COVERAGE:

<table>
<thead>
<tr>
<th>Recombinant GH therapy is considered medically necessary for the following patients:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children with documented GH deficiency (GHD), in order to correct the deficiency.</td>
</tr>
<tr>
<td>Children with documented GHD are considered to be appropriate candidates for GH therapy. GHD is defined as an abnormal response of less than 10 ng/ml to TWO provocative stimulation tests, such as;</td>
</tr>
<tr>
<td>• L-dopa</td>
</tr>
<tr>
<td>• Clonadine</td>
</tr>
<tr>
<td>• Glucagon</td>
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<tr>
<td>• Propranolol</td>
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<tr>
<td>• Arginine</td>
</tr>
<tr>
<td>• Insulin.</td>
</tr>
<tr>
<td>Also, if the child has a documented history of GHD as a result of destructive lesions of the pituitary or as a result of treatment (e.g., ablative pituitary irradiation- usually provided because of a tumor or surgery) they are candidates for GH therapy. In children, GH therapy is not eligible for benefits 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.</td>
</tr>
</tbody>
</table>

**Supportive documentation:**

- Documentation of growth velocity under 5 cm/yr with documentation of height at least 2 standard deviations below mean.
- Bone age as determined by standard x-ray techniques to be two (2) years or more behind chronological age.

Once Growth Hormone deficiency has been established in childhood no further documentation of need is required through age 18.
<table>
<thead>
<tr>
<th>Children with height less than 3\textsuperscript{rd} percentile for chronological age with chronic renal insufficiency.</th>
<th>Chronic renal insufficiency is defined as a serum creatinine of less than 30 mg/dl or a creatinine clearance between 5 and 75 ml/min per 1.73 m\textsuperscript{2}. In patients with chronic renal failure undergoing transplantation, GH therapy is discontinued at the time of transplant.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with AIDS wasting.</td>
<td>AIDS wasting is defined as a greater than 10% of baseline weight loss that cannot be explained by a concurrent illness other than HIV infection. Patients treated with GH must simultaneously be treated by antiviral agents. Therapy is continued until this definition is no longer met.</td>
</tr>
</tbody>
</table>
| Adults with GH deficiency | Adults with GHD are considered to be appropriate candidates for GH therapy. GHD is defined as an abnormal response of less than 10 ng/ml to TWO provocative stimulation tests, such as;  
| | • L-dopa  
| | • Clonadine  
| | • Glucagon  
| | • Propranolol  
| | • Arginine  
| | • Insulin*.  

* Note: The Insulin Provocation test is the preferred test in most adult patients and should be one of the TWO tests provided for documentation unless the patient has a history of seizures or coronary artery disease in which case it would be contraindicated.

Also, if the patient has a documented history of GHD as a result of destructive lesions of the pituitary or as a result of treatment (eg., ablative pituitary irradiation- usually provided because of a tumor or surgery) or trauma they may be candidates for GH therapy. Also, 75% of those children with documented GH deficiency will be found to have sufficient GH as adults. Therefore, once adult height has been achieved, subjects should be retested once for GH deficiency as adults to determine if continuing replacement therapy is necessary. Dosages of GH should be physiologic, not pharmacologic. Physiologic doses are approximately 10 umg/kg per day.

**Note:** If GHD is established as an adult, documentation may be requested that the patient is continuing to benefit from this treatment and that the benefits support continuing treatment with GH. If any patient perceives no benefit, then a trial of withdrawal should be considered.
Patients with Turner’s Syndrome.

Turner’s Syndrome is defined as a patient with a 45, XO genotype.

Patients with Prader-Willi syndrome.

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. GHD has been demonstrated in most tested patients with Prader-Willi syndrome.

The following indications are considered not medically necessary:

<table>
<thead>
<tr>
<th>Indication</th>
<th>Description and Requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pediatric patients born small for gestational age (SGA) who fail to show catch up growth by age 2.</td>
<td>There are no established criteria for SGA 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 mean. Absence of catch-up growth was defined as a height velocity below 1 standard deviation score, adjusted for age.</td>
</tr>
<tr>
<td>Partial GH deficiency.</td>
<td>These patients do not meet the criteria required for GH deficiency. Further lab testing of children without classic GHD to diagnose “partial” GHD, or other abnormalities of GH secretion or bioactivity, is not considered medically necessary. This includes overnight hospitalization of children for testing of spontaneous GH secretion.</td>
</tr>
<tr>
<td>Neurosecretory GH dysfunction.</td>
<td></td>
</tr>
<tr>
<td>Constitutional growth delay.</td>
<td>This is defined as the make-up of the body determined by the genetic, biochemical, and physiologic endowment of the individual, and modified in great measure by environmental factors.</td>
</tr>
</tbody>
</table>

Experimental or investigational applications include but are not limited to the following:

- Non-GH-deficient short stature (except for Turner’s syndrome).
GROWTH HORMONE (GH)
RX501.040
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EFFECTIVE DATE: 12/1/2003

- Constitutional delay (lower than expected growth percentiles compared with their target height percentiles and delayed skeletal maturation when growth velocities and rates of bone age advancement are normal).

- GH therapy in adults to counter effects of aging.

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

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

- Glucocorticoid-induced growth failure.

- Intrauterine growth retardation.

- Short stature after renal dialysis treatment of altered body habitus (e.g., buffalo hump) associated with antiviral therapy in HIV infected patients.

- Promotion of wound healing in burn patients.

**The following diagnostic tests for GHD are considered experimental or investigational:**

- 24 hour continuous monitoring of GH levels.

- Serum levels of insulin-like growth factors (IGF) or insulin-like growth factor–binding protein (IGFBP).

**DESCRIPTION:**

*Human growth hormone (HGH)*, also known as somatotropin, is synthesized in somatotropic cells of the anterior lobe of the pituitary gland. Recombinant GH has been marketed since 1985.

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 those children with classic GHD as defined by a subnormal response (< 10 ng/ml) to GH provocation tests.

However, the ready supply of GH has created interest in expanding its...
use to short-statured children without classic GHD, often referred to as:

- partial GHD,
- neurosecretory GH dysfunction,
- constitutional delay in growth and development (CDGD), or
- idiopathic short stature.

“Classic” GH deficiency is suggested when there is an abnormal growth velocity (typically below the 10th percentile) 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 as outlined below:

- 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 improvement is clinically or emotionally significant for the patient.

There are many ethical considerations regarding GH therapy, most prominently the appropriate informed consent when therapy is primarily requested by the parent due to their particular psychosocial concerns regarding height.

In 2001, Genotropin received a new U.S. Food and Drug Administration (FDA) labeled indication for treatment of pediatric patients born SGA who fail to show catch-up growth by age 2 years. Most children born SGA 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
RATIONAL:

The following discussion focuses on the most controversial aspects of GH use.

**GH Use in Short-Statured Children Without Documented GHD**

While GH therapy in patients with classic GHD is accepted, the use of GH in short-stature patients without GHD (as identified by standard provocation tests) is controversial.

The controversy is related to difficulties in laboratory diagnosis of GHD;

- the lack of pretreatment factors, either laboratory or other criteria such as various measurements of height, skeletal maturity, etc. which can predict response to GH;
- the lack of long-term outcome data to show whether initial gains in growth velocity will result in increased adult height; and
- lack of data to determine if such an increase in height is associated with any beneficial functional or psychosocial outcome.

Surveys of endocrinologists suggest that laboratory measures of GH secretion are of limited usefulness in the decision of whether to initiate therapy. The most useful criteria cited by endocrinologists appear to be abnormal height, growth velocity, and delayed bone age. However, there are inadequate outcome data in terms of final height to validate this approach. These surveys also suggest that GH treatment is sought primarily to treat the potential psychosocial morbidity of short stature, and yet this outcome has not been studied in GH recipients. In addition, other studies have suggested that short stature is only variably related to psychosocial morbidity. There has been 1 controlled trial that examined the behavior of children without documented GHD who were treated with GH due to idiopathic short stature.

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 there have been no demonstrated psychosocial benefits of GH therapy; likewise, there have been no documented psychosocial ill effects of GH treatment.

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.”

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.”

**GH Use in SGA Children**

As noted in the Description section, in 2001, one GH preparation received FDA approval for treatment of SGA children. This FDA approval was based on 4 randomized, open-label controlled clinical trials. Patients were observed for 12 months before being randomized to receive either 0.24 mg/kg/week or 0.48 mg/kg/week GH or no treatment for 24 months. After 24 months all patients received GH. In patients receiving the higher GH dosage of 0.48 mg/kg/wk, the patients' height improved from a baseline of -3.4 standard deviations to -1.7 standard deviations below the mean. In contrast, in the control group the standard deviation score improved to a lesser degree, from -3.1 to -2.9 standard deviations below the mean. The issues associated with this indication for GH are similar to those for other short-stature children without documented GH deficiency. There are no documented functional impairments associated with short stature and no data regarding final adult height in the control or treatment group. It should be noted that the dosage recommended for SGA children, 0.48 mg/kg/week, is a supraphysiologic dose. For example, in patients with documented GHD, in which the intent is to provide normal physiologic replacement levels of GH, the recommended dosage is only 0.24 mg/kg/week. 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, there are inadequate data to document that short-statured youths have either low self-esteem or a higher than average amount of behavioral or emotional problems.

**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 Humatrope and Nutropin were based on the results of randomized, controlled clinical trials that included final adult height as the outcome. 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). The results with Nutropin were similar. While the data regarding Turner’s syndrome are somewhat unique in that final height is known, the clinical significance of a mean increase in height of 3.9 cm (1.75 inches) is unknown.

**GH Therapy in Older Adults without Documented GHD**

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 GHD. 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 GHD. Based on these observations, GH therapy has been investigated in older adult without organic pituitary disease. The policy regarding this off label application is based on a 2001 TEC assessment, which offered the following observations and conclusions:

- In 1998 the American Association of Clinical Endocrinologists (AACE) published clinical guidelines regarding GH use. Regarding the use of GH in adults, the AACE guidelines noted that “the benefits of GH supplementation in aging patients remain to be established.” In 1997, the Growth Hormone Research Society published consensus guidelines for the diagnosis and treatment of adults with GHD. These guidelines state, “partial GH deficiency exists, but further research is needed to distinguish it from physiological causes of reduced GH secretion, e.g., aging. Furthermore, the benefits of treatment of partial GH deficiency remain to be established.”
• Only 6 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, as compared to younger populations. These trials used much higher doses than are currently recommended and suffered from potential bias due to disproportionate numbers of dropouts from adverse events. Bone mineral density outcomes were most often reported, but results did not show consistent time frame (within the time frame tested) and have not been related to fracture rates. Trials tended to report increases in lean body mass and decreases in fat mass in treated patients compared to controls. Not all improvements are statistically significant; different methods of measuring body composition across trials may be affected by GH-induced changes in extra cellular fluid, and may not be comparable.

• 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. Limited results do not suggest marked improvement with GH therapy and, in general, are insufficient to permit conclusions regarding the effectiveness of GH at improving disability and quality of life in older populations.

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"). However, there is minimal published literature regarding the use of GH for this indication. Letters to the editors and small case series dominate the literature. 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. The authors reported improved waist/hip ratio and mid-thigh circumference.

PRICING:

None

REFERENCES:


• BCBSA Technology Assessment Program “Recombant Human Growth Hormone Replacement Therapy in Adults” Volume 11, No. 9 (September 1996)

• BCBSA Technology Assessment Program “Recombinant Human Growth Hormone Therapy in Catabolic Illness” Volume 11, No. 10 (September 1996


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Humatrope, Norditropin, Protropin, Nutropin, Saizen, Serostim.

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