INSTRUCTIONS:

“Medical Policy assists in administering UCare benefits when making coverage determinations for members under our health benefit plans. When deciding coverage, all reviewers must first identify enrollee eligibility, federal and state legislation or regulatory guidance regarding benefit mandates, and the member specific Evidence of Coverage (EOC) document must be referenced prior to using the medical policies. In the event of a conflict, the enrollee’s specific benefit document and federal and state legislation and regulatory guidance supersede this Medical Policy. In the absence of benefit mandates or regulatory guidance that govern the service, procedure or treatment, or when the member’s EOC document is silent or not specific, medical policies help to clarify which healthcare services may or may not be covered. This Medical Policy is provided for informational purposes and does not constitute medical advice. In addition to medical policies, UCare also uses tools developed by third parties, such as the InterQual Guidelines®, to assist us in administering health benefits. The InterQual Guidelines are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice. Other Policies and Coverage Determination Guidelines may also apply. UCare reserves the right, in its sole discretion, to modify its Policies and Guidelines as necessary and to provide benefits otherwise excluded by medical policies when necessitated by operational considerations.”
POLICY DESCRIPTION:

Recombinant human growth hormone (rhGH, somatotropin) is used to treat a variety of childhood diseases affecting growth, including children with growth hormone insufficiency/deficiency, children born small for gestational age, idiopathic short stature, chronic renal insufficiency/failure, Turner syndrome, Prader-Willi syndrome, Noonan syndrome, and short stature homebox-containing gene deficiency (SHOX-D). The primary goals of growth hormone therapy for children with rhGH are the normalization of height and other growth parameters, such as weight and body composition, during childhood, and attainment of normal adult height.

Somatotropin is used as replacement therapy in adults with endogenous growth hormone deficiency, such as those with idiopathic or acquired growth hormone (GH) deficiency. The goal of rhGH therapy is to improve and normalize abnormalities associated with GH deficiency, both in the short and long term. Abnormalities associated with GH deficiency include a variety of metabolic, structural, psychological, and quality-of-life problems.

COVERAGE RATIONALE / CLINICAL CONSIDERATIONS:

I. **Somatotropin** (Recombinant human growth hormone (rhGH)) may be considered **MEDICALLY NECESSARY** for the treatment of patients with any of the following conditions:

1. **Growth hormone (GH) deficiency in Infants**
   
   Demonstration of subnormal growth and provocative growth hormone testing is not required for infants less than 4 months old. In neonates with hypoglycemia, a GH measurement less than 20 ng/mL suggests growth hormone deficiency. Confirmation of diagnosis may be obtained through IGF-1 testing.

2. **Growth hormone (GH) deficiency in children**
   
   For children diagnosed with growth hormone deficiency, the following criteria must be met in order to document medical necessity for growth hormone treatment:
   
   a. **Provocative GH testing:** The patient must have a documented GH deficiency as defined by a diminished serum GH response to stimulation testing of less than 10 ng/mL, or equivalent, based on polyclonal antiserum-based radioimmunoassays. The results of at least two of the following stimulation tests support the diagnosis of growth hormone deficiency: levodopa, insulin-induced hypoglycemia, arginine, clonidine, glucagon, and growth hormone releasing hormone. Due to the risk for hypoglycemia, patients who have hypoglycemia associated with pituitary disease and patients younger than one year of age should not have a provocative hormone test, AND

   b. **Child has one of the following:**
      
      • Subnormal growth velocity: Child's growth velocity is more than 2 standard deviations below the mean for age and gender, OR
      
      • Short stature: For age and gender, the patient's height is more than 1.5 standard deviations score (SDS) from the midparental height or more than 2 standard deviations below the population mean, OR
• Delayed bone-age as documented on x-ray: Bone age should be assessed through radiological examination of the left hand and wrist. Comparison of bone age to chronological age should be documented as abnormal by greater than or equal to two standard deviations below the mean for chronological age, which is generally greater than or equal to 2 years delayed growth, AND

c. Member must not have attained epiphyseal closure as determined by X-ray.

For children, growth rate and skeletal maturation should be documented throughout the treatment course. Therapy should be discontinued regardless of chronologic age if the growth rate is 2 cm or less per year, monitored and reported every 6 months, or if the patient attains expected adult height.

3. Growth hormone (GH) deficiency in adults

For adults diagnosed with growth hormone deficiency, the following criteria must be met in order to document medical necessity for growth hormone treatment:

a. The patient must have a documented diagnosis of somatotropin (growth hormone) deficiency alone or multiple hormone deficiencies (hypopituitarism) resulting from hypothalamic-pituitary disease from known causes (e.g. damage from surgery, cranial irradiation, head trauma, or subarachnoid hemorrhage), AND

b. Before somatropin therapy begins, whether the GH deficiency onset is in childhood or adulthood, the diagnosis must be confirmed with appropriate testing in order to document the diagnosis and likelihood of efficacy of growth hormone treatment.

• The patient must have an abnormal response to one standard growth hormone stimulation test defined as:
  o ITT peak GH ≤ 5 μg/L
  o GHRH+ARG peak GH
    ▪ ≤11 μg/L if body mass index (BMI) < 25 kg/m2
    ▪ ≤8 μg/L if BMI ≥ 25 and < 30 kg/m2
    ▪ ≤4 μg/L if BMI ≥ 30 kg/m2
  o Glucagon peak GH ≤ 3 μg/L
  o Arginine (ARG) peak GH ≤ 0.4 μg/L

  Note: Stimulation tests used to diagnose growth hormone deficiency in adults include insulin tolerance, arginine, growth hormone releasing hormone (GHRH), and glucagon. The insulin tolerance test is the best indicator of growth hormone deficiency. This test is contraindicated in patients with a history of seizures or coronary artery disease. GHRH+ARG test also has been accepted as more accurate than tests using arginine alone.

• For patients with deficiencies of 3 or more other anterior pituitary hormones (ACTH, TSH, prolactin, FSH/LH), and a serum IGF-1 level below the age- and sex-appropriate reference range when off GH therapy, growth hormone deficiency (GHD) is highly probable, and stimulation testing is not necessary in the absence of conditions that lower IGF-1. The probability of GHD in adults ranges from 91% to 100% in the presence of 3 to 4 other
4. **Children with chronic renal insufficiency**
   a. Children with growth failure and chronic renal insufficiency up to the time of kidney transplantation. Patients must be evaluated by a pediatric endocrinologist or a nephrologist. Evaluation of growth hormone secretion is not necessary.
   b. Children who develop chronic renal insufficiency after a kidney transplant and meet above criteria 1a for subnormal growth velocity or skeletal maturation for children.

5. **Children born small for gestational age (SGA)**
   SGA children who meet all of the following criteria:
   a. Child was born small for gestational age (defined as birth weight or length 2 or more standard deviations below the mean for gestational age), AND
   b. Child fails to manifest catch up growth by age of 2 years, defined as height 2 or more SDS below the mean for age and sex.

6. **Children and adults with hypothalamic or pituitary damage**
   Patient has severe GH deficiency as a result of hypothalamic or pituitary disease (e.g., trauma, panhypopituitarism, pituitary adenoma, cranial irradiation, pituitary surgery). Children and adults must meet above criteria 2 and 3 respectively.

7. **Patients with acquired immunodeficiency syndrome (AIDS) wasting syndrome or cachexia**
   Adult patients who meet ALL the following criteria:
   a. The patient must be HIV-positive and have HIV-associated wasting syndrome or cachexia;
   b. The patient must meet ONE of the following criteria:
      - 10% unintentional weight loss over 12 months, OR
      - 7.5% unintentional weight loss over 6 months, OR
      - 5% body cell mass (BCM) loss within 6 months, OR
      - In men: BCM < 35% of total body weight and BMI < 27 kg/m², OR
      - In women: BCM < 23% of total body weight and BMI < 27 kg/m², OR
      - Body mass index (BMI) < 20 kg/m²
   c. The patient must have been taking antiretroviral therapy for greater than or equal to 30 days prior to beginning somatropin therapy and will continue antiretroviral therapy throughout the course of somatropin treatment; and
   d. The patient must be under the guidance of a physician experienced in the diagnosis and management of HIV/AIDS.

8. **Patients with Turner’s syndrome**
   Females with short stature associated with Turner syndrome documented by chromosome analysis. Evaluation of growth hormone secretion is not necessary.

9. **Children with Prader-Willi syndrome**
   Prader-Willi syndrome confirmed by appropriate genetic testing, associated with short stature, and
10. **Burn Injuries**
   GH therapy should be limited to those patients with third-degree burns.

11. **Patients with Noonan syndrome**
   Prepubertal children with short stature (height 2 SDS or more below the mean for chronological age and sex) associated with Noonan syndrome and documented by chromosome analysis.

12. **Children with short stature due to SHOX (short stature homeobox-containing gene) deficiency**
   Children with short-stature homeobox-containing gene (SHOX) deficiency, documented by chromosome analysis, and whose epiphyses are not closed.

13. **Patients with short bowel syndrome receiving specialized nutritional support**
   Patients with symptomatic short bowel syndrome receiving intravenous parenteral nutrition for nutritional support in conjunction with optimal management of short bowel syndrome.

The following FDA-approved indications are considered NOT MEDICALLY NECESSARY:
1. Pediatric patients born small for gestational age (SGA) who fail to show catch-up growth by age 2 years.
2. Children with height standard deviation score of -2.25 or below without documented GH deficiency.

Growth hormone therapy is considered to be EXPERIMENTAL AND/OR INVESTIGATIONAL for the following indications because its effectiveness for these conditions has not been established:
1. Adult obesity/morbid obesity
2. Adult short stature
3. Child short stature without growth hormone deficiency
4. Amyotrophic lateral sclerosis
5. Anabolic therapy to enhance athletic body mass or strength for professional, recreational or social reasons
6. Anabolic therapy to counteract catabolic illness (not HIV)
7. Anti-aging to improve functional status in elderly patients
8. Bone marrow transplantation without total body irradiation (cranial radiation)
9. Bony dysplasia’s (achondroplasia, hypochondroplasia, osteogenesis imperfect, osteoporosis)
10. Chronic fatigue syndrome
11. Corticosteroid-induced short stature, including a variety of chronic glucocorticoid-dependent conditions, such as asthma, inflammatory bowel disease, juvenile rheumatoid arthritis, as well as after renal, heart, liver or bone-marrow transplantation
12. Cystic fibrosis
13. Depression
14. Dilated cardiomyopathy/congestive heart failure/ischemic heart disease
15. Down Syndrome and other syndromes associated with short stature
16. Fibromyalgia
17. Growth hormone neurosecretory dysfunction
18. Hypophosphatemic rickets
19. Infertility/in-vitro fertilization
20. Kidney transplant patients with a functional renal allograft
21. Liver transplantation
22. Metabolic conditions, as an adjunct to nutritional therapy in critically ill catabolic patients receiving specialized nutritional support to promote protein anabolism
23. Muscular dystrophy
24. Myelomeningocele
25. Thalassemia major
26. Spina bifida
27. Wound healing in burn patients if not 3rd degree burns

II. Mecasermin (Increlex®) may be considered MEDICALLY NECESSARY for the long-term treatment of growth failure in children with severe primary IGF-1 deficiency or with growth hormone gene deletion that have developed neutralizing antibodies to growth hormone.

For severe primary IGF-1 deficiency, therapy is proven if the patient meets all the criteria:
   a. Height standard deviation score (SDS) -3.0 and
   b. Basal IGF-1 standard deviation score -3.0 and
   c. Normal or elevated growth hormone (GH)

Mecasermin is considered EXPERIMENTAL AND/OR INVESTIGATIONAL for disorders other than those listed as proven, including patients with secondary forms of IGF-1 deficiency, such as GH deficiency, malnutrition, hypothyroidism, or chronic treatment with pharmacologic doses of anti-inflammatory steroids. Mecasermin is also ineffective for use for growth promotion in patients with closed epiphyses.

**CLINICAL CONSIDERATIONS**

**Clinical Assessment Criteria:**
- Pediatric: Must provide documentation of growth failure, appropriate diagnostic, and all relevant medical records and test results.
- Adult: Must provide documentation of growth hormone deficiency, onset, and all relevant medical records and test results.

**Treatment Schedule:**
- **Children:** Initial authorization for GH therapy in patients meeting criteria will be approved for a 6-month trial. After the trial, continuation of therapy may be reconsidered if the patient has demonstrated a restoration of normal growth and development. Approval is for a maximum of 1 year and must be reviewed annually except for children with pituitary damage (e.g., tumor, radiation, stroke or trauma).

Therapy can be approved for an additional 6-12 months if:
a. Patient height is less than 5'6" for males or 5’1” for females, AND
b. Epiphyses have not closed. Epiphyseal closure is defined as a bone age of 16 years in a male or 14 years in a female on wrist films, AND
c. Child demonstrates improved/normalized growth velocity. [Annual growth velocity in response to therapy is calculated to be > 4.5 cm/year in a pre-pubertal child or > 2.5 cm/year in a post-pubertal child].

- **Adult:** Growth hormone therapy is reviewed annually. IGF-1 levels are reviewed, and thyroid function tests, lipids, regular body weight, and waist/hip ratio measurements are also recommended.

The following numbered **CLINICAL CONSIDERATIONS** correspond to the indications listed in the **COVERAGE RATIONALE** section above:

1. Hypoglycemia may be a presenting feature of hypopituitarism in neonates with GH deficiency. Demonstration of subnormal growth and provocative growth hormone testing is not required for infants less than 4 months old. In neonates with hypoglycemia, a GH measurement less than 20 ng/mL suggests growth hormone deficiency. Confirmation of diagnosis may be obtained through IGF-1 testing as growth hormone deficiency is unlikely in the presence of serum IGF-1 concentrations at or above the mean for age.

2. For children, no criteria have been established for the laboratory diagnosis of GH deficiency, and criteria may vary regionally. The recommended dosage for children with GH deficiency is 0.3 mg/kg per week, divided (and given) into 6 or 7 injections per week. In children, GH therapy is typically discontinued when the growth velocity is less than 2 cm per year, when epiphyseal fusion has occurred, or when the height reaches the 5th percentile of adult height.

3. For adults, proven GH deficiency is defined as:
   a. An abnormal response to TWO provocative stimulation tests, such as L-dopa, clonidine, glucagon's, arginine, GH-releasing hormone (GHRH), or insulin. The insulin tolerance test is considered the best predictor of GH deficiency; however, this test is contraindicated in patients with seizures or coronary artery disease. A provocation test using arginine and GHRH is also acceptable and is considered more stringent than tests using arginine alone or levodopa alone. Although an abnormal GH response has been traditionally defined as less than 10 ng/mL, different tests have different potencies, and the cutoff is likely to be lower when using monoclonal-based GH assays and recombinant human GH reference preparations. Measurement of insulin-like growth factor I (IGF-I) is considered medically necessary to determine adequacy of GH therapy in adults and children. However, the diagnosis of GH deficiency should not rely solely on IGF-I measurements, but must be confirmed by provocative tests solely for GH secretion. Twenty-four hour continuous measurements of GH, serum levels of IGF-I, or serum of levels IGFBP (insulin-like growth factor-binding protein) are considered inadequate to document GH deficiency.
   b. An abnormal response to ONE provocative stimulation test in patients with defined central nervous system pathology, history of irradiation, multiple pituitary hormone deficiency, or a genetic defect.
   c. Low IGF-I concentration in patients with complete hypopituitarism.

Only about 25% of those children with documented GH deficiency will be found to have GH deficiency as adults. Therefore, once adult height has been achieved, subjects should be retested for GH
deficiency to determine if continuing replacement therapy is necessary. These transition patients who require further treatment are usually started at doses of 0.4 to 0.8 mg/day, and tittered to maintenance doses of 1.2 to 2.0 mg/day. Adults with GH deficiency not related to idiopathic deficiency of childhood (e.g., pituitary tumor, pituitary surgical damage, irradiation, trauma) are usually started at 0.1 to 0.3 mg/day; the dose is tittered to clinically desired end points (improved body composition, quality of life, reduction in cardiovascular risk factors), usually resulting in maintenance doses of 0.2 to 0.5 mg/day for men and 0.4 to 1.0 mg/day for women. The FDA cautions that the safety and effectiveness of GH therapy in adults aged 65 and older has not been evaluated in clinical studies. Therefore, it is noted that elderly patients may be more sensitive to the action of GH therapy and may be more prone to develop adverse reactions.

4. Chronic renal insufficiency in children is defined as a serum creatinine of greater than 1.5 mg/dL (or 1.4 for women and 1.7 for men) or a creatinine clearance <75 mL/min per 1.73 m. In patients with chronic renal failure undergoing transplantation, GH therapy is discontinued at the time of transplant or when the growth velocity is less than 2 cm per year, when epiphyseal fusion has occurred, or when the height reaches the 5th percentile of adult height.

5. Genotropin received approval as an orphan drug by the FDA for “long-term treatment of growth failure in children who were born small for gestational age (SGA) who fail to manifest catch-up growth by age 2”. Long-term effects of GH supplementation in these children are unknown. Growth curves plotting growth from birth through age 3 should be submitted for evaluation.

6. Children and adults who have undergone brain radiation and have demonstrated growth hormone deficiency often begin treatment with somatropin when the rate of growth slows significantly.

7. AIDS (acquired immunodeficiency syndrome) wasting is defined as a greater than 10% of baseline weight loss that cannot be explained by a concurrent illness other than HIV (human immunodeficiency virus) infection. Patients treated with GH must simultaneously be treated with antiviral agents. Therapy is continued until this definition is no longer met.

8. Turner’s syndrome is defined as a 45, XO genotype.

9. Prader-Willi syndrome is a genetic disorder characterized by a microdeletion in the long arm of chromosome 15. Clinically, the syndrome presents as a complex multisystem disorder characterized by excessive appetite, obesity, short stature, characteristic appearance, developmental disability, and significant behavioral dysfunction. GH deficiency has been demonstrated in most tested patients with Prader-Willi syndrome. Sleep studies are recommended prior to initiation of growth hormone therapy for obese pediatric patients with Prader-Willi syndrome.

10. GH therapy for burn patients should be limited to those patients with third-degree burns. Children with severe burns have been successfully treated with 0.05 to 0.2 mg/kg recombinant GH (rhGH) per day during acute hospitalization, and for up to 1 year after burn.

11. Noonan syndrome is a relatively common genetic disorder, with an incidence of 1:1000 and 1:4000. The FDA-approved labeling for Norditropin (brand of GH) indicates that not all patients with Noonan syndrome have short stature; some will achieve a normal adult height without treatment. Therefore, the FDA-approved labeling recommends that, prior to initiating GH for a patient with Noonan syndrome, establish that the patient does have short stature.

SHOX is located on the distal ends of the X and Y chromosomes encoding a homeodomain transcription factor responsible for a significant proportion of long-bone growth. Children with mutations or deletions of SHOX, including those with TS who are haplo-insufficient for SHOX have variable degrees of growth impairment, with or without a spectrum of skeletal anomalies consistent with dyschondrosteosis.

13. Growth hormone for patients with short bowel syndrome should be limited to patients who depend on parenteral nutrition for nutritional support in conjunction with optimal management of short bowel syndrome. Specialized nutritional support may consist of a high-carbohydrate, low-fat diet adjusted for individual patient requirements. Optimal management may include dietary adjustments, enteral feedings, parenteral nutrition, fluid, and micronutrient supplements. Zorbtive is administered daily at 0.1mg/kg subcutaneously up to 8 mg/day. Administration of Zorbtive for longer than 4 weeks or repeat courses of GH has not been adequately studied per the FDA indications.

**Short Stature:**

Pediatric patients with short stature. "Short stature" has been defined by the American Association of Clinical Endocrinologists and the Growth Hormone Research Society as height more than 2 standard deviations (SD) below the mean for age and sex. The FDA-approved indication is for children with a height standard deviation score (SDS) of -2.25 below the mean. Using this proposed definition, approximately 1.2% of all children would be defined as having idiopathic short stature and considered potentially treatable under these indications. Note that this indication is considered not medically necessary. Idiopathic short stature is not considered an illness, disease or injury.

**Treatment with somatropin should be discontinued if any of the following apply:**

- Growth velocity increases less than 50% from baseline in the first year of treatment
- Final height is approached and growth velocity is less than 2 cm total growth in 1 year
- There are insurmountable problems with adherence
- Final height is attained

**Contraindications:**

GH therapy is contraindicated in patients with:

- Active malignant disease
- Benign intracranial hypertension (BIH)
- Proliferative or pre-proliferative diabetic retinopathy
- Potential for child-bearing is not a contraindication, but accepted guidelines caution that GH therapy should be discontinued when pregnancy is confirmed
- Critically ill patients who have acute catabolism
- Hypersensitivity to GH or its excipients

**BACKGROUND:**

Human growth hormone (GH), also known as somatotropin, is a product synthesized in the somatotropic cells of the anterior lobe of the pituitary gland. The anabolic effects of GH have been shown to increase
linear growth in children by stimulating the production of insulin-like factor-1 (IGF-1, somatomedin-C), which are synthesized in the liver and other tissues in response to growth hormone stimulation, facilitating cartilage production and its subsequent development into bone. Growth hormone also influences the metabolism of carbohydrates, fats, minerals, and related proteins.

Growth hormone deficiency can occur due to a variety of conditions, such as:

- Pituitary and extrapituitary tumors
- Pituitary dysfunction due to prior surgery or radiation treatment
- Sarcoidosis, and/or other infiltrating disorders
- Idiopathic

Growth hormone deficiency in children is manifested primarily by short stature. In adults, as well as in some children, other abnormalities associated with growth hormone deficiency are often evident. These include changes in body composition, higher levels of low-density lipoprotein (LDL) cholesterol, lower bone density, and a decreased self-reported quality of life compared to healthy peers. Some evidence also suggests that there may be increases in cardiovascular disease and overall mortality, but it is less clear whether growth hormone deficiency is causative for these outcomes.

**GH Treatment:**

Recombinant human growth hormone (rhGH) has been used to treat a variety of childhood diseases affecting growth, including children with growth hormone insufficiency/deficiency, hypothalamic pituitary disease, children born small for gestational age, idiopathic short stature, chronic renal insufficiency/failure, Turner syndrome, Prader-Willi syndrome, Noonan’s syndrome, and short stature homeobox-containing gene deficiency (SHOX-D). The primary goals of the therapy in children are the normalization of height and other growth parameters, such as weight and body composition during childhood, and attainment of normal adult height. The FDA has also approved Serostim for the treatment of human immunodeficiency virus (HIV) associated wasting in adults and Zorbtive for patients with Short Bowel Syndrome (SBS) receiving specialized nutritional support.

Historically GH was obtained from cadaver pituitaries and was available in only limited quantities. Today, biosynthetic rhGH is widely available; consequently the use in children and adults has increased. The wide availability and the demonstrated benefits of GH for a variety of evidence-based indications have resulted in the use of GH in other conditions for which safety and efficacy have not been established.

A major point of controversy is what defines “inadequate secretion of normal endogenous growth hormone,” and what constitutes “growth failure.” Prior to the availability of biosynthetic GH, GH was rationed to children with classic GH deficiency (GHD), as defined by a subnormal response (<10 ng/mL, approximately, depending on GH assay) to GH provocation tests. However, the ready supply of GH has created interest in expanding its use to short stature children without classic GHD, often referred to as partial GH deficiency, neurosecretory GH dysfunction, constitutional delay in growth and development (CDGD), or idiopathic short stature. “Classic” GH deficiency is suggested when the abnormal growth velocity (typically below the 10th percentile) or height is more than 2 standard deviations (SD score) below the current population mean, in conjunction with a chronological age that is greater than the height age and bone age. In practical fact, interest in broadening the use of GH to non-GHD children has resulted in GH evaluation in many children who are simply below the 3rd percentile in height, with or without an abnormal growth velocity. However, these broadened patient selection criteria have remained controversial due to uncertainties in almost every step in the diagnosis and treatment process—selection...
of patients to be tested, limitations in the laboratory testing for GH, establishment of diagnostic cutoffs for normal versus abnormal GH levels, availability of the laboratory tests to predict response to GH therapy, changes in growth velocity due to GH therapy, whether resulting final height is significantly improved, and whether this improvement is clinically or emotionally significant for the patient. In addition, there are many ethical considerations regarding GH therapy, most prominently appropriate informed consent when the therapy is primarily requested by parents due to their particular psychosocial concerns regarding height.

REGULATORY STATUS:

1. **U.S. FOOD AND DRUG ADMINISTRATION (FDA):**

   See Table 1. FDA-Approved Recombinant Human Growth Hormone Products (ATTACHMENTS section).

   - Genotropin, Humatrope, Norditropin, Nutropin, Nutropin AQ, Omnitrope, Saizen, and Tev-Tropin are approved by the U.S. Food and Drug Administration (FDA) for the treatment of children who have growth failure due to an inadequate secretion of normal endogenous growth hormone.  

   - Genotropin and Omnitrope are FDA-approved for the treatment of children with growth failure due to confirmed Prader-Willi syndrome.

   - Genotropin, Humatrope, Norditropin, and Omnitrope are FDA-approved for the treatment of growth failure in children born small for gestational age who fail to manifest catch-up growth by age 2 years.

   - Genotropin, Humatrope, Nutropin, Nutropin AQ, Omnitrope, and Saizen are FDA-approved for the replacement of endogenous growth hormone in adults with GHD who either 1) have adult onset GHD, either alone or associated with multiple hormone deficiencies, as a result of pituitary disease, hypothalamic disease, surgery, radiation therapy, or trauma, or 2) were GH deficient during childhood as a result of congenital, genetic, acquired, or idiopathic causes. Confirmation of GHD in adults may require provocative testing, and adults who were treated with somatropin for GHD in childhood should be reevaluated before continuation of therapy at the reduced dose recommended for GH deficient adults.


   - Norditropin is FDA-approved for the treatment of short stature associated with Noonan syndrome.

   - Nutropin and Nutropin AQ are FDA-approved for the treatment of growth failure associated with chronic renal insufficiency in pediatric patients up to the time of renal transplantation and should be used in conjunction with optimal management of chronic renal insufficiency.

   - Genotropin, Humatrope, Norditropin, Nutropin, and Nutropin AQ are FDA-approved for the long-term treatment of short stature associated with Turner syndrome in pediatric patients.

   - Zorbtive is FDA-approved for the treatment of short bowel syndrome in patients receiving specialized nutritional support and should be used in conjunction with optimal management of this condition.
• Serostim is FDA-approved to be used with concomitant antiretroviral therapy for the treatment of HIV patients with wasting or cachexia to increase lean body mass and body weight, and improve physical endurance.9

• Increlex is indicated for the long-term treatment of growth failure in children with severe primary IGF-1 deficiency (Primary IGFD) or with growth hormone gene deletion who have developed neutralizing antibodies to growth hormone. Severe primary IGFD includes patients with mutations in the growth hormone receptor (GHR), post-GHR signaling pathway, and IGF-1 gene defects.79

2. CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS):
Medicare does not have a National Coverage Determination (NCD) specific for growth hormones. In general, Medicare covers outpatient (Part B) drugs that are furnished "incident to" a physician's service provided that the drugs are not usually self-administered by the patients who take them.

Somatropin 1 mg injection is assigned a status N (item/service packaged into APC rate) for Medicare purposes. Separate payment is not made.


Local Coverage Determinations (LCDs) for growth hormones do not exist at this time. (Accessed July 30, 2014).

3. MINNESOTA DEPARTMENT OF HUMAN SERVICES (DHS):

Minnesota Health Care Programs (MHCP) Enrolled Providers – Pharmacies. Fee-for-Service PA Criteria Sheet – Growth Hormone (January 2016)

Preferred Growth Hormones: Norditropin®, Nutropin®, and Nutropin AQ®

Non preferred Growth Hormones: Humatrope®, Genotropin®, Saizen®, Serostim® [only for AIDS wasting or cachexia], Omnitrope®, Tevtropin®, Zorbtive® [only for patients with Short Bowel Syndrome (SBS)], Zomacton®.

As of May 1, 2012, patients on Genotropin will be required to meet renewal criteria and switch to a preferred product once their current PA for Genotropin expires.

Coverage for Pediatrics
• Prescribing growth hormone (GH) is limited to pediatric endocrinologists or pediatric nephrologists
• If there is no pediatric endocrinologist or pediatric nephrologist in the geographic location, the prescriber must have at least one annual consultation about the patient with the pediatric specialty
• Patients new to GH therapy, must meet criteria and be started on a preferred growth hormone
• Patients continuing GH therapy and having met criteria must be switched to a preferred growth hormone

Minnesota Medicaid may authorize coverage of growth hormone (GH) for children when chronic illness or other causes of growth failure have been ruled out (e.g., hypothyroidism, IBD) and when the following criteria are met:

Indications
A. Indications covered if the child is being treated by pediatric endocrinologist or pediatric
nephrologists:
- Turner's Syndrome
- Prader-Willi Syndrome
- Noonan Syndrome
- Leri-Weill Dyschondrosteosis
- Renal Disease
- Hypoglycemia in newborns with a diagnosis of hypopituitarism or panhypopituitarism
- Acquired Growth Hormone Deficiency (GHD), which can be due to, but is not limited to the following:
  - Pituitary surgery
  - Pituitary insufficiency
  - Radiation treatments
  - Pituitary tumor
  - Trauma
  - Central nervous system tumors
  - Cranial irradiation
  - Panhypopituitarism

B. Pediatric Growth Hormone Deficiency (GHD) Initiation of Therapy (6 month initial authorization) when the child is being treated by pediatric endocrinologist:
- Member must not have attained epiphyseal closure as determined by X-ray
- Member must have failed to respond to at least TWO standard GH stimulation tests (with insulin, levodopa, arginine, propranolol, clonidine, or glucagon), defined as a peak measured GH level of less than 10ng/ml after stimulation
- Documented gender-specific delayed bone age
- Height at initiation of therapy must be > 2 standard deviations below normal mean for age and sex and patient has demonstrated a growth velocity over the past year to be 1 SD below the mean for chronological age

Treatment Continuation

Approval is for a maximum of 1 year and must be reviewed annually except for children with pituitary damage (e.g., tumor, radiation, stroke or trauma).

Therapy can be approved for an additional 6-12 months if:
- Patient height is less than 5'6" for males or 5'1" for females. AND
- Epiphyses have not closed. Epiphyseal closure is defined as a bone age of 16 years in a male or 14 years in a female on wrist films. AND
- Child demonstrates improved/normalized growth velocity. (Annual growth velocity in response to therapy is calculated to be > 4.5 cm/year in a pre-pubertal child or > 2.5 cm/year in a post-pubertal child)
### CLINICAL EVIDENCE:

**SUMMARY:**

These criteria are based on evidence-based guidelines on growth hormone (GH) supplementation from the National Institute of Clinical Excellence (NICE, 2002). Growth hormone has been approved by the U.S. Food and Drug Administration (FDA) for treatment of GH deficiency (GHD) in both children and adults, short stature associated with chronic renal insufficiency (CRI) before renal transplantation, short stature in patients with Turner syndrome (TS), HIV-associated wasting syndrome in adults, idiopathic short stature, treatment of children with short stature associated with Noonan syndrome, short stature homeobox-containing gene deficiency, and treatment of children born small for gestational age (SGA) who fail to manifest catch-up growth. There are several brands of GH (somatropin) on the market, and there is a lack of reliable evidence that any brand of GH is more effective than others for any indication.

### APPLICABLE CODES:

The Current Procedural Terminology (CPT®) codes and HCPCS codes listed in this policy are for reference purposes only. Listing of a service or device code in this policy does not imply that the service described by this code is a covered or non-covered health service. The inclusion of a code does not imply any right to reimbursement or guarantee claims payment. Other medical policies and coverage determination guidelines may apply.

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<td>J2170</td>
<td>Injection, mecasermin, 1 mg</td>
</tr>
<tr>
<td>J2941</td>
<td>Injection, somatropin, 1 mg</td>
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<table>
<thead>
<tr>
<th>ICD-9 Codes</th>
<th>Description</th>
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<tbody>
<tr>
<td>042</td>
<td>Human immunodeficiency virus [HIV]</td>
</tr>
<tr>
<td>253.0</td>
<td>Acromegaly and gigantism</td>
</tr>
<tr>
<td>253.2</td>
<td>Pan hypopituitarism</td>
</tr>
<tr>
<td>253.3</td>
<td>Pituitary dwarfism</td>
</tr>
<tr>
<td>253.7</td>
<td>Iatrogenic pituitary disorders</td>
</tr>
<tr>
<td>259.4</td>
<td>Dwarfism, not elsewhere classified</td>
</tr>
<tr>
<td>579.3</td>
<td>Other and unspecified postsurgical nonabsorption</td>
</tr>
<tr>
<td>579.8</td>
<td>Other specified intestinal malabsorption</td>
</tr>
<tr>
<td>585.1</td>
<td>Chronic kidney disease, Stage I</td>
</tr>
<tr>
<td>585.2</td>
<td>Chronic kidney disease, Stage II (mild)</td>
</tr>
<tr>
<td>585.3</td>
<td>Chronic kidney disease, Stage III (moderate)</td>
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<tr>
<td>585.4</td>
<td>Chronic kidney disease, Stage IV (severe)</td>
</tr>
<tr>
<td>585.5</td>
<td>Chronic kidney disease, Stage V</td>
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<tr>
<td>585.6</td>
<td>End stage renal disease</td>
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<tr>
<td>585.9</td>
<td>Chronic kidney disease, unspecified</td>
</tr>
<tr>
<td>588.0</td>
<td>Renal osteodystrophy</td>
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<tr>
<td>758.6</td>
<td>Gonadal dysgenesis</td>
</tr>
<tr>
<td>759.81</td>
<td>Prader-Willi syndrome</td>
</tr>
<tr>
<td>759.89</td>
<td>Other specified multiple congenital anomalies, so described</td>
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<tr>
<td>764.90</td>
<td>Unspecified fetal growth retardation, unspecified (weight)</td>
</tr>
<tr>
<td>764.91</td>
<td>Unspecified fetal growth retardation, less than 500 grams</td>
</tr>
<tr>
<td>ICD-10 Code</td>
<td>Description</td>
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<tr>
<td>-------------</td>
<td>-------------</td>
</tr>
<tr>
<td>764.92</td>
<td>Unspecified fetal growth retardation, 500-749 grams</td>
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<tr>
<td>764.93</td>
<td>Unspecified fetal growth retardation, 750-999 grams</td>
</tr>
<tr>
<td>764.94</td>
<td>Unspecified fetal growth retardation, 1,000-1,249 grams</td>
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<tr>
<td>764.95</td>
<td>Unspecified fetal growth retardation, 1,250-1,499 grams</td>
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<tr>
<td>764.96</td>
<td>Unspecified fetal growth retardation, 1,500-1,749 grams</td>
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<tr>
<td>764.97</td>
<td>Unspecified fetal growth retardation, 1,750-1,999 grams</td>
</tr>
<tr>
<td>764.98</td>
<td>Unspecified fetal growth retardation, 2,000-2,499 grams</td>
</tr>
<tr>
<td>764.99</td>
<td>Unspecified fetal growth retardation, 2,500 or more grams</td>
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<tr>
<td>799.4</td>
<td>Cachexia</td>
</tr>
<tr>
<td>909.2</td>
<td>Late effect of radiation</td>
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<tr>
<td>990</td>
<td>Effects of radiation, unspecified</td>
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<table>
<thead>
<tr>
<th>ICD-10 Codes</th>
<th>Description</th>
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<tr>
<td>B20</td>
<td>Human immunodeficiency virus [HIV] disease</td>
</tr>
<tr>
<td>E22.0</td>
<td>Acromegaly and pituitary gigantism</td>
</tr>
<tr>
<td>E23.0</td>
<td>Hypopituitarism</td>
</tr>
<tr>
<td>E23.1</td>
<td>Drug-induced hypopituitarism</td>
</tr>
<tr>
<td>E34.3</td>
<td>Short stature due to endocrine disorder</td>
</tr>
<tr>
<td>E34.4</td>
<td>Constitutional tall stature</td>
</tr>
<tr>
<td>E78.71</td>
<td>Barth syndrome</td>
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<td>E78.72</td>
<td>Smith-Lemli-Opitz syndrome</td>
</tr>
<tr>
<td>E89.3</td>
<td>Post-procedural hypopituitarism</td>
</tr>
<tr>
<td>K90.4</td>
<td>Malabsorption due to intolerance, not elsewhere classified</td>
</tr>
<tr>
<td>K90.89</td>
<td>Other intestinal malabsorption</td>
</tr>
<tr>
<td>K91.2</td>
<td>Postsurgical malabsorption, not elsewhere classified</td>
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<tr>
<td>L59.9</td>
<td>Disorder of the skin and subcutaneous tissue related to radiation, unspecified</td>
</tr>
<tr>
<td>N18.1</td>
<td>Chronic kidney disease, stage 1</td>
</tr>
<tr>
<td>N18.2</td>
<td>Chronic kidney disease, stage 2 (mild)</td>
</tr>
<tr>
<td>N18.3</td>
<td>Chronic kidney disease, stage 3 (moderate)</td>
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<tr>
<td>N18.4</td>
<td>Chronic kidney disease, stage 4 (severe)</td>
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<tr>
<td>N18.5</td>
<td>Chronic kidney disease, stage 5</td>
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<td>N18.6</td>
<td>End stage renal disease</td>
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<td>N18.9</td>
<td>Chronic kidney disease, unspecified</td>
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<tr>
<td>N25.0</td>
<td>Renal osteodystrophy</td>
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<tr>
<td>P05.9</td>
<td>Newborn affected by slow intrauterine growth, unspecified</td>
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<tr>
<td>Q55.4</td>
<td>Other congenital malformations of vas deferens, epididymis, seminal vesicles and prostate</td>
</tr>
<tr>
<td>Q87.1</td>
<td>Congenital malformation syndromes predominantly associated with short stature</td>
</tr>
<tr>
<td>Q87.2</td>
<td>Congenital malformation syndromes predominantly involving limbs</td>
</tr>
<tr>
<td>Q87.3</td>
<td>Congenital malformation syndromes involving early overgrowth</td>
</tr>
<tr>
<td>Q87.5</td>
<td>Other congenital malformation syndromes with other skeletal changes</td>
</tr>
<tr>
<td>Q87.81</td>
<td>Alport syndrome</td>
</tr>
<tr>
<td>Q87.89</td>
<td>Other specified congenital malformation syndromes, not elsewhere classified</td>
</tr>
<tr>
<td>Q89.8</td>
<td>Other specified congenital malformations</td>
</tr>
<tr>
<td>Q96.0</td>
<td>Karyotype 45, X</td>
</tr>
<tr>
<td>Q96.1</td>
<td>Karyotype 46, X iso (Xq)</td>
</tr>
<tr>
<td>Q96.2</td>
<td>Karyotype 46, X with abnormal sex chromosome, except iso (Xq)</td>
</tr>
<tr>
<td>Q96.3</td>
<td>Mosaicism, 45, X/46, XX or XY</td>
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</table>
REFERENCES:

HAYES’s Technology Assessments

REFERENCES

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POLICY HISTORY:

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<th>DATE</th>
<th>ACTION/DESCRIPTION</th>
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<td>08/28/2014</td>
<td>Reviewed and approved by the Quality Improvement Advisory and Credentialing Committee (QIACC).</td>
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<tr>
<td>09/01/2014</td>
<td>Published to ucare.org</td>
</tr>
<tr>
<td>08/09/2016</td>
<td>Policy updated and approved by the Medical Policy Committee.</td>
</tr>
<tr>
<td>09/01/2016</td>
<td>Published to ucare.org</td>
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### Table 1. FDA-Approved Recombinant Human Growth Hormone Products

<table>
<thead>
<tr>
<th>Approved Indications / Product Name</th>
<th>Genotropin</th>
<th>Humatrope</th>
<th>Norditropin</th>
<th>Nutropin</th>
<th>Saizen</th>
<th>Serostim</th>
<th>Tev-Tropin</th>
<th>Zorbtive</th>
<th>Omnitrope</th>
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<tbody>
<tr>
<td>Growth failure, peds pts with inadequate endogenous GH</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Growth failure due to Prader-Willi syndrome</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>Yes</td>
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<tr>
<td>Replacement therapy in adults with GH deficiency</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td>Yes</td>
<td></td>
<td></td>
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<tr>
<td>Growth failure assoc. with chronic renal insufficiency</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV wasting or cachexia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Yes</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Children born small for gestational age, who fail to show catch-up growth by age 2 years</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td>Yes</td>
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</tr>
<tr>
<td>Short stature (height Standard Deviation Score &lt;-2.25) in non-GHdeficient peds pts</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
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<tr>
<td>Short stature due to Turner's syndrome (45, XO)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
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<td></td>
<td>Yes</td>
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<tr>
<td>Short bowel syndrome</td>
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<td>Yes</td>
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<tr>
<td>Short stature in peds pts with SHOX (short stature homeobox containing gene) deficiency</td>
<td>Yes</td>
<td></td>
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<td>Yes</td>
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<tr>
<td>Short stature in peds pts with Noonan syndrome</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
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