VENTURA COUNTY HEALTH CARE PLAN

PRIOR AUTHORIZATION POLICY

POLICY: Growth Disorders – Growth Hormone [somatropin] Prior Authorization Policy

- Genotropin®(somatropin injection – Pfizer)
- Humatrope® (somatropin injection – Eli Lilly)
- Norditropin® (somatropin injection – Novo Nordisk)
- Nutropin AQ® (somatropin injection – Genentech)
- Omnitrope® (somatropin injection – Sandoz)
- Saizen® (somatropin injection – EMD Serono)
- Serostim® (somatropin injection – EMD Serono)
- Zomacton™ (somatropin injection – Ferring Pharmaceuticals)
- Zorbtive® (somatropin injection – EMD Serono)

REVIEW DATE: 02/10/2021

OVERVIEW

Indications for somatropin vary among these products. Somatropin is indicated for the following conditions:

- **Growth failure, treatment of pediatric patients**, due to an inadequate secretion of endogenous growth hormone.[1-7]
- **Non-growth hormone deficient short stature (idiopathic short stature)**, treatment, defined by height standard deviation score (SDS) ≤ -2.25 (1.2 percentile), and associated with growth rates unlikely to permit attainment of adult height in the normal range.[1-4,6,7]
- **Adults with growth hormone deficiency (GHD)** for replacement of endogenous growth hormone.[1-7]
- **Children with chronic kidney disease (CKD)**, treatment of growth failure, up to the time of kidney transplantation.[4]
- **Noonan syndrome**, treatment of patients with short stature.[3]
- **Prader Willi syndrome**, treatment of patients with growth failure or short stature.[1,3,7]
- **Short stature homeobox-containing gene (SHOX) deficiency**, treatment of short stature or growth failure in children.[2,6]
- **Small for gestational age (SGA)**, treatment of growth failure or short stature in patients with no catch-up growth by age 2[1,7] to 4 years[2,3,6].
- **Turner syndrome**, treatment of short stature.[1-4,6,7]
- **Short bowel syndrome (SBS)**, treatment, in adult patients receiving specialized nutritional support.[8]
- **Human immunodefiency virus (HIV) infected patients with wasting or cachexia**, treatment, to increase lean body mass (LBM) and body weight, and improve physical endurance.[9]

Growth Hormone Deficiency in Children and Adolescents

Somatropin is indicated for the treatment of growth failure in children due to an inadequate secretion of endogenous growth hormone.[1-7] In these children with GHD, somatropin is effective for increasing final adult height.[31] Somatropin therapy is recommended to normalize adult height and avoid extreme shortness in children and adolescents with GHD.[31] Cranial radiation often causes hypopituitarism, and GHD is a frequent pituitary abnormality seen in children and adults who have undergone cranial radiation.[17] Children who have undergone total body irradiation in preparation for hematopoietic stem cell transplant commonly have GHD and an impaired growth rate; these patients can be treated successfully with growth hormone.[-] Somatropin therapy improves the final height of young children after total body irradiation.[11]

Congenital Hypopituitarism
Somatropin is used in infants and young children with congenital hypopituitarism, that manifests in infancy with hypoglycemia, microgenitalia, hyperbilirubinemia, and multiple anterior pituitary hormone deficiencies.[31] The Pediatric Endocrine Society guidelines suggest that GHD due to congenital hypopituitarism be diagnosed without formal growth hormone provocative testing in a newborn with hypoglycemia who does not attain a serum growth hormone concentration > 5 mcg/L (> 5 ng/mL) and has deficiency of at least one additional pituitary hormone and/or the classical imaging triad (ectopic posterior pituitary and pituitary hypoplasia with abnormal stalk).[31]

Non-Growth Hormone Deficient Short Stature (Idiopathic Short Stature) in Children or Adolescents

Somatropin is indicated for the long-term treatment of idiopathic short stature (non-growth hormone deficient short stature) which is defined by a height SDS > 2.25 (1.2 percentile) and associated with growth rates that are unlikely to permit attainment of adult height in the normal range.[1-4,6,7] The predicted adult heights of these children was < 160 cm (63 inches) for men and < 150 cm (59 inches) in women.[31] The Pediatric Endocrine Society guidelines[31] recommend that the decision to treat idiopathic short stature with somatropin be made on a case-by-case basis after assessing physical and psychological burdens, and discussion of risks and benefits. They recommend against the routine use of somatropin in every child with height SDS ≤ -2.25. In one consensus statement on children with idiopathic short stature from the Growth Hormone Research Society, the Lawson Wilkins Pediatric Endocrine Society, and the European Society for Paediatric Endocrinology Workshop, it was felt that the optimal age for initiating treatment is 5 years to early puberty.[12]

The initial 6-month trial of somatropin is to establish that the child's condition responds to somatropin therapy. Authorization for continued therapy should be based on an adequate clinical response[14] defined as an annualized growth rate that doubles in comparison to the previous year. 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, closure of the epiphyses, and/or attainment of mid-parental height.

Growth Hormone Deficiency in Adults or Transition Adolescents

Somatropin is indicated for the replacement of endogenous growth hormone in adults with GHD, which may present in adults or children as GHD (isolated GHD) or in addition to other pituitary hormone deficiencies (gonadotropin, adrenocorticotropic hormone [ACTH], and/or thyroid-stimulating hormone [TSH] deficiencies).[15] Patients with other anterior pituitary hormone deficiencies are likely to have GHD. In adults, the diagnosis of GHD usually is made in patients with signs and symptoms of hypothalamic-pituitary disease (endocrine, structural, and/or genetic causes); those who have received cranial irradiation or tumor treatment; or those with traumatic brain injury or subarachnoid hemorrhage.[15,16] Onset may be in adulthood or childhood. In childhood, the goal of somatropin therapy is primarily for statural growth. When final adult height is attained, somatropin therapy is no longer required for statural growth. Transition is used to describe the period in adolescence after growth is completed and the need for continued replacement into adulthood is assessed. Ongoing GHD is most likely in patients with multiple pituitary hormone deficits, with or without structural pituitary or peripituitary disease, and/or a history of cranial radiation therapy. Confirmatory growth hormone stimulation testing may not be required in patients, such as with congenital/genetic GHD or multiple pituitary hormone deficiencies. When persistent GHD is documented after completion of adult height, somatropin therapy should be continued to attain full skeletal and muscle maturation during the transition period from childhood to adulthood.[15] In adults with GHD,

somatropin replacement therapy improves abnormalities in substrate metabolism, body composition, and physical and psychosocial function.[15,16]

Growth hormone is not approved by the FDA for the treatment of other conditions in adults who may have a low growth hormone response to growth hormone provocative testing (such as obesity, aging, or depression) or to improve athletic performance.[17,18]

Growth Hormone Stimulation Tests (Adults or Transition Adolescents)
The insulin tolerance test is the gold standard growth hormone stimulation test,[53] but is contraindicated in patients with ischemic heart disease or seizure disorders or in elderly or pregnant patients.[15,16,27] The glucagon stimulation test and the macimorelin test could be considered as alternatives test.[53] The response to all growth hormone stimulation tests show intra-individual variability, and the growth hormone cutoff points vary with the test used. Otherwise healthy obese persons have blunted growth hormone responses to various tests.[30] There is no information on the effects of increased body mass index (BMI) or central adiposity on the insulin tolerance test. When Geref was available [discontinued in the US in 2008], Geref (GHRH) plus arginine was considered the best alternative to the insulin tolerance test in adults.

Macrilen (macimorelin) is the most recently approved test for the diagnosis of adult GHD. Patients in the pivotal trial were 18 to 66 years of age and the BMI ranged from 16 to 40 kg/m^2.[29] Safety and diagnostic performance has not been established in patients with BMI > 40 kg/m^2. Clinical studies established that a maximally stimulated serum growth hormone level of < 2.8 ng/mL (i.e., at the 30, 45, 60, and 90 minute timespoints) after Macrilen administration confirms the presence of adult GHD. Warnings and precautions for Macrilen include QT prolongation, potential for false positive test results with use of strong cytochrome P450 (CYP)3A4 inducers (discontinue and washout strong CYP3A4 inducers before testing), and potential for false negative test results in recent onset hypothalamic disease.

Arginine and levodopa testing have not been systematically evaluated and validated, and because they have a low sensitivity and specificity in adults and transition patients, it is not recommended to utilize these tests in this population.[53] Additionally, the clonidine, levodopa, and arginine alone tests are generally not recommended because very low growth hormone cutoff points are required to achieve adequate specificity.[27]

Adults with childhood onset GHD may have alterations in body composition, bone mineral density, and lipid metabolism that are alleviated by treatment with somatropin.[15,31] However, some children with a diagnosis of GHD have a normal somatotropic axis when retested in late adolescence.[31,52] Re-evaluation of the somatotropic axis in children diagnosed with GHD is required during the transition period. The transition period is the time from late puberty to establishment of adult muscle and bone composition, and encompasses attainment of adult height.[31] Re-evaluation of the somatotropic axis is most conveniently done when growth has slowed to the point where pediatric somatropin dosing will be discontinued (i.e., the growth velocity is < 2 to 2.5 cm/year. Recommendations for transitional care after childhood somatropin treatment from the Pediatric Endocrine Society guidelines[31] are as follows. Patients with multiple (≥ 3) pituitary hormone deficiencies regardless of etiology, or GHD with a documented causal genetic mutation or specific pituitary/hypothalamic structural defect (except ectopic posterior pituitary) be diagnosed with persistent GHD. These guidelines recommend re-evaluation of the somatotropic axis for persistent GHD in persons with 1) GHD and deficiency of only one additional pituitary hormone, 2) idiopathic isolated GHD, 3) idiopathic isolated GHD with or without a small pituitary/ectopic posterior pituitary, and 4) in patients after irradiation. Testing can be done after a trial of at least 1 month off somatropin treatment. The guidelines also recommend growth hormone provocative testing to evaluate the function of the somatotropic axis in the transition period if indicated by a low IGF-1 level. Persons with idiopathic isolated GHD will very likely test sufficient with GH provocative testing. To continue growth hormone therapy in

adulthood, retesting for GHD with GH-stimulation test/s is recommended in most transition patients and at least 1 month after discontinuation of pediatric growth hormone therapy.[53] Retesting is not required in transition patients with evidence of panhypopituitarism (≥ 3 pituitary hormone deficiencies) and low serum IGF-1 levels, patients with genetic defects, and patients with hypothalamic-pituitary structural brain defects.

Adult GHD can be predicted with > 90% accuracy by the presence of three or four pituitary hormone deficiencies in addition to serum IGF-1 concentration that is less than the 2.5th percentile or < -2 SDS.[15,16] This is in the absence of conditions that lower IGF-1. Patients with ≥ 3 pituitary hormone deficiencies and an IGF-1 level below the reference range do not need a growth hormone stimulation test.[16] Because of the nature of the cause of GHD in children with structural lesions with multiple hormone deficiencies and those with proven genetic causes, provocative testing in these adults is not necessary.

Chronic Kidney Disease in Children or Adolescents

Somatropin is indicated for the treatment of growth failure in children with CKD up to the time of kidney transplantation and is effective for increasing the rate of growth.[4] Somatropin therapy has increased final adult height in these patients.[19] An adequate growth response can be assumed if height velocity during the first year of growth hormone treatment is greater than 2 cm per year over basline.[20] This increase is supported by outcomes of controlled-trials specific to patients with chronic kidney disease. In a clinical practice guidelines, for children with CKD, patients who have had a kidney transplant and have persistent growth failure, growth hormone therapy is recommended to be initiated 1 year after transplantation if spontaneous catch-up growth does not occur and steroid-free immunosuppression is not a feasible option.[20]

Noonan Syndrome and Short Stature in Children or Adolescents

Somatropin is indicated for the treatment of children with short stature associated with Noonan syndrome.[3,21] Not all patients with Noonan syndrome have short stature; some will achieve a normal adult height without treatment. The younger the age at start of therapy, the larger the change in height SDS.

Prader-Willi Syndrome

Somatropin is indicated for the treatment of *pediatric* patients who have growth failure due to Prader-Willi syndrome.[1,3,7] Somatropin therapy in children increases linear growth velocity, improves body composition (i.e., decreases the percentage body fat, increases or stabilizes LBM), increases bone mineral density, improves physical strength and agility, and improves final adult height.[22] After final height is attained, there may be potential benefits of somatropin on body composition, peak bone mass, cognition, and quality of life in adults.[22] Somatropin is contraindicated in patients with Prader-Willi syndrome who are severely obese or have severe respiratory impairment.[1,3,7]

Short Stature Homeobox-Containing Gene (SHOX) Deficiency in Children or Adolescents

Somatropin is indicated for the treatment of short stature or growth failure in children with SHOX deficiency.[2,6] SHOX deficiency may result from either deletion of one copy of the SHOX gene or from mutation within or outside one copy of the SHOX gene that impairs the production or function of the SHOX protein. Women with Turner syndrome have only a single copy of the SHOX gene because they lack all or part of their second X chromosome.[23] SHOX deficiency is also the primary cause of short stature in most patients with Léri-Weill dyschondrosteosis (syndrome), and SHOX mutations and deletions are found in patients with idiopathic short stature. In one study consisting of a 2-year control period and a subsequent extension period to final height, short prepubertal patients with SHOX deficiency received somatropin.[24]

Children Born Small for Gestational Age

Somatropin is indicated for the treatment of growth failure in children born SGA who fail to exhibit catch-up growth by age 2[1,7] to 4 years.[2,3,6] SGA is defined as a birth weight and/or birth length that is greater than 2 SD (about the 3rd percentile) below mean normal values after adjusting for gestational age and sex. The

terms SGA and intrauterine growth restriction (retardation) [IUGR] are used interchangeably in this document. In clinical trials, patients born SGA (including children with Silver-Russell syndrome) without catch-up growth who were 2 to 11 years of age had significant increases in growth when treated with somatropin before puberty.[1,3] Optimal duration of therapy once catch-up growth has been attained is not known.

Almost all patients with Silver-Russell syndrome are born SGA, and postnatal catch-up growth does not occur in the majority of children.[44] An expert consensus statement recommends that patients with Silver-Russell syndrome receive treatment with somatropin as soon as possible.[44] Starting therapy at age 2 to 4 years is adequate for the majority of patients. In some cases, somatropin therapy is started in patients less than 2 years of age who have severe fasting hypoglycemia, severe malnutrition, or severe muscular hypotonia. These experts recommend that somatropin therapy be stopped when height velocity is < 2 cm per year over a 6-month period and when bone age is > 14 years in females or > 17 years in males.

Turner Syndrome
Somatropin is indicated for the treatment of short stature associated with Turner syndrome.[1-4,6,7,25,63]

Short Bowel Syndrome
Somatropin is indicated for the treatment of SBS in adults receiving specialized nutritional support.[11]

Human Immunodeficiency Virus-Associated Wasting or Cachexia
Somatropin is indicated for the treatment of HIV-infected adults with wasting (loss of lean body mass [LBM]) or cachexia to increase LBM and body weight, and improve physical endurance.[9] Somatropin therapy increases LBM, decreases fat mass, and increases physical function in patients with HIV-associated wasting. Studies directly comparing somatropin with other therapies (megestrol, oxandrolone, testosterone, and progressive resistance training) for wasting or cachexia in HIV-infection are lacking.[26]

POLICY STATEMENT
Prior Authorization is recommended for prescription benefit coverage of somatropin. All reviews will be directed to a clinician (i.e., pharmacist) for verification of criteria. All approvals are provided for 1 year in duration unless otherwise noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with somatropin as well as the monitoring required for adverse events and long-term efficacy, initial approval requires somatropin to be prescribed by or in consultation with a physician who specializes in the condition being treated. Human growth hormone is FDA-approved for treatment of a limited number of conditions. The FDA has not approved the use of human growth hormone as therapy for anti-aging, longevity, cosmetic or performance enhancement. Federal law prohibits the dispensing of human growth hormone for non-approved purposes. A pharmacy's failure to comply with that law could result in significant criminal penalties to the pharmacy and its employees. Accordingly, a pharmacy may decline to dispense prescriptions for human growth hormone when written by physicians or other authorized prescribers who they believe may be involved in or affiliated with the fields of anti-aging, longevity, rejuvenation, cosmetic, performance enhancement or sports medicine.

Documentation: Documentation is required for use of somatropinas noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, prescription claims records, prescription receipts, and/or other information. For patient cases in which documentation is required, if this documentation has been previously received upon a prior coverage review, the documentation requirement is considered to be met.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

I. Coverage of Genotropin, Humatrope, Norditropin, Nutropin AQ, Omnitrope, Saizen, and Zomacton (all listed products except Serostim and Zorbtive) is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Growth Hormone Deficiency (GHD) in Children or Adolescents.** Approve for *initial* for 1 year therapy in patients who meet the following criteria (A, B, C, D, or E):
   - **A)** Patient meets the following (i or ii and iii):
     - **i.** Patient has had two growth hormone (GH) stimulation tests performed with any of the following agents: levodopa, insulin-induced hypoglycemia, arginine, clonidine, or glucagon AND both tests show an inadequate response as defined by a peak GH response which is below the normal reference range as determined by the testing laboratory; OR
     - **ii.** Patient meets both of the following criteria (a and b):
       - **a)** Patient has had at least one growth hormone stimulation test performed with any of the following agents: levodopa, insulin-induced hypoglycemia, arginine, clonidine, or glucagon AND the test shows an inadequate response as defined by a peak GH response which is below the normal reference range as determined by the testing laboratory; AND
       - **b)** Patient has at least one risk factor for growth hormone deficiency (for example, the height for age curve has deviated downward across two major height percentiles [e.g., from above the 25th percentile to below the 10th percentile]; the child's growth rate is less than the expected normal growth rate based on age and gender; low IGF-1 and/or IGFBP-3 levels; the child has a very low peak growth hormone level on provocative testing as defined by the prescribing physician; the child's growth velocity is less than the 10th percentile for age and gender [height velocity percentile is NOT the same as height-for-age percentile]; the patient is status post craniopharyngioma resection; the patient has optic nerve hypoplasia; the patient has a growth hormone gene deletion); AND

         Note: Some children will achieve stimulated growth hormone concentrations in the normal range as determined by the testing laboratory and could be reviewed for authorization under non-GHD short stature (idiopathic short stature).

     - **iii.** Patient has been evaluated by an endocrinologist.

   - **B)** Patient has *undergone brain radiation or tumor resection* AND meets the following criteria (i and ii):
     - **i.** Patient meets at least ONE of the following criteria (a or b):
       - **a)** Patient has had one growth hormone stimulation test with any of the following agents: levodopa, insulin-induced hypoglycemia, arginine, clonidine, or glucagon AND the test shows an inadequate response as defined by a peak GH response which is below the normal reference range as determined by the testing laboratory; OR
       - **b)** Patient has a deficiency in at least one other pituitary hormone (that is, adrenocorticotropic hormone [ACTH], thyroid-stimulating hormone [TSH], gonadotropin deficiency [luteinizing hormone {LH} and/or follicle stimulating hormone {FSH} deficiency are counted as one deficiency], or prolactin); AND
     - **ii.** Patient has been evaluated by an endocrinologist.

C) Patient has *congenital hypopituitarism* AND meets the following criteria (i and ii):
- **i.** Patient meets at least ONE of the following criteria (a or b):
  - **a)** Patient has had one growth hormone stimulation test with any of the following agents: levodopa, insulin-induced hypoglycemia, arginine, clonidine, or glucagon AND the test shows an inadequate response as defined by a peak GH response which is below the normal reference range as determined by the testing laboratory; OR
  - **b)** Patient has a deficiency in at least one other pituitary hormone (that is, adrenocorticotropic hormone [ACTH], thyroid-stimulating hormone [TSH], gonadotropin deficiency [luteinizing hormone {LH} and/or follicle stimulating hormone {FSH} deficiency are counted as one deficiency], or prolactin) and/or the patient has the imaging triad of ectopic posterior pituitary and pituitary hypoplasia with abnormal pituitary stalk; AND
- **ii.** Patient has been evaluated by an endocrinologist.

D) Patient has *panhypopituitarism* and meets the following criteria (i and ii):
Note: GHD may occur in combination with other pituitary hormone deficiencies and is referred to as hypopituitarism, panhypopituitarism, or multiple pituitary hormone deficiency.

- **i.** Patient meets at least ONE of the following criteria (a, b, or c):
  - **a)** Patient has pituitary stalk agenesis, empty sella, sellar or supra-sellar mass lesion, or ectopic posterior pituitary "bright spot" on magnetic resonance image or computed tomography; OR
  - **b)** Patient has three or more of the following pituitary hormone deficiencies: somatropin (growth hormone), adrenocorticotropic hormone (ACTH), thyroid-stimulating hormone (TSH), gonadotropin deficiency (luteinizing hormone [LH] and/or follicle stimulating hormone [FSH] deficiency are counted as one deficiency), and prolactin; OR
  - **c)** Patient has had one growth hormone stimulation test with any of the following agents: levodopa, insulin-induced hypoglycemia, arginine, clonidine, or glucagon AND the test shows an inadequate response as defined by a peak GH response which is below the normal reference range as determined by the testing laboratory; AND
- **ii.** Patient has been evaluated by an endocrinologist.

E) Patient has had a hypophysectomy (surgical removal of pituitary gland).

Children or Adolescents with Growth Hormone Deficiency (GDH) Continuing Somatropin Therapy (i.e., established on somatropin for ≥ 10 months). Approve for 1 year in patients who meet ONE of the following (A, B, or C):

A) *Patients < 12 years of age.* The height has increased by ≥ 2 cm/year in the most recent year.

B) *Adolescents between ≥ 12 years and ≤ 18 years of age.* Patient meets the following criteria (i and ii):
- **i.** Height has increased by ≥ 2 cm/year in the most recent year; AND
- **ii.** The epiphyses are open.

C) *Adolescents or young adults > 18 years of age.* Patient meets the following criteria (i, ii, and iii):
- **i.** Height has increased by ≥ 2 cm/year in the most recent year; AND
- **ii.** The epiphyses are open; AND
- **iii.** Mid-parental height has *not* been attained.

Note: 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.

Note: Adolescents and young adults with childhood onset GHD who have previously responded to somatropin with increases in height velocity and who have completed linear growth may continue receiving somatropin therapy as a transition adolescent or as an adult. See criteria I.3. (GHD in adults or transition adolescents).

2. **Non-Growth Hormone Deficient Short Stature (Idiopathic Short Stature) in Children or Adolescents.** Approve 6 months of *initial* therapy if the patient meets the following criteria (A, B, C, D, E, and F).
   - **A)** The child is ≥ 5 years of age; AND
   - **B)** Patient's baseline height is less than 1.2 percentile or a standard deviation score (SDS) < -2.25 for age and gender; AND
   - **C)** Patient's growth (height) velocity is ONE of the following (i or ii):
     - **i.** The child is ≥ 5 years of age AND has a growth rate < 4 cm/year; OR
     - **ii.** The growth (height) velocity is less than the 10th percentile for age and gender based on at least 6 months of growth data; AND

     Note: Height velocity percentile is NOT the same as height for age percentile.
   - **D)** Without growth hormone therapy, the patient's predicted adult height is < 160 cm (63 inches) in males or < 150 cm (59 inches) in females; AND
   - **E)** The epiphyses are open; AND
   - **F)** Patient does not have constitutional delay of growth and puberty (CDGP).

Children or Adolescents with Non-Growth Hormone Deficient Short Stature (Idiopathic Short Stature) Continuing Somatropin Therapy. Approve 1 year of continuation therapy if the patient meets ONE of the following criteria (A, B, C, or D):
- **A)** *Patients ≥ 5 years of age who received somatropin on an initial 6-month trial basis.* The annualized growth rate has doubled in comparison to the previous year. Note: For example, if the growth velocity was 3 cm/year for the year prior to treatment, then the growth velocity must be at least 3 cm in 6 months (baseline velocity was 1.5 cm/6 months) or for example, 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); OR
- **B)** *Patients ≥ 5 years and < 12 years of age* (i.e., established on somatropin for ≥ 10 months). The height has increased by ≥ 2 cm/year in the most recent year; OR
- **C)** *Patients ≥ 12 years of age and ≤ 18 years of age* (i.e., established on somatropin for ≥ 10 months). Patient meets the following criteria (i and ii):
  - **i.** Height has increased by ≥ 2 cm/year in the most recent year; AND
  - **ii.** The epiphyses are open.
- **D)** *Adolescents and young adults > 18 years of age* (i.e., established on somatropin for ≥ 10 months). Patient meets the following criteria (i, ii, and iii):
  - **i.** Height has increased by ≥ 2 cm/year in the most recent year; AND
  - **ii.** The epiphyses are open; AND
  - **iii.** Mid-parental height has *not* been attained.

    Note: 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.

3. **Growth Hormone Deficiency in Adults or Transition Adolescents**. Approve for 1 year in patients who meet the following criteria (A, B, C, and D):
   - **A)** The endocrinologist must certify that somatropin is not being prescribed for anti-aging therapy or to enhance athletic ability or for body building; AND
   - **B)** Patient must have a diagnosis of GHD that is one of the following (i or ii): [documentation required for all elements]

i. Childhood onset; OR

ii. Adult onset that results from one of the following: growth hormone deficiency (GHD) alone or multiple hormone deficiencies (hypopituitarism) resulting from pituitary disease, hypothalamic disease, pituitary surgery, cranial radiation therapy, tumor treatment, traumatic brain injury, or subarachnoid hemorrhage; AND

C) Patient meets one of the following criteria (i, ii, or iii):

i. Patient (adult or transition adolescent) has known mutations, embryopathic lesions, congenital or genetic defects, or structural hypothalamic-pituitary defects; [documentation required] OR

ii. Patient meets the following criteria (a, b, and c):

a) Patient (adult onset or transition adolescent) has three or more of the following pituitary hormone deficiencies: Adrenocorticotropic hormone (ACTH), thyroid-stimulation hormone (TSH), gonadotropin deficiency (luteinizing hormone [LH] and/or follicle stimulating hormone (FSH) deficiency are counted as one deficiency), and prolactin [documentation required]; AND

b) The age and gender adjusted serum insulin-like growth factor-1 (IGF-1) must be below the lower limits of the normal reference range for the reporting laboratory [documentation required]; AND

c) Other causes of low serum insulin-like growth factor-1 (IGF-1) have been excluded (e.g., malnutrition, prolonged fasting, poorly controlled diabetes mellitus, hypothyroidism, hepatic insufficiency, oral estrogen therapy).

OR

iii. Patient has had a negative response to one of the following standard growth hormone stimulation tests with the response given for each test and depending on whether an adult or transition adolescent [documentation required];

Adults: Patient meets ONE of the following criteria (a, b, c, d, e, or f): [documentation required for all elements]

Note: If the patient has had a previous trial of an arginine alone test with a peak response of ≤ 0.4 mcg/L, this would meet the criteria for a negative response to a growth hormone stimulation test.

a) Insulin tolerance test (obtaining at least 3 growth hormone levels in at least a 60 minute timeframe [not including a level at timeframe zero], with adequate hypoglycemia being achieved) with peak response ≤ 5.0 mcg/L; OR

b) Glucagon stimulation test (obtaining at least 3 growth hormone levels in at least 180 minute timeframe [not including a level at timeframe zero]) with peak response ≤ 3.0 mcg/L AND the patient's body mass index (BMI) is < 25 kg/m^2; OR

c) Glucagon stimulation test (obtaining at least 3 growth hormone levels in at least 180 minute timeframe [not including a level at timeframe zero]) with a peak response ≤ 3.0 mcg/L AND the patient's body mass index (BMI) is ≥ 25 kg/m^2 and ≤ 30 kg/m^2 with, according to the prescriber, a high pretest probability of GH deficiency; OR

d) Glucagon stimulation test (obtaining at least 3 growth hormone levels in at least 180 minute timeframe [not including a level at timeframe zero]) with a peak response ≤ 1.0 mcg/L AND the patient's body mass index (BMI) is ≥ 25 kg/m^2 and ≤ 30 kg/m^2 with, according to the prescriber, a low pretest probability of GH deficiency; OR

e) Glucagon stimulation test (obtaining at least 3 growth hormone levels in at least 180 minute timeframe [not including a level at timeframe zero]) with peak response ≤ 1.0 mcg/L AND the patient's body mass index (BMI) is > 30 kg/m^2; OR

f) Macrilen™ (macimorelin for oral solution) test (obtaining at least 4 growth hormone levels in at least a 90 minute timeframe [not including a level at timeframe zero]) with peak responses < 2.8 ng/mL (2.8 mcg/L) AND the patient's body mass index (BMI) is ≤ 40 kg/m^2.

Note: The following formula can be used to calculate BMI: BMI equals body weight in kg divided by height meters squared (m^2) [i.e., BMI = kg/m^2].

OR

***Transition Adolescents*:** (The transition period is the time from late puberty to establishment of adult muscle and bone composition, and encompasses attainment of adult height.) The patient meets the following criteria (a and b): [documentation required for all elements]

Note: If the patient has had a trial of a Macrilen test with a peak response of < 2.8 ng/mL (mcg/L), this would meet the criteria for a negative response to a growth hormone stimulation test.

a) Patient has been off somatropin therapy for at least 1 month before retesting with a growth hormone stimulation test; AND

b) Patient meets ONE of the following responses to growth hormone stimulation testing (1, 2, 3, 4, 5 or 6):

(1) Insulin tolerance test (obtaining at least 3 growth hormone levels in at least a 60 minute timeframe [not including a level at timeframe zero], with adequate hypoglycemia being achieved) with peak response ≤ 5.0 mcg/L; OR

(2) Glucagon stimulation test (obtaining at least 3 growth hormone levels in at least 180 minute timeframe [not including a level at timeframe zero]) with peak response ≤ 3.0 mcg/L AND the patient's body mass index (BMI) is < 25 kg/m^2; OR

(3) Glucagon stimulation test (obtaining at least 3 growth hormone levels in at least 180 minute timeframe [not including a level at timeframe zero]) with a peak response of ≤ 3.0 mcg/L AND the patient's body mass index (BMI) is ≥ 25 kg/m^2 and ≤ 30 kg/m^2 with, according to the prescriber, a high pretest probability of GH deficiency; OR

(4) Glucagon stimulation test (obtaining at least 3 growth hormone levels in at least 180 minute timeframe [not including a level at timeframe zero]) with a peak response ≤ 1.0 mcg/L AND the patient's body mass index (BMI) is ≥ 25 kg/m^2 and ≤ 30 kg/m^2 with, according to the prescriber, a low pretest probability of GH deficiency; OR

(5) Glucagon stimulation test (obtaining at least 3 growth hormone levels in at least 180 minute timeframe [not including a level at timeframe zero]) with peak response ≤ 1.0 mcg/L AND the patient's body mass index (BMI) is > 30 kg/m^2; OR

(6) If both the insulin tolerance test AND glucagon stimulation test are contraindicated, the arginine alone test can be used (obtaining at least 3 growth hormone levels in at least 120 minute timeframe [not including a level at timeframe zero]) with a peak response ≤ 0.4 mcg/L;AND

D) Patient has been evaluated by an endocrinologist.

4. **Chronic Kidney Disease in Children or Adolescents.** Approve for *initial* therapy for 1 year for growth failure in children with CKD who meet the following criteria (A and B):
   A) Patient has or had chronic kidney disease (CKD) as defined by an abnormal creatinine clearance; AND
   B) Patient has been evaluated by an endocrinologist or a nephrologist.

Chronic Kidney Disease in Children or Adolescents Continuing Somatropin Therapy (i.e., established on somatropin for ≥ 10 months)**.** Approve for 1 year in patients who meet the following criteria (A and B):

A) Height has increased by ≥ 2 cm/year in the most recent year; AND

B) The epiphyses are open.

5. **Noonan Syndrome in Children or Adolescents.** Approve for *initial* therapy for 1 year in patients who meet the following criteria (A and B):
   A) Patient's baseline height is less than the 5th percentile using a growth chart for children without Noonan syndrome; AND
   B) Patient has been evaluated by an endocrinologist.

   Noonan Syndrome in Children or Adolescents Continuing Somatropin Therapy (i.e., established on somatropin for ≥ 10 months). Approve for 1 year in patients who meet the following criteria (A and B):
   A) Height has increased by ≥ 2 cm/year in the most recent year; AND
   B) The epiphyses are open.

6. **Prader-Willi Syndrome.** Approve for *initial* therapy for 1 year in patients (children or adults) who have been evaluated by an endocrinologist.

   Prader-Willi Syndrome in Patients Continuing Somatropin Therapy (i.e., established on somatropin for ≥ 10 months). Approve for 1 year in patients who meet ONE of the following criteria (A or B):
   A) *Children and adolescents.* The patient meets the following criteria (i and ii):
      i. Height has increased by ≥ 2 cm/year in the most recent year; AND
      ii. The epiphyses are open.
         Note: When the epiphyses are closed and/or the height velocity is < 2 cm/year, the patient can be reviewed for continuation of therapy as an adult with Prader-Willi syndrome.
   B) *Adults or adolescents whose epiphyses are closed and/or whose height velocity is < 2 cm/year* The patient meets the following criteria (i and ii):
      i. This physician must certify that somatropin is not being used for anti-aging therapy or to enhance athletic performance/body building; AND
      ii. Patient must be evaluated by an endocrinologist or in consultation with an endocrinologist.

7. **Short Stature Homeobox-Containing Gene Deficiency in Children or Adolescents.** Approve for *initial* therapy for 1 year in patients who meet the following criteria (A, B, C, and D):
   A) Patient has short stature homeobox-containing gene (SHOX) deficiency demonstrated by chromosome analysis; AND
   B) Epiphyses are open; AND
   C) Patient's baseline height is less than the 3rd percentile for age and gender; AND
   D) Patient has been evaluated by an endocrinologist.

   Short Stature Homeobox-Containing Gene Deficiency in Children or Adolescents Continuing Somatropin Therapy (i.e., established on somatropin for ≥ 10 months). Approve for 1 year in patients who meet the following criteria (A and B):
   A) Height has increased by ≥ 2 cm/year in the most recent year; AND
   B) The epiphyses are open.

8. **Children Born Small for Gestational Age or with Intrauterine Growth Restriction (Retardation) Including Those with Silver-Russell Syndrome.** Approve for *initial* therapy for 1 year in patients who meet the following criteria (A, B, C, and D):
   A) Patient is ≥ 2 years of age; AND

B) Patient was born small for gestational age (SGA), which is defined as birth weight and/or birth length that is > 2 standard deviations (SD) below the mean (< -2 SD) for gestational age and gender, and the patient did not have sufficient catch-up growth before age 2 to 4 years; AND
C) Patient's baseline height is less than the 5th percentile for age and gender; AND
D) Patient has been evaluated by an endocrinologist.

Children Born Small for Gestational Age or with Intrauterine Growth Restriction (Retardation) Including Those with Silver-Russell Syndrome Continuing Somatropin Therapy (i.e., established on somatropin for ≥ 10 months). Approve for 1 year in patients who meet ONE of the following (A, B, or C):
A) *Patients < 12 years of age.* Height has increased by ≥ 2 cm/year in the most recent year.
B) *Patients ≥ 12 years and ≤ 18 years of age.* The patient meets the following criteria (i and ii):
- **i.** Height has increased by ≥ 2 cm/year in the most recent year; AND
- **ii.** The epiphyses are open.

C) *Adolescents and young adults > 18 years of age.* The patient meets the following criteria (i, ii, and iii):
- **i.** Height has increased by ≥ 2 cm/year in the most recent year; AND
- **ii.** Epiphyses are open; AND
- **iii.** Mid-parental height has *not* been attained.
  Note: 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.

9. Turner Syndrome. Approve for *initial* therapy for 1 year in patients with short stature associated with Turner syndrome.

Patients with Turner Syndrome Continuing Somatropin Therapy (i.e., established on somatropin for ≥ 10 months). Approve for 1 year in patients who meet the following criteria (A and B):
A) Height has increased by ≥ 2 cm/year in the most recent year; AND
B) The epiphyses are open.

II. Coverage of Genotropin, Humatrope, Norditropin, Nutropin AQ, Omnitrope, Saizen, Zomacton, and Zorbtive (all listed products except Serostim) is recommended in patients who meet the following criteria:

1. Short Bowel Syndrome in Adults. Approve of *initial* therapy for 1 month if the patient meets the following criteria (A and B):
A) Patient is ≥ 18 years of age; AND
B) Patient is receiving specialized nutritional support (defined as a high carbohydrate, low-fat diet that is adjusted for individual patient requirements and preferences).

Short Bowel Syndrome in Adults Continuing Somatropin Therapy. Approve a second 1-month course of somatropin if the adult patient responded to somatropin therapy with a decrease in the requirement for specialized nutritional support according to the prescriber.

III. Coverage of Serostim is recommended in those who meet the following criteria:

1. Human Immunodeficiency Virus (HIV) Infection with Wasting or Cachexia in Adults. Approve for 6 months in patients who meet ALL of the following criteria (A, B, C, D, and E):
A) Patient is ≥ 18 years of age; AND
B) Patient has ONE of the following (i, ii, or iii):

i. Documented unintentional weight loss of ≥ 10% from baseline; OR
ii. Weight < 90% of the lower limit of ideal body weight; OR
iii. Body mass index (BMI) ≤ 20 kg/m^2; AND
Note: The following formula can be used to calculate BMI: BMI equals body weight in kg divided by height in meters squared (m^2) [i.e., BMI = kg/m^2];

C) Patient has wasting or cachexia that is due to malabsorption, poor diet, opportunistic infection, or depression, and other causes have been addressed prior to starting somatropin; AND
D) Patient has been on antiretroviral therapy or highly active antiretroviral treatment (HAART) for ≥ 30 days prior to beginning Serostim therapy and will continue antiretroviral therapy throughout the course of Serostim treatment; AND
E) Serostim is not being used solely for treatment of alterations in body fat distribution such as increased abdominal girth, lipodystrophy and excess abdominal fat, or buffalo hump.

HIV Infection with Wasting or Cachexia in Adults Continuing Serostim Therapy. Approve up to a 6-month course of Serostim if the patient meets the following criteria (A and B):
A) Patient has been off Serostim for at least 1 month; AND
B) Patient meets criteria III.1.A, B, C, D, and E above.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Genotropin, Humatrope, Norditropin, Nutropin AQ, Omnitrope, Saizen, Serostim, and Zorbtive is not recommended in the following situations:
Note: For some of the following indications, authorization for coverage is not recommended because this indication is excluded from coverage in a typical pharmacy benefit.

1. **Acute Critical Illness Due to Complications Following Surgery, Multiple Accidental Trauma, or with Acute Respiratory Failure.**[1-9] In two 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.**[17,18,32,33] Somatropin is not FDA-approved for anti-aging therapy, to improve functional status in elderly patients, or to treat somatopause. Federal law prohibits the distribution or dispensing of somatropin for non-FDA approved uses. 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-1 status.[16]

3. **Athletic Ability Enhancement.**[18,34] Somatropin is not FDA-approved for athletic performance enhancement or for body building in nonathletes. Federal law prohibits the distribution or dispensing of somatropin for non-FDA approved uses. 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 or improving personal appearance (i.e., to appear leaner and more muscular). Somatropin has been used in supraphysiologic doses alone or in combination with other performance enhancing drugs (PEDs) in

users who are not athletes.[34] Use of PEDs has been linked to an increased risk of death and many adverse effects including cardiovascular, psychiatric, metabolic, endocrine, neurologic, infectious, hepatic, renal, and musculoskeletal disorders.

4. **Central Precocious Puberty.** Children with precocious puberty are often treated with gonadotropin releasing hormone (GnRH) agonists (Lupron® [leuprolide acetate injection]) 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.[35] 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.[35,36]

5. **Chronic Fatigue Syndrome.** There is no evidence of GHD in chronic fatigue syndrome.[37]

6. **Congenital Adrenal Hyperplasia (CAH).**[38,39] The Endocrine Society clinical practice guidelines on CAH due to steroid 21-hydroxylase deficiency recommends against the use of experimental treatment approaches outside of formally approved clinical trials.[39] Children with predicted adult height SD ≤ -2.25 may be considered for growth-promoting treatments in appropriately controlled trials.

7. **Constitutional Delay of Growth and Puberty (CDGP).** These children have delayed skeletal maturation and pubertal development. Administering somatropin does not increase adult height (which is usually normal).[40] Short-term androgen therapy accelerates growth and the rate of pubertal advancement in boys.

8. **Corticosteroid-Induced Short Stature.**[13] This includes a variety of chronic glucocorticoid-dependent conditions, such as asthma, Crohn's disease,[13] juvenile rheumatoid arthritis,[28,41,42] as well as after renal, heart, liver, or bone marrow transplantation.[43] Short-term improvement in growth velocity in children with glucocorticoid-induced suppression has been reported with somatropin therapy. Long-term data are not available.[13] Children being considered for treatment with somatropin should be enrolled in studies that allow careful monitoring and data analysis.

9. **Fibromyalgia.** In one placebo-controlled study, 120 non-GHD adult women with severe fibromyalgia and low levels of IGF-1 were randomized to somatropin 0.006 mg/kg/day for 12 months (dose was adjusted) or placebo for 6 months.[45] Patients receiving placebo initially were switched to somatropin from Months 6 to 12 (open label). Standard therapy for fibromyalgia was continued. After 6 months, there were no differences between somatropin and placebo in the percentage of patients with fewer than 11 positive tender points, mean number of tender points, intensity of pain in every point evaluated, and other measures. After 12 months of somatropin therapy, 53% of patients had less than 11 positive tender points compared with 33% of patients who received placebo and then somatropin for 6 months ($P < 0.05$). At 18 months follow-up evaluation when somatropin was discontinued, impairment in pain perception worsened in both groups but to a lesser extent in the patients on somatropin for 12 months. Further controlled trials are needed with a longer duration,[46] with different doses, and using the 2010 American College of Rheumatology criteria for fibromyalgia. Some patients with fibromyalgia may have adult GHD.

10. **Human Immunodeficiency Virus (HIV)-Infected Patients with Alterations in Body Fat Distribution** (e.g., increased abdominal girth, lipodystrophy and excess abdominal fat, buffalo hump).[26] Somatropin is not indicated for the treatment of HIV-associated adipose redistribution syndrome (HARS). HARS is a subset of HIV lipodystrophy and is defined as maldistribution of body fat characterized by central fat accumulation (lipohypertrophy) with or without lipoatrophy. 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. Safety and efficacy are not established.

11. **Infertility.**[47,10] 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. The authors of a recent meta-analysis concluded there is no evidence of an increased chance of a live birth with use of somatropin.

12. **Obesity.**[48,49] Somatropin is not indicated 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 pusatile release of growth hormone and decreased stimulated growth hormone release. Somatropin therapy does not have significant beneficial effects on obesity in persons without GHD and does not produce significant overall weight loss. Supraphysiologic doses of somatropin have been used to treat obesity. Effects of long-term therapy with somatropin are unknown.

13. **Osteoporosis.**[50,51] Guidelines for treatment or prevention of osteoporosis do not include recommendations for use of somatropin. In one double-blind trial, 80 postmenopausal women with osteoporosis (56% of patients [n = 45/80] had a history of fractures) were randomized to somatropin 0.33 mg/day or 0.83 mg/day or to placebo for three years.[50] The double-blind phase was 18 months and patients on somatropin continued drug for another 18 months and patients on placebo stopped at 18 months. Patients were compared with an age-matched random population sample of women (n = 120). All patients received calcium 750 mg, vitamin D 400 units, and hormone replacement therapy. All women were followed for 10 years total. Bone mineral density increased in the patients receiving somatropin at years 4 and 5, and after 10 years, had decreased to similar levels as before treatment. At 10 years, 28% of women (n = 22/80) had had fractures. In the control group, fractures increased from 8% of patients at baseline to 32% of patients after 10 years. At 10 years, 41% of patients (n = 33/80) had stopped hormone replacement therapy; 23% had started bisphosphonates due to fractures, and 3% had received Forteo® (teriparatide injection). Larger studies are needed to determine the effects of somatropin therapy on bone mineral density and fractures in non-growth hormone deficient persons.

14. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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