

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

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Somatropin (Genotropin[®], Humatrope[®], Norditropin[®], Nutropin[®], Nutropin[®] AQ, Saizen[®], Serostim[®], Tev-Tropin[®], Zorbtive[®]) is considered medically necessary for the following indications (see individual subsections for specific medical necessity criteria requirements for each indication):

Growth Hormone Use in Children:

- growth hormone deficiency in children
- small for gestational age (SGA)
- growth delay in children with chronic renal failure
- Turner Syndrome
- Prader-Willi Syndrome
- Noonan Syndrome

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)

The following somatropin products are preferred brand products:

- Nutropin[®]
- Nutropin AQ[®]
- Saizen[®]
- Serostim[®] (for approved indications only)
- Zorbtive[®] (for approved indications only)

Growth Hormone Use in Children:

- **For growth hormone deficiency in children (including pituitary dwarfism, as well as growth hormone deficiency following cranial irradiation), when ALL of the following criteria are met:**
 - patient must be evaluated for therapy initiation and continuation by an endocrinologist

- auxologic evaluation (stature and growth velocity data), including **ONE** of the following:
 - patient'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
 - patient'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.); history of irradiation, multiple pituitary hormone deficiency (MPHD) (i.e., deficiency of two or more pituitary hormones) or a proven genetic defect affecting the growth hormone axis.
 - low insulin-like growth factor-I (IGF-I) **or** insulin-like growth factor binding protein-3 (IGFBP-3) levels adjusted for chronological age, unless patient is on continuous growth hormone therapy and IGF testing is not performed prior to initiation of therapy
 - other pituitary hormone deficiencies, e.g., thyroid, cortisol or sex steroids, have been ruled out and/or corrected
 - For children with documented panhypopituitarism, defined by the absence of all other anterior pituitary hormones [Luteinizing Hormone(LH), Follicle Stimulating Hormone (FSH), Thyroid Stimulating Hormone (TSH), Adrenocorticotrophic Hormone (ACTH)], it may be assumed that growth hormone is also absent and no stimulation testing is required. Approval of GH in such cases does not require auxologic evaluation or IGF-1 and IGFBP-3 confirmation of this diagnosis.

Reassessment of medical necessity should occur yearly.

Medical necessity for continuation of therapy is contingent upon meeting current initial use criteria and evaluation of response as shown by growth curve chart. Medical necessity for growth promotion ceases when the bony epiphyses have closed.

- **Small for Gestational Age (SGA) when ALL of the following criteria are met:**
 - patient must be evaluated for therapy initiation and continuation by an endocrinologist
 - 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

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

Reassessment of medical necessity should occur yearly.

Medical necessity for continuation of therapy is contingent upon meeting current initial use criteria and evaluation of response as shown by growth curve chart. Medical necessity for growth promotion will cease when the bony epiphyses have closed.

- **For Growth Delay in Children with Chronic Kidney Disease when ALL of the following criteria are met:**
 - patient must be evaluated for therapy initiation and continuation by an endocrinologist
 - renal function at stage 2 chronic kidney disease (or GFR from 60–89 ml/min/1.73m²)
 - patient's height is more than 2 SD below average for the population mean height for age and sex, **and** a height velocity measured over one year to be more than 1 SD below the mean for chronological age, **or** for children over two years of age, a decrease in height SD of more than 0.5 over one year

Reassessment of medical necessity should occur yearly.

Medical necessity for continuation of therapy is contingent upon meeting current initial use criteria and evaluation of response as shown by growth curve chart. Medical necessity for growth promotion will cease when the bony epiphyses have closed.

- **For Turner Syndrome, when ALL of the following criteria are met:**
 - patient must be evaluated for therapy initiation and continuation by an endocrinologist
 - documentation of diagnosis as established by genetic testing
 - patient's height is more than 2 SD below average for the population mean height for age and sex, **and** a height velocity measured over one year to be more than 1 SD below the mean for chronological age, **or** for children over two years of age, a decrease in height SD of more than 0.5 over one year
 - patient must be followed annually by an endocrinologist

Reassessment of medical necessity should occur yearly.

Medical necessity for continuation of therapy is contingent upon meeting current initial use criteria and evaluation of response as shown by growth curve chart. Medical necessity for growth promotion will cease when the bony epiphyses have closed.

- **For Prader-Willi Syndrome, when ALL of the following criteria are met:**
 - patient must be evaluated for therapy initiation and continuation by an endocrinologist
 - diagnosis of Prader-Willi Syndrome is confirmed by appropriate genetic testing
 - long-term treatment of pediatric patients who have growth failure due to Prader-Willi Syndrome and also have a diagnosis of growth hormone deficiency as defined by the above criteria specific to Pediatric Growth Hormone Deficiency

Reassessment of medical necessity should occur yearly.

Medical necessity for continuation of therapy is contingent upon meeting current initial use criteria and evaluation of response as shown by growth curve chart. Medical necessity for growth promotion will cease when the bony epiphyses have closed.

- **For Noonan Syndrome, when ALL of the following criteria are met:**
 - patient must be evaluated for therapy initiation and continuation by an endocrinologist
 - diagnosis of Noonan Syndrome is confirmed by appropriate genetic testing
 - patient's height is more than 2 SD below average for the population mean height for age and sex, **and** a height velocity measured over one year to be more than 1 SD below the mean for chronological age, **or** for children over two years of age, a decrease in height SD of more than 0.5 over one year

Reassessment of medical necessity should occur yearly.

Medical necessity for continuation of therapy is contingent upon meeting current initial use criteria and evaluation of response as shown by growth curve chart. Medical necessity 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:**
 - patient must be evaluated for therapy initiation and continuation by an endocrinologist
 - 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 nanograms per mL when measured by polyclonal antibody (RIA) or less than 2.5 nanograms per mL when measured by monoclonal antibody (IRMA) to at least two provocative stimuli of growth hormone release: Insulin, Levodopa, Clonidine, Arginine, or Glucagon. Only one stimulation test is required where there is a previous diagnosis of GHD from childhood.
- OR**
- GHD has been confirmed by arginine-GHRH testing resulting in plasma growth hormone concentrations of 9 nanograms per mL or less 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 [Luteinizing Hormone (LH), Follicle Stimulating Hormone (FSH), Thyroid Stimulating, Adrenocorticotropic Hormone (ACTH) and Growth Hormone (GH)]

Reassessment of medical necessity should occur yearly.

Medical necessity for continuation of therapy is contingent upon 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), where:**
 - used with special diets and glutamine supplementation
 - patients are currently dependent upon intravenous parenteral nutrition

Authorization to consist of one four-week course of therapy.

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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
- chromosomal anomalies unless otherwise specified as medically necessary
- 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 medical necessity conditions)
- obesity
- osteoporosis

- muscular dystrophy
- infertility
- somatopause
- repeat courses of therapy in Short Bowel Syndrome
- Crohn's disease

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Growth Hormone Use in Children

- idiopathic (i.e., of unknown origin) short stature, also called non-growth hormone deficient short stature

Growth Hormone Use in Adults

- increased athletic performance

General Background

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.

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.

Consensus guidelines are available for several childhood disorders affecting stature and body composition. The American Association of Clinical Endocrinologists (AACE) and the National Institute for Clinical Excellence (NICE) in the United Kingdom proposed appropriate guidelines for use in children. In addition, the Growth Hormone Research Society (GHRS) proposed consensus guidelines for GHD in children and adolescents, and for adult GHD. The pediatric recommendations of GHRS are endorsed by five international organizations and four of five makers of rhGH products. Both GHRS guidelines include recommendations for diagnosis of GHD, as well as rhGH treatment and safety monitoring for children and adults.

The AACE recommended rhGH in children with GHD, Turner's syndrome, chronic renal insufficiency, SGA, and Prader-Willi Syndrome in 2003, based on approved indications and available research. The NICE guidelines, published in 2002, recommend rhGH for the same indications as the AACE guidelines specifically for somatropin, but also includes Prader-Willi syndrome as an appropriate indication for somatropin therapy.

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 Growth Hormone Research Society, 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. Diagnosis may be made based on a stimulus test 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.

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 growth hormone deficiency 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.

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 45,X. 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 United States Pharmacopeial Drug Information (USPDI) states that growth hormone is not indicated for the long-term treatment of pediatric patients who have growth failure due to genetically confirmed Prader-Willi syndrome unless they also have a diagnosis of growth hormone deficiency.

Children born small for gestational age (SGA) may also 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.

From the beginning of the HIV epidemic through the end of 2001, a total of 9074 American children under age 13 were reported to the Centers for Disease Control and Prevention (CDC) as living with AIDS. 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 not increase the final height of many of these children. One-third of children receiving growth hormone therapy in the United States have idiopathic short stature.

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.

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 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.

Two consensus guidelines, one from the AACE and one from the GHRS, provide guidelines for the appropriate diagnosis of adult GHD and treatment of GHD using rhGH. Both define adult growth hormone deficiency as a biochemical disorder of low concentrations of endogenous growth hormone resulting in reduced lean mass, bone mineral density, skin thickness, muscle strength and exercise tolerance. An increase in fat mass, girth at the waist and sweating are also noted. Patients often experience a low sense of well-being. Patients presenting with clinical symptoms are diagnosed when a growth hormone stimulation test raises growth hormone concentrations to fewer than 3 mcg/L by radioimmunoassay. These patients are candidates for rhGH therapy, but doses should begin very low at 0.1 to 0.3 mg per day subcutaneously in the evening. The dose is then titrated at monthly intervals to a maximum of approximately 1 mg per day. Unlike pediatric dosing, these doses are not weight-based, and are relatively small. Patients should receive a thorough evaluation of the efficacy of treatment in order to continue therapy. Practitioners should assess patients for improved quality of life, increased IGF-I concentrations, decreased weight and adiposity, improved bone mineral density, changes in thyroid hormone concentrations, and improved lipid profiles. If a patient shows no improvement by the time the maximum dose is achieved, rhGH should be discontinued. rhGH 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. Insufficient data are available to show the long-term effects of rhGH in adults, but the deficiency in endogenous growth hormone is not curable and, therefore, the need for replacement therapy is lifelong.

Table 2. Effects associated with growth hormone deficiency 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.

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.

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.

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 list of codes may not be all-inclusive.

When medically necessary:

CPT [®] * Codes	Description
	No specific codes

HCPCS Codes	Description
J2940	Injection, somatrem, 1 mg
J2941	Injection, somatropin, 1 mg

ICD-9-CM Diagnosis Codes	Description
	Multiple/varied

*Current Procedural Terminology (CPT[®]) © 2006 American Medical Association: Chicago, IL.

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