

## PRIOR AUTHORIZATION POLICY

- POLICY:** growth hormone [somatropin]
- Genotropin<sup>®</sup>(somatropin injection – Pfizer)
  - Humatrope<sup>®</sup> (somatropin injection – Eli Lilly)
  - Norditropin<sup>®</sup> (somatropin injection – Novo Nordisk)
  - Nutropin AQ<sup>®</sup> (somatropin injection – Genentech)
  - Omnitrope<sup>®</sup> (somatropin injection – Sandoz)
  - Saizen<sup>®</sup> (somatropin injection – EMD Serono)
  - Serostim<sup>®</sup> (somatropin injection – EMD Serono)
  - Zomacton<sup>™</sup> (somatropin injection – Ferring Pharmaceuticals)
  - Zorbtive<sup>®</sup> (somatropin injection – EMD Serono)

**TAC APPROVAL DATE:** 1/16/2019; selected revision 5/8/2019

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### OVERVIEW

Indications for somatropin vary among these products.<sup>1-5, 7-12</sup> Somatropin is indicated for the following conditions:

1. Treatment of pediatric patients who have growth failure due to an inadequate secretion of normal endogenous growth hormone;<sup>3-5,7-10</sup>
2. Treatment of idiopathic short stature, also called non-growth hormone deficient short stature, defined by height standard deviation score (SDS)  $\leq -2.25$  (1.2 percentile), 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;<sup>3-5,7,9-10</sup>
3. Replacement of endogenous growth hormone in adults with growth hormone deficiency (GHD) who meet either of the following two criteria: *Adult Onset:* Patients who have GHD, either alone or associated with multiple hormone deficiencies (hypopituitarism), as a result of pituitary disease, hypothalamic disease, surgery, radiation therapy, or trauma; or *Childhood Onset:* Patients who were growth hormone deficient during childhood as a result of congenital, genetic, acquired, or idiopathic causes;<sup>3-5,7-10</sup>
4. Treatment of growth failure in children with chronic kidney disease (CKD) up to the time of kidney transplantation;<sup>7</sup>
5. Treatment of children with short stature associated with Noonan syndrome;<sup>5</sup>
6. Treatment of pediatric patients who have growth failure due to Prader Willi syndrome;<sup>3,5,10</sup>
7. Treatment of short stature or growth failure in children with short stature homeobox-containing gene (SHOX) deficiency whose epiphyses are not closed;<sup>4,9</sup>
8. Treatment of growth failure in children born small for gestational age (SGA) who fail to manifest catch-up growth by age 2<sup>3,10</sup> to 4 years<sup>4-5,9</sup>;
9. Treatment of short stature associated with Turner syndrome in patients whose epiphyses are not closed;<sup>3-5,7,9-10</sup>
10. Treatment of short bowel syndrome (SBS) in patients receiving specialized nutritional support and in conjunction with optimal management of short bowel syndrome;<sup>11</sup>
11. Treatment of human immunodeficiency virus (HIV) infected patients with wasting or cachexia to increase lean body mass (LBM) and body weight, and improve physical endurance.<sup>12</sup>

Human growth hormone (hGH, somatotropin) is secreted by the anterior pituitary.<sup>1-2</sup> Most of its anabolic effects are mediated by insulin-like growth factor-1 (IGF-1, somatomedin C), which is synthesized in the liver and other tissues in response to growth hormone stimulation. Growth hormone stimulates linear growth in children and influences metabolism of carbohydrates, fats, minerals, and proteins. Somatotropin is produced by recombinant DNA technology and has the same amino acid sequence as naturally occurring hGH (a single polypeptide chain of 191 amino acids).<sup>3-5, 7-12</sup>

### **Growth Hormone Deficiency in Children and Adolescents**

Somatotropin is indicated for the treatment of growth failure in children due to an inadequate secretion of endogenous growth hormone.<sup>3-5,7-10,13</sup> In these children with GHD, somatotropin is effective for increasing final adult height.<sup>13-15,85</sup> Somatotropin therapy is recommended to normalize adult height and avoid extreme shortness in children and adolescents with GHD.<sup>85</sup> Cranial radiation often causes hypopituitarism, and GHD is a frequent pituitary abnormality seen in children and adults who have undergone cranial radiation.<sup>1,16-17</sup> 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.<sup>18-20</sup> Somatotropin therapy improves the final height of young children after total body irradiation.<sup>19-21</sup>

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

Somatotropin 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) below the mean for age, sex, and population group that is associated with growth rates that are unlikely to permit attainment of adult height in the normal range and where diagnostic evaluation has excluded other causes of short stature, including GHD.<sup>3-5,7,9-10,85</sup> The predicted adult heights of these children was < 160 cm (63 inches) for men and < 150 cm (59 inches) in women.<sup>25,85</sup> The Pediatric Endocrine Society guidelines<sup>85</sup> recommend that the decision to treat idiopathic short stature with somatotropin 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 somatotropin in every child with height SDS  $\leq$  -2.25. The use of growth hormone to treat non-growth hormone deficient children with short stature who are otherwise healthy (idiopathic, familial, or constitutional delay of growth and puberty [CDGP]) has been controversial.<sup>1,14,26-28</sup> Patients with CDGP and familial short stature may have heights that are more than 2 SDS below the mean and are growth hormone sufficient.<sup>23</sup> The American Academy of Pediatrics (AAP) concluded that therapy with growth hormone is medically and ethically acceptable for “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.”<sup>14</sup> The mean increase in adult height in children with idiopathic short stature that is attributed to somatotropin therapy (average duration 4 to 7 years) is 3.5 to 7.5 cm.<sup>3-4,7,22-23,29</sup> In controlled trials, in children with idiopathic short stature who were not growth hormone deficient, somatotropin 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.

### **Growth Hormone Deficiency in Adults or Transition Adolescents**

Somatotropin is indicated for the replacement of endogenous growth hormone in adults with GHD,<sup>3-10</sup> which may present in adults or children as GHD (isolated GHD) or in addition to other pituitary hormone deficiencies (gonadotropin, adrenocorticotrophic hormone [ACTH], and/or thyroid-stimulating hormone [TSH] deficiencies).<sup>30-31</sup> 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.<sup>4,30-32</sup> Onset may be

in adulthood or childhood. In childhood, the goal of somatropin therapy is primarily for statural growth.<sup>31</sup> 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; this age group has been arbitrarily defined as between 15 and 25 years of age. Transition patients are adolescents with childhood onset GHD who have been treated with somatropin and have finished linear growth. 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. In general, confirmation of the diagnosis of adult GHD in both groups (i.e., adult onset and childhood onset) usually requires an appropriate growth hormone stimulation test.<sup>3-5,7-8,10</sup> However, confirmatory growth hormone stimulation testing may not be required in patients with congenital/genetic GHD or multiple pituitary hormone deficiencies due to organic disease. 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.<sup>30</sup> Patients with other causes of short stature besides GHD are not treated with somatropin during the transition period between adolescence and adulthood. In adults with GHD, somatropin replacement therapy improves abnormalities in substrate metabolism, body composition, and physical and psychosocial function.<sup>30-32</sup>

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.<sup>31,33-34</sup>

### **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.<sup>7</sup> Somatropin therapy has increased final adult height in these patients.<sup>35</sup> Somatropin is not indicated for the treatment of growth failure *after* kidney transplantation in children. Spontaneous catch-up growth may not occur in some children after kidney transplantation, especially in children aged 6 to 17 years. In one-, two-, and three-year open-label studies and short-term controlled studies, growth velocity has improved with growth hormone therapy in renal allograft recipients.<sup>36</sup> Five years of somatropin therapy following renal transplantation has resulted in a delta Z score of about +0.5 standard deviations (SD).<sup>35</sup>

### **Noonan Syndrome and Short Stature in Children or Adolescents**

Somatropin is indicated for the treatment of children with short stature associated with Noonan syndrome.<sup>5,37</sup> 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. Data from one post marketing observational study indicated somatropin therapy in children with Noonan syndrome improved height SDS at near adult height.<sup>38</sup> Mean age at enrollment was 11.6 years but it is generally accepted that somatropin should be started earlier to maximize final height. This registry and another included patients with cardiac disorders and pulmonic stenosis.

### **Prader-Willi Syndrome**

Somatropin is indicated for the treatment of *pediatric* patients who have growth failure due to Prader-Willi syndrome.<sup>3,5,10</sup> 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.<sup>39-45</sup> 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.<sup>39,43-47</sup> Somatropin is contraindicated in patients with Prader-Willi syndrome who are severely obese or have severe respiratory impairment.<sup>3-5,7-10</sup>

### **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 whose epiphyses are not closed.<sup>4,9</sup> 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.<sup>48</sup> 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.<sup>49</sup> Height SDS from start of somatropin therapy to final height in 16 patients who received somatropin in the control and extension period was  $-1.79 \pm 1.39$  (mean  $\pm$  SD). Height gain was  $43.5 \text{ cm} \pm 10.5 \text{ cm}$ . In these patients, 56% achieved a final height  $> -2$  SD.

### **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<sup>3-5,9-10,50-51</sup> to 4 years.<sup>4-5</sup> SGA is defined as a birth weight and/or birth length that is greater than 2 SD (about the 3<sup>rd</sup> 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.<sup>3,5,52-58</sup> Optimal duration of therapy once catch-up growth has been attained is not known. Limited information is available on somatropin therapy in pubertal adolescents.<sup>55-56</sup> There are no long-term, randomized, controlled, well-powered studies done up to the attainment of adult height.<sup>56,59-60</sup> However, in one pivotal trial in Dutch children (3 to 11 years of age), treatment with somatropin was continued for up to 13 years; mean duration of therapy was 9.5 years in boys and 7.9 years in girls.<sup>5</sup> In all, 72% of children (n = 38/53) reached final height and 63% of children (n = 24/38) who reached final height were within the normal range of their healthy peers using Dutch national reference. The mean final height SDS and the increase in height SDS from baseline to final height were significantly greater with a dose of 0.067 mg/kg/day than with 0.033 mg/kg/day. When patients born SGA delay beginning somatropin therapy until age 9 to 10 years, growth velocity is slower and adult height is shorter compared with children who are treated earlier.<sup>50,61</sup> In one study in Dutch children born SGA who started somatropin therapy near puberty adult height SDS was improved when the dose of somatropin was 2 mg/m<sup>2</sup>/day.<sup>62</sup>

Almost all patients with Silver-Russell syndrome are born SGA, and postnatal catch-up growth does not occur in the majority of children.<sup>115</sup> An expert consensus statement recommends that patients with Silver-Russell syndrome receive treatment with somatropin as soon as possible.<sup>115</sup> 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 in patients whose epiphyses are not closed.<sup>3-5,7,9-10,63</sup> In patients with Turner syndrome who were treated to adult height, average height gains were 5.0 cm to 8.3 cm.<sup>6-7</sup>

### **Short Bowel Syndrome**

Somatropin is indicated for the treatment of short SBS in adults receiving specialized nutritional support in conjunction with optimal management of SBS (which may include dietary adjustments, enteral feedings, parenteral nutrition, and fluid and micronutrient supplements, as needed).<sup>11,64</sup> Therapy for more than 4 weeks has not been adequately studied. Studies are needed that evaluate somatropin therapy during the early active phase of intestinal adaptation (i.e., immediately after bowel resection).<sup>65</sup>

### **Human Immunodeficiency Virus-Associated Wasting or Cachexia**

Somatropin is indicated for the treatment of HIV-infected adults with wasting (loss of LBM) or cachexia to increase LBM and body weight, and improve physical endurance.<sup>12</sup> Wasting in HIV-infected patients can be caused by multiple factors and is characterized by a decrease in body mass of greater than 10% in the absence of other related illnesses, such as opportunistic infections, malignancies, or other identifiable factors.<sup>66</sup> Decreased LBM in HIV-infected patients is associated with an increased risk for mortality. Somatropin therapy increases LBM, decreases fat mass, and increases physical function in patients with HIV-associated wasting.<sup>12,67-69</sup> Studies directly comparing somatropin with other therapies (megestrol, oxandrolone, testosterone, and progressive resistance training) for wasting or cachexia in HIV-infection are lacking.<sup>70-71</sup> In a small number of patients aged 6 to 17 years with HIV-associated failure to thrive, short-term somatropin therapy improved height and weight and reduced protein catabolism.<sup>12,72</sup>

### **POLICY STATEMENT**

Prior authorization is recommended for prescription benefit coverage of somatropin. 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. Non-GHD short stature is approved for an initial 6-month approval duration; SBS in adults is approved for an initial and continuing 4-week approval durations; and HIV infection with wasting or cachexia in adults is approved for an initial and continuing 6-month approval durations. 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 will be required for Growth Hormone Deficiency in Adults or Transition Adolescents where noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, prescription claims records, prescription receipts and/or laboratory data. For Adult and Transition Adolescent 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. This *Growth Hormone Prior Authorization Policy* document applies to the Standard Program.

**Automation:** None.

### **RECOMMENDED AUTHORIZATION CRITERIA**

- I. Coverage of Genotropin, Humatrope, Norditropin, Nutropin, Nutropin AQ, Omnitrope, Saizen, and Zomacton (all listed products except Serostim and Zorbtive) is recommended in patients who meet one of 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) The patient meets the following (i and either ii or iii):

- i. The patient has been evaluated by an endocrinologist; AND
- ii. The 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
- iii. The patient meets both of the following criteria (a and b):
  - a) The 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) The 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 25<sup>th</sup> percentile to below the 10<sup>th</sup> 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 10<sup>th</sup> 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).

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).

B) The patient has *undergone brain radiation or tumor resection* AND meets the following criteria (i and ii):

- i. The patient has been evaluated by an endocrinologist; AND
- ii. The patient meets at least ONE of the following criteria (a or b):
  - a) The 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) The patient has a deficiency in at least one other pituitary hormone (that is, adrenocorticotrophic 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).<sup>85</sup>

- C) The patient has *congenital hypopituitarism* AND meets the following criteria (i and ii):
- i. The patient has been evaluated by an endocrinologist; AND
  - ii. The patient meets at least ONE of the following criteria (a or b):
    - a) The 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) The patient has a deficiency in at least one other pituitary hormone (that is, adrenocorticotrophic 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.<sup>85</sup>

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.<sup>76-77,85</sup> 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).<sup>85</sup>

- D) The patient has *panhypopituitarism* and meets the following criteria (i and ii):
- i. The patient has been evaluated by an endocrinologist; AND
  - ii. 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

Growth hormone stimulation testing is not required. These patients either have severe isolated GHD or multiple pituitary hormone deficiencies.

- b) Patient has three or more of the following pituitary hormone deficiencies: somatropin (growth hormone), adrenocorticotrophic 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) The 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.

GHD may occur in combination with other pituitary hormone deficiencies and is referred to as hypopituitarism, panhypopituitarism, or multiple pituitary hormone deficiency.

- E) The patient has had a hypophysectomy (surgical removal of pituitary gland).

Growth hormone is secreted from the anterior pituitary. These children have GHD.

**Children or Adolescents with Growth Hormone Deficiency (GDH) Continuing Somatropin Therapy** (i.e., established on somatropin for  $\geq 10$  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  $\geq 4$  cm/year in the most recent year.
- B) *Adolescents between  $\geq 12$  years and  $\leq 18$  years of age.* The patient meets the following criteria (i and ii):
  - i. Height has increased by  $\geq 4$  cm/year in the most recent year; AND
  - ii. The epiphyses are open.
- C) *Adolescents or young adults > 18 years of age.* The patient meets the following criteria (i, ii, and iii):
  - i. Height has increased by  $\geq 4$  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 (defined as growth rate  $< 4$  cm/year) 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  $\geq 5$  years of age; AND
- B) The patient's baseline height is less than 1.2 percentile or a standard deviation score (SDS)  $< -2.25$  for age and gender; AND
- C) The patient's growth (height) velocity is ONE of the following (i or ii):
  - i. The child is  $\geq 5$  years of age AND has a growth rate  $< 4$  cm/year; OR
  - ii. The growth velocity is less than the 10<sup>th</sup> percentile for age and gender based on at least 6 months of growth data; AND
- 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) The patient does not have constitutional delay of growth and puberty (CDGP).<sup>23</sup>

**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  $\geq 5$  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. 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  $\geq 5$  years and  $< 12$  years of age* (i.e., established on somatropin for  $\geq 10$  months). The height has increased by  $\geq 4$  cm/year in the most recent year; OR
- C) *Patients  $\geq 12$  years of age and  $\leq 18$  years of age* (i.e., established on somatropin for  $\geq 10$  months). The patient meets the following criteria (i and ii):
  - i. Height has increased by  $\geq 4$  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  $\geq 10$  months). The patient meets the following criteria (i, ii, and iii):
  - i. Height has increased by  $\geq 4$  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.

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.<sup>23</sup>

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<sup>26</sup> 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.

- 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) Patient has been evaluated by an endocrinologist; AND
  - B) The endocrinologist must certify that somatropin is not being prescribed for anti-aging therapy or to enhance athletic ability or for body building; AND
  - C) Patient must have a diagnosis of GHD that is one of the following (i or ii): **[documentation required for all elements]**
    - i. Childhood onset;<sup>3,5,7-8,10,30-31,78</sup> 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
  - D) The patient meets one of the following criteria (i, ii, or iii):
    - i. The patient (adult or transition adolescent) had childhood-onset growth hormone deficiency (GHD) and has known mutations, embryopathic lesions, congenital defects, or irreversible structural hypothalamic-pituitary lesions/damage;<sup>31,85</sup> **[documentation required]** OR
    - ii. The patient meets the following criteria (a, b, and c):
      - a) The patient (adult onset or transition adolescent) has three or more of the following pituitary hormone deficiencies:<sup>30-31,85</sup> 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]**;<sup>31,79</sup> AND

- c) Other causes of low serum insulin-like growth factor-1 (IGF-1) have been excluded<sup>79</sup> (e.g., malnutrition, prolonged fasting, poorly controlled diabetes mellitus, hypothyroidism, hepatic insufficiency, oral estrogen therapy).

OR

- iii. The 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];<sup>30-32</sup>

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

- 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  $\leq 5.0$  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  $\leq 3.0$  mcg/L AND the patient's body mass index (BMI) is  $\leq 25$  kg/m<sup>2</sup>;<sup>73,80</sup> 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 peak response  $\leq 1.0$  mcg/L AND the patient's body mass index (BMI) is  $> 25$  kg/m<sup>2</sup>;<sup>73</sup> OR
- d) 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  $\leq 0.4$  mcg/L;<sup>30-31,82</sup> OR
- e) 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  $\leq 40$  kg/m<sup>2</sup>.

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

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.<sup>85</sup>) The patient meets the following criteria (a and b): [documentation required for all elements]

- a) The patient has been off somatropin therapy for at least 1 month before retesting with a growth hormone stimulation test;<sup>31,85</sup> AND
- b) The patient meets ONE of the following responses to growth hormone stimulation testing (1, 2, 3, or 4):
- (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  $\leq 5.0$  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  $\leq 3.0$  mcg/L AND the patient's body mass index (BMI) is  $< 25$  kg/m<sup>2</sup>; 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 peak response  $\leq 3.0$  mcg/L AND the patient's body mass index (BMI) is  $\geq 25$  kg/m<sup>2</sup> AND a second growth hormone stimulation test with a peak response as stated in transition adolescents b1 or b4 in this section; OR
- (4) 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  $\leq 0.4$  mcg/L.<sup>31,82</sup>

The insulin tolerance test is the gold standard growth hormone stimulation test,<sup>73,81</sup> but is contraindicated in patients with ischemic heart disease or seizure disorders or in elderly or pregnant patients.<sup>30-32,73,81</sup> The glucagon stimulation test is an alternative to the insulin tolerance test.<sup>73,81</sup> 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.<sup>81,83</sup> BMI corrected growth hormone testing cutoffs have only been established for the GHRH (Geref, GHRH Diagnostic) [discontinued in the US in 2008] plus arginine test and for the glucagon test. There is no information on the effects of increased BMI or central adiposity on the insulin tolerance test. There are no normative data by BMI for the arginine test.<sup>84</sup> The American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE) recommended revising the cutoff point for the glucagon stimulation test in adults.<sup>73</sup> The AACE/ACE proposed using 3 mcg/L as the growth hormone cut-point for patients with BMI  $\leq 25$  kg/m<sup>2</sup>, and to consider a lower growth hormone cut-point of 1 mcg/L in patients with BMI  $> 25$  kg/m<sup>2</sup> to reduce over diagnosing adult GHD. They also proposed using the glucagon stimulation test instead of the weight-based glucagon stimulation test. Larger prospective studies of patients with various BMIs and degrees of glucose tolerance are needed to refine the diagnostic accuracy of the 1 mcg/L cut-point when the glucagon stimulation test is used. Studies are needed to determine BMI stratified peak growth hormone cutoff levels to define adult GHD.<sup>80,83-84</sup> When Geref was available, Geref (GHRH) plus arginine was considered the best alternative to the insulin tolerance test in adults.

Macrilen (macimorelin) was recently approved as a test for the diagnosis of adult GHD.<sup>75</sup> Patients in the pivotal trial were 18 to 66 years of age and the BMI ranged from 16 to 40 kg/m<sup>2</sup>. Safety and diagnostic performance has not been established in patients with BMI  $> 40$  kg/m<sup>2</sup>. 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.

Clonidine and levodopa are not useful tests in adults.<sup>31</sup> The clonidine, levodopa, and arginine alone tests are generally not recommended because very low growth hormone cutoff points are required to achieve adequate specificity.<sup>73,81</sup>

**Table 1. Growth Hormone Cutoff Points (mcg/L) for Growth Hormone Stimulation Tests Used in the US by Different Consensus Guidelines for Diagnosis of Adult Growth Hormone Deficiency.<sup>73†</sup>**

Test	GHRS 2007 <sup>32</sup>	AACE 2009 <sup>31</sup>	Endocrine Society 2011 <sup>30</sup>	AACE/ACE 2016 <sup>73</sup>
Insulin tolerance test	< 3.0 mcg/L	≤ 5.0 mcg/L	< 3.0 to 5.0 mcg/L	NDD
GHRH* -arginine				
BMI < 25 kg/m <sup>2</sup>	< 11.0 mcg/L	≤ 11.0 mcg/L	< 11.0 mcg/L	NDD
BMI 25 to 30 kg/m <sup>2</sup>	< 8.0 mcg/L	≤ 8.0 mcg/L	< 8.0 mcg/L	NDD
BMI ≥ 30 kg/m <sup>2</sup>	< 4.0 mcg/L	≤ 4.0 mcg/L	< 4.0 mcg/L	NDD
Glucagon	< 3.0 mcg/L	≤ 3.0 mcg/L	< 3.0 mcg/L	≤ 3.0 mcg/L if BMI is ≤ 25 kg/m <sup>2</sup> ≤ 1.0 mcg/L if BMI is > 25 kg/m <sup>2</sup>
Arginine	NDD	≤ 0.4 mcg/L	NDD	NDD

† Guidelines have not been update to include Macrilen testing; GHRS – Growth Hormone Research Society; AACE – American Association of Clinical Endocrinologists; ACE – American College of Endocrinology; GHRH – Growth hormone releasing hormone; \* No longer available in the US; BMI – Body mass index; NDD – No data described.

Clonidine and levodopa are not useful tests in adults.<sup>31</sup> The clonidine, levodopa, and arginine alone tests are generally not recommended because very low growth hormone cutoff points are required to achieve adequate specificity.<sup>73,81</sup>

Adults with childhood onset GHD may have alterations in body composition, bone mineral density, and lipid metabolism that are alleviated by treatment with somatropin.<sup>30,85</sup> However, some children with a diagnosis of GHD have a normal somatotrophic axis when retested in late adolescence.<sup>85,143</sup> Re-evaluation of the somatotrophic 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.<sup>85</sup> Re-evaluation of the somatotrophic 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<sup>85</sup> 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 somatotrophic 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 somatotrophic 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. Somatropin therapy can be used in individuals with persistent GHD in the transition period. According to the AACE medical guidelines published in 2009, patients with childhood GHD previously treated with somatropin replacement in childhood should be re-tested after final height is achieved and somatropin therapy discontinued for at least 1 month to determine their growth hormone status before considering restarting somatropin therapy.<sup>31</sup> Exceptions include those with one of the following conditions: known mutations; embryonic/congenital defects; irreversible hypothalamic-pituitary structural lesions; and evidence of panhypopituitarism (≥ 3 pituitary hormone deficiencies) and serum IGF-1 levels below the age- and sex- appropriate reference range when the patient is off growth hormone therapy.

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 2.5<sup>th</sup> percentile or < -2 SDS.<sup>30-32,82</sup> 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.<sup>32</sup> 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 with childhood-onset GHD is not necessary.

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 been evaluated by an endocrinologist or a nephrologist; AND
  - B) Patient has chronic kidney disease (CKD) as defined by an abnormal creatinine clearance.

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

- A) Height has increased by  $\geq 2.5$  cm/year in the most recent year; AND
- B) The epiphyses are open.

Evaluation of growth hormone secretion is not necessary.<sup>1,24,86</sup>

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) The patient has been evaluated by an endocrinologist; AND
  - B) The patient's baseline height is less than the 5<sup>th</sup> percentile using a growth chart for children without Noonan syndrome.

**Noonan Syndrome in Children or Adolescents Continuing Somatropin Therapy** (i.e., established on somatropin for  $\geq 10$  months). Approve for 1 year in patients who meet the following criteria (A and B):

- A) Height has increased by  $\geq 2.5$  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  $\geq 10$  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  $\geq 2.5$  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  $< 2.5$  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  $< 2.5$  cm/year*  
The patient meets the following criteria (i and ii):
  - i. The patient must be evaluated by an endocrinologist or in consultation with an endocrinologist; AND
  - ii. This physician must certify that somatropin is not being used for anti-aging therapy or to enhance athletic performance/body building.

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 has been evaluated by an endocrinologist; AND
- D) The patient's baseline height is less than the 3<sup>rd</sup> percentile for age and gender.

**Short Stature Homeobox-Containing Gene Deficiency in Children or Adolescents Continuing Somatropin Therapy** (i.e., established on somatropin for  $\geq 10$  months). Approve for 1 year in patients who meet the following criteria (A and B):

- A) Height has increased by  $\geq 2.5$  cm/year in the most recent year; AND
- B) The epiphyses are open.

Evaluation of growth hormone secretion is not necessary because these children do not have abnormal growth hormone secretion.

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  $\geq 2$  years of age; AND
- B) Patient has been evaluated by an endocrinologist; AND
- C) 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
- D) The patient's baseline height is less than the 5<sup>th</sup> percentile for age and gender.

**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  $\geq 10$  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  $\geq 4$  cm/year in the most recent year.
- B) *Patients  $\geq 12$  years and  $\leq 18$  years of age.* The patient meets the following criteria (i and ii):
  - i. Height has increased by  $\geq 4$  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  $\geq 4$  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.

Evaluation of growth hormone secretion and bone age is not necessary.<sup>24,51</sup> Children born SGA who do not have sufficient catch up growth (height SDS  $< -2.5$ ) by age 2 to 4 years should be considered for treatment with somatropin.<sup>51</sup>

9. **Turner Syndrome.** Approve for *initial* therapy for 1 year in patients with short stature associated with Turner syndrome.<sup>1,3-5,7,14</sup>

**Patients with Turner Syndrome Continuing Somatropin Therapy** (i.e., established on somatropin for  $\geq 10$  months). Approve for 1 year in patients who meet the following criteria (A and B):

- A) Height has increased by  $\geq 2.5$  cm/year in the most recent year; AND
- B) The epiphyses are open.

Evaluation of growth hormone secretion is not necessary because these children do not have abnormal growth hormone secretion.<sup>1,15,24</sup>

**II. Coverage of Genotropin, Humatrope, Norditropin, Nutropin, 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 receiving specialized nutritional support (defined as a high carbohydrate, low-fat diet that is adjusted for individual patient requirements and preferences); AND
- B) Patient is  $\geq 18$  years of age.

**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 prescribing physician.

In some patients somatropin may need to be discontinued for up to 5 days for severe toxicities and resumed.<sup>11</sup> This is FDA-approved dosing.

**III. Coverage of Serostim** is recommended in those who meet the following criteria:<sup>12,67</sup>

**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):<sup>12,67</sup>

- A) Patient is  $\geq 18$  years of age; AND
- B) Patient has ONE of the following (i, ii, or iii):
  - i. Documented unintentional weight loss of  $\geq 10\%$  from baseline; OR
  - ii. Weight  $< 90\%$  of the lower limit of ideal body weight; OR
  - iii. Body mass index (BMI)  $\leq 20$  kg/m<sup>2</sup>; AND
- Note: The following formula can be used to calculate BMI: BMI equals body weight in kg divided by height in meters squared (m<sup>2</sup>) [i.e., BMI = kg/m<sup>2</sup>];
- 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) The patient has been on antiretroviral therapy or highly active antiretroviral treatment (HAART) for  $\geq 30$  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.

Concomitant antiretroviral therapy is necessary since it is possible that somatropin might accelerate viral replication.<sup>12</sup> Clinical trials that established safety and efficacy required that patients have unintentional weight loss of  $\geq 10\%$  from baseline, weight  $< 90\%$  of the lower limit of ideal body weight, or BMI  $\leq 20$  kg/m<sup>2</sup>. Most of Serostim's effects on LBM and work output are apparent after 12 weeks

and these effects are maintained when therapy is continued for an additional 12 weeks. There are no safety and efficacy data from controlled trials in patients treated with Serostim continuously for > 48 weeks or for patients who start, stop, and then restart treatment.<sup>12</sup>

#### **CONDITIONS NOT RECOMMENDED FOR APPROVAL**

Coverage of Genotropin, Humatrope, Norditropin, Nutropin, Nutropin AQ, Omnitrope, Saizen, Serostim, and Zorbtive is recommended in circumstances that are listed in the Recommended Authorization Criteria (FDA-Approved Indications). 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. The following provides rationale for specific Exclusions. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

- 1. Acute Critical Illness Due to Complications Following Surgery, Multiple Accidental Trauma, or with Acute Respiratory Failure.**<sup>3-5,7-9,11-12</sup> 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.**<sup>33-34,87-88</sup> 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.<sup>32</sup>
- 3. Athletic Ability Enhancement.**<sup>34,89-90</sup> 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.<sup>90</sup> 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. Bony Dysplasias (Achondroplasia, Hypochondroplasia).**<sup>1,91-93</sup> Short-term therapy 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.<sup>91</sup> Somatropin therapy may transiently increase growth rate, but there are no studies showing a significant increase in adult height.<sup>91-92</sup> According to AAP guidance for pediatric achondroplasia, growth hormone should only be considered within a research setting.<sup>91</sup> There are very few studies of somatropin therapy in

hypochondroplasia.<sup>92</sup> 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.<sup>92</sup> There are no long-term studies.

- 5. Burn Injury (Extensive) in Children or Adults.** In one randomized, double-blind single-center study, children who were severely burned (> 40% of total body surface area [BSA] 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.<sup>94</sup> Mean total burn size ranged from about 60% to 67% of total BSA. In all, 167 patients began treatment with somatropin and 148 patients with placebo. At the end of 1 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. Objective measures of burn wound or donor site healing were not reported. Although there was no increased mortality in this study, high doses of somatropin in critically ill non-burn patients were associated with increased morbidity and mortality.<sup>95</sup> In one review of randomized controlled trials in children or adults with large burns (> 40% of total BSA), the authors concluded that there is some evidence that somatropin helps burn wounds and donor sites heal more rapidly.<sup>96</sup> High quality studies that are adequately powered are needed.
- 6. Cardiac Transplantation.** Limited information is available.<sup>97</sup> Children being considered for treatment with growth hormone should be enrolled in studies that allow careful monitoring and data analysis.
- 7. Central Precocious Puberty.** Children with precocious puberty are often treated with gonadotropin releasing hormone (GnRH) agonists (Lupron<sup>®</sup> [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.<sup>98</sup> 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.<sup>98-99</sup>
- 8. Chronic Fatigue Syndrome.** There is no evidence of GHD in chronic fatigue syndrome.<sup>100</sup>
- 9. Congenital Adrenal Hyperplasia (CAH).**<sup>101-103</sup> 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.<sup>103</sup> Children with predicted adult height SD  $\leq$  -2.25 may be considered for growth-promoting treatments in appropriately controlled trials.
- 10. Constitutional Delay of Growth and Puberty (CDGP).** These children have delayed skeletal maturation and pubertal development.<sup>15</sup> Administering somatropin does not increase adult height (which is usually normal).<sup>15,104</sup> Short-term androgen therapy accelerates growth and the rate of pubertal advancement in boys.
- 11. Corticosteroid-Induced Short Stature.**<sup>1,15,24</sup> This includes a variety of chronic glucocorticoid-dependent conditions, such as asthma,<sup>15</sup> Crohn's disease,<sup>24</sup> juvenile rheumatoid arthritis,<sup>15,74,105-106</sup> as well as after renal, heart, liver, or bone marrow transplantation.<sup>107-108</sup> Short-term improvement in growth velocity in children with glucocorticoid-induced suppression has been reported with somatropin

therapy. Long-term data are not available.<sup>24</sup> Children being considered for treatment with somatropin should be enrolled in studies that allow careful monitoring and data analysis.

- 12. Crohn's Disease.** Limited information is available in adults receiving somatropin therapy for Crohn's disease.<sup>109</sup> In children with Crohn's disease, somatropin therapy has not been effective in improving final adult height.<sup>110</sup> In one short-term study, somatropin in combination with corticosteroids was more effective than corticosteroids alone in decreasing disease activity (measured using Pediatric Crohn's Disease Activity Index) and increasing linear growth in children and adolescents with moderately active Crohn's disease.<sup>111</sup> 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.
- 13. Cystic Fibrosis.**<sup>112-114</sup> Many clinical trials have been conducted in patients with cystic fibrosis without GHD. One recent critical review of the use of somatropin to improve lung function, growth and quality of life in children and young adults with cystic fibrosis, concluded that there is a modest improvement in height and weight when somatropin is used for 6 to 12 months.<sup>114</sup> But there is no consistent evidence that lung function, muscle strength, clinical condition, or quality of life is improved with somatropin therapy. Long-term, well-designed randomized controlled trials are required to evaluate the efficacy of somatropin in patients with cystic fibrosis.
- 14. Dilated Cardiomyopathy and Heart Failure.** Randomized trials have not demonstrated that somatropin therapy is beneficial in heart failure, other than in patients with a pre-existing deficiency. Further studies are needed.
- 15. Down's Syndrome.**<sup>1,15</sup> 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.
- 16. 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.<sup>116-117</sup> Placebo-controlled trials are short-term (2 to 6 months). In one controlled trial, 139 adults on maintenance hemodialysis were randomized to placebo or somatropin (20, 35, or 50 mcg per kg/day) for 6 months.<sup>118</sup> Therapy with somatropin increased LBM and serum albumin tended to increase.
- 17. Familial Dysautonomia (Riley-Day Syndrome, Hereditary Sensory Autonomic Neuropathy).** In one retrospective review of 13 children with familial dysautonomia who received somatropin, growth velocity increased, especially in the first 6 months.<sup>119</sup> A prospective study with standardized criteria is needed.
- 18. 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.<sup>120</sup> 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,<sup>121</sup> with different doses, and using the 2010

American College of Rheumatology criteria for fibromyalgia. Some patients with fibromyalgia may have adult GHD.

- 19. Hematopoietic Stem Cell Transplant Without Total Body Irradiation or Cranial Radiation.** Somatropin is recommended in patients who have undergone total body irradiation or cranial radiation in preparation for hematopoietic stem cell transplant and have GHD.<sup>18-21</sup> Children conditioned for transplantation with chemotherapy-only regimens do not require somatropin therapy.<sup>20,122</sup>
- 20. Human Immunodeficiency Virus (HIV)-Infected Patients with Alterations in Body Fat Distribution** (e.g., increased abdominal girth, lipodystrophy and excess abdominal fat, buffalo hump).<sup>70,123-126</sup> 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.
- 21. Infertility.**<sup>127-130,6</sup> 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.
- 22. Kidney Transplant Patients (Children) with a Functional Renal Allograft.**<sup>35,131</sup> Somatropin is not indicated for this use. If chronic renal insufficiency develops after transplantation, the patient will meet the criteria for use of somatropin in CKD. In children with a functional renal allograft, four 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.<sup>132</sup> 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 with 2,263 control patients who did not receive somatropin.<sup>35,131</sup> 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 with 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 control patients.
- 23. Liver Transplantation.** Limited information is available from either short-term use or longer use in a limited number of patients.<sup>107-108</sup> 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 one pilot study 43 patients with MSA were randomized, double-blind to somatropin or placebo for 12 months.<sup>133</sup> Of the 26 patients who completed 12 months of treatment without protocol violations, 13 patients had parkinsonian type of MSA and 13 patients 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 GHD. 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<sup>134</sup> and prospective studies<sup>135-136</sup> therapy with somatropin has increased growth velocity and height in carefully selected children with myelomeningocele and GHD. Well-controlled trials are needed.
- 26. Obesity.**<sup>137-138</sup> 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 pulsatile 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.
- 27. Osteogenesis Imperfecta.** There are few studies of somatropin therapy for osteogenesis imperfecta; there is some positive short-term effect on growth velocity but no clear long term effects.<sup>92,139</sup> Somatropin therapy is not recommended until further studies are done.<sup>139</sup>
- 28. Osteoporosis.**<sup>140-141</sup> 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.<sup>140</sup> 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.
- 29. Thalassemia.** Somatropin has been used to treat GHD in short children and adolescents with thalassemia.<sup>142</sup> There are no randomised controlled trials in adults or trials that address the use of growth hormone therapy for more than a year and assess its effect on final height and quality of life. Large well-designed, randomized controlled trials over a longer period with sufficient duration of follow up are needed.
- 30. X-linked Hypophosphatemic Rickets (Familial Hypophosphatemia, Hypophosphatemic Rickets).** In one 3-year open-label study, 16 short pre-pubertal children with X-linked hypophosphatemic rickets who received therapy with somatropin had increased linear growth without progression of body disproportion.<sup>144</sup> Cumulative changes in longitudinal body dimensions were significantly better in the group receiving somatropin compared with a reference population of patients with X-linked hypophosphatemic rickets (P < 0.01).
- 31.** 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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**HISTORY**

Type of Revision	Summary of Changes*	TAC Approval Date
Selected revision	<p>For Turner Syndrome reference to “girls” was deleted and changed to “Patients” for both the initial therapy and for those continuing on therapy as gender is not needed to be specified.</p> <p>In Conditions Not Recommended for Approval, the condition Osteoporosis was revised to remove the descriptors of “(in Postmenopausal Women, Idiopathic in Men or Glucocorticoid-Induced)” as these descriptors are not needed.</p>	08/10/2016
Annual revision	<p>Adult GHD criteria were revised to require that in adults, the glucagon stimulation peak response is <math>\leq 1.0</math> mcg/L and when the patient’s BMI is <math>&gt; 25</math> kg/m<sup>2</sup> and to remove the requirement that a second growth hormone stimulation test is required in these patients. Previously the criteria required a peak response of <math>\leq 3.0</math> mcg/L in patients with a BMI <math>\geq 25</math> kg/m<sup>2</sup> and a second stimulation test. In adults with BMI <math>\leq 25</math> kg/m<sup>2</sup> the peak response to the glucagon stimulation test remains the same at <math>\leq 3</math> mcg/L.</p>	09/21/2016
Annual revision	<ul style="list-style-type: none"> <li>• Children or adolescents who have undergone brain radiation: Added an exception if the patient has a deficiency in one other pituitary hormone (that is, ACTH, thyroid-stimulating hormone, gonadotropin deficiency [luteinizing hormone and/or follicle stimulating hormone deficiency are counted as one deficiency], or prolactin).</li> <li>• Children or adolescents with congenital hypopituitarism: Added an exception if the patient has a deficiency in one other pituitary hormone (that is, ACTH, thyroid-stimulating hormone, gonadotropin deficiency [luteinizing hormone and/or follicle stimulating hormone deficiency are counted as one deficiency], or prolactin); and/or the imaging triad of ectopic posterior pituitary and pituitary hypoplasia with abnormal pituitary stalk.</li> <li>• Idiopathic short stature: In initial criteria, corrected the predicted adult height is <math>&lt; 160</math> cm (previously stated 163 cm).</li> <li>• GHD in Adults or Transition Adolescents Continuing Somatropin Therapy: Added criterion that the diagnosis is either for childhood onset or adult onset.</li> </ul>	10/18/2017
Early annual revision	<ul style="list-style-type: none"> <li>• Growth Hormone Deficiency (GHD) in Children or Adolescents: In patients with growth hormone stimulation testing showing a peak growth hormone response to at least one test of less than 10 ng/mL, the initial criterion was deleted requiring the patient’s baseline height must be less than the 10<sup>th</sup> percentile for age and gender. Criterion regarding growth (height) velocity remains and indicates the rate of growth has slowed significantly. Also added, continuing somatropin therapy is defined as being established on somatropin for at least 10 months.</li> <li>• Non-Growth Hormone Deficient Short Stature (Idiopathic Short Stature) in Children or Adolescents: Continuing somatropin therapy is defined as being established on somatropin for at least 10 months.</li> <li>• Growth Hormone Deficiency in Adults or Transition Adolescents: In GHD in adults, growth hormone stimulation tests were revised to add the Macrilen test as an option in patients with a body mass index less than or equal to 40 kg/m<sup>2</sup>. Macrilen is a new test for GHD in adults. The growth hormone releasing hormone (GHRH) plus arginine test was deleted as a testing option in adults and in transition adolescents. GHRH is not available in the US. Continuing somatropin therapy is defined as being established on somatropin for at least 10 months.</li> <li>• Chronic Kidney Disease in Children or Adolescents, Noonan Syndrome in Children or Adolescents, Prader-Willi Syndrome, Short Stature Homeobox-Containing Gene Deficiency in Children or Adolescents, Children Born Small for Gestational Age or with Intrauterine Growth Restriction (Retardation) Including Those with Silver-Russell Syndrome, and Turner Syndrome: For these conditions, continuing somatropin therapy is defined as being established on somatropin for at least 10 months.</li> </ul>	02/07/2018

Annual revision	<ul style="list-style-type: none"> <li>• Removal of Nutropin (obsolete since 2013)</li> </ul>	01/16/2019
Selected revision	<ul style="list-style-type: none"> <li>• Growth Hormone Deficiency in Children or Adolescents: Criterion related to growth rate and growth velocity percentile were removed. A confirmation of two growth hormone stimulation tests OR one growth hormone stimulation test and a risk factor for growth hormone deficiency was added. Criteria was removed which specified the result of a growth hormone stimulation test was &lt; 10 ng/mL. Criteria was added that the stimulation test show an inadequate response as defined by a peak response below the normal reference range as determined by the testing laboratory. Tumor resection was added to the brain radiation criteria.</li> <li>• Growth Hormone Deficiency in Adults or Transition Adolescents: Growth hormone stimulation tests were updated to include a minimum number of accepted growth hormone values in a specified timeframe required for each test. Criteria was updated for the insulin tolerance test to include information about achieving adequate hypoglycemia. Criterion related to continuation of therapy for Adults and Transition Adolescents were removed. The documentation section of the policy statement was updated to reflect that if documentation had been received upon a prior coverage review, the documentation requirement would be considered met.</li> </ul>	05/08/2019

TAC – Therapeutic Assessment Committee; DEU – Drug Evaluation Unit; GHD – Growth hormone deficiency; BMI – Body mass index; ACTH – Adrenocorticotrophic hormone; HIV – Human immunodeficiency virus; GHRH – Growth hormone releasing hormone. \* For a further summary of criteria changes, refer to respective TAC minutes available at: <http://esidepartments/sites/Dep043/Committees/TAC/Forms/AllItems.aspx>.