

HealthAlliance**MEDICARE**

PURPOSE OF THE POLICY

To define criteria for coverage of growth hormone

STATEMENT OF THE POLICY

Growth hormone will be covered if the contained criteria are met

PROCEDURES

1. Growth Hormone Deficiency in Children and Adolescents:

Health Alliance considers GH replacement medically necessary for children and adolescents with the following indications:

1.1 Idiopathic growth hormone deficiency:

Health Alliance considers GH replacement medically necessary for children and adolescents with growth hormone deficiency (GHD) and growth failure who meet *all* of the following criteria:

- a. Member has failed to respond to at least two standard GH stimulation tests, defined as a serum GH level (peak level) of less than 10 nanograms per milliliter (ng/ml), after stimulation with insulin, levodopa, arginine, propranolol, clonidine, or glucagon.* (However, one abnormal GH test is sufficient for children with defined CNS pathology, history of irradiation, multiple pituitary hormone deficiency (MPHD) or a genetic defect affecting the GH axis); **and**
- b. Appropriate imaging (magnetic resonance imaging (MRI) or computed tomography (CT)) of the brain with particular attention to the hypothalamic-pituitary region has been carried out to exclude the possibility of a tumor; **and**
- c. At least one of the following criteria is met:
 - Child has severe growth retardation with height standard deviation score (SDS) less than 3 SDS below the mean for chronological age and sex; **or**
 - Child has moderate growth retardation with height SDS between -2 and -3 SDS below the mean for chronological age and sex **and** decreased growth rate (growth velocity (GV)** measured over one year below 25th percentile for age and sex); **or**
 - Child exhibits severe deceleration in growth rate (GV** measured over 1 year -2 SDS below the mean for age and sex); **or**
 - Child has decreasing growth rate combined with a predisposing condition such as previous cranial irradiation or tumor; **or**
 - Child exhibits evidence of other pituitary hormone deficiencies or signs of congenital GHD (hypoglycemia, micropallus).

Note: Given the above criteria, further laboratory testing of children without classic GHD to diagnose “partial” GHD, or other abnormalities of GH secretion or bioactivity, is considered *not* medically necessary. This includes overnight hospitalization of children for testing of spontaneous GH secretion.

Note: Measurement of insulin-like growth factor I (IGF-I) is considered medically necessary to determine adequacy of growth hormone therapy in adults and children. However, the diagnosis of growth hormone deficiency should not rely solely on IGF-I measurements, but must be confirmed by provocative tests solely for growth hormone secretion. Measurement of IGF binding protein-2 (IGFBP-2), IGF binding protein-3 (IGFBP-3), and the acid labile subunit of IGF-I are considered experimental and investigational.

Notes:

*** For persons with thyroid deficiency, Health Alliance only accepts results of GH secretion tests that are performed after thyroid deficiency is adequately treated because GH secretion may be subnormal merely as a result of hypothyroidism.**

**** Growth velocity (GV) should be tracked over at least one year.**

1.2 Chronic renal insufficiency:

Health Alliance considers GH replacement prior to renal transplantation medically necessary for children with chronic renal insufficiency and growth retardation who meet *both* of the following criteria:

- a. Child's nutritional status has been optimized, metabolic abnormalities have been corrected, and steroid usage has been reduced to a minimum; *and*
- b. At least one of the following criteria is met:
 - Child has severe growth retardation with height SDS less than 3 SDS below the mean for chronological age and sex; *or*
 - Child has moderate growth retardation with height SDS between -2 and -3 SDS below the mean for chronological age and sex *and* decreased growth rate (GV measured over one year below 25th percentile for age and sex); *or*
 - Child exhibits severe deceleration in growth rate (GV measured over one year -2 SDS below the mean for age and sex).

Note: Consistent with established guidelines for children with chronic renal insufficiency after renal transplantation, Health Alliance does not consider resumption of growth hormone therapy medically necessary until at least 1 year after the transplant to allow time to ascertain whether catch-up growth will occur.

1.3 Turner's syndrome:

Health Alliance considers GH replacement medically necessary for children with Turner's syndrome and growth retardation who meet *all* of the following criteria:

- a. The diagnosis of Turner's syndrome is confirmed by chromosome analysis; *and*
- b. At least one of the following criteria is met:
 - Child has severe growth retardation with height SDS less than 3 SDS below the mean for chronological age and sex; *or*
 - Child has moderate growth retardation with height SDS between -2 and -3 SDS below the mean for chronological age and sex *and* decreased growth rate (GV measured over one year below 25th percentile for age and sex); *or*
 - Child exhibits severe deceleration in growth rate (GV measured over one year -2 SDS below the mean for age and sex).

1.4 Prader Willi syndrome:

Health Alliance considers GH replacement medically necessary for children with Prader Willi syndrome and growth retardation who meet **all** of the following criteria:

- a. The diagnosis of Prader Willi syndrome is confirmed by appropriate genetic testing; **and**
- b. At least one of the following criteria is met:
 - Child has severe growth retardation with height SDS less than 3 SDS below the mean for chronological age and sex; **or**
 - Child has moderate growth retardation with height SDS between -2 and -3 SDS below the mean for chronological age and sex **and** decreased growth rate (GV measured over one year below 25th percentile for age and sex); **or**
 - Child exhibits severe deceleration in growth rate (GV measured over one year -2 SDS below the mean for age and sex).

1.5 Small for gestational age (SGA) children

Health Alliance considers growth hormone supplementation medically necessary for children born small for gestational age, and who meet **all** of the criteria below:

- a. Child was born small for gestational age, defined as birth weight or length 2 or more standard deviations below the mean for gestational age; **and**
- b. Child fails to manifest catch up growth by age 3 years, defined as height 2 or more standard deviations below the mean for age and sex.

Note: Growth curves plotting growth from birth through age 3 should be submitted for evaluation.

1.6 Discontinuation of therapy:

In children and adolescents, GH therapy will be considered not medically necessary if **any** of the following discontinuation criteria is met:

- a. Increase in height velocity is less than 2 cm total growth in one year of therapy; **or**
- b. Gender specific 50th percentile *for age 18* has been reached; **or**
- c. If there is a poor response to treatment, generally defined as an increase in growth velocity of less than 50% from baseline, in the first year of therapy. In children with Prader-Willi syndrome, evaluation of response to therapy should also take into account whether body composition (i.e., ratio of lean to fat mass) has significantly improved; **or**
- d. There are persistent and uncorrectable problems with adherence to treatment.
- e. Significant side effects as documented by prescribing physician

Note: At completion of linear growth (that is, growth rate less than 2 cm/year), available guidelines indicate that GH treatment should be stopped for at least 3 months, and GH status should be re-assessed to determine whether continued GH treatment into adulthood is necessary. Health Alliance will reevaluate the member three or more months after discontinuation of GH therapy to determine if the member fulfills medical necessity criteria for GH treatment at adult doses as set forth below. Note members with severe long-standing multiple pituitary hormone deficiencies, genetic defects or severe organic growth hormone deficiency do not have to undergo growth hormone retesting. Reference "Consensus Guidelines for the Diagnosis and Treatment of Growth Hormone (GH) Deficiency in Childhood and Adolescence: Summary Statement of the GH Research Society", JCE&M, 2000, Vol 85, No 11, pgs 3990-3993

2. Growth Hormone Deficiency in Adults:

Health Alliance considers GH replacement medically necessary for adults who meet the following criteria:

2.1 Destructive lesions of the pituitary:

Health Alliance considers GH treatment of adults with documented GHD medically necessary when *all* of the following criteria are met:

- a. Member has GH deficiency as a result of hypothalamic or pituitary disease (e.g., panhypopituitarism, pituitary adenoma, trauma, cranial irradiation, pituitary surgery) and at least one other hormone deficiency diagnosed (except for prolactin deficiency); *and*
- b. Member is already receiving adequate replacement therapy for any other pituitary hormone deficiencies; *and*
- c. Member has a severe GH deficiency, defined as a peak GH response of less than 9 mU/liter (3 ng/ml) during an insulin tolerance test or a cross-validated GH threshold in an equivalent test (growth hormone releasing hormone, arginine, or glucagon); *and*
- d. Member has a perceived impairment of quality of life (QoL), as demonstrated by a reported score of at least 11 in the disease-specific 'Quality of life assessment of growth hormone deficiency in adults' (QoL-AGHDA) questionnaire (see Figure 1 below).

Health Alliance considers this treatment medically necessary for an initial 9 months, allowing for an initial 3-month period of GH dose titration, followed by a 6-month therapeutic trial period. Subsequent GH treatment is considered medically necessary only if, upon subsequent testing of the effect of this treatment, the member demonstrates a QoL improvement of 7 or more points in QoL-AGHDA score (see Figure 1 below).

2.2 Adults who were growth hormone deficient as children or adolescents:

- a. For adolescents and adults younger than age 25 years with childhood-onset growth hormone deficiency (including idiopathic isolated growth hormone deficiency (IIGHD) or multiple pituitary hormone deficiencies, including growth hormone (MPHD)) who have completed linear growth (growth rate less than 2 cm per year), GH treatment at adult doses is considered medically necessary only in those who have failed to respond to at least two standard GH stimulation tests, defined as a peak GH response of less than 9 mU/liter (3 ng/ml) during an insulin tolerance test and one other cross-validated GH test (growth hormone releasing hormone, arginine, or glucagon). For adults having a low IGF-1 (a marker of insulin response) concentration (standard deviation score less than -2), failure to respond to only one standard GH stimulation test is required. In these members, GH supplementation at adult doses is considered medically necessary until adult peak bone mass is achieved (between 25 and 30 years of age).

Note: Consistent with available guidelines, Health Alliance requires, as a condition of continued authorization of GH therapy at adult doses, that GH therapy be stopped for at least 3 months after completion of linear growth (that is, growth rate less than 2 cm/year), and that GH status should be reassessed. As a condition of continued authorization, Health Alliance requires reassessment of GH status after GH treatment is stopped for at least 3 months before initiating GH

supplementation at adult doses. Health Alliance will reevaluate the member three or more months after discontinuation of GH therapy to determine if the member fulfills medical necessity criteria for GH treatment at adult doses.

- b. For adults over age 25 years with childhood onset growth hormone deficiency (IIGHD or MPHD), GH treatment at adult doses is considered medically necessary if they meet *all* of the following criteria:
- Member has failed to respond to at least two standard GH stimulation tests, defined as a peak GH response of less than 9 mU/liter (3 ng/ml) during an insulin tolerance test and one other cross-validated GH test (growth hormone releasing hormone, arginine, or glucagon). For members having a low IGF-1 (a marker of insulin response) concentrations (SDS less than -2), failure to respond to only one standard GH stimulation test is required; *and*
 - Member has a perceived impairment of quality of life (QoL), as demonstrated by a reported score of at least 11 in the disease-specific 'Quality of life assessment of growth hormone deficiency in adults' (QoL-AGHDA) questionnaire (see Figure 1 below).

2.3 Adults who develop growth hormone deficiency in early adulthood:

- a. GH treatment at adult doses is considered medically necessary for selected members who develop isolated GH deficiency (IIGHD or MPHD) in adolescence or early adulthood, after linear growth is completed but before the age of 25 years. GH treatment at adult doses is considered medically necessary only in those who have failed to respond to at least two standard GH stimulation tests, defined as a peak GH response of less than 9 mU/liter (3 ng/ml) during an insulin tolerance test and one other cross-validated GH test (growth hormone releasing hormone, arginine, or glucagon). For adults having a low IGF-1 (a marker of insulin response) concentration (SDS less than -2), failure to respond to only one standard GH stimulation test is required. In these members, GH supplementation at adult doses is considered medically necessary until adult peak bone mass is achieved (between 25 and 30 years of age).
- b. Following achievement of peak bone mass between 25 and 30 years of age, continued GH treatment is considered medically necessary for adults who meet *all* of the following criteria:
- Member has a severe GH deficiency: GH treatment at adult doses is considered medically necessary only in those who have failed to respond to at least two standard GH stimulation tests, defined as a peak GH response of less than 9 mU/liter (3 ng/ml) during an insulin tolerance test and one other cross-validated GH test (growth hormone releasing hormone, arginine, or glucagon). (For adults having a low IGF-1 (a marker of insulin response) concentration (SDS less than -2), failure to respond to only one standard GH stimulation test is required); *and*
 - Member has a perceived impairment of quality of life (QoL), as demonstrated by a reported score of at least 11 in the disease-specific 'Quality of life assessment of growth hormone deficiency in adults' (QoL-AGHDA) questionnaire (see Figure 1 below).

2.4 AIDS-related wasting:

Health Alliance considers GH supplementation to be medically necessary for HIV-infected persons with involuntary weight loss of greater than 10% of pre-illness baseline body weight or body mass index (BMI) less than 20 kg/m², in the absence of a concurrent illness or medical condition other than HIV infection that would explain these findings, and who have failed to adequately respond or are intolerant to anabolic steroids (e.g., Megace).

3. Dosage:

According to available guidelines, for the first 2-3 months dosage adjustments should be made after monthly assessments of serum levels of IGF-1, and in response to the presence of adverse effects, until a maintenance dose is achieved. As a condition of continued authorization, Health Alliance requires at least annual reassessment of serum levels of IGF-1 in adults and appropriate dosage adjustments, as GH requirements in adults may decrease with age.

4. Continued Authorization:

The continued medical necessity of growth hormone therapy is reviewed at least annually to determine whether growth hormone therapy continues to be medically necessary. The annual medical necessity review focuses on response to therapy, whether discontinuation criteria are met, whether there are any major changes in clinical status affecting the medical necessity of growth hormone supplementation, and verification that the person continues to follow up with the provider and receive appropriate reevaluations and care.

5. Contraindications:

Growth hormone therapy is considered experimental and investigational in persons with any of the following contraindications for which the safety of growth hormone therapy has not been established:

Persons with evidence of tumor activity. In persons with tumors, anti-tumor therapy must be completed before initiating growth hormone therapy; *or*

Critically ill persons (e.g., after complications following open heart or abdominal surgery, multiple trauma, acute respiratory failure or similar conditions); *or*

Persons with known hypersensitivity to growth hormone or to any of its excipients; *or*

Benign intracranial hypertension (BIH); *or*

Diabetic retinopathy; *or*

Women who are pregnant or lactating.

6. Experimental and Investigational Indications:

Health Alliance considers GH therapy to be experimental and investigational for the following indications:

Constitutional delay of growth and development

To promote growth of infants with intrauterine growth retardation or Russell-Silver syndrome

Skeletal dysplasias (e.g., achondroplasia)

Osteogenesis imperfecta

Down syndrome and other syndromes associated with short stature and increased susceptibility to neoplasms (e.g., Bloom syndrome, Fanconi syndrome)

“Somatopause” in older adults

Infertility

Chronic catabolic states, including respiratory failure, pharmacologic glucocorticoid administration, and inflammatory bowel disease

Burn injuries

Obesity
Hypophosphatemic rickets
Muscular dystrophy
Cystic fibrosis
Noonan syndrome
Spina bifida
Juvenile rheumatoid arthritis
Osteoporosis
Post-traumatic stress disorder
Depression
Hypertension
Corticosteroid-induced pituitary ablation.

Note: Growth hormone therapy will be considered medically necessary for persons who meet medical necessity criteria; even if they are also diagnosed with a co-morbid medical condition for which growth hormone therapy is considered not medically necessary or experimental and investigational. For example, growth hormone therapy would be considered medically necessary for a child with Noonan syndrome (an experimental and investigational indication) if the child was also severely growth hormone deficient according to the criteria set forth above.

7. Non-Covered Indications:

Health Alliance considers growth hormone therapy for idiopathic short stature *not* a covered benefit as idiopathic short stature is not considered a disease and the reasons for treatment are cosmetic.

8. Growth Hormone Releasing Hormone (GHRH):

Health Alliance considers GHRH (sermorelin acetate, Geref) medically necessary for members who meet the selection criteria for treatment for growth hormone above, or when GHRH is used as a diagnostic aid in evaluating pituitary function.

9. Pegvisomant (Somavert):

Health Alliance considers pegvisomant (Somavert) medically necessary for the treatment of acromegaly in members who have had an inadequate response to surgery and/or radiation therapy and/or other medical therapies, or for whom these therapies are inappropriate.

Figure 1: Adult Growth Hormone Deficiency Assessment (QoL - AGHDA)