Medical Policy

BlueCross BlueShield of Kansas
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Title: Human Growth Hormone

Pre-Determination of Services IS REQUIRED by the Member's Contract

Prior Authorization Form:
BCBSKS will review Prior Authorization requests
http://www.bcbsks.com/CustomerService/Forms/pdf/15-811_Growth_Hormone_PA.pdf

For information concerning Prior Authorization Prescription Drugs:
http://www.bcbsks.com/CustomerService/PrescriptionDrugs/prior_authorization.htm

Link to Drug List (Formulary):
http://www.bcbsks.com/CustomerService/PrescriptionDrugs/drug_list.htm

Professional
Original Effective Date: February 4, 1986
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Institutional
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Current Effective Date: January 30, 2014

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The BCBSKS Medical Policies contained herein are for informational purposes and apply only to members who have health insurance through BCBSKS or who are covered by a self-insured group plan administered by BCBSKS. Medical Policy for FEP members is subject to FEP medical policy which may differ from BCBSKS Medical Policy.

The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents of Blue Cross and Blue Shield of Kansas and are solely responsible for diagnosis, treatment and medical advice.

If your patient is covered under a different Blue Cross and Blue Shield plan, please refer to the Medical Policies of that plan.

DESCRIPTION

Human growth hormone (GH), also known as somatotropin, is synthesized in somatotropic cells of the anterior lobe of the pituitary gland.

Growth hormone binds to the surface of cells and stimulates the production of insulin growth factor-I (IGF-I). Insulin growth factor is responsible for many of the growth promoting effects attributed to growth hormone. Growth hormone stimulates all aspects of cartilage growth, and one of its major effects is to stimulate the growth of the epiphyseal cartilage plates of long bones. Other body tissues respond to the metabolic effect of growth hormone with increases in bone width and the growth of visceral and endocrine organs, skeletal and cardiac muscle, skin, and connective tissue. It also plays a role in the distribution and metabolism of fat in the body.

Growth hormone deficiency can occur due to a variety of conditions, such as:

- Pituitary tumor
- Pituitary dysfunction due to prior surgery or radiation treatment
- Extrapituitary tumor
- Sarcoidosis, and/or other infiltrating disorders
- Idiopathic

Growth hormone deficiency in children is manifested primarily by short stature. In adults, as well as in some children, other abnormalities associated with growth hormone deficiency are often evident. These include changes in body composition, higher levels of low-density lipoprotein (LDL) cholesterol, lower bone density, and a decreased self-reported quality of life compared to healthy peers. Some evidence also suggests that there may be increases in cardiovascular disease and overall mortality, but it is less clear whether growth hormone deficiency is causative for these outcomes.

Somatropin is polypeptide hormone of recombinant DNA origin and has an amino acid sequence identical to that of human pituitary GH.

Beginning in 1985, recombinant GH has been marketed for a variety of U.S. Food and Drug Administration (FDA)-labeled indications. However, these broadened patient selection criteria have remained controversial due to uncertainties in almost every step in the diagnosis and treatment process—selection of patients to be tested, limitations in the laboratory testing for GH, establishment of diagnostic cutoffs for normal versus abnormal GH levels, availability of the laboratory tests to predict response to GH therapy, changes in growth velocity due to GH therapy, whether resulting final height is significantly improved, and whether this improvement is clinically or emotionally significant for the patient. In addition, there are many ethical considerations regarding GH therapy, most prominently appropriate informed consent when the therapy is primarily requested by the parent due to their particular psychosocial concerns regarding height.

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

Target Drugs

Preferred Growth Hormone	Nonpreferred Growth Hormone
▪ Omnitrope	▪ Genotropin® ▪ Humatrope® ▪ Norditropin® ▪ Nutropin® ▪ Nutropin®AQ ▪ Saizen® ▪ Serostim® ▪ Tev-Tropin® ▪ Zorbtive®

Nonpreferred Growth Hormone products will be approved when the criteria for the preferred growth hormones are met and one of the following is met:

1. The patient's medication history indicated use of the preferred growth hormone product **OR**

2. The patient has documented intolerance, FDA labeled contraindication, or hypersensitivity to the preferred growth hormone product **OR**

3. The prescriber has submitted documentation in support of the use of the non-preferred growth hormone product, for the intended diagnosis which has been reviewed and approved by the Clinical Review pharmacist.

POLICY

A. Pediatric Growth Hormone Therapy

Growth hormone therapy is contractually excluded for those under age 18, except for the following specific conditions:

1. GH Deficiency or insufficiency meeting the following criteria:

   a. Insulin tolerance test with documented hypoglycemia (blood sugars less than 40 mg/dl) and peak GH value of <10ng/ml.

   OR

At least two provocative stimulation tests using arginine, clonidine, glucagon, growth hormone releasing hormone (GHRH), or levodopa with peak GH values <10 ng/ml on all tests.

AND

b. Growth failure as defined by the following age groups:
   - 0-6 months: <34 cm/year
   - 6-12 months: <15 cm/year
   - 1-3 years: <12 cm/year
   - Over three years to puberty (see definition of puberty below): <5 cm/year
   - Puberty (defined as bone age of 10 ½ -12 years for girls and bone age of 12 ½ -141/2 years for boys): <6 cm/year

Note: Growth rates should be tracked over at least one year (except age groups < 1 year).
Continuation of treatment with growth hormone therapy requires a growth rate above 2.5 cm/year.

2. Panhypopituitarism subject to meeting all of the following criteria:
   a. Deficiencies of 3 or more other pituitary hormones (TSH, ACTH, FSH/LH, antidiuretic hormone)
   b. Low IFG-1 concentration

   Note: Growth hormone stimulation testing is not required in these cases. Growth hormone therapy may be approved for life.

3. Turner, Prader-Willi, and Noonan Syndromes With Growth Failure subject to meeting all of the following criteria:
   a. Height less than the 2.5 percentile for age and sex
   b. Growth failure as defined by the following age groups:
      - 0-6 months: <34 cm/year
      - 6-12 months: <15 cm/year
      - 1 - 3 years: <12 cm/year
      - Over three years to puberty (see below definition of puberty): <5 cm/year
      - Puberty (defined as bone age of 10 1/2-12 years for girls and bone age of 12 1/2 -14 1/2 years for boys): <6 cm/year

   Note: Growth rates should be tracked over at least one year one (except age groups < 1 year).
   Growth hormone stimulation testing is not required in these cases.

4. Managing Ongoing Renal Dialysis Patients With Growth Failure subject to meeting all of the following criteria:
   a. End stage renal disease with serum creatinine greater than 1.5 mg/dl or GFR less than 75 ml/min/1.73m2 prior to successful transplant
   b. Under age 18
   c. With open epiphyses
   d. Height less than the 2.5 percentile for age and sex
   e. Growth failure as defined by the following age groups:
      - 0-6 months: <34 cm/year
      - 6-12 months: <15 cm/year
      - 1 – 3 years: <12 cm/year
      - Over three years to puberty (see below definition of puberty): <5 cm/year
      - Puberty (defined as bone age of 10 1/2-12 years for girls and bone age of 12 1/2 -14 1/2 years for boys): <6 cm/year
   f. Complicating factors have been treated including malnutrition and acidosis

   Note: Growth rates should be tracked over at least one year (except age groups < 1 year).
   Growth Hormone stimulation testing is not required.
   Growth Hormone is discontinued at the time of transplantation or other conditions below for termination of GH therapy.

Termination of Growth Hormone Therapy

Growth hormone therapy is no longer covered when any one of the following criteria is met:

1. Epiphyseal fusion has occurred
2. Mid-parental height is achieved. Mid-parental height = (father's height + mother's height) divided by 2, plus 2.5 inches (6.4 cm) (male) or minus 2.5 inches (6.4 cm) (female)
3. Failure to respond to growth hormone therapy with a growth rate of less than 2.5 cm/year

DOCUMENTATION

Documentation needed for predetermination is:

- Growth charts with at least 3 measurements over at least one year
- Growth hormone stimulation testing results
- Other supporting documentation

Length of Approval: Growth hormone therapy approved for life (e.g., panhypopituitarism, or when adult GH therapy requirements are met) will need continued review for benefits.

B. Adult Growth Hormone Therapy

1. Growth hormone therapy is excluded for those over the age of 18 with the following exceptions:
   a. Hypothalamic or pituitary disease or injury and laboratory proven growth hormone deficiency by GH stimulation testing.
   b. Childhood onset of growth hormone deficiency and deficiency is demonstrated by GH stimulation retesting during adulthood
   c. Panhypopituitarism with deficiencies of 3 or more other pituitary hormones (TSH, ACTH, FSH/LH, antidiuretic hormone) and low values for IGF-1

2. Growth hormone stimulation for GH deficiency must be documented by the following criteria:
   a. Insulin tolerance test with documented hypoglycemia (blood sugars less than 40 mg/dl) and peak growth hormone values < 5ng/ml,

      OR

   b. Arginine-GHRH stimulation test (peak growth hormone values <4.1ng/ml)

      OR

   c. Arginine L-Dopa stimulation test (peak growth hormone values <1.5ng/ml)

      OR

   d. Glucagon stimulation test (peak growth hormone values <3ng/ml)

      OR

   e. A below normal level of IFG-1 when associated with panhypopituitarism with documented multiple hormone deficiencies (3 or more deficiencies: TSH, ACTH, FSH/LH, antidiuretic hormone) as a result of pituitary or hypothalamic disease secondary to tumor, surgery, inflammation, radiation therapy, severe head trauma or structural abnormality (septo-optic dysplasia, ectopic neurohypophysis). Growth hormone stimulation testing is not necessary in these cases.

3. Continuation of approval for growth hormone therapy requires some indication of a clinical response to the growth hormone during the first 12 months of therapy: weight loss, improvement on lipid profile, increased bone mass, increased muscle strength or increase of IGF-1 into the normal range. Children on GH therapy who continue growth GH therapy into adulthood or adults with hypopituitarism of recent onset will not exhibit the manifestations of adult GH deficiency and will not show the improvements listed above.

Length of Approval: 12 months
Growth hormone therapy approved for life will need continued review for benefits.

Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Policy Guidelines

1. Only about 25% of those children with documented GH deficiency will be found to have GH deficiency as adults. Therefore, once adult height has been achieved, subjects should be retested for GH deficiency to determine if continuing replacement therapy is necessary.
2. The FDA cautions that the safety and effectiveness of GH therapy in adults aged 65 and older has not been evaluated in clinical studies. Therefore, it is noted that elderly patients may be more sensitive to the action of GH therapy and may be more prone to develop adverse reactions.
3. Growth hormone is contraindicated in patients with PWS, who are severely obese or who have severe respiratory impairment.
4. Insulin tolerance testing is contraindicated in patients with cardiovascular disease, cerebrovascular disease, seizure disorders or patients older than 65 years.
5. Member Contract Language:
   Growth Hormone therapy is covered only for the following:
   If under age 18 and:
   a. Both laboratory proven growth hormone deficiency or insufficiency and significant growth retardation; or
   b. Substantiated Turner's Syndrome, Prader-Willi Syndrome, or Noonan's Syndrome with significant growth retardation; or
   c. Chronic renal insufficiency and end stage renal disease with significant growth retardation prior to successful transplantation; or
   d. Panhypopituitarism

   If age 18 and over and:
   a. Evidence of pituitary or hypothalamic disease or injury and laboratory proven growth hormone deficiency; or
   b. Prior growth hormone therapy for growth hormone deficiency or insufficiency in childhood and laboratory confirmation of continued growth hormone deficiency.

RATIONALE

Outcome Measures in Growth Hormone Research

The most common outcome measure reported in growth hormone research is change in height. For some situations, such as in patients with documented growth hormone deficiency or genetic disorder and short stature, improvements in height alone may be a sufficient outcome measure. However, in most situations, a change in height is not in itself sufficient to demonstrate that health outcomes are improved. There is not sufficient evidence to establish that short stature is associated with substantial impairments in psychological functioning or quality of life, nor is there evidence that increases in height improve these parameters. Similarly, improvements in other measures of body composition such as muscle mass or muscle strength are not in themselves sufficient to establish that health outcomes are improved. Therefore, for most conditions in this literature review, changes in other outcome measures such as functional status, quality of life, or disease-specific clinical outcomes, are necessary to demonstrate an improvement in health outcomes.

Safety of GH treatment

Adverse effects can occur with GH treatment. In children, increased rates of skeletal problems such as worsening of scoliosis can occur in association with a rapid growth spurt. In adults, arthralgias, edema, and carpal tunnel syndrome are common. Less common adverse effects include pancreatitis and gynecomastia. (1, 2)

There is concern that GH treatment may increase the rate of malignancy, particularly de novo leukemia in patients without risk factors. To date, there is insufficient evidence of a causative relationship between GH treatment and malignancy rates. The largest study published to date on the association of growth hormone (GH) treatment with malignancy includes data on 54,996 included in a postmarketing surveillance registry established by Genentech, Inc. (3) The most common indications for GH use among children in the database were idiopathic growth hormone deficiency (GHD) (42.5%), idiopathic short stature (17.8%), organic GH deficiency (15.2%), and Turner's syndrome (9.3%). As of January 1, 2006, a total of 4,084 adverse events (6.2%), including 1,559 (2.4%) serious adverse events and 174 (0.3%) deaths, had been reported. Investigators assessed 19 of 174 deaths (11% of deaths) as related to GH treatment. Twelve of the 19 GH-associated deaths were due to neoplasms (0.1% of children in the registry), and the other 7 deaths were each due to a different cause. Overall, intracranial malignancies of nonpituitary origin were reported in 243 patients; 44 were new-onset malignancies. In addition, extracranial malignancies, including leukemia, were reported in 87 patients; 63 were new-onset extracranial malignancies. The authors reported that 36 new-onset malignancies (intracranial and extracranial combined) occurred in individuals without risk factors; 29 of the 36 cases were confirmed as being enrolled in the registry. The rate of new-onset malignancy did not exceed the rate expected in the general population (standard incidence ratio=1.12, 95% confidence interval [CI]: 0.75 to 1.61). This study lacked a concurrent comparison with untreated patients to compare actual rates of malignancy and other adverse events.

A 2012 analysis of long-term mortality after GH treatment was conducted by Carel and colleagues using French registry and vital statistics data. (4) A total of 6,928 children who initiated GH treatment between 1985 and 1996 were included in the study. Indications for GH therapy included idiopathic isolated GH deficiency (n=5162), neurosecretory dysfunction (n=534), idiopathic short stature (n=871), and born small for gestational age (n=335). The mean dose of GH used was 25 ug/kg/day and the mean treatment duration was 3.9 years.

Patients were followed for a mean of 17.3 years. As of September 2009, follow-up data on vital status were available for 6,558 (94.7%) of participants. Ninety-three of the 6,558 individuals (1.42%) had died. The mortality rate was significantly higher in patients treated with GH than the number that would be expected on the basis of year, sex or age (standardized mortality ratio [SMR]: 1.33, 95% CI: 1.08-1.64). Cox survival analysis found that male sex and higher dose of GH were independent predictors of mortality risk. Examination of the causes of death found a significant increase in mortality due to circulatory system diseases. In addition, there was a significant increase in the number of deaths due to bone tumors (3 observed deaths vs. 0.6 expected deaths) but not other types of cancers or overall cancer deaths. There was also a significant increase in the number of deaths due to cerebral or subarachnoid hemorrhage (4 observed deaths vs. 0.6 expected). The authors noted that the analysis of factors associated with the increased mortality rate was limited by the small number of events in any demographic group or any particular cause of death. Due to the small number of deaths in this sample, conclusions cannot be drawn from these data on the impact of GH therapy on mortality risk. Additional data will be examined as they become available.

Growth Hormone Deficiency

Once a true GH deficiency has been established in association with clinical symptoms of GH deficiency, there is a compelling rationale for treatment with exogenous GH. There are also RCTs that support the benefits of GH replacement in terms of increasing height and alleviating secondary effects of GH deficiency. A few representative trials are discussed below.

Growth hormone deficiency in children

In children with GH deficiency, treatment increases growth velocity and final height. Root and colleagues followed approximately 20,000 children for a period of 9 years as part of the National Cooperative Growth Study (NCGS). (5) Growth velocity improved compared to pre-treatment values, and this improvement was maintained for at least 4 years. For children who were treated for at least 7 years, there were improvements in the mean height standard deviation scores that ranged from 1.3 to 2.5, depending on the specific underlying condition. If treatment is started at an early age, the majority of children can achieve a final height close to that expected from parental height. In a study of 1,258 patients in the Pfizer International Growth Database, the standard deviation for differences between the final height achieved and the midrange of predicted height from parental values ranged between -0.6 and +0.2, depending on the specific underlying condition. (6)

Growth Hormone Deficiency in Adults

In adults with GH deficiency, there is evidence from randomized controlled trials (RCTs) that treatment leads to increases in lean body mass and decreases in body fat. (7) Meta-analyses of RCTs have shown evidence for increases in muscle strength and exercise capacity, although this was not a robust finding across all studies. (8, 9) There is also RCT evidence for improvements in bone mineral density. (10) The evidence on other outcomes such as quality of life, lipid profiles, cardiovascular disease, and total mortality is not consistent and is insufficient to determine whether these outcomes are improved with treatment. (11-14)

Growth Failure Due to Prader-Willi Syndrome

The majority of children with Prader-Willi syndrome have hypothalamic dysfunction and are GH deficient. Use of human growth hormone (HGH) for children with growth failure due to Prader-Willi syndrome is an FDA-approved indication. The value of testing for GH deficiency before treatment in these patients is questionable. None of the clinical studies selected patients for treatment based on presence or absence of GH, nor were results reported separately for those with or without GHD. Information from the product label indicates that the height SDS for Prader-Willi syndrome children in the clinical studies was -1.6 or less (height was in the 10th percentile or lower.)

Several studies have shown patient improvements with use of GH. For example, a 2008 randomized study reported by Festen et al. involving 42 infants and 49 children, showed that GH treatment significantly improved height, body mass index (BMI), head circumference, and body composition. (15)

According to the drug prescribing information, GH therapy use has been associated with sudden death in children with Prader-Willi syndrome. (16) These deaths occurred among children who were severely obese or had severe respiratory impairment; these are now considered to be contraindications to GH treatment use (see Description section of this policy).

For adults with Prader-Willi syndrome, the benefits of GH treatment are less apparent, and treatment of adults with Prader-Willi syndrome is not an FDA-approved indication for GH (Genotropin). In 2012, Sode-Carlsen and colleagues in Scandinavia evaluated GH therapy for adults with genetically verified Prader-Willi syndrome. (17) In the RCT, patients were randomized to receive 12 months of GH treatment or placebo. The authors reported a number of outcomes related to body composition and laboratory test results; they did not specify a primary outcome. In addition, the authors primarily reported within-group outcomes For example, in the GH-treated group, after 1 year, lean body mass increased a mean of 2.25 kg ($p=0.005$ compared to baseline), and fat mass decreased by a mean of 4.2 kg ($p<0.001$ compared to baseline). In the same time period, there was no significant change in lean body mass in the placebo group and a significant increase ($p<0.001$) in fat mass (change in kg was not reported for the placebo group). During the 12-month treatment period, no significant changes were found in either group on other variables including in levels of high-density lipoprotein (HDL)-cholesterol or triglycerides, peak expiratory flow, fasting glucose, fasting insulin and physical function. During the 12-month treatment period, the level of low-density lipoprotein (LDL)-cholesterol decreased significantly more in the GH-treated compared to control group (mean difference of 0.27 mmol/l, $p=0.047$). This study presents insufficient evidence that GH therapy is effective for improving health outcomes in adults with Prader-Willi syndrome.

Conclusions: For patients with documented GH deficiency and clinical manifestations such as short stature, GH replacement has been shown to improve growth velocity and final height achieved. In addition, it can ameliorate the secondary manifestations of GH deficiency seen primarily in older children and adults. Therefore, GH replacement may be considered medically necessary for these indications. For children with Prader-Willi Syndrome and growth failure, GH deficiency is assumed, and GH replacement may be considered medically necessary without documentation of GH deficiency.

Conditions without Growth Hormone Deficiency

GH Use in Children with Short Stature Associated with Chronic Renal Insufficiency

In 2012, Hodson and colleagues published a Cochrane review of RCTs evaluating GH treatment in children with chronic kidney disease. (18) To be included in the review, trials needed to include children 18 years-old or younger who were diagnosed with chronic kidney disease and were pre-dialysis, on dialysis, or post-transplant. In addition, trials needed to compare GH treatment with placebo, no treatment or a different GH regimen and needed to include height outcomes. A total of 7 RCTs with 809 children met the review criteria. Study entry criteria varied e.g., ranging from less than 3rd percentile for chronological age to less than 50th percentile for chronological age. Overall, treatment with GH (28 IU/m2/week) compared with placebo or no specific therapy resulted in a statistically significant increase in height standard deviation score at 1 year (8 studies, mean difference [MD]: 0.82: 95% CI: 0.56 to 1.07). Moreover, a pooled analysis of 7 studies found a significant increase in height velocity at 1 year in the group receiving GH treatment compared to control (MD: 3.88 cm/year, 95% CI: 3.32 to 4.44).

For example, Hokken-Koelega and colleagues in the Netherlands conducted a double-blind placebo-controlled crossover trial in 20 prepubertal children with severe growth retardation and chronic renal failure. (19) Entry criteria included height velocity less than the 25% percentile for chronological age. Patients received 6 months of subcutaneous injection of GH (4 IU/m2 per day) before or after 6 months of placebo injection. There was a 2.9 cm greater increase in height velocity per 6 months with GH compared to placebo. Long-term follow-up data on children in this and other Dutch RCTs (maximum of 8 years of treatment) were published in 2000. (20) GH treatment resulted in significant improvement in the height standard deviation score (SDS) compared to baseline scores (-<0.001). Moreover, the mean height SDS reached the lower end (-2 SDS) of the normal growth chart after 3 years of treatment. Puberty began at a median age that was within the normal range for girls and boys, and GH therapy did not result in significant effects on parathyroid hormone concentration, and there were no radiological signs of renal osteodystrophy.

GH Therapy as a Treatment of Altered Body Habitus Related to Antiretroviral Therapy for HIV Infection

There has been research interest in the use of GH to treat the altered body habitus that may be a complication of antiretroviral therapy for human immunodeficiency virus (HIV) infection. Body habitus changes, also referred to as the fat redistribution syndrome, include thinning of the face, thinning of the extremities, truncal obesity, breast enlargement, or an increased dorsocervical fat pad ("buffalo hump"). (21) However, there is minimal published literature regarding the use of GH for this indication. The literature is dominated by letters to the editors and small case series. The largest case series was reported by Wanke and colleagues who treated 10 HIV-infected patients with fat redistribution syndrome with GH for 3 months. (22) The authors reported improved waist/hip ratio and mid-thigh circumference.

Turner's Syndrome

Short stature is almost universal in Turner's syndrome. Poor growth is evident in utero and further deceleration occurs during childhood and at adolescence. The mean adult height for those with Turner's syndrome is 58 inches (4 feet, 10 inches). Unlike Prader-Willi syndrome, growth hormone deficiency is not seen. The FDA approvals for GH were based on the results of

randomized, controlled clinical trials that included final adult height as the outcome. For example, a group of patients with Turner's syndrome given Humatrope at a dosage of 0.3 mg/kg/week for a median of 4.7 years achieved a final height of 146.0 +/- 6.2 cm (57.5 +/-2.25 inches) compared to an untreated control group who achieved a final height of 142.1 +/- 4.8 cm (56 +/- 2 inches). (23)

In 2007, a Cochrane review identified 4 RCTs (total n=365) evaluating GH for treating Turner's syndrome. (24) Studies included children who had not yet achieved final height, treated children for at least 6 months, and compared GH to placebo or no treatment. Only one trial reported final height, so findings on this outcome could not be pooled. A pooled analysis of 2 trials found that short-term growth velocity was greater in treated than untreated children (MD: 3 cm per year, 95% CI: 2 to 4 cm per year).

Short Stature Due to Noonan Syndrome

In 2007, the FDA approved use of GH (Norditropin) for treatment of short stature in children with Noonan syndrome. This approval was based on a comparative study of 21 children that showed improvement in height and growth velocity in those with short stature due to Noonan syndrome. (25)

GH Therapy for Severe Burns

Mortality was studied in a controlled trial of 54 adult burn patients who survived the first 7 post-burn days. (28) Those patients showing difficulty with wound healing were treated with recombinant human GH (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 ($p<0.05$). (29) For the average 60% TBSA-burned patient, this approximates a length of stay reduction from 46 to 32 days. Singh and colleagues 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%). (30) Demling found significantly improved weight retention and wound healing time with GH or oxandrolone compared to standard treatment in 36 adults with severe burns. (31)

Two Phase III double-blind RCTs 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. (32) The potential for increased mortality prompted additional studies in critically burned pediatric patients. Ramirez and colleagues retrospectively studied 263 pediatric burn patients; those treated with GH had no increase in mortality from matched patients who did not receive GH. (33)

However, an RCT in 56 children with more than 40% total body surface area burns found no benefit of GH alone compared to or in combination with propanolol. (34) Another placebo-controlled trial found no benefit to GH with regard to length of hospitalization in 24 adult patients with severe burns. (35)

GH Therapy to Prevent Growth Delay in Children with Severe Burns

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. (36) Aili Low and colleagues 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. (37)

GH Therapy in Conjunction with Optimal Management of Short Bowel Syndrome.

Short bowel syndrome is experienced by patients who have had 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. The FDA label for Zorbtive indicates that GH has been shown in human clinical trials to enhance the transmucosal transport of water, electrolytes, and nutrients. 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 4-week period had significantly greater reductions in the weekly total volume of intravenous parenteral nutrition required for nutritional support. However, the effects beyond 4 weeks were not evaluated nor were the treatment locations (inpatient vs. outpatient) identified.

A 2010 Cochrane review identified 5 RCTs evaluating GH therapy for treating short bowel syndrome. (38) Studies evaluated GH with or without glutamine treatment. The primary outcome was change in body weight. A pooled analysis of 3 small trials (total n=30) found a statistically significant difference in weight change when patients were treated with GH or placebo (MD, 1.66 kg, 95% CI: 0.69 to 2.63, p=0.0008).

Several published studies have also demonstrated improved intestinal absorption in short bowel syndrome patients receiving parenteral nutrition. (39, 40) However, studies have noted that the effects of increased intestinal absorption are limited to the treatment period. (40, 41) Specialized clinics may offer intestinal rehabilitation for patients with short bowel syndrome; GH may be one component of this therapy.

Practice Guidelines and Position Statements

An Endocrine Society clinical practice guideline on adult growth hormone deficiency, updated in 2011, includes the following statements (62):

- The Task Force recommends that GH therapy of GH-deficient adults offers significant clinical benefits in body composition and exercise capacity
- The Task Force suggests that GH therapy of GH-deficient adults offers significant clinical benefits in skeletal integrity
- The Task Force recommends after documentation of persistent GHD that GH therapy be continued after completion of adult height to obtain full skeletal/muscle maturation during the transition period

In 2009, the American Association of Clinical Endocrinologists (AACE) issued updated guidelines on growth hormone use in growth hormone-deficient adults and transition patients. (64) Evidence-based recommendations include the following:

- Growth hormone deficiency (GHD) is a well-recognized clinical syndrome in adults that is associated with significant comorbidities if untreated
- Growth hormone (GH) should only be prescribed to patients with clinical features suggestive of adult growth hormone deficiency and biochemically proven evidence of adult growth hormone deficiency
- No data are available to suggest that GH has beneficial effects in treating aging and age-related conditions and the enhancement of sporting performance; therefore, the guideline developers do not recommend the prescription of GH to patients for any reason other than the well-defined approved uses of the drug.
- "There is no evidence that one GH product is more advantageous over the other, apart from differences in pen devices, dose increments and decrements, and whether or not the product requires refrigeration; therefore, we do not recommend the use of one commercial GH preparation over another"

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

CPT/HCPCS

96372	Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); subcutaneous or intramuscular
J2940	Injection, somatrem, 1 mg (use this code for Protropin)
J2941	Injection, somatropin, 1 mg (Use this code for Humatrope, Genotropin Nutropin, Biotropin, Genotropin, Genotropin Miniquick, Norditropin, Nutropin, Nutropin AQ, Omintrope, Saizen, Saizen Somatropin RDNA Origin, Zorbtive)
Q0515	Injection, sermorelin acetate, 1 mcg
S9558	Home injectable therapy; growth hormone, including administrative services, professional pharmacy services, care coordination, and ll necessary supplies and equipment, (drugs and nursing visits coded separately) per diem

DIAGNOSES

253.0	Acromegaly and gigantism
253.1	Other and unspecified anterior pituitary hyperfunction
253.2	Panhypopituitarism
253.3	Pituitary dwarfism
253.4	Other anterior pituitary disorders
253.6	Other disorders of neurohypophysis
253.7	Iatrogenic pituitary disorders
253.8	Other disorders of the pituitary and other syndromes of diencephalohypophysial origin
585.3	Chronic kidney disease (CKD), Stage III (Moderate)

585.4 Chronic kidney disease (CKD), Stage IV (Severe)
585.5 Chronic kidney disease (CKD), Stage V
585.6 End stage renal disease (ESRD)
585.9 Chronic kidney disease (CKD), unspecified
758.6 Gonadal dysgenesis (Turner's syndrome)
759.81 Prader-Willi syndrome
759.89 Other specified anomalies, other

ICD-10 DIAGNOSES *(Effective October 1, 2014)*
E22.0 Acromegaly and pituitary gigantism
E22.1 Hyperprolactinemia
E22.2 Syndrome of inappropriate secretion of antidiuretic hormone
E23.0 Hypopituitarism
E23.0 Hypopituitarism
E23.1 Drug-induced hypopituitarism
E23.6 Other disorders of pituitary gland
E24.1 Nelson's syndrome
E89.3 Postprocedural hypopituitarism
N18.3 Chronic kidney disease, stage 3 (moderate)
N18.4 Chronic kidney disease, stage 4 (severe)
N18.5 Chronic kidney disease, stage 5
N18.6 End stage renal disease
Q87.1 Congenital malformation syndromes predominately associated with short stature
Q96.9 Turner's syndrome, unspecified

REVISIONS

01-30-2014	Both Pediatric and Adult Growth Hormone medical policies have been incorporated into the newly titled "Human Growth Hormone" medical policy.
	Updated Description section.
	In Policy section: • Pediatric Growth Hormone policy language was revised from the following: Growth hormone is contractually excluded except for the following specific situations: 1. Deficiency Growth hormone has been approved for reimbursement subject to meeting all of the following criteria: a. Failure to respond (GH less than 10 ng/ml) to two hormones secretagogues (arginine, clonidine, glucagon, insulin, or levodopa) b. Growth failure as defined by the following age groups:☐☐0- 6 months: <34 cm/year • 6 - 12 months: <15 cm/year • 1 - 3 years: <12 cm/year • Over three years to puberty (see definition of puberty below): <5 cm/year • Puberty (defined as bone age of 10 1/2 - 12 years for girls and bone age of 12 1/2 -14 1/2 years for boys): <6 cm/year Note: Growth rates should be tracked over at least one year. Note: Continuation of treatment with growth hormone therapy requires a growth rate above 2.5 cm/year. 2. Insufficiency or Partial Deficiencies Growth hormone has been approved for reimbursement subject to meeting all of the following criteria:

a. Failure to respond (GH less than 15 ng/ml) to two hormones secretagogues (arginine, clonidine, glucagon, insulin, or levodopa)
b. Height less than the 2.5 percentile
c. Growth failure as defined by the following age groups:
- 0 – 6 months: <34 cm/year
- 6 – 12 months: <15 cm/year
- 1 - 3 years: <12 cm/year
- Over three years to puberty (see definition of puberty below): < 5 cm/year
- Puberty (defined as bone age of 10 1/2 -12 years for girls and bone age of 12 1/2 -14 1/2 years for boys): <6 cm/year

Note: Growth rates should be tracked over at least one year.
Note: Continuation of treatment with growth hormone therapy requires a growth rate above 2.5 cm/year.

3. Panhypopituitarism

Growth hormone has been approved for reimbursement subject to meeting all of the following criteria:
a. Deficiencies of 2 or more other pituitary hormones (TSH, ACTH, FSH/LH, antidiuretic hormone)
b. Low values for IGF-1

Note: Growth hormone stimulation testing is not required in these cases.
Note: Growth hormone therapy may be approved for life.

4. Turner, Prader-Willi, and Noonan Syndromes With Growth Failure

Growth hormone has been approved for reimbursement subject to meeting all of the following criteria:
a. Height less than the 2.5 percentile for age and sex
b. Growth failure as defined by the following age groups:
- 0 – 6 months: < 34 cm/year
- 6 – 12 months: < 15 cm/year
- 1 - 3 years: <12 cm/year
- Over three years to puberty (see below definition of puberty): <5 cm/year
- Puberty (defined as bone age of 10 1/2-12 years for girls and bone age of 12 1/2 -14 1/2 years for boys): <6 cm/year

Note: Growth rates should be tracked over at least one year.

Note: Growth hormone stimulation testing is not required in these cases.

5. Managing Ongoing Renal Dialysis Patients With Growth Failure

Growth hormone has been approved for reimbursement subject to meeting all of the following criteria:
a. End stage renal disease with GFR less than 75 ml/min/1.73m2 prior to successful transplant
b. Under age 18
c. With open epiphyses
d. Height less than the 2.5 percentile for age and sex
e. Growth failure as defined by the following age groups:
- 0 – 6 months: <34 cm/year
- 6 – 12 months: < 15 cm/year□ 1 – 3 years: <12 cm/year
- Over three years to puberty (see below definition of puberty): <5 cm/year
- Puberty (defined as bone age of 10 1/2-12 years for girls and bone age of 12 1/2 -14 1/2 years for boys): <6 cm/year

f. Complicating factors have been treated including malnutrition and acidosis

Note: Growth rates should be tracked over at least one year.
Note: Growth Hormone stimulation testing is not required.

Termination of Growth Hormone Therapy

Growth hormone therapy is no longer covered when any one of the following criteria is met:

	1. Epiphyseal fusion has occurred 2. Mid-parental height is achieved. Mid-parental height = (father's height + mother's height) divided by 2, plus 2.5 inches (6.4 cm) (male) or minus 2.5 inches (6.4 cm) (female) 3. Failure to respond to growth hormone therapy with a growth rate of less than 2.5 cm/year NOTE: When a consultant recommends that growth hormone treatment be given for the life of the patient, it will no longer be necessary to re-review for medical necessity. It will be necessary, however, to review for benefits. Such instances may include: 1. Panhypopituitarism, or 2. When adult growth hormone therapy requirements are met (see Adult Growth Hormone policy) Documentation needed for predetermination are: DOCUMENTATION • Growth charts with at least 3 measurements over at least one year • Growth hormone stimulation testing results • Adult Growth Hormone policy language was revised from the following: 1. Growth hormone therapy is excluded for insureds over the age of 18 with the following exceptions: a. Those Insureds over the age 18 with: • Demonstrated hypothalamic or pituitary disease or injury; and • Laboratory proven growth hormone deficiency b. Those Insureds over the age of 18 who have had childhood onset of growth hormone deficiency and have had that deficiency demonstrated by testing during childhood. c. Those Insureds over the age 18 with Panhypopituitarism with deficiencies of 3 or more other pituitary hormones (TSH, ACTH, FSH/LH, antidiuretic hormone) and low values for IGF-1. 2. Growth hormone deficiency must be documented by the following criteria: a. Biochemical testing by means of a subnormal response to standard growth hormone stimulation test (peak growth hormone values <5ng/ml to provocative stimuli). Insulin tolerance test with documented hypoglycemia (blood sugars less that 40mg/dl or 50% decrease from baseline) with symptoms is the standard test. When Insulin Tolerance test is contraindicated in a given insured, Growth Hormone Releasing Hormone/arginine can be used as an alternate testing procedure. L-dopa, glucagon or clonidine is not acceptable secretagogues in adults. OR b. A below normal level of IGF-1 (less than 84 µg/liter) constitutes laboratory proof of growth hormone deficiency when associated with panhypopituitarism with documented multiple hormone deficiencies (3 or more deficiencies: secondary hypothyroidism, ACTH deficiency, gonadotropin deficiency, diabetes insipidus) as a result of pituitary or hypothalamic disease secondary to tumor, surgery, inflammation, radiation therapy, severe head trauma or structural abnormality (septo-optic dysplasia, ectopic neurohypophysis). Growth hormone stimulation testing is not necessary in these cases. 3. Continuation of approval for growth hormone therapy requires some indication of a clinical response to the growth hormone during the first 12 months of therapy; weight loss, improvement on lipid profile, increased bone mass, increased muscle strength or increase of IGF1 into the normal range. Children on growth hormone therapy who continue growth hormone therapy into adulthood or adults with hypopituitarism of recent onset will not exhibit the sequelae of adult growth hormone deficiency and will not show the improvements listed above.

	NOTE: If consultant decides that growth hormone treatment will be given for the rest of the life of the patient, it will no longer be necessary for Medical Review to re-review for medical necessity. It will be necessary, however, to review for benefits. UTILIZATION If growth hormone is approved for an adult, and there has been demonstrative clinical improvement maintained for 1 year or more, periodic review beyond that will be unnecessary for these adults.
	Updated Rationale section.
	In Coding section: ▪ Removed CPT code 90772 (Deleted code 01-01-2009). ▪ Added ICD-10 diagnosis codes. *(Effective October 1, 2014)*
	Updated Reference section.

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