Somatropin is a purified polypeptide hormone of recombinant DNA origin; somatropin contains the identical sequence of amino acids found in human growth hormone; human growth hormone assists growth of linear bone, skeletal muscle, and organs by stimulating chondrocyte proliferation and differentiation, lipolysis, protein synthesis, and hepatic glucose output; stimulates erythropoietin which increases red blood cell mass; exerts both insulin-like and diabetogenic effects; enhances the transmucosal transport of water, electrolytes, and nutrients across the gut.

**Preferred Formulary Status**

**Preferred agents:** Nutropin, Norditropin, and Omnitrope  
**Non-preferred agents:** Humatrope, Saizen, Genotropin, Tev-tropin

- A trial of a preferred agent is required before a non-preferred agent is approved with no grandfathering.

**Recommended Authorization Criteria**

A. Coverage of Genotropin, Humatrope, Norditropin, Nutropin, Nutropin AQ, Omnitrope, Saizen, and Tev-Tropin (all listed products except Serostim and Zorbtive) is recommended in patients who meet one of the following criteria within the scope of their benefit plan:

**FDA Approved Indications**

A1. **Children or adolescents diagnosed with growth hormone deficiency** must meet the following criteria (a through d). Somatropin is FDA approved for the treatment of children with growth failure due to inadequate secretion of normal endogenous growth hormone. In the professional opinion of specialist physicians reviewing the data, we have adopted this criterion.

a) The patient must be evaluated by a pediatric endocrinologist.
b) **Provocative growth hormone testing**: The patient must have a documented growth hormone deficiency as defined by a diminished serum growth hormone response to stimulation testing of < 10 ng/mL. The results of one of the following stimulation tests support the diagnosis of growth hormone deficiency: levodopa, insulin-induced hypoglycemia, arginine, clonidine, or glucagon. One stimulation test is required to exclude normal children. Children severely affected by growth hormone deficiency fail growth hormone stimulation testing. Some children will achieve stimulated growth hormone concentrations above 10 ng/mL and should be reviewed for authorization with criteria A.2. below.

c) **Height**: The patient’s baseline height must be < the third percentile for age and gender (i.e., > 2 standard deviations [SD] below the mean for gender and age);

d) **Growth (height) velocity**: Children aged < 3 years must have a pretreatment growth rate of < 7 cm per year, and children aged 3 years and older must have a growth rate < 4 cm per year OR for a child of any age the growth velocity is < 10th percentile for age and gender based on at least 6 months of growth data.

Authorization can be given for the following conditions where children are growth hormone deficient:

**Children who have undergone brain radiation.** Approve in children who have undergone brain radiation if they meet the criteria for children A.1.a, A.1.b and A.1.d. Children who have undergone brain radiation and have demonstrated growth hormone deficiency often begin treatment with somatropin when the rate of growth slows significantly. Growth hormone deficiency is a frequent complication of total body irradiation and therapy with somatropin is effective in increasing growth rate and final height in children.

**Congenital hypopituitarism.** Approve somatropin for infants or children with congenital hypopituitarism if the patient has been evaluated by a pediatric endocrinologist and meets the criteria for children A.1.b above. These patients are growth hormone deficient. Growth hormone is used in infants and young children with congenital hypopituitarism, which manifests in infancy with hypoglycemia, microgenitalia, hyperbilirubinemia, and multiple anterior pituitary hormone deficiencies.

Patients with pituitary stalk agenesis, empty sella, sellar or supra-sellar mass lesion, or ectopic posterior pituitary “bright spot” on magnetic resonance image or computed tomography must be evaluated by a pediatric endocrinologist, but are not required to have growth hormone stimulation testing. These patients either have severe isolated growth hormone deficiency or multiple pituitary hormone deficiency.

**Children who have had a hypophysectomy (surgical removal of pituitary gland).** Approve. Growth hormone is secreted from the anterior pituitary. These children are growth hormone deficient.

**Patients with growth hormone deficiency who are continuing somatropin therapy.**
In patients who have been receiving somatropin for at least 12 months, the growth rate must have increased significantly in the most recent year according to the prescribing physician. In children or adolescents who respond to growth hormone, the height velocity at least doubles by the end of the first year. Patients should be reviewed annually for growth rate and further authorization is not recommended when the height velocity is < 2.5 cm/year in the most recent year. These criteria do not apply to adolescents with documented hypopituitarism.

In adolescents aged greater than 12 years with prior therapy with somatropin for growth hormone deficiency, the growth rate must have increased significantly in the most recent year according to the prescribing physician, and the epiphyses must be open. In children or adolescents who respond to growth hormone the height velocity at least doubles by the end of the first year. These patients should be reviewed annually for growth rate and x-ray evidence that the epiphyses are not closed. Further
authorization is not recommended when the growth rate is < 2.5 cm/year and/or if the epiphyses are closed. These criteria do not apply to adolescents with documented hypopituitarism.

Adolescents who have previously responded to somatropin with increases in height velocity and who have completed linear growth may be retested for growth hormone deficiency. If appropriate, these patients may receive somatropin therapy as a transition adolescent or an adult. See criteria A3.

In addition, in adolescents or young adults greater than 18 years of age, somatropin should not be authorized when the mid-parental height is attained. Mid-parental height is the father’s height plus the mother’s height divided by 2, plus 2.5 inches if male or minus 2.5 inches if female.

Adult height is achieved when the growth rate is < 2 cm/year and/or the bone age is 15 years in girls or 16 years in boys.

Adolescents and young adults with childhood onset growth hormone deficiency who have completed linear growth (defined as growth rate < 2 cm/year) may be reviewed for treatment of adult growth hormone deficiency. See criteria A3 below.

A2. Non-growth hormone deficient short stature (idiopathic short stature) in children or adolescents whose epiphyses remain open. Coverage of somatropin on a 6-month trial basis is recommended for those who meet all of the following criteria (a through e). In the professional opinion of specialist physicians reviewing the data, we have adopted these criteria.

a) **Height:** The patient’s baseline height must be < the third percentile for age and gender (i.e., > 2 standard deviations [SD] below the mean for gender and age).

b) **Growth (height) velocity:** Children aged < 3 years must have a pretreatment growth rate of < 7 cm per year, and children aged 3 years and older must have a growth rate < 4 cm per year OR for a child of any age the growth velocity is < 10th percentile for age and gender based on at least 6 months of growth data.

c) A **pediatric endocrinologist** must certify that the child’s ability to participate in basic activities of daily living is limited by their short stature (i.e., the degree of growth retardation is considered medically significant by the physician) and the child has a condition for which growth hormone is effective (or will possibly be effective during the initial trial of therapy).

d) A **pediatric endocrinologist** must certify that based on bone-age x-ray, the predicted adult height is < the third percentile. Children with constitutional delay of growth and puberty (CDGP) are excluded from review in this section. (See Exclusions.) Children with Noonan syndrome or SHOX deficiency should be reviewed using the criteria for these conditions.

Children or adolescents with dysmorphic phenotypes such as skeletal dysplasias or Turner syndrome, those born SGA, and those with clearly identified causes of short stature (e.g., celiac disease, inflammatory bowel disease, juvenile chronic arthritis, growth hormone deficiency or growth hormone resistance, hypothyroidism, or Cushing’s syndrome) should be excluded from review for idiopathic short stature.

e) After the 6-month trial, approve for an additional 12-months, if the initial annualized growth rate doubled in comparison to the previous year. The initial 6-month trial of growth hormone is to establish that the child’s condition responds to growth hormone therapy. Authorization for continued therapy should be based on an adequate clinical response defined as an annualized growth rate that doubles in comparison to the previous year (e.g., if the growth velocity was 3 cm/year for the year prior to treatment, then after 6 months of somatropin therapy, the growth velocity must be at least 3 cm in 6 months [1.5 cm/6 months baseline]); or if the growth velocity was 2 cm/year for the year prior to treatment, then after 6 months of somatropin therapy, the growth velocity must be at least 2 cm in 6 months [1 cm/6 months baseline]). Children who show a striking increase in growth velocity during the first 6 to 12 months of somatropin therapy are most likely to
benefit from long-term therapy, and therapy should be discontinued if there is no significant increase in growth rate during the first year. Children who have a significant increase in growth rate after the first 6-month trial and the next 12 months should then be reviewed annually for growth rate and closure of the epiphyses.

**Patients with non-growth hormone deficient short stature (idiopathic short stature) who are continuing somatropin therapy.**

After the first 18 months of therapy (this is in patients who were reviewed after 6 months and received somatropin for another 12 months using criteria e above) or in patients who have been receiving somatropin for at least 12 months, the growth rate must have increased significantly in the most recent year according to the prescribing physician. In children or adolescents who respond to growth hormone, the height velocity at least doubles by the end of the first year. Patients should be reviewed annually for growth rate and further authorization is not recommended when the height velocity is < 2.5 cm/year in the most recent year.

In adolescents greater than 12 years of age with prior therapy with somatropin for idiopathic short stature, the growth rate must have increased significantly in the most recent year according to the prescribing physician and the epiphyses must be open. These patients should be reviewed annually for this growth rate and x-ray evidence that the epiphyses are not closed. Further authorization is not recommended when the growth rate is < 2.5 cm/year and/or if the epiphyses are closed.

In addition, in adolescents greater than 18 years of age, somatropin should not be authorized when the mid-parental height is attained. Mid-parental height is the father's height plus the mother's height divided by 2, plus 2.5 inches if male or minus 2.5 inches if female. Adult height is achieved when the growth rate is < 2 cm/year and/or the bone age is 15 years in girls or 16 years in boys.

The AAP recommends therapy with growth hormone in children whose extreme short stature keeps them from participating in basic activities of daily living and who have a condition for which the efficacy of growth hormone therapy has been demonstrated. There is no reliable way to identify patients likely to respond from those unlikely to respond to growth hormone therapy.

Somatropin is FDA-approved for the long-term treatment of idiopathic short stature (non-growth hormone-deficient short stature) defined by height SDS ≤ -2.25, and associated with growth rates unlikely to permit attainment of adult height in the normal range, in pediatric patients whose epiphyses are not closed and for whom diagnostic evaluation excludes other causes associated with short stature that should be observed or treated by other means. In controlled trials, in children with idiopathic short stature who were not growth hormone deficient, somatropin therapy was effective in increasing final adult height greater than pretreatment predicted adult height. No specific studies have been conducted in pediatric patients with familial short stature.

**A3. Adults diagnosed with growth hormone deficiency** must meet the following criteria (a, b, c, and d):

a. The patient must be evaluated by an endocrinologist.

b. The endocrinologist must certify that somatropin is not being prescribed for anti-aging therapy or to enhance athletic ability or for body building.

c) The patient must have a documented diagnosis of growth hormone deficiency that is one of the following:

*Adult onset:* growth hormone deficiency alone or multiple hormone deficiencies (hypopituitarism) resulting from pituitary disease, hypotalamic disease, pituitary surgery, cranial radiation therapy, tumor treatment, traumatic brain injury, or subarachnoid hemorrhage; or

*Childhood-onset;*
Note: Somatropin is not recommended in adults who had growth hormone for treatment of conditions as children or adolescents that were not due to growth hormone deficiency (e.g., Turner syndrome, idiopathic short stature, or SGA). Retesting these patients when final height is attained is not indicated.

d) Note: d is either i or ii.

i. The patient must have a negative response to one standard growth hormone stimulation test as follows. The cutoff values vary with the test used.

Adults: The insulin tolerance test or the glucagon stimulation test must be used. The peak growth hormone response must be ≤ 5.0 mcg/L for the insulin tolerance test or ≤ 3.0 mcg/L for the glucagon test. If the GH releasing hormone (GHRH) plus arginine test is available, it can be used. See note below. OR

Transition adolescents (adolescents with childhood onset growth hormone deficiency who are transitioning from childhood to adulthood): The patient must be off somatropin for at least one month before retesting. The insulin tolerance test or the glucagon stimulation test must be used. The peak growth hormone response must be ≤ 5.0 mcg/L for the insulin tolerance test or ≤ 3.0 mcg/L for the glucagon test. If the GHRH plus arginine test is available, it can be used. See note below. The transition period is when statural growth is completed, usually before age 20 years (arbitrary age range 15 to 25 years).

Note: rarely, the arginine alone test may be used in adults or transition adolescents if both the insulin tolerance and the glucagon stimulation tests are contraindicated and glucagon is not available. With the arginine test, the peak growth hormone response must be ≤ 0.4 mcg/L.

Note: GHRH (sermorelin, Geref) is no longer available in the U.S. When GHRH was available, GHRH plus arginine was considered the best alternative to the insulin tolerance test in adults. For adults or transition adolescents who have had a GHRH plus arginine test, the peak growth hormone response should be as follows.

- ≤ 11.0 mcg/L in patients with a BMI < 25 kg/m²;
- ≤ 8.0 mcg/L with BMI ≥ 25 and < 30 kg/m²; and
- ≤ 4.0 mcg/L with BMI ≥ 30 kg/m².

A growth hormone stimulation test is not required in adults with childhood-onset growth hormone deficiency who have known mutations, embryopathic lesions, congenital defects, or irreversible structural hypothalamic-pituitary lesions/damage. These patients do not have to meet any of the criteria in di or dii.

OR both of the following:

d) ii. The patient (adult onset or transition adolescent) has 3 or more of the following pituitary hormone deficiencies: adrenocorticotropin hormone (ACTH) deficiency, thyroid stimulating hormone (TSH) deficiency, gonadotropin deficiency (luteinizing hormone [LH] and/or follicle stimulating hormone [FSH] deficiency are counted as one deficiency), and arginine vasopressin (AVP) deficiency (central diabetes insipidus).

AND

Serum IGF-I < 84 μg/liter (11 nmol/liter) using the Esoterix Endocrinology competitive binding RIA OR if another assay is used, the age and gender adjusted serum IGF-I SDS is ≤ -2 or < 2.5 percentile. If other assays are used, the serum IGF-I level reference range should be provided by the laboratory and show an abnormally low IGF-I based on age and gender. In transition adolescents, the IGF-I is determined when the patient has been off somatropin therapy for at least one month. Other causes of low serum IGF-I must be excluded (e.g., malnutrition, prolonged fasting, poorly controlled diabetes mellitus, hypothyroidism, hepatic insufficiency, oral
estrogen therapy) before using IGF-I as a marker of growth hormone deficiency. Serum IGF-I alone is not specific enough for diagnosis.

Patients (adults and transition adolescents) with growth hormone deficiency who are continuing somatropin therapy.
Adults or transition adolescents with prior therapy with somatropin for growth hormone deficiency should be reviewed annually. The patient must be evaluated by an endocrinologist or in consultation with an endocrinologist and this physician must certify that somatropin is not being used for anti-aging therapy or to enhance athletic performance/body building.

Somatropin is FDA-approved for replacement of endogenous growth hormone in adults with growth hormone deficiency who meet either of the two following criteria: 1) adult onset (growth hormone deficiency either alone or associated with multiple hormone deficiencies [hypopituitarism], as a result of pituitary disease, hypothalamic disease, pituitary surgery, cranial radiation therapy, or trauma; or 2) childhood onset (patients who were growth hormone deficient during childhood as a result of congenital, genetic, acquired, or idiopathic causes).

The insulin tolerance test is the gold-standard test for diagnosis of growth hormone deficiency. There is no information of the effects of increased BMI or central adiposity on the insulin tolerance test. There are no normative data by BMI for the glucagon or arginine tests. The insulin tolerance test is contraindicated in patients with ischemic heart disease or seizure disorders or in the elderly. Clonidine and levodopa are not useful tests in adults.

According to the American Association of Clinical Endocrinologists (AACE) medical guidelines patients with childhood growth hormone deficiency previously treated with somatropin replacement in childhood should be re-tested after final height is achieved and somatropin therapy discontinued for at least one month. Exceptions include those with known mutations; embryonic/congenital defects, irreversible hypothalamic-pituitary structural lesions and those with evidence of panhypopituitarism (≥ 3 pituitary hormone deficiencies) and serum IGF-I levels below the age- and sex-appropriate reference range off growth hormone therapy.

Adult growth hormone deficiency can be predicted with > 90% accuracy by the presence of 3 or 4 pituitary hormone deficiencies in addition to serum IGF-1 concentration that is < 2.5 percentile or < -2 SDS. This is in the absence of conditions that lower IGF-I. Patients with ≥ 3 pituitary hormone deficiencies and an IGF-1 level below the reference range do not need a growth hormone stimulation test. Because of the nature of the cause of growth hormone deficiency in children with structural lesions with multiple hormone deficiencies and those with proven genetic causes, a low IGF-1 at least one month off somatropin therapy is sufficient documentation of persistent growth hormone deficiency without additional provocative testing in these adults with childhood-onset growth hormone deficiency.

A4. Turner syndrome. Somatropin is recommended for girls with short stature associated with Turner syndrome, demonstrated by chromosome analysis. Evaluation of growth hormone secretion is not necessary because these children do not have abnormal growth hormone secretion. Somatropin is FDA-approved for treatment of growth failure (treatment of short stature) associated with Turner syndrome.

Girls with Turner syndrome who are continuing somatropin therapy.
After the first year of therapy with somatropin the growth rate must have increased significantly in the most recent year according to the prescribing physician and the epiphyses must be open. These patients should be reviewed annually for this growth rate and x-ray evidence that the epiphyses are not closed. In children or adolescents who respond to growth hormone the height velocity at least doubles by the end of the first year. Patients should be reviewed annually for growth rate and further authorization is not recommended when the growth rate is < 2.5 cm/year in the most recent year and/or the epiphyses are closed.
A5. **Children or adolescents with SHOX (short stature homeobox-containing gene) deficiency.**

   Somatropin is recommended in children with SHOX deficiency, demonstrated by chromosome analysis, and whose epiphyses are not closed. The patient must be evaluated by a pediatric endocrinologist. Somatropin is FDA-approved for the treatment of short stature or growth failure in children with SHOX deficiency whose epiphyses are not closed. Evaluation of growth hormone secretion is not necessary because these children do not have abnormal growth hormone secretion.

   **Children or adolescents with SHOX deficiency who are continuing somatropin therapy.**

   After the first year of therapy with somatropin the growth rate must have increased significantly in the most recent year according to the prescribing physician and the epiphyses must be open. These patients should be reviewed annually for this growth rate and x-ray evidence that the epiphyses are not closed. In children or adolescents who respond to growth hormone the height velocity at least doubles by the end of the first year. Patients should be reviewed annually for growth rate and further authorization is not recommended when the growth rate is < 2.5 cm/year in the most recent year and/or the epiphyses are closed.

A6. **Children or adolescents with chronic renal insufficiency.** Somatropin is recommended for growth failure in children with chronic renal insufficiency up to the time of kidney transplantation. Patients must be evaluated by a pediatric endocrinologist or a nephrologist. Evaluation of growth hormone secretion is not necessary. Somatropin is also recommended in children who develop chronic renal insufficiency after a kidney transplant. In the professional opinion of specialist physicians reviewing the data, we have adopted this criterion. Somatropin is FDA-approved in pediatric patients for the treatment of growth failure associated with chronic renal insufficiency up to the time of renal transplant.

   **Children or adolescents with chronic renal insufficiency who are continuing somatropin therapy.**

   After the first year of therapy with somatropin the growth rate must have increased significantly in the most recent year according to the prescribing physician and the epiphyses must be open. These patients should be reviewed annually for this growth rate and x-ray evidence that the epiphyses are not closed. In children or adolescents who respond to growth hormone the height velocity at least doubles by the end of the first year. Patients should be reviewed annually for growth rate and further authorization is not recommended when the growth rate is < 2.5 cm/year in the most recent year and/or the epiphyses are closed.

A7. **Prader-Willi syndrome.**

   **Children with growth failure due to Prader-Willi syndrome must be evaluated by a pediatric endocrinologist and adults by an endocrinologist.**

   Somatropin is FDA-approved for treatment of pediatric patients who have growth failure due to Prader-Willi syndrome.

   **Patients with Prader-Willi syndrome who are continuing somatropin therapy.**

   In children or adolescents, after the first year of therapy with somatropin, the growth rate must have increased significantly in the most recent year according to the prescribing physician and the epiphyses must be open. These patients should be reviewed annually for this growth rate and x-ray evidence that the epiphyses are not closed. In children or adolescents who respond to growth hormone the height velocity at least doubles by the end of the first year. Children or adolescents should be reviewed annually for growth rate and further authorization is not recommended when the height velocity is < 2.5 cm/year in the most recent year and/or the epiphyses are closed.

   Adults with Prader-Willi syndrome who are on somatropin should be reviewed annually. The patient must be evaluated by an endocrinologist or in consultation with an endocrinologist and this physician must certify that somatropin is not being used for anti-aging therapy or to enhance athletic performance/body building.

A8. **Short children born small for gestational age (SGA) or with intrauterine growth retardation (IUGR) including those with Silver-Russell syndrome.** Somatropin is recommended and patients must
meets the following criteria, a, b, c and d. Evaluation of growth hormone secretion and bone age is not necessary, although some patients may have a diminished serum growth hormone response to stimulation testing and meet the criteria for children described in A.1 [a through c] above.

a. Patient must be evaluated by a pediatric endocrinologist.

b. **Patient must have been born SGA**, which is defined as birth weight and/or birth length that is > 2 SD below the mean for gestational age and gender, and did not have sufficient catch-up growth before age 2 to 4. Most children born SGA will show catch-up growth by age 2.

c. **Age.**
   - Patient is ≥ 2 years of age and ≤ 8 years or
   - If the child is aged > 8 years and prepubertal, coverage is recommended for one year on a trial basis. If growth increases by ≥ 3 cm/year (i.e., in addition to their baseline growth) with therapy, then authorization for continued therapy is recommended. Somatropin therapy should be stopped when the patient is clearly pubertal.
   - If the child is aged > 8 years and is clearly pubertal, then an exception is not recommended. Efficacy has not been established in pubertal adolescents born SGA.

d. **Height.** The patient’s baseline height must be < third percentile for age and gender (i.e., > 2 SD below the mean for gender and age).

**Children born SGA or with IUGR including Silver-Russell syndrome who are continuing somatropin therapy.**

In children ≥ 2 years of age and ≤ 8 years, after the first year of therapy with somatropin the growth rate must have increased significantly in the most recent year according to the prescribing physician. These children should be reviewed annually for this growth rate.

In children > 8 years of age and prepubertal, after the first year of therapy with somatropin the growth rate must have increased by ≥ 3 cm/year in addition to their baseline growth. These patients should be reviewed annually for this growth rate.

In children who respond to growth hormone the height velocity at least doubles by the end of the first year. Further authorization is not recommended when the growth rate is < 2.5 cm/year and/or if the child is clearly pubertal.

Somatropin is FDA approved for treatment of growth failure in children born SGA who fail to manifest catch-up growth by age 2 to 4 years. In the professional opinion of specialist physicians reviewing the data, we have adopted these criteria.

**A9. Children or adolescents with Noonan syndrome.** Patients must be evaluated by a pediatric endocrinologist and the patient’s baseline height must be < third percentile (i.e., > 2 SD below the mean for gender and age for children without Noonan syndrome). Somatropin is FDA-approved for the treatment of children with short stature associated with Noonan syndrome.

**Children or adolescents with Noonan syndrome who are continuing somatropin therapy.**

After the first year of therapy with somatropin the growth rate must have increased significantly in the most recent year according to the prescribing physician and the epiphyses must be open. These patients should be reviewed annually for this growth rate and x-ray evidence that the epiphyses are not closed. In children or adolescents who respond to growth hormone the height velocity at least doubles by the end of the first year. Patients should be reviewed annually for growth rate and further authorization is not recommended when the growth rate is < 2.5 cm/year in the most recent year and/or the epiphyses are closed.
B. Coverage of Genotropin, Humatrope, Norditropin, Nutropin, Nutropin AQ, Omnitrope, Saizen, Tev-Tropin, and Zorbtive (all listed products except Serostim) is recommended in patients who meet the following criteria:

**FDA Approved Indications**

**B1. Short bowel syndrome.** Somatropin is recommended for adults with short bowel syndrome who are receiving specialized nutritional support (defined as a high carbohydrate, low-fat diet that is adjusted for individual patient requirements and preferences). Patient must be aged ≥ 18 years and therapy is limited to one 4-week course per year. In some patients somatropin may need to be discontinued for up to 5 days for severe toxicities and resumed. This is FDA-approved dosing. Patients will be evaluated by a pharmacist and/or a physician on a case-by-case basis to determine a coverage recommendation for the client for patients requesting more than 4 weeks of therapy or more than one 4-week course per year. Somatropin is FDA-approved for the treatment of short bowel syndrome in patients receiving specialized nutritional support.

C. Coverage of somatropin (Serostim) is recommended in those who meet the following criteria:

**FDA Approved Indications**

**C1. Adults with HIV infection with wasting or cachexia** must meet ALL of the following criteria (a through e).

a) The patient must be HIV-positive and have wasting or cachexia. FDA-approved indication.

b) The patient must have one of the following: documented unintentional weight loss of ≥ 10% from baseline, weight < 90% of the lower limit of ideal body weight, or BMI ≤ 20 kg/m². The following formula can be used to calculate BMI: BMI equals body weight in kgs divided by height meters squared (m²) (i.e., BMI = kg/m²). Clinical trials that established safety and efficacy included patients meeting this criterion.

c) The patient must be able to consume or be fed through parenteral or enteral feedings ≥ 75% of maintenance energy requirements based on current body weight. Clinical trials that established safety and efficacy included patients meeting this criterion.

The patient must have been on antiretroviral therapy for ≥ 30 days prior to beginning somatropin therapy and will continue antiretroviral therapy throughout the course of somatropin treatment;

e) Therapy with somatropin should be limited to 24 weeks in these patients.

**Repeat courses.** Repeat 12- or 24-week courses of somatropin may be authorized in patients who have received a previous 12- or 24-week course of somatropin for HIV infection with wasting or cachexia provided that they have been off somatropin for at least 1 month and meet criteria C.1.a, b, c, and d. There is no safety and efficacy data from controlled trials in patients treated with somatropin continuously for greater than 48 weeks or for patients who start, stop, and then restart treatment. Somatropin is FDA-approved for treatment of HIV patients with wasting or cachexia to increase LBM and body weight, and improve physical endurance. Concomitant antiretroviral therapy is necessary since there is the possibility that somatropin might accelerate viral replication.

**C2. HIV-associated failure to thrive.** Children aged < 17 years with HIV-associated failure to thrive must meet the following criteria (a, b, and c):

a) The patient must be able to consume or be fed through parenteral or enteral feedings ≥ 75% of maintenance energy requirements based on current body weight;
The patient must have been on antiretroviral therapy for ≥ 30 days prior to beginning somatropin therapy and will continue antiretroviral therapy throughout the course of somatropin treatment; and

c) The patient should be reevaluated after 12 weeks to assess the risks vs. benefits of somatropin therapy. Children with HIV-associated failure to thrive may require several months of growth hormone therapy.

Somatropin is FDA-approved for treatment of HIV patients with wasting or cachexia to increase LBM and body weight, and improve physical endurance. Limited data have documented somatropin use for HIV-associated failure to thrive in small numbers of patients aged 6 to 17 years. However, the somatropin (Serostim) product information states that safety and effectiveness in pediatric patients with HIV have not been established. Adequate antiretroviral therapy is likely the most critical determinant of growth in most HIV-infected children in the US.

**Exclusions (Limitations)**

Coverage of Genotropin, Humatrope, Norditropin, Nutropin, Nutropin AQ, Omnitrope, Saizen, Tev-Tropin, and Zorbtive (all listed products except Serostim) is not recommended in the following circumstances, unless the criteria in A or B above have been met. For some of the following indications, authorization for coverage is not recommended because this indication is excluded from coverage in a typical pharmacy benefit. (Note: this is not a level of evidence, but is a reason for exclusion from coverage.)

1. **Acute critical illness due to complications following surgery, multiple accidental trauma, or with acute respiratory failure.** In 2 placebo-controlled trials, in non-growth hormone deficient adults (n = 522) with these conditions, there was a significant increase in mortality (42% vs. 19%) in patients treated with somatropin compared to those on placebo.

2. **Aging (i.e., antiaging); to improve functional status in elderly patients; and somatopause.** Somatropin is not FDA-approved for anti-aging therapy. There are no long-term studies assessing somatropin efficacy and safety for anti-aging therapy. Short-term therapy with somatropin may improve some measures of body composition, including increased muscle mass, reduced total body fat, improved skin elasticity, and reduced rate of bone demineralization, but does not have positive effects on strength, functional capacity, or metabolism. Somatropin is associated with considerable adverse effects in non-growth hormone deficient adults (e.g., carpal tunnel syndrome, soft tissue edema, arthralgias, glucose intolerance, increased serum lipids). Another concern is the possible increased risk of cancer with long-term use of somatropin and the potentiating effects of IGFs on cancer. Somatropin is not indicated for the age-related decrease in growth hormone/IGF-I status.

3. **Athletic ability (enhancement).** Somatropin is not indicated for anabolic therapy to increase body mass or strength for professional or recreational reasons. Short term administration of somatropin to increase strength and endurance in athletes is no more effective than training alone and somatropin should not be administered to athletes or other persons for the purpose of enhancing athletic ability.

4. **Bone marrow transplantation without total body irradiation (cranial radiation).** Somatropin is recommended in patients who have undergone cranial radiation in preparation for bone marrow transplantation and have growth hormone deficiency. Children conditioned for bone marrow transplantation with chemotherapy-only regimens do not require somatropin therapy.

5. **Bony dysplasias (achondroplasia, hypochondroplasia).** Short-term treatment with somatropin increases growth velocity in some patients, but there are no prospective studies assessing linear growth until achievement of final adult height. Achondroplasia is the most common form of bony dysplasia, and somatropin treatment is not effective in significantly increasing stature. Somatropin therapy may transiently increase growth rate, but there are no studies showing a significant increase in adult height. According to AAP guidance for pediatric achondroplasia, growth hormone should only be considered within a research setting. There are very few studies of somatropin therapy in hypochondroplasia. Results are better when somatropin is given at puberty because these patients lack the normal pubertal growth spurt. Effects on
final height are not known. Other forms of skeletal dysplasias are very rare and no conclusions about the use of somatropin can be drawn. There are no long-term studies.

6. **Burn injury (severe) in children.** In a randomized, double-blind single-center study, children who were severely burned (> 40% total body surface area burn) received placebo (n = 94) or somatropin 0.5 mg/kg/day (n = 37), 0.1 mg/kg/day (n = 41), or 0.2 mg/kg/day (n = 23) from hospital discharge to 12 months post-burn. Mean total burn size ranged from about 60 to 67% total body surface area. In all, 167 patients began treatment with somatropin and 148 patients with placebo. At the end of one year, 101 patients on somatropin and 94 patients on placebo were analyzed. Patients were followed for another 12 months after somatropin or placebo were stopped. Height, weight, and LBM increased significantly with somatropin therapy. At 12 and 18 months post-burn, cardiac output was decreased in the somatropin groups. Cardiac output is increased post-burn due to the hypermetabolism that occurs post-burn. Many other parameters were evaluated. Further studies are needed.

7. **Cardiac transplantation.** Limited information is available. Children being considered for treatment with growth hormone should be enrolled in studies that allow careful monitoring and data analysis.

8. **Central precocious puberty.** Children with precocious puberty are often treated with gonadotropin releasing hormone (GnRH) agonists (leuprolide acetate injection [Lupron®]) to suppress pituitary gonadal activity, to slow the advancement of bone age (prevent premature fusion of the epiphyseal growth plates), and to improve adult height. In some patients GnRH agonist therapy may result in marked deceleration of bone growth and may result in adult height that is less than the midparental height. Somatropin has been used in girls when growth velocity decreases or if it appears that the targeted adult height will not be attained. This is not an FDA-approved indication for somatropin. There are no large well-controlled trials on the efficacy and safety of adding somatropin to GnRH agonist therapy in these children or the effect on final height.

9. **Chronic fatigue syndrome.** There is no evidence of growth hormone deficiency in chronic fatigue syndrome.

10. **ConGenital adrenal hyperplasia.** Limited information is available. In a well-designed, single-center study, 14 patients with congenital adrenal hyperplasia due to 21-hydroxylase deficiency who were predicted > 1 SD below their midparental target height received somatropin for a mean duration of 4.4 ± 1.5 years and luteinizing hormone releasing hormone analog (leuprolide acetate) to delay epiphyseal fusion until final height. Patients were matched at the start of somatropin therapy with a patient with congenital adrenal hyperplasia who was treated only with glucocorticoids and a mineralocorticoid if indicated. In the group treated with somatropin, final height SD score was -0.4 ± 0.8 which was significantly better than the untreated group (-1.4 ± 1.1; P = 0.01). Mean final adult height in the somatropin group was 171.5 ± 6.1 cm for males (vs. 163.1 ± 5.6 cm without somatropin) and 163.6 ± 3.4 cm in females (vs. 158.4 ± 8.4 cm without somatropin). Six of 15 untreated patients ended with final adult heights that were below their baseline height predictions.

11. **Constitutional delay of growth and puberty.** These children have delayed skeletal maturation and pubertal development. Administering somatropin probably does not increase adult height (which is usually normal anyway). Short-term androgen therapy accelerates growth and the rate of pubertal advancement in boys.

12. **Corticosteroid-induced short stature,** including a variety of chronic glucocorticoid-dependent conditions, such as asthma, Crohn’s disease, juvenile rheumatoid arthritis, as well as after renal, heart, liver, or bone marrow transplantation. Short-term improvement in growth velocity in children with glucocorticoid-induced suppression has been reported. Long-term data are not available. Children being considered for treatment with somatropin should be enrolled in studies that allow careful monitoring and data analysis.

13. **Crohn’s disease.** Limited information is available. In a double-blind, placebo-controlled pilot study, 19 adults with moderate to severe active Crohn’s disease who received somatropin for 4 months had a significant decrease in Crohn’s Disease Activity Index (CDAI). The number of patients entering remission
was not reported. In children with Crohn’s disease, somatropin therapy has not been effective in improving final adult height. Long-term data are not available. In a short-term study, somatropin in combination with corticosteroids was more effective than corticosteroid alone in decreasing disease activity (measured using Pediatric CDAI [PCDAI]) and increasing linear growth in children and adolescents with moderately active Crohn’s disease. This study also showed that somatropin therapy was steroid sparing. Further larger, long-term studies are needed to determine the optimal dose, length of therapy, duration of response, effect on endoscopic healing, ability to maintain suppression of disease activity, and safety.

14. **Cystic fibrosis.** In a prospective multicenter trial, 61 prepubertal children with cystic fibrosis who were ≤ 25th percentile for height and weight were randomized to daily somatropin therapy or no treatment for one year. After 1 year, treatments were crossed over. Patients on somatropin had significantly greater gain in height, weight, lean mass, and bone mineral content. There were fewer hospitalizations in the somatropin-treated group. There was no difference in pulmonary function between groups. After stopping therapy, there was sustained effect for increased height and weight velocity and for accrual of bone mineral. In a small randomized study, 20 patients with cystic fibrosis (aged 10 to 23 years) received somatropin or placebo for 12 months. Patients in the somatropin group had moderately improved exercise capacity but pulmonary function did not improve. Long-term studies are not available. Children being considered for treatment with somatropin should be enrolled in studies that allow careful monitoring and data analysis.

15. **Dilated cardiomyopathy and heart failure.** According to American College of Cardiology/American Heart Association (ACC/AHA) guidelines for chronic heart failure, randomized trials have not demonstrated that somatropin therapy is beneficial in heart failure, other than in patients with a preexisting deficiency. Further studies are needed.

16. **Down's syndrome.** Short-term acceleration of growth with somatropin therapy has occurred in children with this syndrome; however, no prospective studies have assessed linear growth until achievement of final adult height.

17. **End-stage renal disease in adults undergoing hemodialysis.** Large long-term studies are required to assess the effects of somatropin on nutritional status, quality of life, morbidity, and mortality. Placebo-controlled trials are short-term (2 to 6 months). In a controlled trial, 139 adults on maintenance hemodialysis were randomized to placebo or 20, 35, or 50 mcg/kg/day of somatropin for 6 months. Therapy with somatropin increased LBM and serum albumin tended to increase. A long-term study is needed to determine if mortality and morbidity is reduced.

18. **Familial dysautonomia** (Riley-Day syndrome, hereditary sensory autonomic neuropathy). In a retrospective review of 13 children with familial dysautonomia who received somatropin, growth velocity increased, especially in the first 6 months. A prospective study with standardized criteria is needed.

19. **Fibromyalgia.** In one placebo-controlled study, somatropin produced a modest improvement in patients with fibromyalgia who had low levels of IGF-1; symptoms worsened when somatropin was discontinued. Further controlled trials are needed. Some patients may have adult growth hormone deficiency.

20. **HIV-infected patients with alterations in body fat distribution** (e.g., increased abdominal girth, buffalo hump). Somatropin is not FDA-approved for the treatment of HIV-associated adipose redistribution syndrome (HARS). HARS is a subset of HIV lypodystrophy and is defined as maldistribution of body fat characterized by central fat accumulation (lipohypertrophy) with or without lipatrophy. In HARS, fat may also accumulate in the upper body subcutaneous area such as the dorsocervical area (buffalo hump). These changes may be associated with metabolic disturbances (insulin resistance, glucose intolerance, dyslipidemia) and belly image distress. According to the product labeling for somatropin, an initial 12-week treatment with somatropin resulted in decreased visceral adipose tissue (VAT), trunk fat, and patient-reported belly-reported distress. The clinical significance of these changes (i.e., improved cardiovascular risk profile or compliance with highly active antiretroviral therapy [HAART]) has not been studied. The clinical efficacy of somatropin for the treatment of HARS was assessed in 2 double-blind, placebo-controlled trials. Both studies had a 12-week induction phase. Study 1 had a 12-week maintenance phase and Study 2 had a 24-week maintenance phase. Patients with diabetes or glucose intolerance were
excluded. At Week 12, in both studies, VAT decreased significantly compared to placebo. During the maintenance phase in Study 2, VAT accumulated to the same extent in patients treated with somatropin 2 mg every other day (QOD) and placebo. In Study 1 during the maintenance phase patients who were initially treated with somatropin 4 mg daily during induction and then 4 mg QOD had less reaccumulation of VAT, trunk fat and total body fat.

21. Infertility. Clinical trials indicate that somatropin is not useful as an adjunct during in vitro fertilization, for induction of ovulation in polycystic ovary syndrome, or for assisted reproductive technology.

22. Kidney transplant patients (children) with a functional renal allograft. Somatropin is not FDA-approved for this indication. If chronic renal insufficiency develops after transplantation, the patient will meet the criteria for use of somatropin in chronic renal insufficiency. In children with a functional renal allograft, 4 randomized controlled studies showed that short-term (6 to 12 months) somatropin therapy was effective in increasing growth velocity and did not increase the incidence of graft rejection. Data from the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) database were analyzed for growth, allograft function, and adverse effects over 5 years in 513 patients who received somatropin therapy (not given continuously throughout the 5 years of the study) and compared to 2,263 controls who did not receive somatropin. Children < 10 years of age who received somatropin had a greater increase in height than older children ($P < 0.001$; difference in mean cumulative increment in height during the 5 years was 3.6 cm). Final adult height was superior in the patients treated with somatropin compared to the control group ($P < 0.001$); the $z$ scores were significantly different but the difference in cm was not given. Allograft function and graft failure rate were similar in the somatropin-treated patients and controls.

23. Liver transplantation. Limited information is available from either short-term use or longer use in a limited number of patients. Children being considered for treatment with somatropin should be enrolled in studies that allow careful monitoring and data analysis.

24. Multiple system atrophy (MSA). In a pilot study 43 patients with MSA were randomized, double-blind to somatropin or placebo for 12 months. Of the 26 patients who completed 12 months of treatment without protocol violations, 13 had parkinsonian type of MSA and 13 had the cerebellar type. The mean total Unified Parkinson’s Disease Rating Scale (UPDRS) score (the primary endpoint) increased in both groups, indicating deterioration of the disease at 6 months and further deterioration at 12 months with no difference between treatments. There was a trend for less increase for the somatropin-treated patients than for the placebo group. Further studies are needed.

25. Myelomeningocele. Some persons with myelomeningocele have growth hormone deficiency. Studies of somatropin therapy in children with myelomeningocele include a heterogeneous group of patients (different levels of myelomeningocele lesions, previous surgical procedures, complicating medical disorders, scoliosis, contractures). These factors could also compromise adult height. In retrospective and prospective studies therapy with somatropin has increased growth velocity and height in carefully selected children with myelomeningocele and growth hormone deficiency. Well-controlled trials are needed.

26. Obesity. Somatropin therapy is not FDA-approved for the treatment of obesity. Low growth hormone levels are a consequence of central obesity and not a cause. Obesity is associated with decreased basal and pulsatile release of growth hormone and decreased stimulated growth hormone release. Somatropin therapy does not have significant beneficial effects on obesity in persons without growth hormone deficiency and does not produce significant overall weight loss. Doses of somatropin used to treat obesity have been supraphysiological. Effects of long-term treatment of obesity with somatropin are unknown.

27. Osteogenesis imperfecta. There are few studies of somatropin therapy for osteogenesis imperfecta; there is some positive short-term effect on growth velocity but there is no clear cut long term effects. Somatropin therapy is not recommended as first line therapy until further studies are done.

28. Osteoporosis, postmenopausal women, idiopathic in men, or glucocorticoid-induced. Guidelines for treatment or prevention of osteoporosis do not include recommendations for use of somatropin. In an 18-month placebo-controlled trial, 80 postmenopausal women with osteoporosis (56% had had fractures) were
randomized to somatropin 0.33 mg/day or 0.83 mg/day or placebo. All patients received calcium, vitamin D, and hormone replacement therapy. Patients on somatropin continued on drug for an additional 18 months. Bone mineral content increased up to 14% with the 0.83 mg/day dose. Larger studies are needed to determine the effects of somatropin therapy on bone mineral density and fractures in non-growth hormone deficient persons.

29. Thalassemia. Somatropin has been used to treat growth hormone deficiency in short children with thalassemia. The value of somatropin therapy in short children with thalassemia without growth hormone deficiency is controversial and requires more study.

30. X-linked hypophosphatemic rickets (familial hypophosphatemia, hypophosphatemic rickets). There are insufficient data of sufficient quality to recommend somatropin therapy. Larger randomized well designed trials are needed to determine if somatropin therapy changes longitudinal growth, mineral metabolism, endocrine, renal function, bone mineral density, and body proportions or has any adverse effects.

Coverage of Serostim is not recommended in the following circumstances: HIV-infected patients with alterations in body fat distribution (e.g., increased abdominal girth, buffalo hump). Safety and efficacy are not established.

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Reviewed:

References

1. Express Scripts, Inc. monograph dated 03/16/2011