BlueCross BlueShield of Kansas City

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Human Growth Hormone

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Policy

BCBSKC will provide coverage for human growth hormone when it is determined to be medically necessary because the criteria shown below are met.

When Policy Topic is covered

Recombinant human GH therapy may be considered **medically necessary** for the following patients (see specific patient selection criteria in Policy Guidelines):

1. Children with proven GH deficiency
2. Children with height less than 3rd percentile for chronologic age with chronic renal insufficiency
3. Patients with AIDS wasting
4. Adults with proven GH deficiency
5. Patients with Turner's syndrome
6. Children with growth failure due to Prader-Willi syndrome
7. Patients with short stature due to Noonan syndrome
8. Promotion of wound healing in burn patients
9. Prevention of growth delay in children with severe burns
10. Patients with short bowel syndrome receiving specialized nutritional support in conjunction with optimal management of short bowel syndrome

When Policy Topic is not covered

The following FDA-approved indications are considered **not medically necessary**:

1. Pediatric patients born small for gestational age (SGA) who fail to show catch-up growth by age 2 years

2. Children with height standard deviation score of -2.25 or below without documented GH deficiency

Investigational applications for recombinant human growth hormone therapy include, but are not limited to, the following:

3. Constitutional delay (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)

4. In conjunction with gonadotropin-releasing hormone (GnRH) analogs as a treatment of precocious puberty

5. GH therapy in older adults without proven deficiency

6. Anabolic therapy except for AIDS provided to counteract acute or chronic catabolic illness (e.g., surgery outcomes, trauma, cancer, chronic hemodialysis, chronic infectious disease) producing catabolic (protein wasting) changes in both adult and pediatric patients

7. Anabolic therapy to enhance body mass or strength for professional, recreational, or social reasons

8. Glucocorticoid-induced growth failure

9. Short stature due to Down's syndrome

10. Treatment of altered body habitus (e.g., buffalo hump) associated with antiviral therapy in HIV-infected patients

11. Treatment of obesity

12. Treatment of cystic fibrosis

13. Treatment of idiopathic dilated cardiomyopathy

14, Treatment of juvenile idiopathic or juvenile chronic arthritis

15. Treatment of children with "genetic potential" (i.e., lower than expected height percentiles based on parents' height

Policy Guidelines

The numbered guidelines correspond to the indications listed in the Policy section above.

Medically Necessary Indications:

1. Both children and adults with proven GH deficiency are considered appropriate candidates for GH therapy.

For adults, proven GH deficiency is defined as:

a. An abnormal response to TWO provocative stimulation tests, such as L-dopa, clonidine, glucagons, arginine, GH-releasing hormone (GHRH), or insulin. The insulin tolerance test is considered the best predictor of GH deficiency; however, this test is contraindicated in patients with seizures or coronary artery disease. A provocation test using arginine and GHRH is also acceptable and is considered more stringent than tests using arginine alone or levodopa alone. Although an abnormal GH response has been traditionally defined as less than 10 ng/ml, different tests have different potencies, and the cutoff is likely to be lower when using monoclonal-based GH assays and recombinant human GH reference preparations. 24-hour continuous measurements of GH, serum levels of IGF-I, or serum of levels IGFBP are considered inadequate to document GH deficiency.
b. An abnormal response to ONE provocative stimulation test in patients with defined central nervous system pathology, history of irradiation, multiple pituitary hormone deficiency, or a genetic defect.
c. Low IGF-I concentration in patients with complete hypopituitarism.

For children, proven GH deficiency is defined as:

a. An abnormal response of less than 10 ng/ml to at least two provocative stimulation tests, such as insulin, levodopa, arginine, clonidine or glucagon; AND
b. Delayed bone age: 2 standard deviations or more below the 50th percentile for age and gender (this does not apply to children with subnormal GH levels due to pituitary surgery or radiation therapy); AND
c. Evidence that the patient does not have other reasons for short stature, including hypothyroidism; AND
d. One of the following:
    i. Height less than the 3rd percentile for normal or 2 standard deviations below the 50th percentile for age; OR

ii. Growth velocity less than the 10th percentile of normal as tracked over at least one year.

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 or when epiphyseal fusion has occurred.

2. Chronic renal insufficiency is defined as a serum creatinine of greater than 1.5 mg/dL (or 1.4 for women and 1.7 for men) or a creatinine clearance <75 mL/min per 1.73 m2. 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.
3. AIDS (acquired immunodeficiency syndrome) wasting is defined as a greater than 10% of baseline weight loss that cannot be explained by a concurrent illness other than HIV (human immunodeficiency virus) infection. Patients treated with GH must simultaneously be treated with antiviral agents. Therapy is continued until this definition is no longer met.
4. Adults with GH deficiency are defined as in No. 1 above. 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. These transition patients who require further treatment are usually started at doses of 0.4 to 0.8 mg/day, and titered to maintenance doses of 1.2 to 2.0 mg/day. Adults with GH deficiency not related to idiopathic deficiency of childhood (e.g., pituitary tumor, pituitary surgical damage, irradiation, trauma) are usually started at 0.1 to 0.3 mg/day; the dose is titered to clinically desired end points (improved body composition, quality of life, reduction in cardiovascular risk factors), usually resulting in maintenance doses of 0.2 to 0.5 mg/day for men and 0.4 to 1.0 mg/day for women. The FDA cautions that the safety and effectiveness of GH therapy in adults aged 65 and over 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.
5. Turner’s syndrome is defined as a 45, XO genotype.
6. Prader-Willi syndrome 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. GH deficiency has been demonstrated in most tested patients with Prader-Willi syndrome.
7. GH therapy for burn patients should be limited to those patients with 3rd-degree burns.
8. Children with severe burns have been successfully treated with 0.05 to 0.2 mg/kg rhGH per day during acute hospitalization and for up to 1 year after burn.
9. Growth hormone for patients with short bowel syndrome should be limited to patients receiving specialized nutritional support 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. Optimal management may include dietary adjustments, enteral feedings, parenteral nutrition, fluid, and micronutrient supplements. Zorbtive is administered daily at 0.1mg/kg subcutaneously up to 8 mg/day. Administration of Zorbtive for longer than 4 weeks has not been adequately studied per the FDA indications.

Not Medically Necessary Indications:

1. Pediatric patients born small for gestational age. There are no established criteria for small for gestational age or “catch-up” growth. However, in the data submitted to the FDA as part of the approval process, the mean height of enrolled patients was at least 2 standard deviations below the mean. Absence of catch-up growth was defined as a height velocity below 1 standard deviation score, adjusted for age.

2. Pediatric patients with short stature. "Short stature" has been defined by the American Association of Clinical Endocrinologists and the Growth Hormone Research Society as height more than 2 standard

deviations (SD) below the mean for age and sex. The FDA-approved indication is for children with a height standard deviation score (SDS) of -2.25 below the mean. Using this proposed definition, approximately 1.2% of all children would be defined as having idiopathic short stature and considered potentially treatable under these indications. Note that this indication is considered not medically necessary.

Considerations

Members are required to use the preferred (formulary) product prior to non-preferred (non-formulary) products.

This Blue Cross and Blue Shield of Kansas City policy statement is consistent with the Blue Cross and Blue Shield Association Policy 5.01.06.

Description of Procedure or Service

Recombinant human growth hormone (GH) is FDA approved for a variety of indications and is also proposed for various non-labeled indications such as cystic fibrosis and treatment of older adults without documented GH deficiency.

Background

Human growth hormone (GH), also known as somatotropin, is synthesized in somatotropic cells of the anterior lobe of the pituitary gland. Beginning in 1985, recombinant GH has been marketed for a variety of U.S. Food and Drug Administration (FDA) -labeled indications as follows:

	Genotropin (Pharmacia)	**Humatrope (Lilly)**	**Norditropin (Novo-Nordisk)**	**Nutropin (Genen-tech)**	**Saizen (Serono)**	**Serostim (Serono)**	**Tev-Tropin (Ferring)**	**Zorbtive (Serono)**
Growth failure, peds pts with inadequate endogenous GH	yes	yes	yes	yes	yes		yes	
Growth failure due to Prader-Willi syndrome	yes							

Replacement therapy in adults with GH deficiency	yes	yes	yes	yes	yes	
Growth failure associated with chronic renal insufficiency				yes		
HIV wasting or cachexia						yes
Children born small for gestational age, who fail to show catch-up growth by age 2 years	yes	yes (new indication as of 3/09)	yes (new indication as of 10/08)			
Short stature (height SDS $\leq$ -2.25) in non-GH-deficient peds pts	yes	yes		yes		
Short stature due to Turner's syndrome	yes	yes	yes	yes		

(45, XO)			
Treatment of short bowel syndrome			yes
Short stature in peds pts with SHOX (short stature homeobox-containing gene) deficiency	yes		
Short stature in peds pts with Noonan syndrome		yes	

A major point of controversy is what defines “inadequate secretion of normal endogenous growth hormone,” and what constitutes “growth failure.” Prior to the availability of biosynthetic GH, GH was rationed to children with classic GH deficiency (GHD), as defined by a subnormal response (<10 ng/mL, approximately, depending on GH assay) to GH provocation tests. However, the ready supply of GH has created interest in expanding its use to short-stature children without classic GHD, often referred to as partial GH deficiency, neurosecretory GH dysfunction, constitutional delay in growth and development (CDGD), or idiopathic short stature. “Classic” GH deficiency is suggested when the abnormal growth velocity (typically below the 10th percentile) or height is more than 2 standard deviations (SD score) below the current population mean, in conjunction with a chronological age that is greater than the height age and bone age. In practical fact, interest in broadening the use of GH to non-GHD children has resulted in GH evaluation in many children who are simply below the 3rd percentile in height, with or without an abnormal growth velocity.

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.

In 2001, Genotropin received an FDA-labeled indication for treatment of pediatric patients born small for gestational age who fail to show catch-up growth by age 2 years. Most children born small for gestational age normalize their stature during infancy, but about 15% maintain an exceptionally short stature at least throughout childhood. Epidemiologic surveys have suggested that the average adult height of men and women who did not exhibit catch-up growth as children is 5 ft 6 inches in men and

5 ft 1 inch in women. 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.

Genotropin is the only recombinant GH product that is FDA-approved for treatment of Prader-Willi syndrome (PWS). According to the product label, Genotropin is contraindicated in patients with Prader-Willi syndrome (PWS) who are severely obese or who have severe respiratory impairment.

On July 25, 2003, the FDA approved Humatrope for use in non-GH-deficient short stature, defined by the manufacturer as a height standard deviation score (SDS) of -2.25 below the mean. This new indication for GH was the first indication that is based on short stature alone, without an underlying etiology. In May 2008, Genotropin was also approved for this indication.

Rationale

The policy was created in 1997 and was updated regularly with searches of the MEDLINE database. In 2008, the policy was updated on three potential indications: Prader-Willi syndrome, Noonan syndrome, and cystic fibrosis. A search of the MEDLINE database, covering the period June 2008 through July 2011, focused on the areas of idiopathic short stature, children with tall parents, and children with growth hormone deficiency (GHD).

Safety of GH treatment

The largest study published to date on safety of growth hormone (GH) treatment includes data on 54,996 included in a postmarketing surveillance registry established by Genentech, Inc. (1) The study was initiated due to concerns about long-term safety of GH, in particular, cases of de novo leukemia in patients without risk factors. The most common indications for GH use among children in the database were idiopathic 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). The results of this study provide some evidence that the rate of malignancies was not increased in patients treated with GH. However, the registry study lacked a concurrent comparison with untreated patients to compare actual rates of malignancy and other adverse events.

GH treatment for various indications

GH Use in Children with Idiopathic Short Stature (i.e., without documented GH deficiency or underlying pathology)

Is GH effective at increasing the adult height of children with idiopathic short stature?

Several meta-analyses have been published. Most recently, Deodati and colleagues identified 3 randomized controlled trials (RCTs) and 7 non-randomized controlled trials. (2) To be included in the meta-analysis, studies needed to include pre-pubertal children with initial short stature (more than 2 standard deviations [SD] below the mean) and peak GH response greater than 10 ug/L. In addition, participants needed to have no previous growth hormone therapy and no comorbid conditions that could impair growth. Adult height was defined as a growth rate of less than 1.5 cm/year or bone age was 15 years in females and 16 years in adults. The primary efficacy outcome was the difference between groups in adult height; this was measured as an SD score (SDS, also known as a z-score). The investigators considered a mean difference in height of more than 0.9 SD scores (about 6 cm) to be a satisfactory response to GH therapy. Only one of the RCTs was placebo-controlled, and that study had a high dropout rate (40% in the treated group and 65% in the placebo group).

In the 3 RCTs (total n=115), the mean adult height (primary efficacy outcome) was -1.52 SDS for treated children and -2.30 SDS for untreated children. The difference between groups significantly favored the treated group; mean difference=0.65 SDS (about 4 cm), 95% CI: 0.40 to 0.91 SDS, p<0.001. The mean adult height in the 7 non-randomized studies was -1.7 SDS for treated children and -2.1 SDS for untreated children. The mean difference between groups was 0.45 SDS (3 cm), 95% CI: 0.18 to 0.73 and was statistically significant favoring the treated group, p<0.001. Although GH treatment resulted in a statistically significant increase in adult height in the treated group, according to the a priori definition of a satisfactory response, the difference was not clinically significant. Moreover, there was a lack of high-quality placebo-controlled RCTs.

In 2009, a Cochrane review of RCTs evaluating GH therapy for idiopathic short stature in children and adolescents was published. (3) A total of 10 RCTs met eligibility criteria, which included being conducted in children who had normal GH secretion, normal size for gestational age at birth, and no evidence of chronic organic disease. In addition, studies needed to compare GH treatment to placebo or no treatment and provide GH treatment for at least 6 months. Three studies were placebo controlled and the other 7 compared GH therapy to no treatment. Unlike the Deodati review described above, (2) studies were not required to report final adult height. Nine out of 10 studies in the Cochrane review were short-term and reported intermediate outcomes. A pooled analysis of 3 studies reporting growth velocity at 1 year found a statistically significantly greater growth velocity in treated compared to untreated children. The weighted mean difference (WMD) was 2.84 (95% CI: 2.06 to 2.90). Five studies reported height SDSs, but there was heterogeneity among studies and their findings were not pooled. These data suggest that GH has an effect on height in children with idiopathic short stature in the short term but that evidence on GH's effects on adult height is extremely limited.

In summary, recent systematic reviews have found that GH treatment may result in increases in height gain for children with idiopathic short stature, but the difference in height gain may not be clinically significant. The absolute difference in height in these studies is in the range of 3-4cm, and children treated with GH remain below average in height, with heights that are between 1 and 2 standard deviations below the mean at the end of treatment. These studies do not follow treated patients long enough to determine the ultimate impact of GH on final adult height.

What is the impact of GH treatment on self-esteem and quality of life in children with idiopathic short stature?

Advocates of GH therapy often cite the potential psychosocial impairments associated with short stature. However, several RCTs have addressed this topic, and they have not found better self-esteem, psychological functioning, or quality of life in children treated with GH compared to controls. These studies are described briefly below:

In 2004, Ross and colleagues published findings on psychological adaptation in 68 children with idiopathic short stature without GH deficiency. (4) Children (mean age, 12.4 years) were randomized to receive GH therapy (n=37) or placebo (n=31) 3 times per week until height velocity decreased to less than 1.5 cm per year. At baseline and then yearly, parents and children completed several psychological instruments including the Child Behavior Checklist (CBCL) and Self-Perception Profile (SPP). No significant associations were found between attained height SDS or change in height SDS and annual changes in scores on the CBCL. There were no significant differences between groups on any CBCL summary scales in years 1 and 2, but in year 4, there were significantly higher scores on the CBCL summary scales in the group receiving GH treatment. There were no significant differences between groups on the SPP at any follow-up point. In conclusion, short stature in this study was not associated with problems in psychological adaptation or self-concept.

Theunissen and colleagues in the Netherlands published a trial in 2002 in which 40 prepubertal children with idiopathic short stature were randomly assigned to GH treatment (n=20) or a control group (n=20). (5) Parents and children were interviewed at baseline and at 1 and 2 years to obtain information on health-related quality of life (HRQOL) and children's self-esteem. At the 2-year follow-up, satisfaction with current height was significantly associated with improvement in children's reported health-related quality of life, social functioning, and other psychosocial measures. However, satisfaction with height did not differ significantly between the treatment and control groups. The data

from this study do not support the hypothesis that GH treatment improves HRQOL in children with idiopathic short stature.

In 1996, Downie and colleagues examined the behavior of children without documented GH deficiency who were treated with GH due to idiopathic short stature. (6) Across measures of behavior, including IQ, self-esteem, self-perception, or parental perceptions of competence, there were no significant differences between the control and treatment groups, either at baseline or after 5 years of GH therapy. The authors concluded that while no psychosocial benefits of GH therapy have been demonstrated, likewise, no documented psychosocial ill effects of GH treatment have been demonstrated.

In summary RCTs have not found that short stature is associated with psychological problems, in contrast to the expectations of some advocates. In addition, the available trials have not reported a correlation between increases in height and improvements in psychological functioning.

In light of the published research on the impact of GH on health outcomes for children with idiopathic short stature, and because this group of children is healthy (i.e., no identified pathology or hormone deficits) and thus should avoid unnecessary exposure to long-term medical treatment, GH treatment for children with idiopathic short stature is considered not medically necessary.

GH Use in Small for Gestational Age (SGA) Children

A meta-analysis of RCTs evaluating GH treatment for children born small for gestational age was published in 2009. (7) Four trials with a total of 391 children met the eligibility criteria (birth height or weight below 2 SDS and initial height less than 2 SDS). The GH dose ranged from 33 to 67 ug/kg in the RCTs, and the mean duration of treatment was 7.3 years. Mean adult height in the 4 studies was -1.5 SDS in the treated group and -2.4 SDS in the untreated group. The adult height in the treated group was significantly higher than that of controls; mean difference=0.9 SDS (5.7 cm), $p<0001$. There was no difference in adult height between the 2 doses of 33 and 67 ug/kg per day. The authors commented that it is unclear whether the gain in adult height associated with GH treatment “is of sufficient clinical importance and value to warrant wide-spread treatment of short children born SGA…”

There are very minimal data regarding the psychosocial outcomes of short pediatric or adult stature related to intrauterine growth retardation and how these outcomes may be affected by GH therapy. As noted above, data are inadequate to document that short-stature youths have either low self-esteem or a higher than average number of behavioral or emotional problems.

For both small for gestational age children and short-stature children, an additional strategy to achieve target adult heights is to combine GH therapy with gonadotropin hormone releasing (GnRH) analogs, which prolong the prepubertal growth period. The combined therapy is intended to increase the critical pubertal height gain by delaying the fusion of the epiphyseal growth plates, thus prolonging the period during which GH is active. This therapy has been suggested for children who are considered short when they enter puberty. (8-10)

GH use in children with “genetic potential” (i.e., lower than expected height percentiles based on parents’ height)

No randomized or non-randomized studies were identified that evaluated the efficacy, safety, and/or psychosocial impacts of treating this group of children with GH therapy.

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 ft 10 inches). Unlike Prader-Willi syndrome, GHD 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). (11)

In 2007, a Cochrane review identified 4 RCTs (total n=365) evaluating GH for treating Turner's syndrome. (12) 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 (mean difference [MD], 3 cm per year, 95% CI: 2 to 4 cm per year).

GH Therapy in Conjunction with GnRH Therapy as a Treatment of Precocious Puberty

Precocious puberty is generally defined as the onset of secondary sexual characteristics before 8 years of age in girls and 9 years in boys. Central precocious puberty is related to hypothalamic pituitary gonadal activation, leading to increase in sex steroid secretion, which accelerates growth and causes premature fusion of epiphyseal growth plates, thus impacting final height. Children with precocious puberty are often treated with GnRH (gonadotropin-releasing hormone) analogs to suppress the pituitary gonadal activity, to slow the advancement of bone age, and to improve adult height. Several long-term studies have reported that treatment with GnRH analogs is associated with improved adult height in most cases, particularly in those with the most accelerated bone age progression at treatment onset, the shortest predicted height, and the greatest difference between the target height and the predicted height. (13-15) In contrast, patients with a slowly progressive form in which the predicted height does not change after 2 years of follow-up may not require any treatment. In another subset of patients, GnRH analog therapy may be associated with a marked deceleration of bone growth that may ultimately result in an adult stature that is less than the targeted midparental height. GH may be offered to these patients in order to achieve the targeted adult height. There have been no RCTs comparing final adult height in those treated with GnRH analogs alone versus GnRH analogs combined with growth hormone therapy, and the largest case series includes 35 patients. Case series suggest that GH is most commonly offered as an adjunct to GnRH analogs when the growth velocity drops below the 25th percentile for chronologic age. (16, 17) A series of comparative case series that have included final adult heights have been reported by the same group of investigators from Italy. This group of investigators is the only one to have reported final adult heights. The most recent reports focus on a group of 17 girls with precocious puberty and a growth velocity below the 25th percentile who were treated with a combination of GnRH and GH, and 18 girls who refused treatment with adjunctive GH. (17) Those in the combined group attained a significantly greater adult height (161.2 +/- 4.8 cm) than the "control" group (156.7 +/- 5.7 cm) This small study is inadequate to permit scientific conclusions. Tuvemo and colleagues reported on the results of a trial that randomized 46 girls with precocious puberty to receive either GnRH analogs or GnRH analogs in addition to GH. (18) Of interest, all the participants were adopted from developing countries; precocious puberty is thought to be common in such cross-cultural adoptions. Criteria for participation in this trial did not include predicted adult height or growth velocity. After 2 years of treatment, the mean growth and predicted adult height were greater in those receiving combined treatment compared to those receiving GnRH analogs alone. The absence of final height data limits interpretation of this trial.

As noted here, the "not medically necessary" status of other applications of GH for non-GH deficient short-stature children is based on the absence of a functional impairment associated with a less than predicted final adult height. While these same considerations may apply to using GH therapy as a component of therapy for precocious puberty, the "investigational" status of this indication is based on lack of final height data from controlled trials.

GH Therapy in Older Adults without Documented Growth Hormone Deficiency

The GH secretion rate decreases by an estimated 14% per decade after young adulthood; mean levels in older adults are less than half those of a young adult. However, mean GH levels in older adults are greater than age-matched adults with diagnosed GH deficiency. Older individuals experience changes in body composition, loss of muscle mass, and decreases in bone mineral density that are similar to changes seen in adults with biochemically verified GH deficiency. Based on these observations, GH therapy has been investigated in older adults without organic pituitary disease. The policy regarding this off-label application is based on a 2001 TEC Assessment, (19) which offered the following observations and conclusions:

- Only 8 small controlled trials with at least 10 patients per treatment arm have examined the effect of GH therapy on older patients who may have partial GH deficiency. Overall, these trials reported improved bone density, increased lean body mass, and decreased fat mass in rhGH-treated versus control arms. However, results were not statistically significant and consistent across trials. Information on physical performance and quality of life outcomes was insufficient to draw conclusions regarding functional and long-term benefits from rhGH treatment. In 3 of 6 trials, noticeably fewer patients were evaluable in the treated than in the control arms. All trials used starting rhGH doses that were above the currently recommended range.

- It is not possible to prove effectiveness of GH treatment or lack thereof unless otherwise similar groups of treated versus non-treated patients are compared over a sufficient length of time to allow detection of any significantly and clinically different results. Currently limited results do not document clinically significant benefits with rhGH therapy, and they have potential for bias. The available evidence is insufficient to determine whether rhGH improves health outcomes in adults with age-related GH deficiency.

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 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"). (20) 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. (21) The authors reported improved waist/hip ratio and mid-thigh circumference.

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 (22). 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 ($p<0.05$). (23) For the average 60% TBSA-burned patient, this approximates a length of stay reduction from 46 to 32 days. Singh et al. (24) 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%). Demling (25) found significantly improved weight retention and wound healing time with GH or oxandrolone compared to standard treatment in 36 adults with severe burns.

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. (26) The potential for increased mortality prompted additional studies in critically burned pediatric patients. Ramirez et al. (27) retrospectively studied 263 pediatric burn patients; those treated with GH had no increase in mortality from matched patients who did not receive GH.

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. (28) Another placebo-controlled trial (29) found no benefit to GH with regard to length of hospitalization in 24 adult patients with severe burns.

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. (30) Aili Low et al. (31) 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.

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. (32) 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. (33, 34) However, studies have noted that the effects of increased intestinal absorption are limited to the treatment period. (33, 35) Specialized clinics may offer intestinal rehabilitation for patients with short bowel syndrome; GH may be one component of this therapy.

Growth hormone deficiency due to Prader-Willi Syndrome

Use of human growth hormone (HGH) for patients with growth failure due to Prader-Willi syndrome is an FDA-approved indication. Most patients with this syndrome have hypothalamic dysfunction and GH deficiency. Numerous studies have shown patient improvements with use of GH. For example, a recent 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. (36) Recently deaths have been reported in Prader-Willi patients who are being treated with GH. (37) 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 recommend sleep studies and correction of underlying airway obstruction before initiating GH treatment in these patients.

Questions have been raised about the value of testing for GH deficiency before treatment in these patients. The majority of patients with Prader-Willi syndrome are GH deficient. A number of recent clinical studies on use of GH in Prader-Willi syndrome were reviewed. In none of these studies were patients selected for treatment based on presence or absence of GH, nor were results reported separately for those with or without GHD (and thus no differential impact was noted.) One older study did describe a series of Prader-Willi syndrome patients treated with GH that were GH deficient. (38) However, the FDA approval is for those with Prader-Willi syndrome and growth failure, thus this “growth failure” indication is added to the policy statement. 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.)

Contraindications and precautions for use of GH in Prader-Willi syndrome are provided in the Description section of this policy. This information followed reports of fatalities after initiating therapy with GH in some patients with Prader-Willi syndrome.

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. (39)

Cystic Fibrosis

Since use of HGH is not FDA approved for this indication, this use is considered investigational. A systematic review identified 10 controlled trials evaluating GH for treating patients with cystic fibrosis. (40) One study was placebo-controlled, 8 compared GH therapy to no treatment and the remaining trial compared GH alone to glutamine or glutamine plus GH. In one study, patients were treated with GH for 4 weeks and in the other studies, duration of treatment ranged from 6 months to 1 year. There were insufficient data to determine the effect of GH on most health outcomes including frequency of intravenous antibiotic treatment, quality of life, and bone fracture. Data could be pooled, however, on frequency of hospitalizations although the authors did not report the number of studies included in their meta-analyses. In trials with a duration of at least 1 year, there was a significantly lower rate of hospitalizations per year in the group receiving GH therapy (pooled effect size=-1.62, 95% CI: -1.98 to -1.26). The authors commented that GH is a promising therapy for treatment of cystic fibrosis, but there are a number of important research questions that must be answered; in particular, there is a need for high-quality studies on health outcomes.

Practice Guidelines and Position Statements

In 2010, the National Institute of Health and Clinical Excellence (NICE) in the U.K. issued guidance on human growth hormone for growth failure in children. (41) NICE recommends GH as a possible treatment for children with growth failure who have any of the following conditions:

- Growth hormone deficiency
- Turner syndrome
- Prader-Willi syndrome
- Chronic renal insufficiency
- Small for gestational age and have growth failure at 4 years
- Short stature homeobox (SHOX) gene deficiency

In 2009, the American Association of Clinical Endocrinologists (AACE) issued updated guidelines on growth hormone use in growth hormone-deficient adults and transition patients. (42) 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.

In January 1997, the American Academy of Pediatricians (AAP) published a document that recommended the following patient selection criterion for children with short stature not associated with classic GH deficiency:

“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.” (43)

In addition, the AAP noted:

“Numerous considerations argue against widespread administration of GH therapy to other short children. First, the therapy’s risk benefit ratio in this population is not established. There could be unknown long-term risks, and the treatment could result in either no increase or only an insignificant increase in final adult height. . . . Even if the clinical data show a positive risk benefit ratio, however, the benefits of GH therapy will inevitably remain somewhat elusive. Individual children may escape the stigma of being very short, but a group of very short children will always exist. 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.”

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Billing Coding/Physician Documentation Information

J2941 Injection, somatropin, 1mg

S9558 Home injectable therapy; growth hormone, including administrative services, professional pharmacy services, coordination of care, and all necessary supplies and equipment (drugs and nursing visits coded separately), per diem

Additional Policy Key Words

Growth Hormone Replacement Therapy, Recombinant Human
Human Growth Hormone Replacement Therapy, Recombinant
Precocious Puberty, Growth Hormone
Recombinant Human Growth Hormone Replacement Therapy

Related Topics

N/A

Policy Implementation/Update Information

10/2000	New Policy – Growth Hormone Therapy in Children
10/2001	Reviewed – no changes made
10/2002	Reviewed – no changes made
06/2003	Revised – to include intrauterine growth retardation as investigational
07/2003	Revised – to include small for gestational age (SGA) as not medically necessary
10/2003	Reviewed – no changes made
05/2004	Revised – to reflect BCBSA policy 5.01.06
10/2004	Reviewed – no changes made
10/2005	Revised – to reflect BCBSA policy 5.01.06 with new statement of medical necessity for treatment of short bowel syndrome, and to include use in conjunction with GnRH, treatment of obesity, cystic fibrosis, idiopathic dilated cardiomyopathy, and juvenile idiopathic arthritis as investigational.
10/2006	Reviewed – no changes made
10/2007	Reviewed – no changes made
08/2008	Revised – Policy updated with for Prader Willi syndrome, Noonan syndrome, and cystic fibrosis. Reference numbers 43 to 46 added. “Growth failure” added to medically necessary indication for Prader-Willi syndrome; Noonan syndrome changed to medically necessary indication; no other changes in policy statement.
10/2008	Reviewed – no changes made
10/2009	Reviewed – no changes made
10/2010	Reviewed – no changes made
10/2011	Reviewed – no changes made
10/2012	Revised – to reflect BCBSA policy 2.01.06
10/2013	Literature review update
08/2014	Proven GH failure in children defined and added to policy
10/2014	Reviewed – no changes made