

## Corporate Medical Policy

### Growth Hormone

<b>File Name:</b>	growth_hormone
<b>Origination:</b>	8/1996
<b>Last CAP Review:</b>	7/2011
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<b>Last Review:</b>	7/2011

#### Description of Procedure or Service

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Growth Hormone (GH), also called Somatotropin, is a hormone produced by the pituitary gland under the influence of the hypothalamus portion of the brain. It stimulates the growth of bone, muscle, skin, blood cells and most tissues and organs of the body.

When the pituitary gland fails to produce normal or adequate amounts of hormone, both children and adults experience physical and metabolic consequences. In children, there is a failure to grow at normal rates with resulting short stature (defined in this policy, below).

Adults with inadequate GH production may experience abnormal weight gain with increased body fat content, decreased lean body mass (muscle and bone), decreased exercise capacity and endurance, decreased muscle mass and strength, decreased bone density, reduced cardiac performance, an impaired sense of well-being and depression.

Synthetic recombinant GH may be used to treat the clinical consequences of natural GH deficiency. Synthetic GH is also used to treat several conditions that are not clearly associated with a deficiency in production of GH, such as AIDS wasting syndrome, Short Bowel Syndrome, Turner's Syndrome, infants who are Small for Gestational Age (SGA), pediatric burn patients, and children with Chronic Renal Insufficiency (CRI). Some of these conditions may be associated with a deficiency of other intermediary molecules involved in the growth process, such as IGF-1 (also called Somatomedin C) or IGFBP-3, which can also be measured.

\*\*\*See also the BCBSNC policy titled, "Treatment for Severe Primary IGF-1 Deficiency".

\*\*\**Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.*

#### Policy

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**BCBSNC will provide coverage for Growth Hormone (GH) when it is determined to be medically necessary because the medical criteria and guidelines shown below are met.**

#### Benefits Application

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This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

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## When Growth Hormone is covered

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- A. **In children** (under age 18) with open epiphyses, GH therapy may be considered medically necessary and is eligible for coverage for the following conditions:
1. Children who have growth failure due to inadequate secretion of GH, as documented by failure of at least one GH stimulation test (e.g., L-dopa, clonidine, glucagon, propranolol, arginine, or insulin challenge test), and as documented by serial height/length and weight records showing linear growth failure (**defined in Policy Guidelines below**), and who are persistently under the 3rd percentile (i.e., > 1.88 SD below mean for age and sex) in height.
    - a. Documentation of significant growth deceleration is sufficient for children with history of relevant CNS pathology or history of brain irradiation.
    - b. Neonates with hypoglycemia and growth hormone deficiency (one abnormal GH test is sufficient for hypoglycemic neonates in whom growth hormone deficiency is suspected)
  2. Female children with Turner Syndrome who are under the 5th percentile in height.
  3. Children with SHOX (short stature homeobox-containing gene) deficiency who are persistently under the 3rd percentile (i.e., > 1.88 SD below mean for age and sex) in height.
  4. Children with growth failure due to Prader-Willi Syndrome (PWS) or Noonan Syndrome.
  5. Children with severe burns (3rd degree) have been successfully treated with GH during their hospitalization and for up to 1 year after burn to prevent observed growth delays. Treatment can be covered for no more than one year after discharge from hospital. There is no evidence of benefit for treatment beyond one year. (See also C.3 below.)
  6. Children who were born small for gestational age (SGA) or with intrauterine growth retardation (IUGR) in whom the birth weight and/or length were more than 2 standard deviations (SD) below the mean for the gestational age, and fail to show catch-up growth by age 2 (defined as a height velocity below 1 standard deviation score, adjusted for age). For children with intrauterine growth retardation (IUGR) or who are small for gestational age (SGA) who have been previously treated with Growth Hormone, coverage may be continued if the criteria under 9.a-d below are met and the medical records indicate that the child met the criteria above at the time of initiation of Growth Hormone therapy.
  7. Children with chronic renal failure or insufficiency (defined as GFR [glomerular filtration rate] of < 75 ml/min/1.73m<sup>2</sup>) resulting in short stature (i.e., persistently under 3rd percentile in height). GH therapy should be discontinued at the time of kidney transplant. GH therapy may be resumed one year following kidney transplant if catch up growth has not occurred.
  8. A 6 month trial of growth hormone may be considered medically necessary in children who do not fail a growth hormone (GH) stimulation test but are identified to have biochemical abnormalities in the growth hormone metabolic pathway and meet the following criteria: (\*\*NOTE\*\*These cases should be reviewed by the Medical Director for individual consideration.\*\*)

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- a. Persistently below the 1.2 percentile in height, (2.25 standard deviation below the mean for age & sex or >2 standard deviations below the mid parental height percentile); and
  - b. Growth velocity <25th percentile for bone age; and
  - c. Bone age > 2 standard deviations below the mean for age; and
  - d. Low serum insulin-like growth factor 1 (IGF-1, also called Somatomedin C) and/or insulin-like growth factor binding protein 3 (IGFBP3). \*\*\*Children whose height is >3.0 SD below age-matched mean and whose IGF-1 levels are also >3 SD below mean may be diagnosed with primary IGF-1 deficiency. See policy, Treatment for Severe Primary IGF-1 Deficiency.
9. Continued pediatric GH therapy is considered medically necessary, and will be covered, if, after a suitable course of initial therapy (6 - 12 months) **ALL** of the following apply:
- a. Increase in growth velocity over pre-treatment level is >50 percent; and
  - b. Annual growth velocity in response to therapy is calculated to be > 4.5 cm/year in a pre-pubertal child or > 2.5 cm/yr in a post-pubertal child; and
  - c. Expected final adult (estimated mid-parental) height has not been achieved; and
  - d. Epiphyses have not closed. Epiphyseal closure is defined as a bone age of 16 years in a male or 14 years in a female on wrist films. Note: Wrist films for bone age must be obtained annually for renewal submission for girls > 10 years old and boys > 12 years old.
- B. Adults** with inadequate GH production may experience any of the following symptoms: abnormal weight gain with increased body fat content, decreased lean body mass (muscle and bone), decreased exercise capacity and endurance, decreased muscle mass and strength, decreased bone density, reduced cardiac performance, impaired sense of well-being and depression. In adults, GH therapy may be considered medically necessary and is eligible for coverage for the following conditions:
1. Adult onset symptomatic GH deficiency associated with low GH levels (documented by failure of at least two GH stimulation tests). 24-hour continuous measurements of GH, serum levels of IGF-1, or serum levels of IGFBP-3 are considered inadequate to document GH deficiency.
  2. Childhood onset symptomatic GH deficiency, where persistent GH deficiency is documented by at least one failed GH stimulation test performed at least 3 months after the cessation of prior GH therapy.
  3. Adult onset symptomatic GH deficiency associated with multiple hormone deficiencies (i.e., panhypopituitarism), as a result of pituitary disease, hypothalamic disease, surgery, radiation therapy, or trauma. The diagnosis of panhypopituitarism is established when either one of the two following criteria (a or b) are met:
    - a. At least 2 additional hormone deficiencies (other than GH) requiring hormone replacement therapy are documented (e.g., TSH, ACTH, ADH or gonadotropin hormones) as well as failure of at least 1 GH stimulation test, OR
    - b. Three pituitary hormone deficiencies (other than GH) requiring hormone

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replacement therapy (where clinically appropriate) are documented AND a low IGF-1 level (below 80 ng/ml) is documented in lieu of GH stimulation testing.

4. Renewal of coverage for adult GH therapy may be granted on an annual basis without additional testing if the original documentation of failed GH stimulation testing is made available with the request for renewal of coverage, and there is continued clinical benefit in symptoms or signs.
- C. **Other conditions** in which GH therapy may be considered medically necessary and are eligible for coverage include the following:
1. HIV cachexia or "wasting syndrome," defined by unintentional weight loss of at least 10 percent of baseline weight, or BMI < 20 kg/m<sup>2</sup>, not attributable to other causes (such as AIDS-associated diarrhea, infection, malignancy or depression), when optimal anti-viral therapy has been instituted. Therapy is continued until this definition is no longer met.
  2. Short Bowel Syndrome (SBS), defined as the inability to maintain adequate nutritional status without parenteral (intravenous) supplementation required at least 5 days/week for a total of at least 3,000 calories/week, due to surgical or functional loss of small bowel.
    - a. Continued coverage for Short Bowel Syndrome will be approved on a quarterly basis (every 3 months) when continued benefit is documented by a sustained decrease in IV nutritional requirements and sustained weight.
  3. Promotion of wound healing in children or adults with 3rd degree burns.

## When Growth Hormone is not covered

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- A. When none of the conditions under "When Covered" are present, OR when any of the conditions for continued therapy ("renewal criteria") are not met, the use of GH therapy will be considered not medically necessary.
- B. The use of Growth Hormone for short stature in patients with no proven Growth Hormone deficiency (e.g., idiopathic short stature without evidence of biologic impairment of the growth hormone pituitary axis) is not covered. It is considered cosmetic.
- C. Investigational conditions. The use of GH therapy is considered investigational and is not covered for certain conditions, including but not limited to:
  1. Constitutional delay (defined as lower than expected height percentiles compared with their target height percentiles and delayed skeletal maturation when growth velocities and rates of bone age advancement are normal.)
  2. Therapy for geriatric patients, defined as age > 65.
  3. Anabolic therapy provided to counteract acute or chronic catabolic illness due to surgery outcomes, trauma (except for children with severe burns or for promotion of wound healing in children or adults with third degree burns), cancer, chronic hemodialysis (except as specified above for chronic renal insufficiency) or chronic infectious disease producing catabolic (protein wasting) changes in both adult and pediatric patients (except for the specific covered indication of AIDS wasting noted above, under "When GH is Covered".)

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4. Anabolic therapy provided to enhance body mass or strength for professional, recreational or social reasons.
  5. Glucocorticoid-induced growth failure.
  6. Short stature after renal transplantation.
  7. Short stature due to Bloom or Down Syndrome.
  8. Treatment of altered body habitus (e.g., buffalo hump) associated with antiviral therapy in HIV infected patients.
  9. Precocious puberty.
  10. Obesity.
  11. Cystic fibrosis.
  12. Idiopathic dilated cardiomyopathy.
  13. Infertility.
  14. Juvenile rheumatoid (or idiopathic chronic) arthritis.
  15. Chronic hepatitis.
  16. Diabetes.
- D. Contraindications. The use of synthetic GH is contraindicated and should not be used in the following individuals:
1. Children or adults with active malignancies or other tumors.
  2. Patients with a known sensitivity to any ingredients in the synthetic GH product.
  3. Patients with proliferative or preproliferative diabetic retinopathy.
  4. Patients with benign intracranial hypertension (BIH), also called pseudotumor cerebri.
  5. Critically ill patients (e.g., post-surgical, ICU, respiratory failure or multiple trauma patients).
- Pregnant or lactating females.

## Policy Guidelines

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### **Growth Hormone (GH) may be subject to prior approval and/or medical review**

- A. Growth data to be documented.
1. Growth data must include serial heights and weights plotted on standard clinical growth charts with appropriate age and gender standards compatible with those endorsed by the CDC (available at: [http://www.cdc.gov/nchs/about/major/nhanes/growthcharts/clinical/\\_charts.htm](http://www.cdc.gov/nchs/about/major/nhanes/growthcharts/clinical/_charts.htm))

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- B. GH therapy should be discontinued when there is poor adherence to the treatment regimen for any reason.
- C. The calculation of growth velocity must be normalized for "bone age" (not the chronological age).

## **Billing/Coding/Physician Documentation Information**

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This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at [www.bcbsnc.com](http://www.bcbsnc.com). They are listed in the Category Search on the Medical Policy search page.

*Applicable service codes: J2940, J2941.*

*Human growth hormone, Growth hormone, GH, HGH, Genotropin, Humatrope, Norditropin, Norditropin Nordiflex, Nutropin, Nutropin AQ, Omnitrope, Saizen, Serostem, Tev-Tropin, Somatotropin, Zorbtive.*

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

## **Scientific Background and Reference Sources**

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AMA Dry Information - 1995

TEC Bulletin - 2/1996

Lawson Wilkins Ped. End. Soc., Guidelines for the use of growth hormone in children with short stature, *The Journal of Pediatrics*, 1995; 127:857-67.

BCBSA Medical Policy Reference Manual - 11/1997

USPDI - 1999

AHFS Dry Information - 1999

BCBSNC Corporate Pharmacist - 3/1999

Independent Consultant Review - 3/1999

Medical Policy Advisory Group - 12/1999

Independent Consultant Review - 3/2000

Specialty Matched Consultant Advisory Panel - 10/2000.

Medical Policy Advisory Group - 10/2000

TEC Assessment, Volume 16, No. 11 - 11/2001

BCBSA Medical Policy Reference Manual, 2/15/2002; 5.01.06

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Genentech: Products - Product Information.

[www.genentech.com/gene/products/information/opportunistic/nutropin/insert.jsp](http://www.genentech.com/gene/products/information/opportunistic/nutropin/insert.jsp) - 4/2002

Specialty Matched Consultant Advisory Panel - 7/2002

BCBSA Medical Policy Reference Manual, 5/15/2002; 5.01.06

BCBSA Medical Policy Reference Manual [Electronic Version]. 5.01.06, 12/17/03.

Department of Health and Human Services. (2003, December 4) FDA approval letter to Serono, Inc., Pamela Williamson-Joyce. Retrieved on 5/7/04 from <http://www.fda.gov/cder/foi/applletter/2003/21597,20604slr026ltr.pdf>

Specialty Matched Consultant Advisory Panel - 6/2004

BCBSA Medical Policy Reference Manual [Electronic Version]. 5.01.06, 7/15/2004

Specialty Matched Consultant review, 9/2005

Specialty Matched Consultant Advisory Panel - 5/2006

CDC. National Center for Health Statistics. Clinical growth charts. Retrieved 5/18/2006 from [http://www.cdc.gov/nchs/about/major/nhanes/growthcharts/clinical\\_charts.htm](http://www.cdc.gov/nchs/about/major/nhanes/growthcharts/clinical_charts.htm)

Specialty Matched Consultant review, 1/2007

Hartman ML, et al. Which patients do not require a GH stimulation test for the diagnosis of adult GH deficiency? *J Clin Endocrinol Metab*, February 2002, 87(2):477-485.

Molitch ME, et al. Clinical practice guideline, Evaluation and treatment of adult growth hormone deficiency: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*, May 2006, 91(5):1621-1634.

American Association of Clinical Endocrinologists. Medical guidelines for clinical practice for growth hormone use in adults and children - 2003 update. *Endocrine Practice*, 2003, 9(No.1):64-76.

American Association of Clinical Endocrinologists (AACE). Medical guidelines for clinical practice for growth hormone use in adults and transition patients-2009 update. *Endocr Pract*. 2009;15(Suppl 2). Retrieved on August 11, 2011 from <http://www.aace.com/pub/pdf/guidelines/GrowthHormoneGuidelines.pdf>

Specialty Matched Consultant Advisory Panel 8/2010

BCBSA Medical Policy Reference Manual [Electronic Version]. 5.01.06, 6/12/2008

## Policy Implementation/Update Information

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8/96	Original policy issued.
3/99	Revised. Included approved adult indications. Changed policy guidelines for adults to include one provocative stimulation test instead of two.
5/99	Reformatted; description of service changed and medical term definitions added.

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- 12/99 Medical Policy Advisory Group
- 4/00 Revised. Removed statement, "Children with Turner's syndrome, i.e., a 45, XO genotype", and "Serum levels of insulin-like growth factors (IGF) or insulin-like growth factor binding protein (IGFBP)"; and changed policy guidelines for adults to include two provocative stimulation tests instead of one. Revised statement that "this drug is prior approved for PCP only" and changed to "this drug may require prior approval". System coding changes.
- 10/00 Specialty Matched Consultant Advisory Panel review. No change recommended in criteria. System coding changes. Medical Policy Advisory Group review. No change in criteria. Approve.
- 12/00 Following sentence moved from Scientific Background section to Policy Implementation section; New 2001 HCPCS codes added; Q2014, Q2015, Q2016. System coding changes.
- 7/01 J2352, Q2014 removed from coding section. System changes.
- 5/02 Revised to include Prader-Willi Syndrome as a covered indication. Added children with height less than 3rd percentile for chronologic age with chronic renal insufficiency to covered indications. Revised under when it is not covered to include Growth Hormone as not medically necessary for pediatric patients born small for gestational age (SGA) who fail to show catch-up growth by age 2. Revised under Policy Guidelines section for use in children and adults to include one provocative stimulation test instead of two. Format changes. Codes J2940 and J2941 added and codes Q2015 and Q2016 deleted from the Billing and Coding section.
- 8/02 Specialty Matched Consultant Advisory Panel review 7/1/2002. No criteria changes. Format changes.
- 10/02 Revised under when it is not covered to include treatment of altered body habitus (e.g., buffalo hump) associated with antiviral therapy in HIV-infected patients.
- 8/03 Added statement to not covered section to indicate that growth hormone given to treat short stature in the absence of growth hormone deficiency is not covered. It is considered cosmetic. FDA - approved indications for Growth Hormone therapy that are cosmetic are not covered.
- 4/04 Benefits Application and Billing/Coding sections updated for consistency.
- 6/24/04 Specialty Matched Consultant Advisory Panel review. Added the name "Zorbtive™" to Description of Procedure or Service and to the Policy Key Words section. Added new indication of "Short Bowel Syndrome." under section When Growth Hormone (GH) is Covered. Corrected statement under Policy Guidelines section from "Chronic renal insufficiency is defined as a serum creatinine of less than 30 mg/dl" to "Chronic renal insufficiency is defined as a serum creatinine of greater than 1.5mg/dL". References added. Notification date 6/24/04. Effective date 8/26/04.
- 10/20/05 Two Specialty Matched Consultants reviewed the policy in September 2005. The "Description of Procedure or Service" section was revised. Under "When Growth Hormone is covered" a statement was added; "Note: The Medical Policy on Growth Hormone is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician." Small for gestational age and intrauterine growth retardation was added as a covered indication. In the "When Growth Hormone is not covered" section "precocious puberty, obesity,

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cystic fibrosis, idiopathic dilated cardiomyopathy and juvenile idiopathic arthritis" were added which are off-label indications and considered investigational. The "Policy Guidelines" section was revised to include specific criteria for intrauterine growth retardation and small for gestational age. A statement regarding the FDA caution in regards to use in adults over the age of 65 was added. The "Medical Definitions" section was updated. New brand names for growth hormone were added to the description and to the "Policy Key Words" section. References added.

- 6/19/06 Specialty Matched Consultant Advisory Panel review 5/18/06. Added additional information to "When Growth Hormone is covered" section, under the first criteria bullet to indicate "(documentation should include sequential growth chart data utilizing clinical growth charts which are consistent with those available through the CDC at [http://www.cdc.gov/nchs/about/major/nhanes/growthcharts/clinical\\_charts.htm](http://www.cdc.gov/nchs/about/major/nhanes/growthcharts/clinical_charts.htm) )". References added
- 10/2/06 Added "Omnitrope" to "Description" and "Key Words" section. Removed lab values from B.1 and B.2. under the "Policy Guidelines" section. It now states "B.1. For children and adults, Growth Hormone deficiency is defined as an abnormal response to one provocative stimulation tests (e.g., L-dopa, clonidine, glucagon, propranolol, arginine, or insulin challenge test). B.2. Chronic renal insufficiency is defined as elevated serum creatinine concentrations or a lower than normal creatinine clearance/glomerular filtration rate, less than 75 ml/ min per 1.73 m2.
- 2/12/07 A Specialty Matched Consultant reviewed the criteria for the added new indication 1/2007. Clarified "Somatropin has been marketed under multiple brand names including but not limited to:" in the "Description" section. In the section, "When Growth Hormone is Covered" added reference to the "Policy Guidelines" section for additional information. Added an additional covered indication; number "2. A 6 month trial of growth hormone may be considered medically necessary in children who do not fail a growth hormone (GH) stimulation test but are identified to have biochemical abnormalities in the growth hormone metabolic pathway" and listed criteria. Under the "When Not Covered" section, clarified number 1, added "chronic infectious disease" to number 3.d., and "or juvenile chronic arthritis" to 3.n. Added number 6 to the "Policy Guidelines" section regarding to growth velocity. References added.
- 7/14/08 Specialty Matched Consultant Review panel review 4/29/08. Reformatted the "When Covered", "When Not Covered", and "Policy Guidelines" sections. "Noonan syndrome" removed from the "When Not Covered" section and added to the "When Covered" section; "#4. Children with growth failure due to Prader-Willi Syndrome (PWS) or Noonan Syndrome." Reference to "AIDS" was changed to "HIV" in # C.1.in the "When Covered" section. References added. (btw)
- 6/22/10 Policy Number(s) removed (amw)
- 9/28/10 Specialty Matched Consultant Advisory Panel review 8/2010. Added the following statements to When Covered section: "a. Documentation of significant growth deceleration is sufficient for children with history of relevant CNS pathology or history of brain irradiation. b. Neonates with hypoglycemia and growth hormone deficiency (one abnormal GH test is sufficient for hypoglycemic neonates in whom growth hormone deficiency is suspected)" and "GH therapy may be resumed one year following kidney transplant if catch up growth has not occurred." References updated. (mco)
- 8/30/11 Specialty Matched Consultant Advisory Panel review 7/27/11. Policy accepted as written. (adn)

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Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.