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**Coverage Policy Number** ..... **IP0452**

# Somatropin

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## Related Coverage Resources

Mecasermin
Unassigned Drug or Biologic Code Medical Precertification

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## Overview

This policy supports medical necessity review for the following growth hormone (somatropin) products:

- **Genotropin®**(somatropin injection)
- **Humatrope®** (somatropin injection)
- **Norditropin Flexpro®** (somatropin injection)
- **Nutropin AQ®** (somatropin injection)
- **Omnitrope®** (somatropin injection)
- **Saizen®** (somatropin injection)
- **Serostim®** (somatropin injection)
- **Zomacton™** (somatropin injection)
- **Zorbtive®** (somatropin injection)

Additional criteria that support the review for medical necessity exceptions of non-covered products are located in the Non-Covered Product Table by the respective plan type and drug list where applicable.

Receipt of sample product does not satisfy any criteria requirements for coverage.

## Medical Necessity Criteria

**I. Somatropin products (Genotropin, Humatrope, Norditropin Flexpro, Nutropin AQ, Omnitrope, Saizen, or Zomacton) are considered medically necessary when ONE of the following is met:**

1. **Growth Hormone Deficiency (GHD) in a Child or Adolescent.** Individual meets **ONE** of the following criteria:
   - A. **ALL** of the following:
     - i. Documentation of **BOTH** of the following:
       - a. Diagnostic evaluation including **BOTH** of the following:
         - I. Other pituitary hormone deficiencies (for example, thyroid, cortisol or sex steroids) have been ruled out and/or corrected prior to time of testing
         - II. **TWO** growth hormone stimulation tests performed with any of the following agents: levodopa, insulin-induced hypoglycemia, arginine, clonidine, or glucagon **AND** both tests show a growth hormone response of less than 10 ng/mL
       - b. **ONE** of the following:
         - I. Height is more than two [2] standards of deviation (SD) below average for the population mean height for age and sex, and **ONE** of the following:
           - 1) One-year height velocity more than one standard of deviation (SD) below the mean for chronological age
           - 2) 2 years of age or older, and there is a decrease in height of more than 0.5 standards of deviation (SD) over one year
         - II. One-year height velocity is more than two standards of deviation (SD) below the mean for age and sex
         - III. Height velocity is more than 1.5 standards of deviation (SD) below the mean sustained over two years
     - ii. Medication prescribed by, or in consultation with, an endocrinologist
     - iii. Non-Covered Product Criteria is met, refer to below table(s)

   - B. Documentation of Cranial or Whole Body irradiation and **BOTH** of the following:
     - i. Medication prescribed by, or in consultation with, an endocrinologist
     - ii. Non-Covered Product Criteria is met, refer to below table(s)

   - C. **ALL** of the following:
     - i. **ONE** of the following:
       - a. Defined central nervous system pathology (for example, empty sella syndrome, interruption of pituitary stalk, hypoplasia of the pituitary gland, craniofacial developmental defects, pituitary or hypothalamic tumors)
       - b. Undergone tumor resection
     - ii. **ONE** of the following:
       - a. **ONE** growth hormone stimulation test with any of the following agents: levodopa, insulin-induced hypoglycemia, arginine, clonidine, or glucagon AND the test shows a growth hormone response of less than 10 ng/mL
       - b. Deficiency in at least **ONE** other pituitary hormone (for example, adrenocorticotropic hormone, thyroid-stimulating hormone, gonadotropin [luteinizing hormone and/or follicle stimulating hormone deficiency are counted as one deficiency], or prolactin)
     - iii. Medication prescribed by, or in consultation with, an endocrinologist
     - iv. Non-Covered Product Criteria is met, refer to below table(s)

   - D. Congenital hypopituitarism and **BOTH** of the following:
     - i. Medication prescribed by, or in consultation with, an endocrinologist
     - ii. Non-Covered Product Criteria is met, refer to below table(s)

E. Multiple pituitary hormone deficiencies and **ALL** of the following:
    i. **BOTH** of the following:
        a. **THREE** or more of the following pituitary hormone deficiencies: somatropin (growth hormone), adrenocorticotropic hormone, thyroid-stimulating hormone, gonadotropin (luteinizing hormone and/or follicle stimulating hormone deficiency are counted as one deficiency), and prolactin
        b. **ONE** growth hormone stimulation test with any of the following agents: levodopa, insulin-induced hypoglycemia, arginine, clonidine, or glucagon **AND** the test shows a growth hormone response of less than 10 ng/mL

        Note: If the individual has had one growth hormone stimulation test and the peak growth hormone response was less than 10 ng/mL, this would satisfy criteria for an approval.

    ii. Medication prescribed by, or in consultation with, an endocrinologist
    iii. Non-Covered Product Criteria is met, refer to below table(s)

F. Hypophysectomy (surgical removal of pituitary gland) and **BOTH** of the following:
    i. Medication prescribed by, or in consultation with, an endocrinologist
    ii. Non-Covered Product Criteria is met, refer to below table(s)

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2. **Non-Growth Hormone Deficient Short Stature (Idiopathic Short Stature) in a Child or Adolescent.** Individual meets **ALL** of the following criteria:
    A. 5 years of age or older
    B. Baseline height is less than or equal to 1.2 percentile or a standard deviation score (SDS) less than or equal -2.25 for age and gender
    C. Growth (height) velocity is **ONE** of the following:
        i. Growth rate less than 4 cm/year
        ii. Growth (height) velocity is less than the 10th percentile for age and gender based on at least 6 months of growth data
    D. Without growth hormone therapy, the individual's predicted adult height is less than 160 cm (63 inches) in males or less than 150 cm (59 inches) in females
    E. The epiphyses are open
    F. Individual does not have constitutional delay of growth and puberty
    G. Non-Covered Product Criteria is met, refer to below table(s)

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3. **Growth Hormone Deficiency of Defined Etiology in an Adult or Transition Adolescent.** Individual meets **ALL** of the following criteria:
    A. According to the prescriber, somatropin is not being prescribed for anti-aging therapy or to enhance athletic ability or for body building
    B. Documented diagnosis of growth hormone deficiency based on **ONE** of the following:
        i. Childhood onset
        ii. Adult onset that results from **ONE** of the following:
            a. growth hormone deficiency alone or multiple hormone deficiencies (hypopituitarism) resulting from pituitary disease
            b. hypothalamic disease
            c. pituitary surgery
            d. cranial radiation therapy
            e. tumor treatment
            f. traumatic brain injury
            g. subarachnoid hemorrhage

C. **ONE** of the following criteria:
    i. Individual has known perinatal insults OR congenital or genetic defects
    ii. **ALL** of the following:
        a. **THREE** or more of the following pituitary hormone deficiencies: adrenocorticotropic hormone, thyroid-stimulation hormone, gonadotropin deficiency (luteinizing hormone and/or follicle stimulating hormone deficiency are counted as one deficiency), and prolactin
        b. The age and gender adjusted serum insulin-like growth factor-1 is below the lower limit of the normal reference range for the reporting laboratory
        c. Other causes of low serum insulin-like growth factor-1 have been excluded (e.g., malnutrition, prolonged fasting, poorly controlled diabetes mellitus, hypothyroidism, hepatic insufficiency, oral estrogen therapy)
        d. For an adult: Negative response to **ONE** of the following standard growth hormone stimulation tests:
            1. For insulin, levodopa, clonidine, arginine, or glucagon: growth hormone response of less than 5 ng/mL when measured by polyclonal antibody (RIA) or less than 2.5 ng/mL when measured by monoclonal antibody (IRMA) to one provocative stimuli of growth hormone release
            2. For macimorelin: **BOTH** of the following:
                A. Maximum serum growth hormone level observed after stimulation of less than 2.8 ng/ml for the 4 blood draws
                B. Body mass index (BMI) less than or equal to 40 $kg/m^2$

D. Medication is being prescribed by, or in consultation with, an endocrinologist
E. Non-Covered Product Criteria is met, refer to below table(s)

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4. **Chronic Kidney Disease (CKD) in a Child or Adolescent.** Individual meets **ALL** of the following criteria:
    A. Individual has or had chronic kidney disease (CKD) as defined by **ONE** of the following:
        i. Glomerular filtration rate less than 60 milliliters/minute
        ii. Renal function at stage 2 or more advanced Chronic Kidney Disease
    B. Persistent growth failure as defined as **ONE** of the following:
        i. Baseline height is less than the 5th percentile for age and gender
        ii. Individual's 6 to 12 month height velocity is more than two SD below the mean for age and sex
        iii. Individual's height velocity is more than 1.5 SD below the mean sustained over two years
    C. Medication is being prescribed by, or in consultation with, an endocrinologist or a nephrologist
    D. Non-Covered Product Criteria is met, refer to below table(s)

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5. **Noonan Syndrome in a Child or Adolescent.** Individual meets **ALL** of the following criteria:
    A. Diagnosis of Noonan Syndrome is confirmed by **ONE** of the following:
        i. Genetic testing
        ii. If genetic testing does not definitively confirm the diagnosis, the prescriber has made a clinical diagnosis of Noonan syndrome (examples of clinical diagnosis include abnormal facial features [high forehead, epicanthic folds, etc.], pulmonary valve stenosis and/or hypertrophic cardiomyopathy, first-degree relative with Noonan syndrome, mild developmental delay)
    B. Persistent growth failure as defined as **ONE** of the following:
        i. Baseline height is less than the 5th percentile for age and gender
        ii. Individual's 1 year height velocity is more than two SD below the mean for age and sex
        iii. Individual's height velocity is more than 1.5 SD below the mean sustained over two years
    D. Medication is being prescribed by, or in consultation with, an endocrinologist
    E. Non-Covered Product Criteria is met, refer to below table(s)

6. **Prader-Willi Syndrome.** Individual meets **ALL** of the following criteria:
    A. Diagnosis of Prader-Willi Syndrome is confirmed by genetic testing
    C. Medication is being prescribed by, or in consultation with, an endocrinologist
    D. Non-Covered Product Criteria is met, refer to below table(s)

7. **Short Stature Homeobox-Containing Gene Deficiency in a Child or Adolescent.** Individual meets **ALL** of the following criteria:
    A. Diagnosis of Short Stature Homeobox-Containing Gene Deficiency is confirmed by genetic testing
    B. The epiphyses are open
    C. Persistent growth failure as defined as **ONE** of the following:
        i. Baseline height is less than the 5th percentile for age and gender
        ii. Individual's 1 year height velocity is more than two SD below the mean for age and sex
        iii. Individual's height velocity is more than 1.5 SD below the mean sustained over two years
    E. Medication is being prescribed by, or in consultation with, an endocrinologist
    F. Non-Covered Product Criteria is met, refer to below table(s)

8. **Children Born Small for Gestational Age (SGA) or with Intrauterine Growth Restriction Including a Child with Silver-Russell Syndrome.** Individual meets **ALL** of the following criteria:
    A. 2 years of age or older
    B. **BOTH** of the following:
        i. Born small for gestational age, which is defined as birth weight and/or birth length that is greater than 2 standard deviations (SD) below the mean (less than -2 SD) for gestational age and gender
        ii. Insufficient catch-up growth before age 2 to 4 years
    C. Baseline height is less than the 5th percentile for age and gender
    D. Medication is being prescribed by, or in consultation with, an endocrinologist
    E. Non-Covered Product Criteria is met, refer to below table(s)

9. **Turner Syndrome.** Individual meets **ALL** of the following criteria:
    A. Diagnosis of Turner Syndrome is confirmed by genetic testing
    B. Persistent growth failure as defined as **ONE** of the following:
        i. Baseline height is less than the 5th percentile for age and gender
        ii. Individual's 1 year height velocity is more than two SD below the mean for age and sex
        iii. Individual's height velocity is more than 1.5 SD below the mean sustained over two years
    C. Non-Covered Product Criteria is met, refer to below table(s)

**Employer Group Non-Covered Products and Criteria:**

| Non-Covered Product | Criteria |
|---|---|
| **Humatrope** (somatropin injection) | Documented intolerance to **BOTH** of the following:<br>1. **Genotropin** [requires prior authorization]<br>2. **Omnitrope** [requires prior authorization] |
| **Norditropin Flexpro** (somatropin injection) | Documented intolerance to **BOTH** of the following:<br>1. **Genotropin** [requires prior authorization]<br>2. **Omnitrope** [requires prior authorization] |
| **Nutropin AQ** (somatropin injection) | Documented intolerance to **BOTH** of the following:<br>1. **Genotropin** [requires prior authorization]<br>2. **Omnitrope** [requires prior authorization] |

| Non-Covered Product | Criteria |
|---|---|
| | |
| **Saizen** (somatropin injection) | Documented intolerance to **BOTH** of the following:<br>1. **Genotropin** [requires prior authorization]<br>2. **Omnitrope** [requires prior authorization |
| **Zomacton** (somatropin injection) | Documented intolerance to **BOTH** of the following:<br>1. **Genotropin** [requires prior authorization]<br>2. **Omnitrope** [requires prior authorization |

**Individual and Family Plan Non-Covered Products and Criteria:**

| Non-Covered Product | Criteria |
|---|---|
| **Norditropin Flexpro** (somatropin injection) | Documented intolerance to **BOTH** of the following:<br>1. **Genotropin** [requires prior authorization]<br>2. **Humatrope** [requires prior authorization] |
| **Nutropin AQ** (somatropin injection) | Documented intolerance to **BOTH** of the following:<br>1. **Genotropin** [requires prior authorization]<br>2. **Humatrope** [requires prior authorization] |
| **Omnitrope** (somatropin injection) | Documented intolerance to **BOTH** of the following:<br>1. **Genotropin** [requires prior authorization]<br>2. **Humatrope** [requires prior authorization] |
| **Saizen** (somatropin injection) | Documented intolerance to **BOTH** of the following:<br>1. **Genotropin** [requires prior authorization]<br>2. **Humatrope** [requires prior authorization] |
| **Zomacton** (somatropin injection) | Documented intolerance to **BOTH** of the following:<br>1. **Genotropin** [requires prior authorization]<br>2. **Humatrope** [requires prior authorization] |

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**II. Zorbtive (somatropin injection) is considered medically necessary when the following is met:**

1. **Short Bowel Syndrome.** Individual meets **ALL** of the following criteria:
   A. 18 years of age or older
   B. Receiving specialized nutritional support (for example, a high carbohydrate, low-fat diet that is adjusted for individual patient requirements and preferences)
   C. Current dependence upon intravenous (IV) parenteral nutrition

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**III. Serostim (somatropin injection) is considered medically necessary when the following is met:**

1. **Human Immunodeficiency Virus Infection with Wasting or Cachexia in an Adult.** Individual meets **ALL** of the following criteria:
   A. 18 years of age or older
   B. **ONE** of the following:
      i. Documented unintentional weight loss of at least 10% from baseline
      ii. Weight less than 90% of the lower limit of ideal body weight
      iii. Body mass index (BMI) 20 $kg/m^2$ or lower
   C. Wasting or cachexia that is due to malabsorption, poor diet, opportunistic infection, or depression, and other causes have been addressed prior to starting somatropin

D. Current antiretroviral therapy or highly active antiretroviral treatment for at least 30 days prior to beginning Serostim therapy and will continue antiretroviral therapy throughout the course of Serostim treatment
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
F. Documented failure , contraindication or intolerance to appetite stimulants and/or other anabolic agents

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

## Reauthorization Criteria

I. Continuation of Genotropin, Humatrope, Norditropin Flexpro, Nutropin AQ, Omnitrope, Saizen, or Zomacton is considered medically necessary for **ALL** covered diagnoses when the above medical necessity criteria are met AND **ONE** of the following:
    1. Less than 12 years of age: Height has increased by at least 2 cm/year in the most recent year
    2. 12 years of age to 17 years of age AND **BOTH** of the following:
        a. Height has increased by at least 2 cm/year in the most recent year
        b. Epiphyses are open
    3. 18 years of age and older
        a. Documentation of beneficial response

II. Continuation of Zorbtive is considered medically necessary for Short Bowel Syndrome in an Adult when the above medical necessity criteria are met **AND** beneficial response is demonstrated by the following:
    1. Decrease in the requirement for specialized nutritional support.

III. Serostim is considered medically necessary for Human Immunodeficiency Virus Infection with Wasting or Cachexia in an Adult when the above medical necessity criteria are met AND there is documentation of beneficial response.

## Authorization Duration

Initial approval duration:
1. Growth Hormone Deficiency (GHD) in a Child or Adolescent (including pituitary dwarfism): up to 12 months
2. Non-Growth Hormone Deficient Short Stature (Idiopathic Short Stature) in a Child or Adolescent: up to 12 months
3. Growth Hormone Deficiency of Defined Etiology in an Adult or Transition Adolescent: up to 12 months
4. Chronic Kidney Disease (CKD) in a Child or Adolescent: up to 12 months
5. Noonan Syndrome in a Child or Adolescent: up to 12 months
6. Prader-Willi Syndrome: up to 12 months
7. Short Stature Homeobox-Containing Gene Deficiency in a Child or Adolescent: up to 12 months
8. Children Born Small for Gestational Age (SGA) or with Intrauterine Growth Restriction Including a Child with Silver-Russell Syndrome: up to 12 months
9. Turner Syndrome: up to 12 months
10. Short Bowel Syndrome in an Adult: up to 1 month
11. Human Immunodeficiency Virus Infection with Wasting or Cachexia in an Adult: up to 6 months

Reauthorization approval duration:
1. Growth Hormone Deficiency (GHD) in a Child or Adolescent (including pituitary dwarfism): up to 12 months
2. Non-Growth Hormone Deficient Short Stature (Idiopathic Short Stature) in a Child or Adolescent: up to 12 months
3. Growth Hormone Deficiency of Defined Etiology in an Adult or Transition Adolescent: up to 12 months

4. Chronic Kidney Disease (CKD) in a Child or Adolescent: up to 12 months
5. Noonan Syndrome in a Child or Adolescent: up to 12 months
6. Prader-Willi Syndrome: up to 12 months
7. Short Stature Homeobox-Containing Gene Deficiency in a Child or Adolescent: up to 12 months
8. Children Born Small for Gestational Age (SGA) or with Intrauterine Growth Restriction Including a Child with Silver-Russell Syndrome: up to 12 months
9. Turner Syndrome: up to 12 months
10. Short Bowel Syndrome in an Adult: up to 1 month
11. Human Immunodeficiency Virus Infection with Wasting or Cachexia in an Adult: up to 6 months

## Conditions Not Covered

Any other use is considered experimental, investigational or unproven, including the following (this list may not be all inclusive):

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., Anti-Aging), to Improve Functional Status in an Elderly Patient, 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 somatotropin 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 mid-parental 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 recommend 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.** 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 Patient 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.

## Background

**OVERVIEW**

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

- **Growth hormone deficiency (GHD) or 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 , and associated with growth rates unlikely to permit attainment of adult height in the normal range.[1-4,6,7]
- **Adults with GHD** for replacement of endogenous growth hormone.[1-7]
- **Children with chronic kidney disease**, 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**, treatment, in adults receiving specialized nutritional support.[8]
- **Human immunodefiency virus (HIV)-infected patients with wasting or cachexia**, treatment, to increase lean body mass and body weight, and improve physical endurance.[9]

**Growth Hormone Deficiency (GHD) 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, 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 are < 160 cm (63 inches) for men and < 150 cm (59 inches) in women.[31] The Pediatric Endocrine Society guidelines (2016) 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.[31] 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 (2008), 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 defined as an annualized growth rate that doubles in comparison to the previous year.[14] 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 (GHD) 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, and/or thyroid-stimulating hormone 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.[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 (growth hormone releasing hormone) plus arginine was considered the best alternative to the insulin tolerance test in adults.

Macrilen (macimorelin oral solution) 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.

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 insulin-like growth factor (IGF)-1 level. Persons with idiopathic isolated GHD will very likely test sufficient with growth hormone provocative testing. To continue growth hormone therapy in adulthood, retesting for GHD with growth hormone 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 2.5 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 chronic kidney disease 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 baseline.[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 chronic kidney disease, 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 lean body mass), 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 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 short bowel syndrome 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) or cachexia to increase lean body mass and body weight, and improve physical endurance.[9] Somatropin therapy increases lean body mass, 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]

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