MEDICAL MUTUAL®

Drug Policy

Policy:	**95015**	**Initial Effective Date: 06/22/1995**
Code(s):	**HCPCS J2170, J2940, J2941 and Q0515**	**Annual Review Date: 10/17/2024**
SUBJECT:	**Growth Stimulating Drugs** - **Genotropin (somatropin injection)** - **Humatrope (somatropin injection)** - **Increlex (mecasermin)** - **Norditropin (somatropin injection)** - **Nutropin AQ (somatropin injection)** - **Omnitrope (somatropin injection)** - **Saizen (somatropin injection)** - **Serostim (somatropin injection)** - **Zomacton (somatropin injection)** - **Zorbtive (somatropin injection)** - **Skytrofa (lonapegsomatropin injection)** - **Sogroya* (somapacitan injection)** - **Ngenla (somatrogon-ghla injection)**	**Last Revised Date: 10/17/2024**

*Sogroya is non-formulary under pharmacy benefits

☒Subject to Site of Care

Prior approval is required for some or all procedure codes listed in this Corporate Drug Policy.

Initial and renewal requests for the medication(s) listed in this policy are subject to site of care management. When billed under the medical benefit, administration of the medication will be restricted to a non-hospital facility-based location (i.e., home infusion provider, provider's office, free-standing ambulatory infusion center) unless the member meets the site of care exception criteria. To view the exception criteria and a list of medications subject to site of care management please click here.

Definition: Exogenous growth hormone (recombinant human, rhGH) is a polypeptide hormone with metabolic effects similar to endogenous human growth hormone (GH). Produced in the pituitary gland, endogenous growth hormone activates production of insulin-like growth factor-1 (IGF-1) and other peptides that: modulate lipid, carbohydrate and protein metabolism; and stimulate development of bone, cartilage, skeletal muscle and gonadal tissue, leading to longitudinal growth. Inadequate secretion or impairment of growth hormone activity during childhood and adolescence may result in short stature, growth hormone deficiency with growth failure and other medical conditions.

Exogenous growth hormone products approved by the U.S. Food and Drug Administration include somatropin (Humatrope®, Nutropin®, Serostim®, Saizen®, Norditropin®, Genotropin®, Zorbtive®, Omnitrope®, Zomacton™). These products are intended for treatment of children with growth failure due to inadequate secretion of endogenous growth

hormone and in adults with growth hormone deficiency, either alone or associated with multiple hormone deficiencies, short bowel syndrome and human immunodeficiency virus (HIV)-associated wasting.

Human insulin-like growth factor-1 (rhIGF-1) is a polypeptide produced by recombinant DNA technology with properties similar to endogenous IGF-1 IGF-1 is produced in response to growth hormone stimulation and is necessary for normal bone, cartilage and organ growth. It is the principal mediator of growth hormone for statural growth and insulin secretion. Inability to produce adequate levels of IGF-1 leads to primary insulin growth factor deficiency and consequent growth failure (inability to achieve a height within normal range).

Mecasermin (Increlex®,) has been approved by the U.S. Food and Drug Administration for treatment of both growth failure due to severe primary IGF-1 deficiency and growth hormone gene deletion with neutralizing antibodies to growth hormone in children.

Somapacitan (SOGROYA®) is a human growth hormone analog indicated for replacement of endogenous growth hormone in adults with growth hormone deficiency. Somapacitan is a reversible albumin-binding growth hormone derivative, which extends the half-life and enables once weekly dosing.

Skytrofa, a weekly human growth hormone product, is indicated for the treatment of pediatric patients ≥ 1 year of age who weigh at least 11.5 kg and have **growth failure due to an inadequate secretion of endogenous growth hormone**.

POLICY STATEMENT:
Prior authorization is recommended for prescription benefit coverage of somatropin, mecasermin and somapacitan. All approvals are provided for 1 year in duration unless otherwise noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with somatropin/mecasermin/somapacitan as well as the monitoring required for adverse events and long-term efficacy, initial approval requires somatropin/mecasermin/somapacitan to be prescribed by or in consultation with a physician who specializes in the condition being treated. Criteria for patients who are continuing on somatropin/mecasermin/sompacitan are provided. 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. The Site of Care Medical Necessity Criteria applies to initial therapy and reauthorizations. *

Preferred Product Criteria^

Trade Name	Exception
Genotropin	**1.** Approve.
Omnitrope	**1.** Approve.
Humatrope	**1.** For the Basic Formulary, approve if the patient has tried both of the preferred products (Genotropin and Omnitrope)~.

	2. For the National Preferred Formulary/ACA Advantage Formulary, this product is non-formulary and the patient must use one of the covered formulary products (Genotropin, Omnitrope).
Trade Name	**Exception**
Norditropin	**1.** For the Basic Formulary, approve if the patient has tried both of the preferred products (Genotropin and Omnitrope)~. **2.** For the National Preferred Formulary/ACA Advantage Formulary, this product is non-formulary and the patient must use one of the covered formulary products (Genotropin, Omnitrope)
Nutropin AQ	**1.** For the Basic Formulary, approve if the patient has tried both of the preferred products (Genotropin and Omnitrope)~. **2.** For the National Preferred Formulary/ACA Advantage Formulary, this product is non-formulary and the patient must use one of the covered formulary products (Genotropin, Omnitrope).
Saizen	**1.** For the Basic Formulary, approve if the patient has tried both of the preferred products (Genotropin and Omnitrope)~. **2.** For the National Preferred Formulary/ACA Advantage Formulary, this product is non-formulary and the patient must use one of the covered formulary products (Genotropin, Omnitrope).
Zomacton	**1.** For the Basic Formulary, approve if the patient has tried both of the preferred products (Genotropin and Omnitrope)~. **2.** For the National Preferred Formulary/ACA Advantage Formulary, this product is non-formulary and the patient must use one of the covered formulary products (Genotropin, Omnitrope).

^ Preferred Product Criteria apply to both initial therapy and reauthorization requests using pharmacy benefits.

Recommended Authorization Criteria
Coverage of growth hormones is recommended in those who meet the following criteria:

Food and Drug Administration (FDA)-Approved Indications

1. **Pediatric Growth Hormone Deficiency**
   Coverage is provided for (Genotropin, Humatrope, Norditropin, Nutropin/Nutropin AQ, Saizen, Zomacton, Omnitrope, Skytrofa, Ngenla). Approve for 1 year in patients who meet the following (A, B, C and D):
   A. Patient must meet one of the following criteria (i, ii, or, iii):
      i. Patient's height must be below the third percentile for their age and gender related height; OR

ii. Growth velocity subnormal 2 standard deviations from the age-related mean; OR
iii. Delayed skeletal maturation 2 standard deviations below the age/gender related mean; AND

B. Epiphyses must be confirmed as open in patients 10 years of age and older; AND
C. The patient has been evaluated by an endocrinologist; AND
D. Patient must meet one of the following criteria (i or ii):
i. Growth hormone deficiency confirmed by any 2 provocative stimulation tests (levodopa, insulin-induced hypoglycemia, arginine, clonidine, or glucagon) [Note: the peak growth hormone response should be < 10 ng/mL] [NOTE: one test including co-administration of two agents will count as meeting this requirement] OR by low insulin growth factor-1 (IGF-1) a.k.a. somatomedin C, and low IGF binding protein-3 (IGFBP-3) levels; OR
ii. If none of the coverage points related to height (i.e., height below the third percentile for age and gender related height, growth velocity >2 standard deviations from the bone age related mean, or skeletal maturation >2 standard deviations below the age/gender related mean) are met, coverage is provided if growth hormone deficiency has been confirmed by 2 provocative stimulation tests [NOTE: one test including co-administration of two agents will count as meeting this requirement]; AND low IGF-1 AND IGF-BP3; OR
iii. For Ngenla requests, if none of the above (i or ii) are met, the patient has had a hypophysectomy (surgical removal of the pituitary gland) leading to inadequate secretion of endogenous growth hormone; AND
E. Preferred Product Criteria in above table must be met (for pharmacy benefit requests)~; AND
F. Site of care must be met*

Pediatric Growth Hormone Deficiency (GDH) Continuing Somatropin Therapy (i.e., established on **requested** therapy for ≥ 10 months). Approve for 1 year in patients who meet ONE of the following (A, B, or C, AND D AND E):
A. *Patients < 12 years of age.* The height has increased by ≥ 2 cm/year in the most recent year; OR
B. *Adolescents between ≥ 12 years and ≤ 18 years of age.* The patient meets the following criteria (i and ii):
i. Height has increased by ≥ 2 cm/year in the most recent year; AND
ii. The epiphyses are open; OR
C. *Adolescents or young adults > 18 years of age.* The patient meets the following criteria (i, ii, and iii):
i. Height has increased by ≥ 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; AND
D. Preferred Product Criteria in above table must be met (for pharmacy benefit requests)~; AND
E. Site of care must be met*

Dosing in Pediatric Growth Hormone Deficiency:
Genotropin, Omnitrope: SubQ: Weekly dosage: 0.16 to 0.24 mg/kg divided into equal doses 6 to 7 days per week.
Humatrope: SubQ: Weekly dosage: 0.18 to 0.3 mg/kg divided into equal doses 6 to 7 days per week.

Norditropin: SubQ: Weekly dosage: 0.17 to 0.24 mg/kg/week (0.024 to 0.034 mg/kg/**day**) divided into equal doses 6 to 7 days per week.
Nutropin, Nutropin AQ: SubQ: Weekly dosage: 0.3 mg/kg divided into equal daily doses; pubertal patients: ≤0.7 mg/kg divided into equal daily doses.
Saizen: SubQ: Weekly dosage: 0.18 mg/kg divided into equal daily doses **or** as 0.06 mg/kg/dose administered 3 days per week **or** as 0.03 mg/kg/dose administered 6 days per week.
Tev-Tropin: SubQ: ≤0.1 mg/kg/dose 3 days per week.
Zomacton: SubQ: Weekly dosage: 0.18 to 0.3 mg/kg/week (0.026 to 0.043 mg/kg/day) divided into equal doses and administered either 3, 6, or 7 days per week.
Ngenla: SUBQ: 0.66 mg/kg/dose once **weekly**; individualize dose based on growth velocity, body weight, and insulin-like growth factor-1 (IGF-1); treat with the lowest effective dose ([Ref]). Discontinue treatment if there is evidence of epiphysial growth plate closure.
Note: Therapy should be discontinued when patient has reached satisfactory height, when epiphyses have fused, or when the patient ceases to respond. Some guidelines recommend discontinuing therapy when growth velocity is <2 to 2.5 cm/year

2. **Growth failure in Chronic Renal Disease, Noonan Syndrome, Turner Syndrome, Small for Gestational Age, Intrauterine Growth Restriction including Silver-Russell Syndrome, and Prader-Willi Syndrome**
   Coverage is provided for (Genotropin, Humatrope, Norditropin, Nutropin/Nutropin AQ, Saizen, Zomacton, Omnitrope). Approve for 1 year in patients who meet ONE of the following (A, B, C, D or E AND F AND G):
   - **A.** Pediatric growth failure due to chronic renal failure (in situations where the patient has not undergone a renal transplant), as defined by an abnormal creatinine clearance (provocative tests not required); OR
   - **B.** Growth failure in children born small for gestational age (SGA) or interuterine growth restriction (including Silver-Russell Syndrome) who fail to manifest catch up growth by age 2 defined as birth weight, birth length, or both that are more than 2 standard deviations below mean normal values following adjustment for age and gender and the patient's baseline height is less than the 5th percentile for age and gender (provocative tests not required); OR
   - **C.** Pediatric growth failure due to Turner's syndrome (provocative tests not required); OR
   - **D.** Treatment of short stature associated with of Prader-Willi syndrome (provocative tests not required), OR
   - **E.** Treatment of short stature associated with Noonan Syndrome if the patient's baseline height is less than the 5th percentile using a growth chart for children without Noonan Syndrome (provocative tests not required); AND
   - **F.** The patient has been evaluated by an endocrinologist (all conditions) or a nephrologist (only chronic renal disease) ; AND
   - **G.** Site of care must be met*

Continuation therapy is provided for (Genotropin, Humatrope, Norditropin, Nutropin/Nutropin AQ, Saizen, Zomacton, Omnitrope) in patients who meet one of the following criteria and site of care must be met*

- Growth failure in children SGA, growth failure due to Turner's syndrome, Noonan Syndrome or chronic renal failure; benefit approved for 12 months and is renewable in the presence of open epiphyses and a growth response of 4.5 cm/yr (prepubertal growth rate) or 2.5 cm/yr (post-pubertal growth rate).
- Prader-Willi Syndrome; benefit approved for 12 months and is renewable in the presence of an increase in lean body mass (or decrease in fat mass).

Dosing in Growth failure in Chronic Renal Disease, Noonan Syndrome, Turner Syndrome, Small gestational age, and Prader-Willi Syndrome:

Growth failure secondary to chronic kidney disease (CKD): *Nutropin, Nutropin AQ:* SubQ: Weekly dosage: ≤0.35 mg/kg divided into daily injections; continue until the time of renal transplantation.
Dosage recommendations in patients treated for CKD who require dialysis:
Hemodialysis: Administer dose at night prior to bedtime or at least 3 to 4 hours after hemodialysis to prevent hematoma formation from heparin.
CCPD: Administer dose in the morning following dialysis.
CAPD: Administer dose in the evening at the time of overnight exchange.
Noonan syndrome: *Norditropin*: SubQ: Weekly dosage: ≤0.46 mg/kg/week (≤0.066 mg/kg/**day**) divided into equal doses 6 to 7 days per week.
Turner syndrome:
Genotropin, Omnitrope: SubQ: Weekly dosage: 0.33 mg/kg divided into equal doses 6 to 7 days per week.
Humatrope: SubQ: Weekly dosage: ≤0.375 mg/kg divided into equal doses 6 to 7 days per week.
Norditropin: SubQ: Weekly dosage: ≤0.47 mg/kg/week (≤0.067 mg/kg/**day**) divided into equal doses 6 to 7 days per week.
Nutropin, Nutropin AQ: SubQ: Weekly dosage: ≤0.375 mg/kg divided into equal doses 3 to 7 days per week.
Prader-Willi syndrome:
Genotropin, Omnitrope: SubQ: Weekly dosage: 0.24 mg/kg divided into equal doses 6 to 7 days per week
Norditropin: SubQ: Weekly dosage: 0.24 mg/kg/week (0.034 mg/kg/**day**) divided into equal doses 6 to 7 days per week
Small for gestational age:
Genotropin, Omnitrope: SubQ: Weekly dosage: ≤0.48 mg/kg divided into equal doses 6 to 7 days per week.
Humatrope: SubQ: Weekly dosage: ≤0.47 mg/kg divided into equal doses 6 to 7 days per week.
Norditropin: SubQ: Weekly dosage: ≤0.47 mg/kg/week (≤0.067 mg/kg/**day**) divided into equal doses 6 to 7 days per week.
Alternate dosing (small for gestational age): In older/pubertal children or children with very short stature (ie, height SDS <–3), consider initiating therapy at higher doses (eg, 0.067 mg/kg/day [0.48 mg/kg/week]) and then consider reducing the dose (eg, gradually towards 0.033 mg/kg/day [0.24 mg/kg/week]) if substantial catch-up growth observed during the first few years of therapy. In younger children (~<4 years) with less severe short stature (ie, baseline height SDS values between -2 and -3), consider initiating therapy with lower doses (eg, 0.033 mg/kg/day [0.24 mg/kg/week]) and then titrating the dose upwards as needed.

3. Growth Hormone Deficiency in Adults or Transition Adolescents

Initial Therapy coverage is provided for (Genotropin, Humatrope, Norditropin, Nutropin/Nutropin AQ, Saizen, Zomacton, Omnitrope, Sogroya): Approve for 1 year in patients who meet the following (A, B, C, D and E):

A. The patient has been evaluated by an endocrinologist; AND
B. The endocrinologist must certify that growth hormone is not being prescribed for anti-aging therapy or to enhance athletic ability or for body building; AND
C. The patient must have a diagnosis of Growth Hormone Deficiency that is one of the following (i or ii)~:
  i. Childhood onset; OR
  ii. Adult onset that results from one of the following: growth hormone deficiency (GHD) alone or multiple hormone deficiencies (hypopituitarism) resulting from pituitary disease, hypothalamic disease, pituitary

surgery, cranial radiation therapy, tumor treatment, traumatic brain injury, or subarachnoid hemorrhage; AND

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 ~; 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: 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~; 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~; AND

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

OR

iii. 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 ~

Adults: The patient meets ONE of the following criteria (a, b, c, d, or e)~:

a) Insulin tolerance test with peak response ≤ 5.0 mcg/L; OR

b) Glucagon stimulation test with peak response ≤ 3.0 mcg/L AND the patient's body mass index (BMI) is ≤ 25 kg/m^2 OR

c) Glucagon stimulation test with peak response ≤ 1.0 mcg/L AND the patient's body mass index (BMI) is > 25 kg/m^2 OR

d) If both the insulin tolerance test AND glucagon stimulation test are contraindicated, the arginine alone test can be used with a peak response ≤ 0.4 mcg/L OR

e) Macrilen™ (macimorelin for oral solution) test with peak responses < 2.8 ng/mL (2.8 mcg/L)AND the patient's body mass index (BMI) is ≤ 40 kg/m^2.
Note: The following formula can be used to calculate BMI: BMI equals body weight in kg divided by height meters squared (m^2) [i.e., BMI = kg/m^2].

OR

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

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

b) The patient meets ONE of the following responses to growth hormone stimulation testing (1, 2, 3, or 4)~:

(1) Insulin tolerance test with peak response ≤ 5.0 mcg/L; OR

(2) Glucagon stimulation test with peak response ≤ 3.0 mcg/L AND the patient's body mass index (BMI) is < 25 kg/m^2; OR

(3) Glucagon stimulation test with peak response ≤ 3.0 mcg/L AND the patient's body mass index (BMI) is ≥ 25 kg/m^2 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 with a peak response ≤ 0.4 mcg/L; AND

E. Site of care must be met*

Growth Hormone Deficiency (GHD) in Adults or Transition Adolescents Continuing Somatropin or Somapacitan Therapy (i.e., established on somatropin/somapacitan for ≥ 10 months). Approve for 1 year in patients who meet the following criteria (A, B, C and D) every 12 months:

A) Patient must have a diagnosis of GHD that is one of the following (i or ii):

i. Childhood onset; OR

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

B. The patient has been evaluated by an endocrinologist or in consultation with an endocrinologist; AND

C. This physician must certify that somatropin is not being used for anti-aging therapy or to enhance athletic performance/body building; AND

D. Site of care must be met*

Dosing in Adult Growth Hormone Deficiency:

Growth hormone deficiency: Adjust dose based on individual requirements: To minimize adverse events in older or overweight patients, reduced dosages may be necessary. During therapy, dosage should be decreased if required by the occurrence of side effects or excessive IGF-I levels.

Weight-based dosing: **Note:** Obese patients are more likely to experience adverse effects when treated with a weight-based regimen; use is not recommended.

Norditropin: SubQ: Initial dose: 0.004 mg/kg/day; dose may be increased up to a maximum of 0.016 mg/kg/day.

Nutropin, Nutropin AQ: SubQ: ≤0.006 mg/kg/day; dose may be increased up to a maximum of 0.025 mg/kg/day in patients ≤35 years, or up to a maximum of 0.0125 mg/kg/day in patients >35 years

Humatrope: SubQ: ≤0.006 mg/kg/day; dose may be increased up to a maximum of 0.0125 mg/kg/day

Genotropin, Omnitrope: SubQ: Weekly dosage: ≤0.04 mg/kg divided into equal doses 6 to 7 days per week; dose may be increased at 4- to 8-week intervals to a maximum of 0.08 mg/kg/week

Saizen: SubQ: ≤0.005 mg/kg/day; dose may be increased to ≤0.01 mg/kg/day after 4 weeks.

Zomacton: SubQ: 0.006 mg/kg/day; dose may be increased up to a maximum of 0.0125 mg/kg/day

Sogroya: Initiate with 1.5mg and increase dose by 0.5mg every 2-4 weeks until desired response is achieved.

Non-weight-based dosing:

Manufacturer labeling: SubQ: Initial: ~0.2 mg/day (range: 0.15 to 0.3 mg/day); may increase every 1 to 2 months by 0.1 to 0.2 mg/day based on response and/or serum IGF-I levels.

Alternative recommendations (off-label; AACE [Cook 2009]): SubQ: Initial dose:

<30 years: 0.4 to 0.5 mg/day (higher doses may be needed if transitioning from pediatric treatment)

30 to 60 years: 0.2 to 0.3 mg/day

Lower initial doses (0.1 to 0.2 mg/day) may be needed in patients with diabetes or glucose intolerance. Adjust dose by 0.1 to 0.2 mg/day in 1- to 2-month intervals.

Dosage adjustment with estrogen supplementation: Larger doses of somatropin may be needed for women taking oral estrogen replacement products; dosing not affected by topical products

4. **Short Stature Homeobox-Containing Gene (SHOX) Deficiency in Children or Adolescents** (Genotropin, Humatrope, Norditropin, Nutropin/Nutropin AQ, Saizen, Zomacton, Omnitrope): Approve for 1 year in **p**atients who meet the following (A, B, C, D and E):
   - **A.** Patient has 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 3rd percentile for age and gender; AND
   - **E.** Site of care must be met*

Continuation of therapy is provided for Short Stature Homeobox-Containing Gene (SHOX) Deficiency in Children or Adolescents in the presence of the following:

A. Benefit approved for 1 year if the patient's height has increased by greater than or equal to 2.5 cm/yr in the most recent year; **AND**
B. The epiphyses are open; AND
C. Site of care must be met*

Dosing in SHOX deficiency: *Humatrope:* SubQ: Weekly dosage: 0.35 mg/kg divided into equal doses 6 to 7 days per week

5. **HIV infection with Wasting or Cachexia**

Coverage is provided for **Serostim**® for the treatment of HIV Infection with Wasting or Cachexia in the presence of the following: Approve for 3 months in **p**atients who meet the following (A, B, C, D and E):

- **A)** Patient is 18 years of age; **AND**
- **B)** Wasting syndrome is not attributable to other causes such as; depression, MAC, chronic infectious diarrhea, or malignancy (Kaposi's sarcoma limited to the skin or mucous membranes is covered); **AND**
- **C)** Wasting syndrome confirmed by ONE of the following:
  - i. Unintentional weight loss of 10% of body weight; OR
  - ii. Patient's weight is 90% or less than the lower limit of ideal body weight; OR
  - iii. BMI less than or equal to 20 kg/m^2; **AND**
- **D)** Optimal antiretroviral therapy (ART) has been attempted and will be continued during course of Serostim therapy; AND
- **E)** Growth hormone therapy is not being requested solely for treatment of alterations in body fat distribution such as lipodystrophy or buffalo hump; AND
- **F)** Site of care must be met*

Continuation therapy is provided for **Serostim**® for the treatment of HIV Infection with Wasting or Cachexia in the presence of the following:

- Benefit approved for 3 months and is renewable in the presence of weight stabilization or increase if the patient has been off of therapy for at least 1 month AND site of care must be met*

Dosing in HIV-associated wasting, cachexia:
Serostim: SubQ: Initial: 0.1 mg/kg once daily at bedtime (maximum: 6 mg/day); patients at risk for side effects (eg, glucose intolerance) may be started at 0.1 mg/kg every other day. Adjust dose (ie, reduce the total daily dose or the number of doses per week) if needed to manage side effects.
Daily dose based on body weight:
<35 kg: 0.1 mg/kg
35 to 45 kg: 4 mg
45 to 55 kg: 5 mg
>55 kg: 6 mg

6. Growth Failure in Children with Severe Primary IGF-1 deficiency or With Growth Hormone Deletion
Coverage is provided for **Increlex®** in the treatment of growth failure in children with severe primary IGF-1 deficiency or with growth hormone gene deletion who have developed neutralizing antibodies to growth hormone in the presence of the following. Approve for 1 year in patients who meet the following (A, B, C, D, E, F and G):

A) Patient's height standard deviation score must be ≤ -3.0 at baseline; **AND**
B) The basal IGF-1 score must be below the lower limits of normal for the reporting lab; **AND**
C) The patient must have normal or elevated growth hormone (except for patients with growth hormone gene deletion); **AND**
D) Epiphyses must be confirmed as open in patients 10 years of age; **AND**
E) Diagnosis made by an endocrinologist; **AND**
F) Not used concurrently with growth hormones or corticosteroids; AND
G) The patient is 2 years of age or older; AND
H) The patient has developed neutralizing antibodies to growth hormone; AND
I) Site of care must be met*

Continuation therapy is provided for **Increlex®** in the treatment of growth failure in children with severe primary IGF-1 deficiency or with growth hormone gene deletion who have developed neutralizing antibodies to growth hormone in the presence of the following:

- Benefit approved for 12 months and is renewable in the presence of open epiphyses and a growth response of 4.5 cm/yr (prepubertal growth) or 2.5 cm/yr (post-pubertal growth) and site of care must be met*

Dosing in Primary insulin-like growth factor-1 deficiency (IGFD): SubQ: Children ≥2 years and Adolescents: Initial: 0.04-0.08 mg/kg twice daily; if tolerated for 7 days, may increase by 0.04 mg/kg/dose (maximum dose: 0.12 mg/kg twice daily). Must be administered within 20 minutes of a meal or snack; omit dose if patient is unable to eat. Reduce dose if hypoglycemia occurs despite adequate food intake; dose should not be increased to make up for ≥1 omitted dose.

7. Short Bowel Syndrome

Coverage is provided for **Zorbtive®** and Genotropin, Humatrope, Norditropin, Nutropin/Nutropin AQ, Saizen, Zomacton, Omnitrope: for the treatment of Short Bowel Syndrome in Adults. Approve for 4 weeks if following criteria are met (A, B and C):

A) Patient is receiving nutritional support; AND
B) Patient is over 18 years of age; AND
C) site of care must be met*

Continuation therapy is provided for **Zorbtive®** and Genotropin, Humatrope, Norditropin, Nutropin/Nutropin AQ, Saizen, Zomacton, Omnitrope for the treatment of Short Bowel Syndrome in the presence of the following:

- Benefit is renewable for 1 month in situations where the patient is deriving clinical benefit (e.g., the patient is experiencing a decrease in intravenous nutrition requirements) AND site of care must be met*

Dosing in Short-bowel syndrome: *Zorbtive:* SubQ: 0.1 mg/kg once daily for 4 weeks (maximum: 8 mg/day)

Conditions Not Recommended for Approval
Coverage of Genotropin, Humatrope, Norditropin, Nutropin, Nutropin AQ, Omnitrope, Saizen, Serostim, Tev-Tropin, Zorbtive and Increlex is recommended in circumstances that are listed in the Recommended Authorization Criteria (FDA-Approved Indications). 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.)

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1. **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 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. 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. Patients with CDGP and familial short stature may have heights that are more than 2 SDS below the mean and are growth hormone sufficient. 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." The mean increase in adult height in children with idiopathic short stature that is attributed to somatropin therapy (average duration 4 to 7 years) is 3.5 to 7.5 cm. In controlled trials, in children with idiopathic short stature who were not growth hormone deficient, somatropin therapy was effective in increasing final adult height greater than pretreatment predicted adult height. No specific studies have been conducted in pediatric patients with familial short stature.

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

3. **Acute Critical Illness Due to Complications Following Surgery, Multiple Accidental Trauma, or with Acute Respiratory Failure.** 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.

4. **Aging (i.e., Antiaging); To Improve Functional Status in Elderly Patients; and Somatopause.** 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.

5. **Athletic Ability Enhancement.** 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. 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.

6. **Bony Dysplasias (Achondroplasia, Hypochondroplasia).** 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. Somatropin therapy may transiently increase growth rate, but there are no studies showing a significant increase in adult height. According to AAP guidance for pediatric achondroplasia, growth hormone should only be considered within a research setting. There are very few studies of somatropin therapy in hypochondroplasia. Results are better when somatropin is given at puberty because these patients lack the normal pubertal growth spurt. Effects on final height are not known. Other forms of skeletal dysplasias are very rare and no conclusions about the use of somatropin can be drawn. There are no long-term studies.

7. **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.[94] 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. 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. High quality studies that are adequately powered are needed.

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

9. **Central Precocious Puberty.** Children with precocious puberty are often treated with gonadotropin releasing hormone (GnRH) agonists (Lupron® [leuprolide acetate injection]) to suppress pituitary gonadal activity, to slow the advancement of bone age (prevent premature fusion of the epiphyseal growth plates), and to improve adult height. In some patients GnRH agonist therapy may result in marked deceleration of bone growth and may result in adult height that is less than the midparental height. Somatropin has been used in girls when growth velocity decreases or if it appears that the targeted adult height will not be attained. 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.

10. **Chronic Fatigue Syndrome.** There is no evidence of GHD in chronic fatigue syndrome.

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

12. **Crohn's Disease.** Limited information is available in adults receiving somatropin therapy for Crohn's disease. In children with Crohn's disease, somatropin therapy has not been effective in improving final adult height. 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.[111] 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.** 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. 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.** 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. 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. 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. 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. 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, 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. Children conditioned for transplantation with chemotherapy-only regimens do not require somatropin therapy.

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). 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.** 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.** 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 was effective in increasing growth velocity and did not increase the incidence of graft rejection. Data from the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) database were analyzed for growth, allograft function, and adverse effects over 5 years in 513 patients who received somatropin therapy (not given continuously throughout the 5 years of the study) and compared with 2,263 control patients who did not receive somatropin. Children < 10 years of age who received somatropin had a greater increase in height than older children ($P < 0.001$; difference in mean cumulative increment in height during the 5 years was 3.6 cm). Final adult height was superior in the patients treated with somatropin compared 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. 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. 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[134] and prospective studies therapy with somatropin has increased growth velocity and height in carefully selected children with myelomeningocele and GHD. Well-controlled trials are needed.

26. **Obesity.** 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.

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. Somatropin therapy is not recommended until further studies are done.[139]

28. **Osteoporosis.** 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. 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. There are no randomized 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. 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. **Congenital Adrenal Hyperplasia (CAH).** The Endocrine Society clinical practice guidelines on CAH due to steroid 21-hydroxylase deficiency recommends against the use of alternative treatment approaches such as growth hormone and/or treatment to delay puberty or epiphyseal fusion for most children with CAH. Children with predicted adult height SD $\leq$ -2.25 may be considered for growth-promoting treatments in appropriately controlled trials.

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

Prior approval is required for HCPCS Codes J2170, J2940, J2941 and Q0515

~ Documentation Requirements:

The Company reserves the right to request additional documentation as part of its coverage determination process. The Company may deny reimbursement when it has determined that the services performed were not medically necessary, investigational or experimental, not within the scope of benefits afforded to the member and/or a pattern of billing or other practice has been found to be either inappropriate or excessive. Additional documentation supporting medical necessity for the services provided must be made available upon request to the Company. Documentation requested may include patient records, test results and/or credentials of the provider ordering or performing a service. The Company also reserves the right to modify, revise, change, apply and interpret this policy at its sole discretion, and the exercise of this discretion shall be final and binding.

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Edits and Denials:

Prior approval: Children (≤17 years): Prior approval is required for growth stimulating drugs **(HCPCS Codes J2170, J2940, J2941 and Q0515)**. Requests for prior approval will be authorized by a nurse reviewer if submitted documentation meets criteria outlined within Corporate Medical Policy. Prior approval is required on a yearly basis.

Requests for prior approval will be forwarded to a qualified reviewer if submitted documentation does not meet criteria outlined within Corporate Medical Policy.

Adults (≥18 years): Prior approval is required for growth stimulating drugs **(HCPCS Codes J2170, J2940, J2941 and Q0515)**. Requests for prior approval will be forwarded to a specialty matched physician reviewer†. Prior approval is required on a yearly basis.

†**Note:** Prior approval requests received for a member age ≥18 years ***must*** be reviewed by a specialty matched physician consultant.

TOPPS: Claims received with **HCPCS Codes J2170, J2940, J2941 and Q0515** will edit with **Remark Code M3M or M4M** and will be adjudicated in accordance with the Corporate Medical Policy.

Note: If a course of treatment has already been initiated prior to April 1, 2009, members currently taking growth stimulating drugs for the treatment of idiopathic short stature (non-growth hormone deficient short stature) or

constitutional delayed growth will continue to receive benefits based upon reimbursement policies in place at the time the course of treatment was approved.

Appeals: Children (≤17 years): Appeals submitted to Medical Review will be approved by a nurse reviewer if documentation meets criteria outlined within Corporate Medical Policy.

Appeals submitted to Medical Review will be forwarded to the Chief Medical Officer or specialty matched physician consultant reviewer if documentation does not meet criteria outlined within Corporate Medical Policy.

Adults (≥18 years): Appeals submitted to Medical Review will be forwarded to the Chief Medical Officer or specialty matched physician reviewer.

Liability: A participating provider will be required to write off charges denied as not medically necessary.

HCPCS Code(s):	
J2170	Injection, mecasermin, 1 mg
J2940	Injection, somatrem, 1 mg
J2941	Injection, somatropin, 1 mg
Q0515	Injection, semorelin acetate, 1 microgram