



California  
Department of  
Health Services

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May 1, 2006

N.L.: 06-0506  
Index: Growth Hormone  
Supercedes N.L.s:  
19-0997, 25-0791 and  
20-0789

TO: ALL COUNTY CALIFORNIA CHILDREN'S SERVICES (CCS)  
ADMINISTRATORS, MEDICAL CONSULTANTS, CHIEF/SUPERVISING  
THERAPISTS, STATE CHILDREN'S MEDICAL SERVICES (CMS)  
BRANCH STAFF AND REGIONAL OFFICE STAFF

SUBJECT: GROWTH HORMONE

### **I. Purpose**

This Numbered Letter supercedes CCS Numbered Letters 19-0997, 25-0791, and 20-0789; and delineates policy for diagnostic evaluation of potential Growth Hormone Deficiency (GHD) and for treatment with Growth Hormone (GH) therapy.

### **II. Background**

Title 22, California Code of Regulations Section 41819 (b) states that "CCS applicants with at least one of the following conditions shall be medically eligible for participation in the CCS program: ...growth hormone deficiency". There has been confusion as to when to determine eligibility for the CCS program and when to authorize GH treatment.

GHD is the medical condition of inadequate production or secretion of GH and its effects on children and adults. GH is a polypeptide hormone which stimulates growth and cell reproduction. GHD may be an isolated deficiency or occur in association with deficiencies of other pituitary hormones. Deficiency of GH produces significantly different problems at various ages. In newborn infants the primary manifestations may be hypoglycemia, exaggerated jaundice or microphallus. In later infancy and childhood, growth failure may be a major effect. Adults with GHD may have increased body fat, decreased musculature, poor bone density, depression, hyperlipidemia, and be at increased risk for atherosclerotic heart disease. GHD is treated by GH replacement.

GHD in children may result from:

1. Abnormalities in the hypothalamus. This, the most common cause of GHD, is referred to as idiopathic isolated GHD and seems to often result from deficient hypothalamic secretion of Growth Hormone-Releasing Hormone (GHRH).
2. Anatomic malformations of the brain (isolated or in association with more extensive developmental defects, particularly craniofacial midline abnormalities) or genetic defects (e.g., genetic abnormalities of the pituitary gland or genes for GH production or GHRH synthesis). These causes are referred to as congenital GHD.
3. Intracranial lesions/tumors, especially craniopharyngiomas, cranial or craniospinal irradiation, head trauma, and central nervous system infection. These forms of GHD are referred to as acquired GHD.

In the past decade there have been significant advances in: genetic testing, high-resolution neuroimaging, and the ability to measure serum insulin-like growth factor 1 (IGF-1) and insulin-like growth factor-binding protein 3 (IGFBP-3). These emerging tools have helped with diagnosing GHD, but because there is no single gold-standard test, there is still limitation in the ability to make a definitive diagnosis of GHD in children.

Historically, endocrinologists have relied on GH stimulation testing to diagnose GHD, but in recent years, stimulation tests have been found to lack reliability, accuracy, and the ability to predict who will benefit from GH therapy. Endocrinologists are currently diagnosing GHD based on the integration of historical, clinical (including body measurements and physical findings), neuroradiologic (cranial MRI), biochemical data (e.g., IGF-1 and IGFBP-3), and/or genetic testing (e.g., mutations of: GHRH Receptor; GH1, growth hormone gene; Pit-1, pituitary specific transcription factor 1; Prop-1, prophet of Pit-1; Hes-1, homeo box gene expressed in embryonic stem cells; or Lhx-3, LIM homeo box protein 3).

For some children treated with GH, the need may continue for late adolescent/adult GH replacement if the child/adolescent has persistent and complete hypopituitarism, structural disease (e.g., craniopharyngioma), or inherited structural defects, GHD will most likely persist into adulthood, so no retesting is required for continued GH therapy. For idiopathic isolated GHD of childhood, retesting for GHD

by a stimulation test must be done to confirm the presence of persistent GHD prior to reinstatement of GH therapy, if the endocrinologist had previously recommended discontinuing therapy. This testing is done after the adolescent is off GH for at least 6-12 months. The peak GH level must be less than 5  $\mu$ /L to be eligible for treatment with GH for adult GHD.

In addition to GHD, GH has been FDA approved as a therapy for groups of CCS clients: individuals with renal failure/insufficiency and individuals with the wasting disease associated with HIV infection. GH has also been approved for the treatment of other conditions that are not CCS eligible medical conditions, e.g., Turner syndrome, Prader-Willi syndrome, idiopathic short stature, and for small for gestational age infants who have not caught up in height.

There are a small number of children who do not have classic GHD described in the paragraphs above, but they may have severe growth failure from an inadequate target cell response to GH, resistance or insensitivity to GH, bioinactive or biodeficient GH, or deficiency of IGF-1. Some of these children may respond to GH.

### **III. Policy**

Effective the date of this letter the following are CCS program policies.

#### **A. Diagnostic Services:**

Diagnostic evaluation services for potential GHD shall be authorized for children/adolescents with clinical evidence of growth failure when there is one or more of the following clinical criteria are present::

1. Height more than 3 Standard Deviations (SD) below the mean for age;
2. Height more than 1.5 SD below the mid-parental height (average of biological mother's and father's heights);
3. Height more than 2 SD below the mean and a 1-year height velocity more than 1 SD below the mean for chronologic age;
4. A 1-year decrease of more than 0.5 SD in height (in children over 2 years of age);

5. In the absence of short stature, a 1-year height velocity more than 2 SD below the mean, or a 2-year height velocity more than 1.5 SD below the mean (may occur in GHD manifesting during infancy or in organic, acquired GHD);
6. Signs indicative of an intracranial lesion;
7. Signs of multiple pituitary hormone deficiencies (MPHD); or
8. Neonatal symptoms and signs of GHD (e.g., unexplained hypoglycemia, exaggerated jaundice, or microphallus in males).

B. Treatment Services:

1. Authorization for GH therapy shall be issued when the CCS paneled pediatric endocrinologist at the authorized CCS approved Endocrine Center has presented documentation of the presence of GHD and the child is both financially and residentially eligible for the CCS program.
2. Authorization for GH therapy shall be issued when there is a request for a CCS client from:
  - a. A CCS approved Renal Special Care Center (SCC) for a child with chronic renal insufficiency/failure; or
  - b. A CCS approved Immunology/Infectious Disease SCC for the treatment of the wasting associated with HIV infection that has failed to improve with the use of Megace or Marinol.
3. The authorization for GH therapy shall continue, as long as the child remains financially and residentially eligible for the CCS program and until:
  - a. Growth is considered complete (e.g., evidence of epiphyseal closure); or
  - b. There is no longer documentation of medical necessity by the CCS approved SCC (e.g., unresponsiveness to GH therapy).
4. Upon request from a CCS approved Endocrine SCC, GH may be restarted or continued in adolescents with documented GHD who have achieved adult height, but who are experiencing the symptoms of adult GHD.

5. The medical eligibility for individuals who have growth failure from inadequate target cell response to GH, resistance or insensitivity to GH, bioinactive or biodeficient GH, or deficiency of IGF-1 should be evaluated on an individual basis.

#### **IV. Policy Implementation**

- A. A Service Authorization Request (SAR) for Service Code Grouping 02 shall be issued to the Endocrine SCC either for the diagnosis of GHD or the ongoing care of a client diagnosed with GHD.
- B. A SAR for the dispensing of GH shall be issued to a pharmacy. This SAR shall also include all the necessary injection supplies.
- C. Before renewing the GH authorization, a minimum of an annual SCC evaluation documenting continued medical necessity of the GH therapy shall be requested and reviewed by CCS program staff.

If there are questions regarding this policy, please contact your Regional Office Medical Consultant.

**Original signed by Marian Dalsey, M.D., M.P.H.**

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