



CIGNA PHARMACY COVERAGE POLICY

The following Coverage Policy applies to all plans administered by CIGNA Companies including plans administered by Great-West Healthcare, which is now a part of CIGNA.

Subject Somatropin (Genotropin[®], Humatrope[®], Norditropin[®], Nutropin[®], Nutropin[®] AQ, Omnitrope[®], Saizen[®], Serostim[®], Tev-Tropin[®], Zorbtive[®])

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Table of Contents

Coverage Policy	1
General Background	6
Coding/Billing Information	14
References	14
Policy History.....	21

Hyperlink to Related Coverage Policies

Mecasermin (Increlex[®])

INSTRUCTIONS FOR USE

Coverage Policies are intended to provide guidance in interpreting certain **standard** CIGNA HealthCare benefit plans as well as benefit plans formerly administered by Great-West Healthcare. Please note, the terms of a participant's particular benefit plan document [Group Service Agreement (GSA), Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a participant's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a participant's benefit plan document **always supercedes** the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable group benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. Proprietary information of CIGNA. Copyright ©2010 CIGNA

Coverage Policy

The following somatropin products are preferred brand products:

- Humatrope[®]
- Saizen[®]

Non-preferred brand somatropin (Genotropin[®], Norditropin[®], Nutropin[®], Nutropin AQ[®], Omnitrope[®], Serostim[®] and Tev-Tropin[®]) will only be covered when there is a failure, contraindication, or intolerance to BOTH preferred brand somatropin products.

Zorbtive is only covered as preferred brand for its FDA approved indication.

Zorbtive is a non-preferred brand product on the Great West HealthCare Drug List.

CIGNA covers somatropin as medically necessary for the following conditions (see individual subsections for specific coverage criteria requirements for each indication):

Growth Hormone Use in Children:

- growth hormone deficiency in children
- growth hormone use following cranial irradiation
- small for gestational age (SGA)
- growth delay in children with chronic renal failure
- Turner Syndrome
- Prader-Willi Syndrome
- Noonan Syndrome
- SHOX (short stature homeobox-containing gene) gene deletion

Growth Hormone Use in Adults:

- for growth hormone deficiency in adults
- for the continuation of therapy from growth hormone deficiency in childhood
- treatment of AIDS Wasting (Serostim only)
- treatment of Short Bowel Syndrome (Zorbtive only)

Summary of Diagnosis and Stimulation Testing Requirements

Diagnosis	Stimulation Testing Requirements
Pediatric Uses:	
Growth Hormone Deficiency in children (including pituitary dwarfism)	2
<ul style="list-style-type: none"> • Defined CNS pathology such as empty sella syndrome, interruption of pituitary stalk, hypoplasia of the pituitary gland, craniofacial developmental defects, pituitary or hypothalamic tumors, etc. 	1
<ul style="list-style-type: none"> • Multiple Pituitary Hormone Deficiency (MPHD) 	1
<ul style="list-style-type: none"> • Genetic defect along GH axis 	1
<ul style="list-style-type: none"> • Panhypopituitarism in children 	None
<ul style="list-style-type: none"> • Cranial irradiation history 	None
<ul style="list-style-type: none"> • Whole body irradiation history 	None
Small for Gestational Age (SGA)	None
Chronic Kidney Disease	None
Turner Syndrome	None
Prader-Willi Syndrome	None
Noonan Syndrome	None
SHOX Gene Deletion	None
Adult Uses:	
Growth Hormone Deficiency in adults	1
<ul style="list-style-type: none"> • Panhypopituitarism in adults 	None
AIDS Wasting (Serostim only)	None
Short Bowel Syndrome (Zorbtive only)	None

(See individual subsections for specific coverage criteria requirements for each indication)

Growth Hormone Use in Children:

For a history of cranial or whole body irradiation it may be assumed that GH is absent and neither stimulation testing nor auxologic evaluation (stature and growth velocity data) is required.

- **For growth hormone deficiency in children (including pituitary dwarfism), when ALL of the following criteria are met:**
 - auxologic evaluation (stature and growth velocity data), including **ONE** of the following:
 - individual's height is more than two standards of deviation (SD) below average for the population mean height for age and sex, **AND** a height velocity measured over one year is more than one SD below the mean for chronological age, **OR** for children over two years of age, there is a decrease in height SD of more than 0.5 over one year
 - individual's height velocity measured over one year is more than two SD below the mean for age and sex **OR** more than 1.5 SD below the mean sustained over two years
 - diagnostic evaluation, including **ALL** of the following:
 - growth hormone response of less than 10 ng/mL to at least two provocative stimuli of growth hormone release: Insulin, Levodopa, L-Arginine, Clonidine, Glucagon. One abnormal growth hormone stimulation test is sufficient for children with defined central nervous system (CNS) pathology (e.g., empty sella syndrome, interruption of pituitary stalk, hypoplasia of the pituitary gland, craniofacial developmental defects, pituitary or hypothalamic tumors, etc.); multiple pituitary hormone deficiency (MPHD) (i.e., deficiency of two or more pituitary hormones) or a proven genetic defect affecting the growth hormone axis.
 - other pituitary hormone deficiencies, e.g., thyroid, cortisol or sex steroids, have been ruled out and/or corrected prior to time of testing
 - for children with either documented panhypopituitarism, defined by the absence of all other anterior pituitary hormones [Luteinizing Hormone(LH), Follicle Stimulating Hormone (FSH), Thyroid Stimulating Hormone (TSH), Adrenocorticotropic Hormone (ACTH)].
 - Standard re-auth criteria apply:
 - **Yearly reassessment for reauthorization of coverage is required.**
 - **Coverage for continuation of therapy requires meeting current initial use criteria and evidence of a beneficial response as shown by growth curve chart**
 - **Coverage for growth promotion will cease when the bony epiphyses have closed.**
- **Small for Gestational Age (SGA) when ALL of the following criteria are met:**
 - child was born small for gestational age, defined as birth weight and/or length at least two standard deviations below the mean for gestational age
 - child fails to manifest catch-up growth by two years of age, defined as height at least two standard deviations below the mean for age and sex

Yearly reassessment for reauthorization of coverage is required.

Coverage for continuation of therapy requires meeting current initial diagnosis criteria only and evidence of a beneficial response as shown by growth curve chart. Coverage for growth promotion will cease when the bony epiphyses have closed.

Note: For consideration for Russell Silver Syndrome or chromosomal anomalies, please refer to end criteria section listing experimental, unproven, investigational indications.

- **For Growth Delay in Children with Chronic Kidney Disease when ALL of the following criteria are met:**
 - renal function at stage 2 chronic kidney disease (or GFR from 60–89 ml/min/1.73m²)
 - auxologic evaluation (stature and growth velocity data), including **ONE** of the following:
 - individual's height is more than two standards of deviation (SD) below average for the population mean height for age and sex, **AND** a height velocity measured over one year

- is more than one SD below the mean for chronological age, **OR** for children over two years of age, there is a decrease in height SD of more than 0.5 over one year
- individual's height velocity measured over one year is more than two SD below the mean for age and sex **OR** more than 1.5 SD below the mean sustained over two years

Yearly reassessment for reauthorization of coverage is required.

Coverage for continuation of therapy requires meeting current initial use criteria and evidence of a beneficial response as shown by growth curve chart. Coverage for growth promotion will cease when the bony epiphyses have closed.

- **For Turner Syndrome, when ALL of the following criteria are met:**
 - documentation of diagnosis as established by genetic testing
 - auxologic evaluation (stature and growth velocity data), including **ONE** of the following:
 - individual's height is more than two standards of deviation (SD) below average for the population mean height for age and sex, **AND** a height velocity measured over one year is more than one SD below the mean for chronological age, **OR** for children over two years of age, there is a decrease in height SD of more than 0.5 over one year
 - individual's height velocity measured over one year is more than two SD below the mean for age and sex **OR** more than 1.5 SD below the mean sustained over two years

Yearly reassessment for reauthorization of coverage is required.

Coverage for continuation of therapy requires meeting current initial diagnosis criteria only and evidence of a beneficial response as shown by growth curve chart. Coverage for growth promotion will cease when the bony epiphyses have closed.

- **For Prader-Willi Syndrome, when ALL of the following criteria are met:**
 - diagnosis of Prader-Willi Syndrome is confirmed by appropriate genetic testing
 - auxologic evaluation (stature and growth velocity data), including **ONE** of the following:
 - individual's height is more than two standards of deviation (SD) below average for the population mean height for age and sex, **AND** a height velocity measured over one year is more than one SD below the mean for chronological age, **OR** for children over two years of age, there is a decrease in height SD of more than 0.5 over one year
 - individual's height velocity measured over one year is more than two SD below the mean for age and sex **OR** more than 1.5 SD below the mean sustained over two years

Yearly reassessment for reauthorization of coverage is required.

Coverage for continuation of therapy requires meeting current initial diagnosis criteria only and evidence of a beneficial response as shown by growth curve chart. Coverage for growth promotion will cease when the bony epiphyses have closed.

- **For Noonan Syndrome, when ALL of the following criteria are met:**
 - diagnosis of Noonan Syndrome is confirmed by appropriate genetic testing
 - auxologic evaluation (stature and growth velocity data), including **ONE** of the following:
 - individual's height is more than two standards of deviation (SD) below average for the population mean height for age and sex, **AND** a height velocity measured over one year is more than one SD below the mean for chronological age, **OR** for children over two years of age, there is a decrease in height SD of more than 0.5 over one year
 - individual's height velocity measured over one year is more than two SD below the mean for age and sex **OR** more than 1.5 SD below the mean sustained over two years

Yearly reassessment for reauthorization of coverage is required.

Coverage for continuation of therapy requires meeting current initial diagnosis criteria only and evidence of a beneficial response as shown by growth curve chart. Coverage for growth promotion will cease when the bony epiphyses have closed.

- **For SHOX (short stature homeobox-containing gene) gene deletion treatment when ALL of the following criteria are met:**
 - diagnosis of SHOX gene deletion is confirmed by appropriate genetic testing
 - auxologic evaluation (stature and growth velocity data), including **ONE** of the following:
 - individual's height is more than two standards of deviation (SD) below average for the population mean height for age and sex, **AND** a height velocity measured over one year is more than one SD below the mean for chronological age, **OR** for children over two years of age, there is a decrease in height SD of more than 0.5 over one year
 - individual's height velocity measured over one year is more than two SD below the mean for age and sex **OR** more than 1.5 SD below the mean sustained over two years

Yearly reassessment for reauthorization of coverage is required.

Coverage for continuation of therapy requires meeting current initial diagnosis criteria only and evidence of a beneficial response as shown by growth curve chart. Coverage for growth promotion will cease when the bony epiphyses have closed.

Growth Hormone Use in Adults:

- **For Growth Hormone Deficiency in Adults, when ALL of the following conditions are met:**
 - the etiology of Growth Hormone Deficiency (GHD) is a result of destructive hypothalamic or pituitary disease, radiation therapy, surgery or trauma **OR** is a result of documented GHD in childhood
 - appropriate evaluation of stimulation testing:
 - GHD has been confirmed by growth hormone response of less than 5 ng/mL when measured by polyclonal antibody (RIA) or less than 2.5 ng/mL when measured by monoclonal antibody (IRMA) to one provocative stimuli of growth hormone release: Insulin, Levodopa, Clonidine, Arginine, or Glucagon.
 - OR**
 - [Test currently unavailable, however when historically used] GHD had been confirmed by arginine-GHRH testing resulting in plasma growth hormone concentrations of < 11ng/mL with a BMI of <25, < 8ng/mL with a BMI of 25-30, and < 4ng/mL with a BMI ≥30 when measured by monoclonal antibody (IRMA)
 - other pituitary hormone deficiencies, e.g., thyroid, cortisol or sex steroids, have been ruled out and/or corrected
 - no stimulation testing is required where it would not be expected to produce a clinical response, e.g., for a diagnosis of panhypopituitarism, defined by the absence of all anterior pituitary hormones [Lutenizing Hormone (LH), Follicle Stimulating Hormone (FSH), Thyroid Stimulating, Adrenocorticotrophic Hormone (ACTH) and Growth Hormone (GH)]

Yearly reassessment for reauthorization of coverage is required

Coverage for continuation of therapy requires meeting current initial use criteria

- **Treatment of AIDS Wasting (Serostim only), where:**
 - there has been weight loss greater than 10% of pre-illness baseline body weight or body mass index (BMI) less than 20 kg/m²
 - there has been documented failure, intolerance, or contraindication to appetite stimulants and/or other anabolic agents
 - there is continuous use of antiviral therapy

Initial authorization to be limited to 12 weeks' duration

- **Treatment of Short Bowel Syndrome (Zorbtive only), when:**
 - used with special diets and glutamine supplementation
 - individuals are currently dependent upon intravenous parenteral nutrition

Authorization to consist of one four-week course of therapy

CIGNA does not cover somatropin for the following indications because they are considered experimental, investigational or unproven (this list may not be all-inclusive):

Growth Hormone Use in Children:

- intrauterine growth restriction (IUGR)
- Russell-Silver Syndrome
- skeletal dysplasias, for example, achondroplasia
- osteogenesis imperfecta
- Down Syndrome and other syndromes associated with short stature and malignant diathesis
- continuation of growth hormone treatment for growth promotion once epiphyses are closed
- deletion of chromosome 18q
- chromosomal anomalies unless otherwise specified as covered
- precocious puberty
- juvenile rheumatoid arthritis
- Crohn's disease
- repeat courses of therapy in Short Bowel Syndrome

Growth Hormone Use in Adults:

- continuation of growth hormone treatment from childhood use once epiphyses are closed (except as defined in adult growth hormone coverage conditions)
- obesity
- osteoporosis
- muscular dystrophy
- infertility
- somatopause
- repeat courses of therapy in Short Bowel Syndrome
- Crohn's disease

CIGNA does not cover somatropin for the diagnosis/treatment/management of the following conditions because they are considered not medically necessary (this list may not be all-inclusive):

- idiopathic (i.e., of unknown origin) short stature, also called non-growth hormone deficient short stature in children
- approved GH therapy in combination with GnRH therapy to prolong pre-pubertal state
- increased athletic performance in adults

FDA Approved Indications

Human growth hormone products currently available in the United States are exclusively produced from recombinant technology in the form of somatropin. There are no expected differences in efficacy between recombinant human growth hormone (rhGH) products made by different companies because the molecular structure is the same for each brand name for somatropin. Additionally, consensus guidelines and many trials do not distinguish between products in describing the safety and efficacy of rhGH. Clinicians generally agree that the products are therapeutically equivalent, despite differences in the FDA-approved indications for each product.

FDA Recommended Dosing

Recommended dosing for growth hormone is based on each agent and its formulation of somatropin concentration. Each agent provides dosing parameters for pediatric and adult use within its FDA label. Providers should refer to the specific FDA recommended dose for the chosen agent.

Drug Availability

Each formulation is available in an injection form. Please refer to the specific agent's FDA product information availability.

General Background

Pharmacology

Somatropin is identical to endogenous growth hormone (GH). Endogenous growth hormone is produced in the anterior pituitary gland. It stimulates the production of insulin-like growth factor-I (IGF-I), resulting in decreased insulin use by peripheral tissues, increased breakdown of lipids, and increased muscle mass. This "anti-insulin" effect promotes linear growth in children and development of normal muscle mass, reduced adiposity, and improved exercise tolerance in children and adults. Recombinant human growth hormone functions in an identical way to endogenous growth hormone. For most indications, it is replacing a natural deficiency of endogenous hormone, and in a few indications it is used to overcome resistance to the effects of growth hormone. When given by intravenous (IV) administration, the elimination half-life of somatropin is approximately 20 to 30 minutes. When given by subcutaneous (SC) or intramuscular (IM) administration, the elimination half-life of somatropin is three to five hours. Somatropin is metabolized via classical protein catabolism in both the liver and kidneys. In renal cells, at least a portion of the breakdown products are returned to the systemic circulation.

Guidelines

Consensus guidelines are available for several childhood disorders affecting stature and body composition. The diagnosis of GHD is confirmed by measurements of growth hormone secretion, commonly following stimulation by a provocative agent(s). The American Association of Clinical Endocrinologists (AACE), the National Institute for Clinical Excellence (NICE), and the Growth Hormone Research Society (GHRS) all consider a growth hormone response of less than 10 ng/mL supportive of the diagnosis of GHD.

AACE

The following are the AACE 2009 recommendations:

GH should only be prescribed to patients with clinical features suggestive of adult GHD and biochemically proven evidence of adult GHD. 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 AACE does not recommend the prescription of GH to patients for any reason other than the well-defined approved uses of the drug.

Patients with childhood-onset GHD (COGHD) previously treated with GH replacement in childhood should be retested after final height is achieved and GH therapy discontinued for at least 1 month to ascertain their GH status before considering restarting GH therapy. Exceptions include those with known mutations, those with embryopathic/congenital defects, those with irreversible hypothalamic-pituitary structural lesions, and those with evidence of panhypopituitarism (at least 3 pituitary hormone deficiencies) and serum IGF-I levels below the age- and sex-appropriate reference range off GH therapy. For childhood GH treatment of conditions other than GHD, such as Turner's syndrome and idiopathic short stature, there is no proven benefit to continuing GH treatment in adulthood; hence, there is no indication to retest these patients when final height is achieved.

The preferred GH stimulation test to establish the diagnosis of adult GHD in patients with COGHD is the insulin tolerance test (ITT). Acceptable alternative stimulation tests include the GHRH+arginine (ARG) test, the glucagon test, and, rarely, the ARG test alone.

The ITT remains the gold-standard test for diagnosing adult GHD. Acceptable alternative stimulation tests to diagnose adult GHD include the GHRH+ARG test, the glucagon test, and, rarely, the ARG test alone. Appropriate GH cut points based on body mass index (BMI) should be used with the GHRH+ARG test, because BMI has a well-validated effect on GH responses to GHRH and ARG stimulation. In patients where the ITT is not desirable and when recombinant GHRH is not available, the glucagon test is a reliable alternative, but not the levodopa and clonidine tests.

On restarting GH therapy, the starting dose of GH in transition patients should be approximately 50% of the dose between the pediatric doses required for growth and the adult dose.

Traumatic brain injury and aneurysmal subarachnoid hemorrhage are now recognized conditions causing GHD. However, in patients with these conditions, GHD may be transient; therefore, it is recommended GH stimulation testing to be performed at least 12 months after the event.

Dosing of GH replacement therapy in all patients should be individualized. There are insufficient data regarding its safety to make recommendations about the use of GH during pregnancy.

There is no evidence that one GH product is more advantageous over the other, apart from differences in pen devices, dose increments and decrements, and whether or not the product requires refrigeration; therefore, the AACE does not recommend the use of one commercial GH preparation over another.

Adults with GHD have an increased risk of cardiovascular morbidity and mortality; therefore, cardiovascular parameters to consider monitoring during follow-up include fasting lipid profile, systolic and diastolic blood pressure, heart rate, and electrocardiogram results, while more expensive and complex examinations such as echocardiogram and carotid echo-Doppler examinations should be performed only if clinically indicated. Adults with GHD have an increased risk of developing osteopenia and osteoporosis; therefore, it is recommended to measure bone mineral content and bone mineral density (BMD) in GH-deficient patients before starting GH therapy. If the initial bone dualenergy X-ray absorptiometry (DEXA) scan is abnormal, repeat bone DEXA scans are recommended at 2- to 3-year intervals to assess the need for additional bone-treatment modalities.

In GH-deficient adults on GH replacement therapy with pituitary microadenomas or postsurgery residual pituitary tumor, periodic magnetic resonance imaging should be undertaken to assess the size of the tumor. Adults with GHD have diminished quality of life (QOL); therefore, we recommend a specific questionnaire be administered to adults with GHD before they begin GH treatment; subsequently, these adults should be evaluated annually to determine whether there is a change or sustained impact of GH therapy on QOL. No data are available regarding the optimal length of GH replacement; therefore, we recommend that if patients on GH replacement report significant QOL benefits and objective improvements in biochemistry and body composition, then GH treatment should be continued indefinitely. However, if the patient reports neither subjective nor objective benefits, then it is reasonable to consider discontinuing GH treatment altogether.

If diabetes mellitus is diagnosed during GH therapy, or if GH therapy is considered for patients with concurrent diabetes mellitus, adjustments in anti-diabetic medications and treatment with low-dose GH therapy may be necessary. Alternatively, it is reasonable to withhold or discontinue GH therapy and to optimize the treatment of the diabetes before reconsidering later resumption of low-dose GH replacement in these patients.

Growth hormone treatment is contraindicated in patients with a previous history of malignancy or in the presence of active malignancy. No data are available to suggest that GH therapy is associated with causing or accelerating recurrences of pituitary-region tumors; therefore, we recommend continued long-term surveillance of patients with pituitary-region tumors regardless of whether or not these patients are treated with GH therapy.

NICE

NICE has issued a technology appraisal (2010) recommending the use of HGH (somatropin) as a possible treatment for children with growth failure associated with the following conditions:

- growth hormone deficiency
- Turner syndrome
- Prader–Willi syndrome
- chronic renal insufficiency
- growth failure at 4 years or older and were born small for gestational age
- short stature homeobox-containing gene (SHOX) deficiency.

NICE recommend that treatment should continue until the child stops growing unless growth is slow in the first year of treatment or the child doesn't wish to carry on with the treatment. Endocrinologists should carefully consider weight and height before stopping treatment in children with Prader–Willi syndrome.

The 2003 NICE recommendations for adults remain the same. In 2003, NICE recommended that rhGH should be used only for adults with severe growth hormone deficiency that is severely affecting their quality of life.

GHRH

The GHRH proposed consensus guidelines for GHD in children and adolescents remain current. The pediatric recommendations of GHRH are endorsed by five international organizations and four of five makers of rhGH products. GHRH guidelines include recommendations for diagnosis of GHD, as well as rhGH treatment and safety monitoring for children and adolescents.

Testing for GHD should be undertaken with an intention to treat in patients with hypothalamic–pituitary disease, those who have received cranial irradiation, and those with TBI or sub-arachnoid hemorrhage. The diagnosis of severe GHD is straightforward but partial GHD is not adequately defined. Testing may indicate isolated GHD; however, idiopathic isolated GHD occurring de novo in the adult is not a recognized entity. Insulin-induced hypoglycemia, combined administration of GHRH with arginine or GHRP, and glucagon are validated stimulatory tests for the diagnosis of GHD in the adult. A low IGF-I is a reliable diagnostic indicator of GHD in patients with hypopituitarism; however, a normal IGF-I does not rule out GHD. Assay standardization remains an important unresolved issue. Universally adopted calibrators for GH and IGF-I assays are required. The availability of age- and sex-specific normative data for IGF-I assays would be highly advantageous to clinical management. The benefits of GH replacement have been demonstrated throughout life. Thus, GH status should be reevaluated in the transition age for continued GH replacement to achieve full somatic development. Replacement therapy should be individualized based on the titration against the serum IGF-I levels and the absence of adverse events.

Clinical Efficacy

Pediatric Diagnoses

Growth hormone deficiency (GHD) in children typically produces symptoms of short stature, increased central obesity, a high-pitched voice, lethargy, a prominent forehead and hypoglycemia, in addition to low concentrations of growth hormone. GHD may be congenital (genetic) or acquired (see Table 1). Growth hormone deficiency in children varies. Some children may have a total absence of growth hormone that results in severe growth retardation, pudgy appearance and delayed skeletal maturation. Other children may only have a partial deficiency that can lead to a slightly shorter stature. The diagnosis of GHD is difficult because up to 60% of children with normal growth may have peak growth hormone concentrations that may support a diagnosis of GHD in as many as three separate tests.

No one laboratory test has sufficient diagnostic sensitivity and specificity to serve as a gold standard for the diagnosis of pediatric growth hormone deficiency (GHD). Therefore, clinical diagnosis of GHD in children is supported by a combination of appropriate clinical, auxological, biochemical and radiological investigations. According to consensus guidelines from the GHRH, children should undergo extensive clinical and biochemical assessments to confirm diagnosis before subjecting them to injections and costs associated with many years of rhGH therapy.

For children, the diagnostic algorithm can be complicated with many possible variations. The focus should be on auxological measurements, particularly growth velocity. Clinical criteria include a height or growth velocity more than two standards of deviation (SD) below the mean for age and sex. This correlates with the third percentile for height. In addition to focusing on growth, other screening laboratory tests should be performed to rule out other causes of disease, or the cause of GHD should be verified (e.g., pituitary cancer). The following general tests should be used to screen for common causes of poor growth before embarking on growth hormone provocative stimulation testing: complete blood count (CBC) with differential, sedimentation rate (i.e., looking for inflammatory processes), hepatic and renal function tests, chromosomes in females (i.e., to exclude Turner syndrome), and thyroid function tests.

Many biochemical assays for endogenous growth hormone (GH), insulin-like growth factor I (IGF-I), and insulin-like growth factor binding protein-3 (IGFBP-3) are available, but the tests using monoclonal antibodies are preferred for more accurate results. Release of endogenous growth hormone is possible by administration of arginine, clonidine, glucagon, L-dopa, insulin (to produce hypoglycemia), or growth hormone releasing hormone. Traditionally, practitioners use the insulin stimulus test as the gold standard; however, no test has both high sensitivity and specificity. False positive responses occur in patients with normal pituitary function as well as

false negative responses in pituitary deficient patients. Evaluation of growth hormone reserve should not be based upon the results of one single provocative test.

Diagnosis may be made based upon stimulus testing in combination with current height and predicted adult height assessments. Generally, a peak concentration of < 5 ng/mL in response to a growth hormone stimulus test is considered to be diagnostic with a higher sensitivity for severe GHD. Many clinicians consider values < 10 ng/mL abnormal, and this value is frequently used to support moderate to severe growth hormone deficiency. Caution should be exercised in patients with risk factors for a falsely low stimulus test result. These include obesity, use of aminophylline or amphetamines, and concurrent high cortisol and low thyroid hormone levels.

IGF-I and IGFBP-3 should also be measured. IGF-I and IGFBP-3 levels that are more than two SD below normative reference ranges adjusted for age, sex, and pubertal status strongly suggest an abnormality in the growth hormone axis if other causes of low IGF (e.g., malnutrition, liver disease, renal insufficiency, diabetes, and hypothyroidism) have been excluded. Even in patients with GHD, it is possible to have IGF-1 and IGFBP-3 levels within the normal range.

Genetic evaluations and magnetic resonance imaging (MRI) of the pituitary gland may also assist with the diagnosis of GHD. However, these tests are not required for definitive diagnosis. Cerebral MR imaging of the hypothalamic-pituitary region has proven to be a useful tool in defining the anatomical abnormalities that are associated with GHD. Profound GHD is uncommon in patients with normal MRI findings, with the exception of those with genetic causes.

Table 1 - Causes of GHD in children

Cause	Comments
Congenital deficiency	May occur due to anatomical malformations of the brain or genetic defects.
Acquired deficiency	May occur due to tumors of the pineal, hypothalamic, or pituitary region, or optic gliomas. Craniopharyngiomas are the most common. CNS irradiation may also impair pituitary function; children with brain tumors treated with high-dose radiation are at highest risk.
Chronic renal insufficiency	Not completely reversed by renal transplantation, but does improve with growth hormone therapy.
Turner's syndrome	Syndrome occurs due to deletions or mutations of one of the X chromosomes. It is associated with short stature, and growth hormone therapy improves growth in these patients.

Children born small for gestational age (SGA) may benefit from rhGH. SGA is defined as birth weight and/or length at least two standard deviations below the mean for gestational age. Some SGA children may be from -2.9 to -3.4 standards of deviation below the population average, and children may not catch up prior to puberty. Most children born with SGA achieve catch-up growth in length during the first six to twelve months of life. However, approximately 10% of children born with SGA will remain at least two standard deviations below the mean for height throughout childhood and adolescence and into adulthood. Before growth hormone therapy for a child born with SGA is considered, it is important to wait until the spontaneous catch-up phase is completed, which usually occurs by the time a child is two to three years of age. Impaired fetal growth has multiple causes, including maternal, placental, and fetal factors, although the cause is often not clear. The reason for short stature may be from abnormal patterns of endogenous GH release with low GH, IGF-I and IGF-binding protein concentrations.

About 32 in one million children under 15 years old have renal failure, defined as the need for dialysis or transplant. Many more children have chronic renal insufficiency (CRI), defined as a creatinine clearance of less than 30 mL/min. Pre-pubertal children with CRI experience growth retardation of two or more standards of deviation below the average height for their age. Although renal transplantation results in improved growth, it does not fully allow children with CRI to attain expected adult height. Growth hormone therapy can overcome some of the resistance to growth hormone seen in uremic patients. This resistance to GH may be due to increased concentrations of binding proteins for growth hormone and a reduced availability of insulin-like growth factor-I (IGF-I). Additionally, fewer GH receptors are found in the liver, resulting in reduced IGF-I action. Growth hormone does not improve renal function, but it increases growth velocity in children.

Turner's syndrome is a chromosomal disorder occurring exclusively in girls with an absence or a defect in chromosome 45X. The disorder results in lack of sexual development at puberty, short stature, webbed neck and a variety of heart defects. Turner's syndrome is diagnosed in approximately one in 2000 to 3000 live female births. The reason for short stature in nearly all girls with Turner's syndrome is probably from an impaired response to GH rather than a deficiency of the hormone. Treatment with growth hormone, anabolic steroids and estrogen are required to improve physical and sexual development.

Prader-Willi syndrome affects multiple systems resulting in infantile hypotonia and failure to thrive, hypogonadism, short stature, learning disabilities and hyperphagia beginning at one to three years of age that leads to obesity. Prader-Willi syndrome is rare, occurring in approximately one in 10,000 to 25,000 live births; approximately 17,000 to 22,000 children in the U.S. have Prader-Willi syndrome. Sixty percent of children (primarily boys) diagnosed with Prader-Willi syndrome have abnormal chromosomes; either a three to four million base-pair deletion of the paternal chromosome 15q11q13, or both fifteenth chromosomes are inherited from the mother.

The primary outcomes observed in clinical evaluations of rhGH therapy in PWS include changes in growth, body composition, fat utilization, physical strength and agility, cardiovascular risk factors, and behavior. Doses of rhGH used in PWS efficacy trials range from 0.02 to 0.07 mg/kg/day. The benefit of rhGH in the management of PWS is increased height, and possible reduction in fat mass with increased muscle mass. In a consensus statement by Lee et al, children with PWS do have growth hormone dysregulation and rhGH therapy should be considered for these patients as it is for other children with growth hormone deficiencies. The FDA has approved the treatment of growth hormone for short stature in Prader-Willi syndrome.

Noonan syndrome is a genetic disorder that causes abnormal development of multiple parts of the body. It used to be called Turner-like syndrome because certain symptoms (webbing of neck and abnormally shaped chest) resembled those seen in Turner syndrome. Management focuses on controlling the disease's symptoms and complications. Growth hormone may be used to treat short stature in some people who have Noonan syndrome.

SHOX is an acronym for the short stature homeobox-containing gene. The SHOX gene codes for a key transcription factor that plays a critical role in controlling human stature primarily through regulation of chondrocyte development. The SHOX gene is located on the human sex chromosomes (X and Y), and two functional copies of the gene are required for normal growth. SHOX deficiency (SHOX-D) is present when one copy (or very rarely, both copies) of the SHOX gene has undergone deletion or mutation. SHOX deficiency may be inherited in a dominant fashion from an affected parent and passed on to offspring, or may occur spontaneously in a family with no other affected members. Patients with SHOX deficiency may present with a broad phenotypic spectrum ranging from isolated short stature with no distinguishing clinical features to short stature with moderate to severe skeletal dysplasia (Léri-Weill syndrome).

Children with AIDS often develop a wasting syndrome as with adults or a failure to thrive, with inadequate growth or development. Limited research suggests that growth hormone supplementation may help to normalize physical growth and appearance.

Approximately 45,000 people are hospitalized for burns each year with approximately half of these being admitted to specialized burn units. The number of patients with severe burns of > 60% of body surface area is less than 5% of admissions. The metabolic goal of rhGH therapy in children and adults with severe burns is primarily anti-catabolic. Rather than increased growth and physical appearance, burn patients benefit from rhGH therapy by improving nitrogen balance, reducing protein wasting and increasing wound healing.

Children are diagnosed with idiopathic short stature when they are at or below the 5th percentile for height, but who have normal serum growth hormone responses to stimuli. Conflicting research suggests that growth hormone therapy may or may not increase the final height of many of these children. If it did increase height these children are still considered short by stature into adulthood. GH for ISS is FDA approved and one-third of children receiving growth hormone therapy in the United States have idiopathic short stature.

Adult Diagnoses

Adults with GHD may have a congenital form of the disease or they may acquire GHD from damage to the pituitary occurring later in life. The primary goal of rhGH therapy in these patients is not linear growth, but reversal of risk for problems such as abnormal body composition, osteopenia, cardiac failure, and hyperlipidemia. Patients may also benefit from an improved quality of life. Adults with GHD are at increased risk of death due to coronary artery disease based on data from 849 patients in three retrospective studies. Additionally, these adults may suffer from the effects summarized in Table 2. Patients with adult-onset deficiency will experience more severe effects than those with childhood-onset deficiency.

The use of rhGH to treat adults with growth hormone deficiency remains controversial. Although recognized as a clinical syndrome for a decade, the disorder's diagnosis and management are not completely defined. Some are not convinced that a deficiency of growth hormone accounts for the syndrome that those patients with GHD experience. Adult-onset GHD appears to increase the mortality rate from cardiovascular, respiratory and cerebrovascular causes; however, many patients have deficiencies of other gonadal hormones, thyroid releasing hormones, or corticosteroids. Gonadotropin deficiency, over-treatment of hypothyroidism, or Cushingoid syndrome from over-replacement of corticosteroids, and irradiation of tumors may also serve as risk factors for increased mortality in patients with hypopituitarism. If GHD could be defined as a single factor in increased mortality, no data of the long-term use of rhGH defines whether or not it reduces mortality in this population. Currently, it is used to correct significant physical and psychological factors such as abnormal body habitus and reduced sense of well-being.

Table 2 - Effects Associated with GHD in adults

Category	Effects
Body composition	Increased fat mass, central obesity, decreased muscle mass and strength, low total body water
Metabolic disorders	Increased serum lipid concentrations (VLDL and LDL) with decreased HDL concentrations, insulin resistance, hyperinsulinemia, stimulated growth hormone concentrations less than 3 mcg/mL.
Cardiovascular	Decreased heart size and cardiac output, increased risk for atherosclerotic plaques, and a nearly doubled risk for cardiac mortality, increased plasminogen activator inhibitor and fibrinogen concentrations increasing risk for thrombosis
Bone	Decreased bone mineral density and bone mineral content
Quality of life and personal well-being	Decreased energy, vitality, physical mobility, and sexual function. Feelings of social isolation and emotional lability.

An estimated 800,000 to 900,000 people currently live with HIV infection in the U.S. As of December 2001, the total number of cases of AIDS reported to the Centers for Disease Control and Prevention was 807,075 in adults and adolescents. The wasting syndrome associated with AIDS involves an involuntary loss of 10% of body weight (including lean muscle mass) in combination with fever, diarrhea and weakness. This is a result of increased energy expenditure with inefficient use of energy sources and altered hormone function. This disorder is an AIDS-defining condition that often leads to death. A recent development in the treatment of AIDS-wasting syndrome is the use of rhGH to control loss of body mass where androgens, megestrol and dronabinol were frequently used in the past to stimulate weight gain and appetite.

Finally, short bowel syndrome (SBS) is a complication of removing 50% or more of the small intestine. The most common indication for bowel removal is Crohn's disease. Diarrhea is the primary symptom of patients with SBS, although cramping, bloating and heartburn are also common. Many people with SBS are malnourished and severely dehydrated because their remaining small intestine is unable to absorb enough water, vitamins and other nutrients from food. Patients with SBS often present with weakness, fatigue, depression, weight loss, bacterial infections and food sensitivities. Growth hormone is used with special diets and glutamine supplementation in improving nutrient absorption and utilization in SBS patients.

Ongoing Studies

Other adult uses for which growth hormone has been studied without conclusive benefit include obesity, osteoporosis, muscular dystrophy, infertility, increased athletic performance and somatopause in the elderly. This agent is not currently recommended for these indications.

Growth hormone has also been used in children with the following conditions, although there are no prospective studies that assess linear growth until final height is achieved: hypochondroplasia, Down syndrome, spinal cord defects, hypophosphatemic rickets, juvenile chronic arthritis, Duchenne muscular dystrophy, and cystic fibrosis.

Some studies have shown that administering GnRH with recombinant human GH may lead to an improvement in the final height of GHD children, but published results are few and sometimes conflicting. A central issue is the selection of the patients likely to benefit from such a combined therapy. Although we did not find that administration of GnRHa in combination with rGH resulted in a clear overall positive effect on the final height of GHD children in comparison with rGH treatment alone, the results of our study suggest that two populations might benefit particularly from combined GnRHa-rGH replacement therapy. As already reported by some researchers, a beneficial effect on the shortest girls at the onset of puberty was observed in our study. Interestingly, we found that another population, GHD children of either sex with a history of IUGR, might also benefit from such a combination therapy. Further prospective studies are required to confirm these preliminary results in this particular group of patients who already benefit from treatment with recombinant human GH.

The literature on the final effect of the addition of GnRHa to GH in GHD children is limited. Adding GnRHa in early puberty to GHD patients who have been treated with GH, or in whom GH and GnRHa are started simultaneously, enables the patients to reach their genetic target, whereas FH of patients on GH alone is about 1 SD score below MPH SD score. This result is of similar size as the efficacy of GnRHa in idiopathic short stature.

Adverse Reactions

Somatropin produces relatively few significant adverse effects. The most common side effects of somatropin therapy include pain at injection site and arthralgias. Rare adverse effects have been identified in international databases of thousands of children receiving recombinant human growth hormone (rhGH), namely, the National Cooperative Growth Study (Genentech), the Kabi International Growth Study (Pharmacia), and OZGROW (sponsored by the Australian government and Pharmacia). The most prominent disorders include idiopathic intracranial hypertension (IIH), slipped capital femoral epiphyses (SCFE), hyperglycemia and diabetes, cancers, and antibodies to rhGH.

Adverse effects that occur more in adults than in children are carpal tunnel syndrome, joint swelling, and peripheral edema. These adverse effects are associated with fluid retention and are seen shortly after initiating GH therapy and are dose-dependent. Fluid retention may resolve on its own or may require dosage reductions. Increased left ventricular wall size was noted after 42 months in some patients; however, doses were noted to be too high. Another concern of GH therapy in adults is the increase in lipoprotein-A concentrations, since this is associated with coronary heart disease. The significance of this increase, however, is not currently known. Additional rare findings in GH-treated patients include increased pigmentation, nevi growth, gynecomastia, and pancreatitis.

Drug Interactions/Contraindications

Although formal drug interaction studies have not been conducted, limited published data indicate that growth hormone treatment increases cytochrome P450 (CP450) mediated antipyrine clearance. These data suggest that growth hormone administration may alter the clearance of compounds known to be metabolized by CP450 liver enzymes (e.g., corticosteroids, sex steroids, anticonvulsants, cyclosporine). When growth hormone is administered in combination with other drugs known to be metabolized by CP450 liver enzymes, careful monitoring should occur. Concomitant excessive glucocorticoid treatment may prevent optimal response to somatropin. If glucocorticoid replacement therapy is required, the glucocorticoid dosage and compliance should be monitored carefully to avoid either adrenal insufficiency or inhibition of growth-promoting effects.

Somatropin is contraindicated when there is any evidence of active malignancy. Prior to the institution of somatropin therapy, antimalignancy treatment must be completed with evidence of remission. Somatropin should not be initiated to treat patients with acute critical illness due to complications following open heart or abdominal surgery, multiple accidental trauma or to patients with acute respiratory failure. Somatropin is also contraindicated in patients with Prader-Willi syndrome who are severely obese or have severe respiratory impairment. Additionally, somatropin is not indicated for the long-term treatment of pediatric patients who have growth failure due to genetically confirmed Prader-Willi syndrome, unless patients with Prader-Willi syndrome

also have a diagnosis of growth hormone deficiency. Somatropin should not be used for growth promotion in pediatric patients with closed epiphyses. Somatropin should also be discontinued if a contraindication arises, such as active malignancy, intracranial hypertension, second and third trimester of pregnancy, or the development of diabetic retinopathy.

Coding/Billing Information

Note: This section is not in use.

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Policy History

Pre-Merger Organizations	Last Review Date	Policy Number	Title
CIGNA HealthCare	5/30/2008	4012	Somatropin (Genotropin [®] , Humatrope [®] , Norditropin [®] , Nutropin [®] , Nutropin [®] AQ, Omnitrope [®] , Saizen [®] , Serostim [®] , Tev-Tropin [®] , Zorbtive [®])
Great-West Healthcare	11/2007	-----	Somatropin

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Connecticut General Life Insurance Company has acquired the business of Great-West Healthcare from Great-West Life & Annuity Insurance Company (GWLA). Certain products continue to be provided by GWLA (Life, Accident and Disability, and Excess Loss). GWLA is not licensed to do business in New York. In New York, these products are sold by GWLA’s subsidiary, First Great-West Life & Annuity Insurance Company, White Plains, N.Y.