, acquired, or idiopathic causes.

In general, confirmation of the diagnosis of adult growth hormone deficiency in both groups usually requires an appropriate growth hormone stimulation test. However, confirmatory growth hormone stimulation testing may not be required in patients with congenital/genetic growth hormone deficiency or multiple pituitary hormone deficiencies due to organic disease.

Nutropin⁴, Nutropin AQ⁵

Nutropin and Nutropin AQ are indicated for:

Pediatric Patients

- The long-term treatment of growth failure due to a lack of adequate endogenous GH secretion.
- The treatment of growth failure associated with chronic renal insufficiency up to the time of renal transplantation. Growth hormone therapy should be used in conjunction with optimal management of chronic renal insufficiency.
- The long-term treatment of short stature associated with Turner syndrome.
- The long-term treatment of idiopathic short stature, also called non-growth hormone-deficient short stature, defined by height SDS ≤ -2.25 , and associated with growth rates unlikely to permit attainment of adult height in the normal range, in pediatric patients whose epiphyses are not closed and for whom diagnostic evaluation excludes other causes associated with short stature that should be observed or treated by other means.

Adult Patients

- The replacement of endogenous growth hormone in adults with growth hormone deficiency who meet either of the following two criteria:
 - Adult Onset: Patients who have adult growth hormone deficiency, either alone or associated with multiple hormone deficiencies (hypopituitarism), as a result of pituitary disease, hypothalamic disease, surgery, radiation therapy, or trauma; or
 - Childhood Onset: Patients who were growth hormone deficient during childhood as a result of congenital, genetic, acquired, or idiopathic causes.

In general, confirmation of the diagnosis of adult growth hormone deficiency in both groups usually requires an appropriate growth hormone stimulation test. However, confirmatory growth hormone stimulation testing may not be required in patients with congenital/genetic growth hormone deficiency or multiple pituitary hormone deficiencies due to organic disease.

Omnitrope⁶

Omnitrope is indicated for:

Pediatric Patients

- The long-term treatment of pediatric patients who have growth failure due to an inadequate secretion of endogenous growth hormone.

Adult Patients

- The long-term replacement therapy in adults with growth hormone deficiency (GHD) of either childhood- or adult- onset etiology. GHD should be confirmed by an appropriate growth hormone stimulation test.

Saizen⁷

Saizen is indicated for:

Pediatric Patients

- The treatment of children with growth failure due to inadequate secretion of endogenous growth hormone.

Adult Patients

- The replacement of endogenous growth hormone in adults with growth hormone deficiency who meet either of the following two criteria:
 - Adult Onset: Patients who have growth hormone deficiency, either alone or associated with multiple hormone deficiencies (hypopituitarism), as a result of pituitary disease, hypothalamic disease, surgery, radiation therapy, or trauma; or
 - Childhood Onset: Patients who were growth hormone deficient during childhood as a result of congenital, genetic, acquired, or idiopathic causes.

In general, confirmation of the diagnosis of adult growth hormone deficiency in both groups usually requires an appropriate growth hormone stimulation test. However, confirmatory growth hormone stimulation testing may not be required in patients with congenital/genetic growth hormone deficiency or multiple pituitary hormone deficiencies due to organic disease.

Serostim⁸

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. Concomitant antiretroviral therapy is necessary.

Tev-Tropin⁹

Tev-Tropin is indicated only for the treatment of children who have growth failure due to an inadequate secretion of normal endogenous growth hormone.

Zorbtive¹⁰

Zorbtive is indicated for the treatment of Short Bowel Syndrome in patients receiving specialized nutritional support. Zorbtive therapy should be used in conjunction with optimal management of Short Bowel Syndrome. Specialized nutritional support may consist of a high carbohydrate, low-fat diet, adjusted for individual patient requirements and preferences. Nutritional supplements may be added according to the discretion of the treating physician. Optimal management of Short Bowel Syndrome may include dietary adjustments, enteral feedings, parenteral nutrition, fluid and micronutrient supplements, as needed.

TABLE

Product	Indications
Genotropin [®]	Pediatric GHD, TS, ISS, PWS, SGA, Adult GHD
Humatrope [®]	Pediatric GHD, TS, ISS, SHOX, Adult GHD
Norditropin [®]	Pediatric GHD, TS, Noonan syndrome, Adult GHD
Nutropin [®]	Pediatric GHD, CRI, TS, Idiopathic SS, Adult GHD
Nutropin AQ [®]	Pediatric GHD, CRI, TS, Idiopathic SS, Adult GHD
Omnitrope [™]	Pediatric GHD, Adult GHD
Saizen [®]	Pediatric GHD, Adult GHD
Serostim [®]	HIV wasting or cachexia
Tev-Tropin [®]	Pediatric GHD
Zorbtive [®]	Short bowel syndrome

GHD = growth hormone deficiency; CRI = chronic renal insufficiency; TS = Turner syndrome; ISS = idiopathic short stature; SHOX = Short Stature Homeobox-containing gene; PWS = Prader-Willi syndrome; SGA = small for gestational age.

Description

The growth hormone (GH) preauthorization and step-therapy program is intended to optimize the utilization of growth hormone supplementation in conditions where efficacy has been established, in patients identified through product labeling and clinical guidelines, and utilization of cost-effective products in the GH class. The conditions where the administration of growth hormone is determined to be medically necessary are: children with growth hormone deficiency (GHD), adults with GHD, children with chronic renal insufficiency, promotion of wound healing in burn patients, Turner syndrome, Prader-Willi syndrome, Noonan syndrome, pediatric SHOX, AIDS-associated wasting, pediatric patients born small for gestational age (SGA), short bowel syndrome, and idiopathic short stature. The criteria is based on available medical literature and evidence provided in the package labeling of the FDA approved growth hormone products and there is little evidence that there is a difference in the efficacy and safety of these products. Therefore, the GH preauthorization program utilizes a protocol where patients must have tried and failed the formulary agent, Omnitrope, prior to receiving a non-formulary agent.

Criteria

1. Is this an initial request for growth hormone therapy?
If yes, see initial request section.
If no, see renewal request section.

Initial Request

2. Does the patient have a diagnosis of or meet one of the following uses for GH:
 - a. Child with growth hormone deficiency (GHD)
 - b. Adults with GHD
 - c. Child with chronic renal insufficiency
 - d. Promotion of wound healing in burn patients
 - e. Prader-Willi syndrome (PWS)
 - f. Turner syndrome
 - g. Pediatric SHOX deficiency
 - h. Short bowel syndrome
 - i. Noonan syndrome
 - j. HIV-wasting (AIDS-wasting) syndrome
 - k. Small for gestational age (SGA)
 - l. Idiopathic short stature

If a, continue to 3. If b, continue to 6. If c, continue to 8. If d-h, continue to 10. If i, continue to 11. If j, continue to 13. If k, continue to 15. If l, continue to 16.

Child GHD

3. Does the child meet one or more of the following:
 - a. Height more than 2 SD below the mean for age and sex
 - b. Height more than 1.5 SD below the midparental height
 - c. Height more than 2 SD below the mean and a height velocity over 1 year more than 1 SD below the mean for chronological age
 - d. A 0.5 SD decrease or more in height of 1 year in those patients 2 years of age or older

If yes to a, b, c, or d, continue to 4.

If no, deny.

4. Are the child's epiphyses closed as seen on x-ray?

If yes, deny.

If no, continue to 5.

5. Has the child failed two of the following stimulation tests (<10 ng/mL) and/or IGF-I/IGFBP-3 studies (only one stimulation test if IGF-I/IGFBP-3 information is provided or the patient has documented history of GHD as a result of pituitary lesions or treatment)?

Tests: insulin, glucagon, arginine, levodopa, clonidine, propranolol, and exercise growth hormone stimulation

If yes, human growth hormone is approved for 12 month. Continue to 18.

If no, deny.

Adult GHD

6. Has the adult failed two of the following stimulation tests (<5 ng/mL) and IGF-I/IGFBP-3 studies?

Tests: insulin, glucagon, arginine, levodopa, clonidine, propranolol, and exercise growth hormone stimulation

If yes, continue to 7.

If no, deny.

7. Is the deficiency the result of congenital, genetic, or acquired causes (i.e., pituitary disease or tumor, hypothalamic disease, surgical damage, cranial irradiation, etc.)?

If yes, human growth hormone is approved for 12 months. Continue to 18.

If no, deny.

Child – Chronic Renal Insufficiency

8. Does the child have a creatinine clearance less than or equal to 75 mL/min per 1.73m²?
If yes, continue to 9.
If no, deny.
9. Is the child height SDS < -1.88 (3rd percentile) or height velocity SDS < -2?
If yes, human growth hormone is approved for 12 months. Continue to 18.
If no, deny.

Burns, PWS, Turner syndrome, SHOX deficiency, Short bowel syndrome

10. Is the patient diagnosed with or have:
- a. third degree burns
 - b. PWS with height SDS -1.6 or lower
 - c. Turner syndrome
 - d. SHOX deficiency
 - e. Short bowel syndrome and dependent on specialized nutritional support
- If a-d, human growth hormone is approved for 12 months. Continue to 18.
If e, human growth hormone is approved for 4 weeks. Continue to 18.
If no, deny.

Noonan syndrome

11. Is the patient diagnosed with Noonan syndrome?
If yes, continue to 12.
If no, deny.
12. Does the child meet all of the following:
- a. Height 2 SD or more below the mean for chronological age and sex
 - b. Patient has no serious heart failure or congenital heart disease
 - c. Height velocity is measured over 1 year prior to start of therapy and is 1 or more standard deviations below the mean for age and sex
 - d. Patient is prebuteral or epiphyses are not closed
- If yes to a-d, human growth hormone is approved for 12 months. Continue to 18.
If no, deny.

AIDS/HIV wasting

13. Is the patient diagnosed with AIDS/HIV and meets CDC definition of HIV-wasting?
If yes, continue to 14.
If no, deny.
14. If the patient on concurrent treatment with antiretroviral agents?
If yes, human growth hormone is approved for 12 weeks. Continue to 18.
If no, deny.

Small for gestational age

15. Does the child meet all of the following:
- a. At least 2 years of age
 - b. Birth weight or length below 3rd percentile for gestational age
 - c. Height below 2 standard deviations for chronological age if catch up growth is not observed by 2 years of age
- If a-c, human growth hormone is approved for 12 months. Continue to 18.
If no to any, deny.

Idiopathic short stature

16. Is the child diagnosed with idiopathic short stature?
If yes, continue to 17.
If no, deny.

17. Does the child demonstrate a height SDS of -2.25 or below and does not have epiphyses closure?
If yes, human growth hormone is approved for 12 months. Continue to 18.
If no, deny.

Step-Therapy

18. Is Omnitrope the growth hormone product being requested?
If yes, approve for previously stated duration indicated above for condition.
If no, continue to 19.
19. Is the patient being prescribed Serostim for HIV-wasting (AIDS-wasting) syndrome or Zorbtive for short bowel syndrome?
If yes, approve for previously stated duration indicated above for condition.
If no, continue to 20.
20. Has the patient tried and failed (provide proper documentation) the formulary product, Omnitrope?
If yes, approve requested nonformulary product for stated duration indicated above for condition.
If no, continue to 21.
21. Does the patient have a contraindication or documented intolerance to Omnitrope?
If yes, provide proper documentation and approve for stated duration indicated above for condition.
If no, deny.

Renewal Request

2. Does the patient have a diagnosis of or meet one of the following uses for GH:
- a. Child with growth hormone deficiency (GHD)
 - b. Adults with GHD
 - c. Child with chronic renal insufficiency
 - d. Prader-Willi syndrome
 - e. Turner syndrome
 - f. Pediatric SHOX deficiency
 - g. Noonan syndrome
 - h. Small for gestational age (SGA)
 - i. Idiopathic short stature
 - j. HIV-wasting (AIDS-wasting) syndrome
- If a, continue to 3. If b, continue to 5. If c, continue to 6. If d-i, continue to 7. If j, continue to 8.

Child GHD

3. Is the child's growth rate greater than 2 cm/year?
If yes, continue to 4.
If no, deny.
4. Is the child's epiphyses closed as determined by x-ray?
If yes, deny.
If no, approve for 12 months.

Adult GHD

5. Is the patient's IGF-I concentration in the normal range for age and sex?
If yes, approve for 12 months.
If no, deny.

Child – Chronic Renal Insufficiency

6. Does the child meet all of the following:
 - a. Growth velocity greater than 2 cm/year
 - b. Epiphyses are open as determined by x-ray
 - c. Awaiting transplant

If a-c, approve for 12 months.

If no, deny.

PWS, Turner syndrome, SHOX deficiency, Noonan syndrome, SGA, Idiopathic short stature

7. Does the child meet all of the following:
 - a. Growth velocity greater than 2 cm/year
 - b. Epiphyses are open as determined by x-ray

If a-b, approve for 12 months.

If no, deny.

HIV-wasting (AIDS-wasting) syndrome

8. Continuation beyond 12 weeks requires medical review based on most of the effect of GH on work output and lean body mass is apparent after 12 weeks of therapy. Safety or efficacy data does not go beyond 24 weeks.

If continuation is requested, forward for review.

Step-Therapy

9. Is Omnitrope the growth hormone product being requested?
If yes, approve for previously stated duration indicated above for condition.
If no, continue to 10.

10. Has the patient tried and failed (provide proper documentation) the formulary product, Omnitrope?
If yes, approve requested nonformulary product for stated duration indicated above for condition.
If no, continue to 11.

11. Does the patient have a contraindication or documented intolerance to Omnitrope?
If yes, provide proper documentation and approve for stated duration indicated above for condition.
If no, deny.

Rationale

Children with Growth Hormone Deficiency

Growth hormone deficiency (GHD) in children generally results from defects in the hypothalamus with the most common reason of idiopathic GHD resulting from the lack of GHRH secretion.¹¹ Other causes of GHD in children results from pathological instances such as pituitary tumors or genetic anomalies that affect *GH* gene or other genes responsible for pituitary cell maturation and development.¹¹ The diagnosis of GHD in children requires a multifaceted process involving clinical, auxological, radiological, and biochemical assessment.^{11,12} It is recommended that children not be evaluated for GHD until other possibilities of growth failure are explored.^{11,12} These include hypothyroidism, Turner syndrome, chronic disease, and skeletal disorders.^{11,12} It is possible, however, that short stature is the only characteristic present to suggest GHD.¹²

Criteria have been developed to help clinicians investigate for GHD and these include: severe short stature, height more than 1.5 standard deviations (SD) below the midparental height (average of both parent's heights), height more than 2 SD below the mean and a height velocity over 1 year more than 1 SD below the mean for chronological age or a 0.5 SD decrease or more in height of 1 year in those patients 2 years of age or older, when short stature is absent a more than 2 SD below the mean 1-year height velocity or a more than 1.5 SD below the mean 2-year height velocity (may arise in GHD during infancy or acquired, organic GHD), signs of an intracranial lesion, signs indicative of multiple pituitary

hormone deficiencies, and neonatal signs and symptoms of GHD.^{11,12} The definition of severe short stature varies as the American Association of Clinical Endocrinologists (AACE) defines severe short stature as height more than 2 SD below the population mean and the GH Research Society defines severe short stature as a height more than 3 SD below the mean.^{11,12}

For children, no criteria have been established for the laboratory diagnosis of GH deficiency as there is little agreement on specific criteria within the pediatric endocrinology community.^{11,13,14} Since there is no standard agreement on GHD criteria, the diagnosis of GHD must combine clinical, radiological, auxologic, and biochemical information.¹¹ Stimulation tests have been utilized to help with the diagnosis of GHD. These tests include insulin, glucagon, arginine, levodopa, clonidine, propranolol, and exercise growth hormone stimulation.¹¹⁻¹³ Many of these tests have limited data available on their specificity and sensitivity.¹¹ When conducting a stimulation test the reference range typically used for GHD is a peak GH concentration below 10 ng/mL.¹¹ Depending on the type of GHD the stimulation test alone may not be the best determinant of GHD since some non-GHD patients can have similar GH in which insulin-like growth factor (IGF-I) and insulin-growth factor binding protein (IGFBP-3) may be helpful in the diagnosis.¹¹ As long as non-GHD causes have been ruled out, the IGF-I/IGFBP-3 value of 2 SD below the mean is generally used to exhibit support for GHD.¹¹

Based on the information presented by the AACE and the GH Research Society, growth hormone may be approved for patients that have a height more than 2 SD below the mean for age and sex, or height more than 1.5 SD below the midparental height, or height more than 2 SD below the mean and a height velocity over 1 year more than 1 SD below the mean for chronological age, or a 0.5 SD decrease or more in height of 1 year in those patients 2 years of age or older. This information combined with the failure of two stimulation tests (or one stimulation test if IGF-I/IGFBP-3 information is provided or the patient has documented history of GHD as a result of pituitary lesions or treatment). Documentation that the epiphyses have not closed is also required. Those patients whose epiphyses have closed will need to meet guidelines for adults with GHD below. The recommended dosage for children with GH deficiency is 0.3 mg/kg per week, divided into daily or 6 times per week injections. In children, GH therapy is typically discontinued when the growth velocity is less than 2 cm per year, when epiphyseal fusion has occurred, or when the height reaches the 5th percentile of adult height.

Adults with Growth Hormone Deficiency

Guidelines developed for the use of GH in adults with GHD are categorized into three categories: previous GHD in childhood, acquired GHD secondary to disease or condition, and idiopathic GHD.¹⁵ Individuals included in the childhood GHD category are those who were growth hormone deficient during childhood as a result of congenital, genetic, acquired, or idiopathic causes.¹⁵ Acquired GHD in adults is generally caused by a pituitary adenoma. GHD can progress based on either the tumor size and anatomical location or due to treatment of the mass with radiotherapy or surgery.¹⁵ Guidelines suggest that the probability of GH recovery is less likely when compared to other pituitary hormones (i.e., ACTH, TSH, gonadotropins).¹⁵ Idiopathic GHD in the adult population is rare and relates to difficulty in diagnosing since linear growth is no longer as evident as compared to GHD in children. Adult idiopathic GHD usually presents with truncal obesity in patients not clinically obese and GH effect is decreased upon conduction of stimulation tests, however, obese patients generally have normal IGF-I levels. Testing of idiopathic adult GHD should include GH response to stimulation along with IGF-I levels, of which should fall below the lower limit of normal based on age corrected values.

Stimulation tests include the insulin tolerance test (ITT), growth hormone releasing hormone (GHRH) plus arginine, arginine alone, clonidine, levodopa, and levodopa plus arginine. Recommendations from the adult GHD guidelines recommend the ITT and GHRH-arginine stimulation tests as the specificity and sensitivity of both tests were above 90%.^{11,15} The other tests mentioned are not as highly recommended by the guidelines. Results of the stimulation tests indicating possible GHD is ≤ 5 ng/mL (≤ 5 μ g/L). As mentioned previously, IGF-I levels should also be obtained. Low IGF-I alone does not indicate GHD as lower levels are observed in conditions such as malnutrition, hepatic disease, poorly controlled diabetes, and hypothyroidism.¹¹ Low IGF-I in absence of these circumstances are helpful in the GHD diagnosis. Other situations, such as deficiencies of three or more pituitary axes, can indicate the presence of GHD and stimulation tests are not necessarily required.¹⁵

The decision to use GH in adults should include: individualized dosing regimens versus weight-based regimens, dosage of GH should start low and should be titrated based on response and side effects, contraindicated in patients with active malignancies, consideration of patient age, gender, and estrogen status, and treatment should be monitored every 1 to 2 months during dose titration followed by semiannual visits once dose has stabilized.¹⁵

Based on the guidelines and package labeling, GH therapy for adult GHD may be approved in patients with an abnormal response to two standard stimulation tests with results of 5 ng/mL or less, documentation of serum IGF-I below normal (standard deviation less than -2), and the deficiency is the result of congenital, genetic, or acquired causes (i.e., pituitary disease or tumor, hypothalamic disease, surgical damage, cranial irradiation, etc.). Serum IGF-I suggests GHD in absence of conditions that lower IGF-I levels such as malnutrition, hepatic disease, poorly controlled diabetes, and hypothyroidism.

Children with Chronic Renal Insufficiency

Package labeling, clinic trials, and literature reviews have provided evidence that children with chronic renal insufficiency benefit from growth hormone therapy and that treatment with growth hormone can provide catch-up growth to obtain normal adult height.^{4,5,16-18} The reason for growth failure in these patients can be attributed not to GH deficiency, but rather abnormalities in the GH/IGF-I axis.¹⁶ Compounding these abnormalities are nutritional and metabolic issues due to the disease process.¹⁶ Recommendations are to correct the nutritional and metabolic issues prior to initiating GH therapy.^{11,16} A literature review proposed treatment algorithm indicates GH therapy should be considered in patients with chronic renal insufficiency as defined a creatinine clearance ≤ 75 mL/min per 1.73 m^2 , and height SDS < -1.88 (3rd percentile) or height velocity SDS < -2 .¹⁶ In patients with chronic renal failure undergoing transplantation, GH therapy is discontinued at the time of transplant or when the growth velocity is less than 2 cm per year, when epiphyseal fusion has occurred, or when the height reaches the 5th percentile of adult height. GH therapy posttransplantation is not recommended.¹¹ Patients may be approved for GH therapy under these conditions and GH therapy should be discontinued as outlined above.

Promotion of Wound Healing in Burn Patients

Mortality was studied in a controlled trial of 54 adult burn patients who survived the first 7 post-burn days.¹⁹ Those patients showing difficulty with wound healing were treated with recombinant human growth hormone (rhGH) and compared to those healing at the expected rate with standard therapy. Mortality of rhGH treated patients was 11% compared to 37% not receiving rhGH ($p=0.027$). 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 burned for the treatment group ($p<0.05$).²⁰ For the average 60% TBSA-burned patient, this approximates a length of stay reduction from 46 to 32 days. Singh, et al., studied 2 groups of patients ($n=22$) with comparable third-degree burns; those who received GH had improved wound healing and lower mortality (8% vs. 44%).²¹ Another study found significantly improved weight retention and wound healing time with GH or oxandrolone compared to standard treatment in 36 adults with severe burns.²²

Two phase III double-blind randomized controlled trials of GH treatment in adults following cardiac or abdominal surgery, multiple trauma, or acute respiratory failure found increased in-hospital mortality rates in patients who received GH.²³ The potential for increased mortality prompted additional studies in critically burned pediatric patients. 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.²⁴

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.²⁵ Another placebo-controlled trial found no benefit to GH with regard to length of hospitalization in 24 adult patients with severe burns.²⁶

Children with severe burns show significant growth delays for up to 3 years after injury. GH treatment in 72 severely burned children for 1 year after discharge from intensive care resulted in significantly increased height in a placebo-controlled, randomized, double-blinded trial.²⁷ Another study found that

GH treatment in severely burned children during hospitalization resulted in significantly greater height velocity during the first 2 years after burn compared to a similar group of untreated children.²⁸

The use of GH in these groups of patients is limited to those patients with 3rd degree burns. GH may be approved for up to one year as the longest length of time observed in study protocols were no longer than 12 months.

Prader-Willi Syndrome

Prader-Willi syndrome (PWS) is a genetic disorder characterized by a microdeletion in the long arm of chromosome 15. Clinically, the syndrome presents as a complex multisystem disorder characterized by excessive appetite, obesity, short stature, characteristic appearance, developmental disability, and significant behavioral dysfunction.^{29,30} Most PWS patients have hypothalamic dysfunction and GH deficiency has been demonstrated in most tested patients with PWS.^{29,30} Reviews of the literature have provided randomized studies that show GH treatment significantly improved height, body mass index (BMI), head circumference, and body composition.^{29,30} However, recently deaths have been reported in PWS patients who are being treated with GH.^{31,32} A number of these deaths occurred in children with morbid obesity, respiratory or sleep disorders. Airway obstruction has been hypothesized as a potential cause; however, the exact role of GH is not certain. Because of this, many specialists now recommend sleep studies and correction of underlying airway obstruction before initiating GH treatment in these patients.^{1,33} According to the product labeling, GH is contraindicated in patients with Prader-Willi syndrome (PWS) who are severely obese, have a history of upper airway obstruction or sleep apnea, or have severe respiratory impairment.¹

Questions have been raised about the value of testing for GH deficiency before treatment in these patients, however, the majority of patients with PWS are GH deficient. The FDA approval is for those with Prader-Willi syndrome and growth failure.¹ Information from the product label indicates that the height standard deviation score for Prader-Willi syndrome children in the clinical studies was -1.6 or less (height was in the 10th percentile or lower.) The approval of GH in these patients is based on documentation of a diagnosis of PWS and height -1.6 SDS or lower.

Turner Syndrome

Short stature is almost universal in Turner syndrome (TS).^{34,35} Poor growth is evident in utero and further deceleration occurs during childhood and at adolescence. The mean adult height for those with Turner syndrome is 58 inches (4 ft 10 inches). Unlike Prader-Willi syndrome, GH deficiency is not seen. The diagnosis of Turner's syndrome should be confirmed by a peripheral blood karyotype showing 45, XO genotype. The FDA approvals for products with this indication were based on the results of randomized, controlled clinical trials that included final adult height as the outcome.^{1,4,5} A group of patients with Turner's syndrome indicated height improvement can be observed in most patients and normalized in other patients.³⁶⁻³⁹ Early initiation of GH therapy can possibly result in more significant increases in adult height even though the average height increase with GH therapy was 4cm (1.75 inches) over controls^{1,4,5}. A final height of 150cm is considered the height goal for patients with Turner's syndrome.³⁵ Current guidelines recommend GH therapy should continue until the bone age is 14 years and height increases have slowed to less than 2cm per year, or a satisfactory height has been achieved.³⁵

Pediatric SHOX

Short stature homeobox-containing gene (SHOX) deficiency generally results from either a mutation within the SHOX gene or a mutation elsewhere that impedes the function or production of the SHOX protein, or from deletion of a copy of SHOX.² SHOX deficiency also plays a role in TS as the genetic anomaly associated with TS encodes SHOX which contributes to the short stature in these patients.⁴⁰ A randomized control trial evaluated the use of growth hormone in SHOX deficient patients who were not GH deficient. The study included three arms, one of which recruited TS patients; placebo, GH, and GH use in TS. Evidence from the trial indicated that those patients receiving GH had a statistically significant increase in height velocity over placebo in the first year (8.7cm vs. 5.2cm, $P < 0.001$), and this continued in the second year of the study (7.3cm vs. 5.4cm, $P < 0.001$).⁴⁰ GH treatment in SHOX deficiency is indicated in pediatric patients up to the time of epiphyses closure since the treatment is for short stature and not for GH deficiency as outlined in the clinical trial.

Noonan Syndrome

Noonan syndrome (NS) is inherited genetic disorder which includes the following features of the syndrome: short stature, congenital heart defects (pulmonary valve stenosis, hypertrophic cardiomyopathy), chest deformity, and coagulation defects (non-exhaustive listing).⁴¹⁻⁴⁴ The syndrome is similar to TS, however, females are the only affected group in TS and NS affects both genders equally.⁴¹⁻⁴⁴ NS patients are generally not GH deficient, however, it is plausible that the GH/IGF pathways are compromised.⁴¹⁻⁴⁴ Based on package labeling, those patients indicated for GH treatment with NS are: height 2 standard deviations or more below the mean for chronological age and sex, patient has no serious heart failure or congenital heart disease, cardiac function is measured regularly, height velocity is measured over 1 year prior to start of therapy and is 1 or more standard deviations below the mean for age and sex, and the patient is prepubertal or epiphyses are not closed.³

Short Bowel Syndrome

Short bowel syndrome (SBS) is experienced by patients who have had one-half or more of the small intestine removed with resulting malnourishment because the remaining small intestine is unable to absorb enough water, vitamins, and other nutrients from food. Zorbive is the only approved growth hormone product for SBS. Human clinical studies provided in product labeling showed the administration of growth hormone enhanced the transmucosal transport of water, electrolytes, and nutrients.¹⁰ This information was retrieved from a phase III clinical trial in which patients dependent on intravenous (IV) parenteral nutrition received growth hormone (either with or without glutamine) over a 4-week period had significantly greater reductions in the weekly total volume of IV parenteral nutrition required for nutritional support. However, the effects beyond 4 weeks were not evaluated nor were the treatment locations (inpatient vs. outpatient) identified. Several published studies have also demonstrated improved intestinal absorption in SBS patients receiving parenteral nutrition.^{45,46} However, studies have noted the effects of increased intestinal absorption are limited to the treatment period.⁴⁵⁻⁴⁷

HIV-wasting Syndrome (AIDS-wasting Syndrome)

The Centers for Disease Control and Prevention (CDC) definition of HIV-associated wasting is >10% involuntary weight loss plus either chronic diarrhea (2 loose stools daily for >30 days) or chronic weakness and documented fever for >30 days (intermittent or constant) in the absence of a concurrent condition other than HIV infection that might explain these findings. A randomized, placebo-controlled trial evaluating growth hormone use in HIV-infected patients with an unintentional weight loss of at least 10% while on antiretroviral therapy observed a body weight increase of 1.6kg in the growth hormone group versus 0.1kg in the control group ($P=0.011$) after 12 weeks of therapy. Lean body mass and body fat were also analyzed in the clinical trial. Lean body mass increased significantly over placebo (3.0kg vs. -0.1kg, $P<0.001$) and body fat decreased significantly over placebo (-1.7kg vs. -0.3kg, $P<0.001$).⁴⁹ Product labeling indicates trials up to 24 weeks and long-term safety information have not been formally presented.^{8,50} A review on the treatment of wasting in these patients provides recommendations on the use of appetite-stimulating drugs (i.e., megestrol acetate, dronabinol). Appetite-stimulating medications should be reserved for those patients with reduced food intake and weight loss. Growth hormone use is indicated in patients with >10% of baseline weight loss that cannot be explained by a concurrent illness other than HIV infection and concurrent treatment with antiretroviral agents. Therapy is continued until this definition is no longer met.

Pediatric Patients Born Small for Gestational Age

Most children born small for gestational age normalize their stature during infancy, but about 15% maintain an exceptionally short stature at least throughout childhood.⁵¹ GH has been investigated in these children, based in part on the hypothesis that a GH resistance is a possible etiology of the growth retardation.¹¹ The use of GH in pediatric patients born small for gestational age (SGA) is based on product labeling provided evidence based on 4 randomized, open-label, controlled trials that the use of GH is efficacious in this patient population by improving SDS scores.¹ Patients were observed for 12 months before being randomized to receive either 0.24 mg/kg/week or 0.48 mg/kg/week GH or no treatment for 24 months. After 24 months all patients received GH. In patients receiving the higher dosage of 0.48 mg/kg/wk, the patients' height improved from a baseline of -3.4 standard deviations to -1.7 standard deviations below the mean. In contrast, in the control group the standard deviation score

improved to a lesser degree, from -3.1 to -2.9 standard deviations below the mean. Other studies have followed the use of GH for extended periods of time with the treatment groups achieving heights greater than placebo.^{52,53} Patients may be approved for GH therapy based on clinical trials and guidelines as follows: child with short stature at least 2 years of age, birth weight or length below 3rd percentile for gestational age, and height below 2 standard deviations for chronological age if catch up growth is not observed by 2 years of age.^{11,52} Treatment continues until final height is obtained, the epiphyses close, or growth rate falls below 2 cm/year.

Idiopathic Short Stature

Idiopathic short stature (ISS), also known as non-growth hormone short stature, is defined by approved product labeling as height SD score (SDS) of -2.25 or less and epiphyses are not closed, associated with growth rates unlikely to permit attainment of adult height in the normal range, and for whom diagnostic evaluation excludes other causes associated with short stature that should be observed or treated by other means.² This definition is from the approval of a growth hormone product supported by data indicating a significant increase in final height with GH treatment compare to placebo; average increases ranged from 1.25 to 2.8 inches, depending on the trials, which differed in patient baseline characteristics, GH dose, administration, and length of treatment.^{2,54,55} A recent meta-analysis of 10 controlled and 28 uncontrolled trials estimate a benefit on adult height of 1.6 to 2.4 inches.⁵⁶

There are benefits to final adult height with GH therapy as just described, however, significant improvements to adaptation, psychosocial function, and quality of life in adolescents with ISS remains controversial.^{55,57} The American Academy of Pediatrics (AAP) has stated, "Therapy with GH is medically and ethically acceptable in patients whose extreme short stature keeps them from participating in basic activities of daily living and who have a condition for which the efficacy of GH therapy has been demonstrated." The AAP continued, "On a broader scale, the best 'therapy' for these children would be a campaign against the current prejudice against short people instead of an implicit medical reinforcement of such prejudice."⁵⁸

In light of the controversial topic of psychosocial and quality of life improvement adult height has been improved in these patients. Growth hormone may be approved in patients that demonstrate a height SDS of -2.25 or below.

Step Therapy

The process of preauthorization requires that the formulary hGH product, Omnitrope, be utilized prior to approval of a non-formulary growth hormone medication. Contraindications, intolerance, or failure to Omnitrope will be reviewed for use of a non-formulary product. Documentation of each will be requested and shall include hypersensitivity reactions to Omnitrope (and others as noted in the product labeling) and documentation that the reaction is not due to the active ingredient, somatropin, but rather to the type of product.

The pharmacology review conducted by the FDA concluded that the chemical structure of Omnitrope is identical to hGH.⁵⁹ Growth hormone products used in GHD (and other indications) are all approved as containing the identical sequence of 191 amino acids constituting the naturally occurring pituitary human growth hormone.¹⁻¹⁰ Omnitrope was FDA approved based on clinical trials conducted comparing Omnitrope to Genotropin.^{6,60} The FDA approved Omnitrope based on non-inferiority efficacy to another growth hormone product based on multiple characteristics including:⁶¹

- Omnitrope and other rhGH (recombinant human growth hormone) consist of one active ingredient (somatropin)⁶¹
- hGH has been used extensively with a history comprising of safety and efficacy endpoints thoroughly published and described in the medical literature⁶¹
- Characteristics such as hGH chemical structure (i.e., hGH is a single chain, 191 amino acid, non-glycosylated protein) that allow for comparisons between two rhGH products⁶¹

Recombinant human growth hormone has been approved in multiple other conditions and there are numerous preparations available.⁶² A pediatric Pharmacy and Therapeutics committee reviewed the

growth hormone class and concluded there are “no observable differences in the results obtained among the different preparations as long as the regimen follows currently approved daily injections. Many of the products are available in a variety of injection devices that are meant to make administration more appealing and easier. At this time, there is no evidence that clinical outcome differs among the various injection systems, although there may be patient and parent preference for some of these devices.”⁶²

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Billing/Coding

CODES	NUMBER	DESCRIPTION
GPI	3010002000****	Somatropin
	3010002010****	Somatropin (non-refrigerated)
HCPCS	J2941	Injection, somatropin, 1 mg
Type of Service	Prescription Drug	
Place of Service	Outpatient	

Update Information

Date	Action	Reason
01/01/09	Replace Medical Policy criteria	Pharmacy department will begin to review.
7/1/09	Update Criteria	Added step-therapy language as formulary product should be used prior to the use of non-formulary medications. Criteria updated with this language as well as the "rationale" section.

Preauthorization Criteria History

10/30/08	Reviewed and approved by QMC
01/01/09	Preauthorization criteria original effective date
04/30/09	New Criteria/Step-Therapy reviewed and approved by QMC
07/01/09	Updated criteria/step-therapy effective date
04/2010	Next Review