Subject: Recombinant Human Growth Hormone (somatropin)_ PEDIATRIC Growth Hormone Deficiency ▪ Growth Failure in Children and Adolescents with Classic GHD [under 18 years] ▪ Neonatal Hypoglycemia Related to GHD ▪ Transition from Childhood to Adult Growth Hormone Therapy: Continuation of Therapy After Completion of Linear Growth	**Original Effective Date:** 7/5/2007
Policy Number: MCP-004-A	**Revision Date(s):** 4/28/2010, 4/27/2011, 3/14/2017
Review Date(s): 4/28/2010, 4/27/2011, 3/14/2017, 7/10/2018	

DISCLAIMER

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (i.e., will be paid for by Molina) for a particular member. The member's benefit plan determines coverage. Each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their providers will need to consult the member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this MCP document and provide the directive for all Medicare members.

SUMMARY OF EVIDENCE/POSITION

This policy addresses the coverage of **recombinant human growth hormone (rhGH, somatotropin)** for the treatment of Growth Failure in Children and Adolescents with Classic GHD [under 18 years], including 'Neonatal Hypoglycemia Related to GHD' and 'Transition from Childhood to Adult Growth Hormone Therapy: Continuation of Therapy After Completion of Linear Growth' when appropriate criteria are met. The intent of this drug policy is to ensure appropriate selection of patients for therapy based on product labeling, clinical guidelines, and clinical studies.

- **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 (TS), Prader-Willi syndrome (PWS), Noonan syndrome, and short stature homeobox-containing gene deficiency (SHOX-D).

  The primary goals of rhGH therapy for children are the normalization of height and other growth parameters, such as weight and body composition, during childhood, and attainment of normal adult height.[J]

- **Somatotropin** is used as replacement therapy in adults with endogenous growth hormone deficiency (GHD), such as those with idiopathic or acquired GHD.
  - Human growth hormone (hGH, somatotropin) is secreted by the anterior pituitary. Most of its anabolic effects are mediated by insulin-like growth factor-I (IGF-I, somatomedin C), which is synthesized in the liver and other tissues in response to growth hormone stimulation. Growth hormone stimulates linear growth in children and influences metabolism of carbohydrates, fats, minerals, and proteins. Somatropin is produced by

recombinant DNA technology and has the same amino acid sequence as naturally occurring hGH (a single polypeptide chain of 191 amino acids).

- 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.

❖ Growth hormone treatment is <u>not</u> authorized for treatment of short stature in the absence of a growth hormone deficiency or for the majority of other conditions in which growth hormone has not been shown to provide clinical benefits or improvements in functional impairment or long-term health outcomes.

❖ Molina Healthcare authorize rhGH therapy if there is a significant physical functional impairment and treatment with rhGH treatment can be reasonably expected to improve the physical functional impairment of the member as a result of an illness, disease or injury.

EQUIVALENCE OF PRODUCTS

❖ Growth hormone products are equally safe and effective, although they differ in how the medication is prepared and injected.

❖ No clinical trials have been conducted to evaluate the comparative efficacy or safety of available synthetic growth hormone products.

- ➢ There is a lack of reliable evidence that any one brand of GH is superior to other brands for medically necessary indications.

- ➢ Omnitrope brand of GH is the PREFERRED brand of GH for Molina Healthcare since other brands (e.g., *Genotropin, Humatrope, Norditropin, Nutropin, Nutropin AQ, Saizen*) of GH are not as cost-effective brand of growth hormone and highly expected to produce equivalent therapeutic results for the treatment of the member's disease. Other brands of GH will be considered NON-PREFERRED and not authorized unless the member has a documented contraindication or intolerance PREFERRED brand of GH (Omnitrope).

- ➢ If the PREFERRED brand (Omnitrope) does not have the labeled indication for member's diagnosis, Molina Healthcare will select the most cost-effective brand of GH that has the required labeling indication.

❖ **PREFERRED AGENT: OMNITROPE** may be authorized when ALL of the following criteria for member's specific diagnosis are met.

- ❒ **Omnitrope vial: Medicaid**
- ❒ **Omnitrope pen: Marketplace**

❖ **NON-PREFERRED products:** ALL of the following criteria for member's specific diagnosis are met <u>AND</u> when a preferred growth hormone product is contraindicated or not tolerated.

CLASSIFICATION: Hormones and Hormone Modifiers; Pituitary Hormones; Growth hormone modifiers

FDA INDICATIONS

FDA-approved indication does not, in itself, dictate coverage. Molina coverage Policy may not recommend coverage for all FDA-approved indications. Please review this policy in its entirety for indications covered by Molina Healthcare.

The covered FDA-approved indications are conditions that are considered medically necessary; however it is not inclusive of all conditions which may be approved by the Medical Reviewer. At the discretion of the Medical Director and on a **case-by-case basis,** Molina Healthcare may consider authorization of the biologic therapy addressed in this Policy for members with exceptional circumstances and for members with severe disease who may fall outside of the defined criteria. Molina Healthcare reserves the right to update this Policy and revise coverage criteria to include or omit any off-label condition(s) as necessary based on medical literature and clinical studies that may become available.

The **PREFERRED** agent of Molina Healthcare brand of GH, **OMNITROPE,** is indicated in bold-faced type.
Available as: Omnitrope: Cartridge 5, 10 mg; Vial 5.8mg

The indications highlighted below are addressed in this policy.

FDA-Approved Indication	Brands
Growth failure in children due to inadequate secretion of endogenous growth hormone ****ADRESSED IN THIS POLICY****	Genotropin, Humatrope, Norditropin, Nutropin, Nutropin AQ, **Omnitrope,** Saizen, Zomacton
Growth failure associated with Noonan syndrome (NS) **REFER TO: MCP-004-B**	Norditropin
Growth failure associated with Prader-Willi syndrome (PWS) **REFER TO: MCP-004-B**	Genotropin, **Omnitrope**
Growth failure associated with Turner syndrome (TS) **REFER TO: MCP-004-B**	Genotropin, Humatrope, Norditropin, Nutropin, Nutropin AQ , **Omnitrope**
Short stature homeobox–containing (SHOX) gene deficiency **REFER TO: MCP-004-B**	Humatrope
Growth failure associated with CRI/CKD **REFER TO: MCP-004-C**	Nutropin, Nutropin AQ
Children born small for gestational age (SGA) who fail to manifest catch-up growth **REFER TO: MCP-004-C**	Genotropin, Humatrope, Norditropin, **Omnitrope**
Idiopathic Short Stature (ISS) ****REFER TO 'EXCLUSIONS' SECTION****	Genotropin, Humatrope, Nutropin, Nutropin AQ
Growth hormone deficiency in adults **REFER TO: MCP-004-D**	Genotropin, Humatrope, Norditropin, Nutropin, Nutropin AQ, **Omnitrope,** Saizen
Short bowel syndrome (SBS) **REFER TO: MCP-004-D**	Zorbtive
Wasting or cachexia associated with HIV *HIV: human immunodeficiency virus* **REFER TO: MCP-004-D**	Serostim

CLASSIFICATION: Hormones and Hormone Modifiers; Pituitary Hormones; Growth Hormone Modifiers

RECOMMENDATIONS/COVERAGE CRITERIA

- Members authorized for GH therapy under previous Molina Healthcare GH policy (MCP) may be authorized for continuation of therapy in accordance with MCP continuation of therapy criteria
- Members receiving GH therapy without previous authorization by Molina Healthcare GH policy may be considered for continuation of therapy in accordance with MCP initiation criteria (per member's clinical data prior to initiation of therapy) and MCP continuation criteria (per member's current clinical data)
- Members previously treated with GH therapy but who have had treatment subsequently discontinued may be considered for re-initiation of therapy in accordance with MCP initial treatment criteria and continuation criteria except growth velocity

PEDIATRIC GROWTH HORMONE DEFICIENCY (GHD)

Growth Failure in Children and Adolescents with Classic GHD [under 18 years]

- Recombinant human growth hormone (rhGH, somatotropin) is <u>not</u> a covered benefit for treatment of short stature in the absence of a growth hormone deficiency or for conditions in which growth hormone has not been shown to provide clinical benefits or improvements in functional impairment or long-term health outcomes.
- For adolescents whose epiphyses have closed, refer to Adult GH MCP.

COVERAGE CRITERIA

Recombinant GH therapy (rhGH, somatotropin) may be authorized for members who meet **ALL** of the following criteria [ALL]

1. Prescriber specialty [ONE]

   ❒ Prescribed and managed by a board-certified pediatric endocrinologist or pediatric nephrologist

   ❒ For Neonates: Refer to 'Neonates' criteria in the following section

2. Age/Gender/Restrictions

   ❒ 18 years of age or younger (*If member is older than 18 years, reference 'Adult' criteria*)

3. <u>Labs/Reports/Documentation required</u> [ALL]
   All of the following documentation requested for the criteria below must be submitted for review

   ❒ Open epiphyses confirmed by bone age x-ray of the left hand and wrist (12 years of age and older only)
   †*X-ray must be taken within 6 months of request.*
   - ❍ Males: not to exceed 16 0/12 years of age
   - ❍ Females: not to exceed 14 0/12 years of age

   ❒ Thyroid function tests are within **normal** range (TSH 0.4 - 4.0 mIU/L)
   NOTE: Documentation of normal thyroid function (TSH) required
   NOTE: If TSH level is not within normal range, TSH deficiency should be corrected
   - ➢ *Hypothyroidism is indicated by an elevated serum TSH, which is defined as a TSH concentration above the upper limit of the normal TSH reference range, which is usually 4 to 5 mU/L in most laboratories.*
   - ➢ *Untreated/undiagnosed hypothyroidism may decrease response to therapy; monitor thyroid function test periodically and initiate/adjust thyroid replacement therapy as needed.*

❒ Other causes of GHD or secondary medical illnesses that affect GH have been ruled out [*including but not limited to: liver/kidney disease, chronic systemic disease, intracranial malignancy or tumor, growth-inhibiting medication(s), endocrine disorders, cranial tumors, cranial irradiation, chronic systemic disease, infections of the central nervous system, genetic syndromes, skeletal disorders, or other organic causes*]

❍ Other pituitary hormone deficiencies have been ruled out and/or corrected prior to time of testing [e.g. adrenocorticotropin hormone (ACTH), thyroid stimulating hormone (TSH), gonadotropin deficiency (leutinizing hormone [LH] and/or follicle stimulating hormone [FSH] are counted as 1 deficiency), prolactin, or arginine vasopressin (VAP) deficiency]

❍ Nutritional status has been optimized, metabolic abnormalities have been corrected, and steroid usage has been reduced to a minimum

❍ History of malignancy: Anti-malignancy treatment must be completed AND evidence of complete remission for at least 12 months free of recurrence[J]

Pediatric Uses	
Diagnosis	**Stimulation Testing Requirements**
GHD in children (including pituitary dwarfism)	2
Diagnosis of CNS system pathology (empty sella syndrome, interruption of pituitary stalk, hypoplasia of pituitary gland, craniofacial developmental defects, pituitary or hypothalamic tumors, etc.)	1
History of cranial irradiation	1
Multiple Pituitary Hormone Deficiency (MPHD)	1
Genetic defect along GH axis	1
Panhypopituitarism [absence of all other anterior pituitary hormones (LH, FSH, TSH, ACTH)]	None
Pituitary surgery	None

❒ **BIOCHEMICAL GH DEFICIENCY documented by ONE (1) of the following: [ONE: A OR B]**
NOTE: GH provocative stimulation tests include L-dopa, clonidine, propranolol, glucagon, arginine, and insulin-induced hypoglycemia

A. TWO (2) GH stimulation tests with serum peak level of less than 10 ng/mL [ng/mL = nanograms per milliliter (or microgram/L)] or an abnormal response as otherwise determined by the testing lab. Submit laboratory documentation.

- *Both stimulation tests may be performed simultaneously.*
- *There is no real "gold standard" for the diagnosis of GHD. There is general consensus that a diagnosis of impaired GH secretion can be confirmed only if subnormal GH secretion is observed during two different GH stimulation tests.*
- *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 GHD should not rely solely on IGF-I measurements, but must be confirmed by provocative tests solely for GH secretion. Measurement of IGF binding protein-2 (IGFBP-2), IGF binding protein-3 (IGFBP-3), and the acid labile subunit of IGF-I are considered experimental and investigational.*

B. ONE (1) GH stimulation test with serum peak level below 10 ng/mL [ng/mL = nanograms per milliliter (or microgram/L)] or an abnormal response as otherwise determined by the testing lab for the following diagnosis: [ONE]

- ❍ **Defined CNS pathology** [i.e. empty sella syndrome, interruption of pituitary stalk, hypoplasia of the pituitary gland, craniofacial developmental defects, pituitary or hypothalamic tumors, etc., history of irradiation or genetic conditions associated with GHD]

  **In a patient with known pathology of the central nervous system, other pituitary hormone defects, or a genetic defect, one test is sufficient to establish the diagnosis*

- ❍ **Multiple Pituitary Hormone Deficiencies (MPHD):** THREE (3)* or more pituitary axes (i.e., TSH, LH, FSH, ACTH, ADH) defined as at least 2 other pituitary hormone deficiencies in addition to GHD
  - ➢ *MPHD refers to the condition when the pituitary is not producing two or more of these hormones; if all the hormones produced by the pituitary are affected this condition is known as panhypopituitarism.*

❒ **AUXOLOGIC EVALUATION (STATURE AND GROWTH VELOCITY DATA)**
Auxology (comparison of the child's growth pattern to established gender and ethnicity norms) is the clinical basis for the diagnosis of GHD in children.

Documented by **ONE (1)** of the following: **[ONE]**

1) Severe growth retardation: Standing height of more than 3 standard deviation below the mean for chronological age, gender, and ethnic background
OR
2) Moderate growth retardation: Standing height that is 2 SD to 3 SD below the mean for chronologic age AND with growth deceleration [growth velocity less than the 25th percentile for age/gender] tracked over at least 1 year documented by ONE (1) of the following: [ONE]
- ❍ 2 heights measured by an endocrinologist at least 6 months apart (≥ 1 year)
- ❍ 4 heights measured by a primary physician at least 6 months apart (≥ 2 years)

OR
3) Severe deceleration in growth rate: Growth Velocity of 2 SDS (or 3rd percentile) below the mean for age and gender as measured over 1 year (or 3rd percentile for chronologic age and gender)
OR
4) Delayed skeletal maturation: Comparison of bone age to chronological age should be documented as abnormal by greater than or equal to 2 SDs below the mean for chronological age, which is generally greater than or equal to 2 years delayed growth
NOTE: Bone age estimation from x-ray of left wrist and hand
OR
5) Hypothalamic-pituitary dysfunction (e.g., microphallus, septo-optic dysplasia, intracranial tumor, history of cranial irradiation) with decelerating growth

❍ Imaging Studies [RECOMMENDED but NOT REQUIRED. SUBMIT IF AVAILABLE]†
Magnetic Resonance Imaging (MRI) of the hypothalamic-pituitary area to rule out tumors, investigate for structural causes of GHD, and to evaluate the severity and prognosis of the deficiency. †Criterion is not required for authorization; however Prescriber is requested to submit if available for documentation.
- ➢ *MRI without contrast is sufficient; MRI contrast helpful if anatomy is not normal on regular MRI.*
- ➢ *The Endocrine Society guidelines do not specifically state MRI testing is required, however most endocrinologists order imaging as standard practice.*[AMR Reviewer2017]

4. Contraindications/Exclusions
   - ❒ Authorization to continue GH therapy will not be authorized if ANY of the following has occurred: [ANY]
     - ❍ Hypersensitivity to somatropin or any component of the formulation
     - ❍ Growth promotion in pediatric patients with closed epiphyses
     - ❍ Progression or recurrence of any underlying intracranial lesion or actively growing intracranial tumor
     - ❍ Acute critical illness caused by complications following open-heart or abdominal surgery, multiple accidental trauma or acute respiratory failure
     - ❍ Active malignancy
       - ➢ *Due to the potent anabolic effects, GH therapy is contraindicated in children with active malignancies and is generally withheld until after completion of successful therapy for a malignancy.*
     - ❍ Active proliferative or severe non-proliferative diabetic retinopathy

CONTINUATION of Therapy for GHD in children [under 18 years of age]

Recombinant GH therapy (rhGH, somatotropin) may be authorized for continuation of therapy if meet ALL of the following criteria are met: [ALL]

1. Member meets current initial diagnosis criteria

2. 18 years of age or younger

3. Compliance with GH therapy as verified by Prescriber and member's medication fill history
NOTE: GH therapy should be discontinued and will not be authorized when there is poor adherence to the treatment regimen for any reason.

4. Labs/Reports/Documentation required [ALL]
All of the following documentation requested for the criteria below must be submitted for review

- ❒ Open epiphyses confirmed by bone age x-ray of the left hand and wrist (12 years of age and older only)
  ***** *X-ray must be taken within 6 months of request.*
  - ❍ Males: not to exceed 16 0/12 years of age
  - ❍ Females: not to exceed 14 0/12 years of age

- ❒ Expected adult height has not been reached (calculated using mid-parental height)
  - ➢ *Mid-parental height = (father's height + mother's height) divided by 2, plus 2.5 inches (male) or minus 2.5 inches (female)*

- ❒ Positive response as documented by growth curve chart : [AS APPLICABLE]

  - ❍ First year of therapy: [ONE]
    - o A doubling of pre-treatment growth rate
    - o An increase in growth rate of 2.5 cm/year or more

  - ❍ After the first year of therapy: Growth rate remains above 2.5 cm/year (*does not apply to children with prior documented hypopituitarism*)

- ❑ Thyroid function tests are within normal range (TSH 0.4 - 4.0 mIU/L)

5. Contraindications/Exclusions

- ❒ Authorization to continue GH therapy will not be authorized if ANY of the following has occurred: [ANY]
  - ❍ Hypersensitivity to somatropin or any component of the formulation
  - ❍ Growth promotion in pediatric patients with closed epiphyses
  - ❍ Progression or recurrence of any underlying intracranial lesion or actively growing intracranial tumor
  - ❍ Acute critical illness caused by complications following open-heart or abdominal surgery, multiple accidental trauma or acute respiratory failure
  - ❍ Active malignancy
  - ❍ Active proliferative or severe non-proliferative diabetic retinopathy

6. Discontinuation

- ❒ Treatment with rhGH should be discontinued if ANY of the following apply: [ANY]
  - ❍ Bone age ≥ 16 years (male), or ≥ 14 years (female) is reached
  - ❍ Attained height at any age is greater than or equal to the 5th percentile for adults (65 inches for men and 60 inches for women) using the latest publicly available CDC Growth Charts
    - o Mid-parental adult height has been achieved [Mid-parental height = (father's height + mother's height) divided by 2, plus 2.5 inches (male) or minus 2.5 inches (female)]
    - o Epiphyseal fusion has occurred
  - ❍ Increase in height velocity is less than 2.5 centimeters (cm) total growth in one year of therapy*
    **Therapy should be discontinued regardless of chronologic age if the growth rate is 2.5 cm or less per year, monitored and submitted every 12 months at reauthorization review*
  - ❍ Poor response to treatment, generally defined as an increase in growth velocity of less than 50% from baseline, in the first year of therapy
  - ❍ Persistent and uncorrectable problems with adherence to treatment
  - ❍ Adverse reactions or side effects

ADMINISTRATION, QUANTITY LIMITATIONS, AND AUTHORIZATION PERIOD

Consult the manufacturer's labeling for more detailed information on dosage and administration of this drug, cautions, precautions, contraindications, potential drug interactions, laboratory test interferences, and acute toxicity.

Recommended Dosing Regimen

- ❒ Up to 0.47 mg/kg SC per week divided into equal doses given 6 to 7 times per week

Authorization Limit [ALL APPLICABLE]

- ❑ **Prior to Completion of Linear Growth: [ONE]**
  - ❍ Initial therapy authorization period: 6 months
  - ❍ Continuation of therapy authorization period: 12 months OR until maximum bone age is met, whichever is shorter (in males up to 16 0/12 years of age; in females, up to 14 0/12 years of age)

- ❒ **Continuation of Therapy After Completion of Linear Growth** (after linear growth is complete, member is transitioned to "adult dosing" if criteria for transitional/ongoing GH treatment is met): Member will be re-evaluated per 'TRANSITIONAL CARE AFTER CHILDHOOD GH TREATMENT' criteria after GH treatment has been stopped for at least 3 months to determine growth hormone status. *****Refer to 'TRANSITIONAL CARE AFTER CHILDHOOD GH TREATMENT'*****

- ❑ Quantity limitation sufficient for a 30-day supply per fill based on FDA-approved dosages
  - ➢ *Total vials of GH required calculated by dividing total milligrams (mg) of GH for 12 months by size of vials (mg/vial)*
  - ➢ *Calculation: Multiply number of mg per dose by number of doses per week = mg/week. Multiply mgs/week by 52 weeks = total mgs/year. Divide mgs/year by number of mg per vial = number of vials for 12 month period.*

Route of Administration [ALL]

- ❑ GH therapy is considered a **self-administered** medication and is deemed appropriate for self-administration or administration by a caregiver (i.e., not a healthcare professional). Provider-administered setting such as an outpatient hospital, ambulatory surgical suite, physician office, or emergency facility will not be authorized.
  NOTE: The status of an individual member, such as the ability to administer the medication, is not a consideration in determining whether a medication is defined as self-administered.

- ❑ If member meets all criteria and approval for therapy is authorized, medication will be dispensed by a specialty pharmacy vendor at the discretion of Molina Healthcare. Self-administered medications may not be dispensed for self-administration and billed through the medical benefit by a provider. These agents must be dispensed through a participating pharmacy.

NEONATAL HYPOGLYCEMIA RELATED TO GROWTH HORMONE DEFICIENCY (GHD)

1. Prescriber specialty [ONE]
   - ❒ Prescribed and managed by a board-certified neonatologist (in the neonatal period)

2. Age/Gender/Restrictions
   - ❒ 30 days old or less at time of diagnosis

3. Labs/Reports/Documentation required [ALL]
   All of the following documentation requested for the criteria below must be submitted for review

   - ❒ Presence of neonatal hypoglycemia in the absence of a metabolic disorder

   - ❒ Other metabolic disorders have been ruled out as a cause of hypoglycemia (e.g., prematurity, delayed feedings, hyperinsulinism, birth asphyxia, insulin-dependent diabetic mothers)
     NOTE: Chart documentation indicating that other metabolic disorder have been ruled out as a cause of hypoglycemia through clinical work-up must be submitted

   - ❒ Randomly assessed GH level less than 20ng/mL as confirmed by polyclonal radioimmunoassay (RIA)
     ****No stimulation test required for neonates****
     - ➢ *A GH level should always be measured in the presence of neonatal hypoglycemia in the absence of a metabolic disorder. A random GH measurement in a polyclonal RIA of less than 20 mg/L would suggest GHD in the newborn. An IGFBP-3 measurement is of value for the diagnosis of GHD in infancy.*[1]

   - ❒ Thyroid function tests are within **normal** range (TSH 0.4 - 4.0 mIU/L)
     NOTE: Documentation of normal thyroid function (TSH) required
     NOTE: If TSH level is not within normal range, TSH deficiency should be corrected
     - ➢ *Hypothyroidism is indicated by an elevated serum TSH, which is defined as a TSH concentration above the upper limit of the normal TSH reference range, which is usually 4 to 5 mU/L in most laboratories.*
     - ➢ *Untreated/undiagnosed hypothyroidism may decrease response to therapy; monitor thyroid function test periodically and initiate/adjust thyroid replacement therapy as needed.*

   - ❒ Other pituitary hormone deficiencies [i.e. Cortisol, Adrenocorticotropic Hormone (ACTH)] have been evaluated, ruled out, and/or corrected prior to time of testing

   - ❒ Imaging: Appropriate imaging (magnetic resonance imaging [MRI] or computed tomography [CT]) of the brain with particular attention to the hypothalamic pituitary region to exclude the possibility of *pituitary or hypothalamic neoplasms or congenital abnormalities*

4. Contraindications/Exclusions
   - ❒ Authorization to continue GH therapy will not be authorized if ANY of the following has occurred: [ANY]
     - ❍ Hypersensitivity to somatropin or any component of the formulation
     - ❍ Progression or recurrence of any underlying intracranial lesion or actively growing intracranial tumor
     - ❍ Active malignancy
     - ❍ Active proliferative or severe non-proliferative diabetic retinopathy

CONTINUATION of Therapy for Neonatal Hypoglycemia Related to Growth Hormone Deficiency

Refer to 'CONTINUATION of Therapy for GHD in children [under 18 years of age]'

ADMINISTRATION, QUANTITY LIMITATIONS, AND AUTHORIZATION PERIOD

Consult the manufacturer's labeling for more detailed information on dosage and administration of this drug, cautions, precautions, contraindications, potential dprug interactions, laboratory test interferences, and acute toxicity.

Recommended Dosing Regimen

- ❒ GHD (ped): 0.16 to 0.24 mg/kg SC per week divided into 6 to 7 doses daily[J]

Authorization Limit [ALL APPLICABLE]

- ❑ **Prior to Completion of Linear Growth:**
  - ❍ Initial therapy authorization period: 6 months
  - ❍ Continuation of therapy authorization period: 12 months

- ❒ **Continuation of Therapy After Completion of Linear Growth** (after linear growth is complete, member is transitioned to "adult dosing" if criteria for transitional/ongoing GH treatment is met): Member will be re-evaluated per 'TRANSITIONAL CARE AFTER CHILDHOOD GH TREATMENT' criteria after GH treatment has been stopped for at least 3 months to determine growth hormone status. *****Refer to 'TRANSITIONAL CARE AFTER CHILDHOOD GH TREATMENT'*****

- ❑ Quantity limitation sufficient for a 30-day supply per fill based on FDA-approved dosages
  - ➢ *Total vials of GH required calculated by dividing total milligrams (mg) of GH for 12 months by size of vials (mg/vial)*
  - ➢ *Calculation: Multiply number of mg per dose by number of doses per week = mg/week. Multiply mgs/week by 52 weeks = total mgs/year. Divide mgs/year by number of mg per vial = number of vials for 12 month period.*

Route of Administration [ALL]

- ❑ GH therapy is considered a **self-administered** medication and is deemed appropriate for self-administration or administration by a caregiver (i.e., not a healthcare professional). Provider-administered setting such as an outpatient hospital, ambulatory surgical suite, physician office, or emergency facility will not be authorized.
  NOTE: The status of an individual member, such as the ability to administer the medication, is not a consideration in determining whether a medication is defined as self-administered.

- ❑ If member meets all criteria and approval for therapy is granted, medication will be dispensed by a specialty pharmacy vendor at the discretion of Molina Healthcare. Self-administered medications may not be dispensed for self-administration and billed through the medical benefit by a provider. These agents must be dispensed through a participating pharmacy.

TRANSITION FROM CHILDHOOD TO ADULT GROWTH HORMONE THERAPY
Continuation of Therapy After Completion of Linear Growth

The transition period is the period from late puberty to establishment of adult muscle and bone composition, and encompasses attainment of adult height. As attainment of adult or near-adult height is an easily measurable variable, re-evaluation of the somatotropic axis is most conveniently performed when growth has slowed to the point when pediatric GH dosing will be discontinued.

Since all children with GHD will not require continued treatment into adulthood, the transition period is significant. The transition period can be defined as beginning in late puberty the time when near adult height has been attained, and ending with full adult maturation (6-7 years after achievement of adult height). During this period ongoing growth hormone therapy may be necessary to attain somatic maturation, normal intermediary metabolism and appropriate quality of life. Once adult height has been achieved, subjects should be retested for GH deficiency to determine if continuing replacement therapy is necessary. The level of GH considered normal for an adult is much lower than that for a child, especially one undergoing the pubertal growth spurt.

The American Association of Clinical Endocrinologists published guidelines in 2009 that stressed the need for and use of GH for continued treatment of persistently GH-deficient transition and adult patients. The metabolic improvements and long-term benefit with continuation of GH treatment in GH-deficient adolescents transitioning to adulthood remains uncertain. Mauras N et al.

COVERAGE CRITERIA

Recombinant GH therapy (rhGH, somatotropin) may be authorized for the treatment of adolescents and young adults with childhood onset GHD, who have completed linear growth **as defined by growth rate less than 2 cm per year** and meets ALL of the following criteria below: **[ALL]**

1. Member has completed linear growth as defined by growth rate **less than 2 cm per year**

2. GH treatment has been discontinued for at least THREE (3) months after completion of linear growth[GHRS, J]

3. Member meets ONE (1) of following sets of criteria are met: **[ONE: A OR B]**

   A. GH treatment has been stopped for at least THREE (3) months AND the diagnosis of GHD has been reconfirmed as follows: [ONE]

   - ❒ **Idiopathic isolated GHD [ONE: 1 OR 2]**

     1) Subnormal response to **TWO (2)** provocative GH stimulation tests: **[TWO]**
     [*ng/mL = mcg/L*]
     - ❍ ITT [5.1mcg/L]
     - ❍ Arginine: [4.1mcg/L]
     - ❍ Glucagon [2.5-3 mcg/L, 1 mcg/L for obese patients and 3mcg/L in normal weight[J]]
     - ❍ Arginine/GHRH [4.1mcg/L OR cutoff value varies by waist circumference, body mass index (BMI), and age: peak GH values ≤ 11 ng/mL if body mass index [BMI] < 25 kg/m^2; ≤ 8 ng/mL if BMI ≥ 25 and < 30 kg/m^2; ≤ 4 ng/L if BMI ≥ 30 kg/m^2]
     - ❍ Arginine/L-Dopa [peak GH ≤ 1.5 ng/mL]
     - ❍ EXCEPTION to GH provocation tests: NOT required for members where it would not be expected to produce a clinical response (in absence of all pituitary hormones): [ANY]
       - o Surgical removal of the pituitary
       - o Panhypopituitarism (criteria below)

2) Subnormal response to ONE (1) provocative test (*similar to the stimulation tests and values above criterion*) **AND** low IGF-1/IGFBP-3 level *based on specific laboratory reference range*

B. GH treatment has been stopped for at least ONE (1) month AND the diagnosis of GHD has been reconfirmed with the documented presence of ANY of the following conditions: [ANY]
Due to the irreversible nature of the cause of the GHD in children with structural lesions with multiple hormone deficiencies and those with proven genetic causes, a low insulin-like growth factor I (IGF-I) level at least ONE (1) month off GH therapy is sufficient documentation of persistent GHD without additional provocative testing (level of evidence, moderate).

- ❒ Multiple Pituitary Hormone Deficiencies: Subnormal response *(similar to the stimulation tests and values above criterion)* to ONE (1) provocative GH test AND/OR low IGF-1/IGFBP-3 level *based on specific laboratory reference range*

- ❒ GH reassessment through stimulation testing is not required for the following members: [ANY]
  - ❍ Severe GHD in childhood due to a genetic cause: Genetic mutations associated with deficient GH production or secretion (e.g.GH-1 or GHRH-R)
  - ❍ Structural hypothalamic-pituitary disease
  - ❍ Central nervous system tumors
  - ❍ Severe GHD and the receipt of high-dose cranial radiation therapy
  - ❍ Panhypopituitarism: defined by at least 3 pituitary hormone deficiencies (ACTH, TSH, FSH, LH, prolactin)
    AND
    IGF-1 level below the normal range for age and gender, based on specific lab reference values (IGF-1 while not receiving growth hormone therapy)
    NOTE: Peak GH level must be adjusted if monoclonal-based assay or recombinant human GH reference preparations are used, based upon specific lab reference values

Informational Note
Member needs to be off GH therapy for 3 months after completion of growth regardless of cause of GHD. Exceptions:
- Idiopathic GHD: member should be off GH therapy for at 3 months before GHD diagnosis is reconfirmed
- Diagnoses specified under 3.B. above: member should be off GH therapy for at 1 month before GHD diagnosis is reconfirmed

4. Contraindications/Exclusions
- ❒ Authorization to continue GH therapy will not be authorized if ANY of the following has occurred: [ANY]
  - ❍ Hypersensitivity to somatropin or any component of the formulation
  - ❍ Growth promotion in pediatric patients with closed epiphyses
  - ❍ Progression or recurrence of any underlying intracranial lesion or actively growing intracranial tumor
  - ❍ Acute critical illness caused by complications following open-heart or abdominal surgery, multiple accidental trauma or acute respiratory failure
  - ❍ Active malignancy
    - ➢ *Due to the potent anabolic effects, GH therapy is contraindicated in children with active malignancies and is generally withheld until after completion of successful therapy for a malignancy.*
  - ❍ Active proliferative or severe non-proliferative diabetic retinopathy

ADMINISTRATION, QUANTITY LIMITATIONS, AND AUTHORIZATION PERIOD

Consult the manufacturer's labeling for more detailed information on dosage and administration of this drug, cautions, precautions, contraindications, potential drug interactions, laboratory test interferences, and acute toxicity.

Recommended Dosing Regimen [ALL]

- ❒ After linear growth is complete, member is transitioned to "adult dosing" if ALL criteria in this section are met for ongoing GH treatment: GHD (adults): 0.04-0.08 mg/kg/week
  Adults: Initially, not more than 0.04 mg/kg SC per week divided into 7 equal daily injections, preferably administered in the evening. Increase dose as needed at 4-8 week intervals to a maximum of 0.08 mg/kg per week as 7 equal daily injections.

- ❒ To optimize the GH dose for an adolescent during the transition period, initiate with the adult dose and then titrate to a serum IGF-I level in the upper portion of the normal range for age and gender

Authorization Limit [ALL]

- ❒ Authorization period: May authorize up to 12 months

- ❒ Quantity limitation sufficient for a 30-day supply per fill based on FDA-approved dosages
  - *Total vials of GH required calculated by dividing total milligrams (mg) of GH for 12 months by size of vials (mg/vial)*
  - *Calculation: Multiply number of mg per dose by number of doses per week = mg/week. Multiply mgs/week by 52 weeks = total mgs/year. Divide mgs/year by number of mg per vial = number of vials for 12 month period.*

Route of Administration [ALL]

- ❒ GH therapy is considered a **self-administered** medication and is deemed appropriate for self-administration or administration by a caregiver (i.e., not a healthcare professional). Provider-administered setting such as an outpatient hospital, ambulatory surgical suite, physician office, or emergency facility will not be authorized.
  NOTE: The status of an individual member, such as the ability to administer the medication, is not a consideration in determining whether a medication is defined as self-administered.

- ❒ If member meets all criteria and approval for therapy is authorized, medication will be dispensed by a specialty pharmacy vendor at the discretion of Molina Healthcare. Self-administered medications may not be dispensed for self-administration and billed through the medical benefit by a provider. These agents must be dispensed through a participating pharmacy.

PREFERRED/NON-PREFERRED

PREFERRED
OMNITROPE may be authorized when ALL of the criteria for member's diagnosis has been met: [APPLICABLE]

- ❒ Omnitrope vial: Medicaid
- ❒ Omnitrope pen: Marketplace

NON-PREFERRED
A NON-PREFERRED product may be authorized when ALL criteria for member's diagnosis has been met in addition to:

- ❒ Failure or inadequate clinical response to the PREFERRED agent documented to ANY of the following: [ANY]
  - ❍ Inadequate clinical response from previous trial of PREFERRED product. Documentation of trial and failure of the preferred GH product required either through previous claims history or by member's medical records.
  - ❍ Member's diagnosis is not an FDA-labeled indication of the PREFERRED product (Omnitrope)
  - ❍ Allergy, *labeled contraindication, or clinical intolerance of the PREFERRED product (Omnitrope)
    *Contraindications/Exclusions to Omnitrope includes the following: [ANY]
    - o Documented sensitivity to benzyl alcohol (a preservative in Omnitrope 5 Pen and Omnitrope 5.8mg/vial) and to phenol (a preservative in Omnitrope 10 Pen)
      NOTE: Genotropin or Humatrope contains a different preservative
    - o Children under the age of 3: Benzyl alcohol should not be used in children under the age of 3. Omnitrope 5 & 5.8mg which contains benzyl alcohol as a preservative is contraindicated in children under the age of 3. Omnitrope 10 should be used in children under the age of 3 as it does not contain benzyl alcohol.

COVERAGE EXCLUSIONS

This policy only addresses the indications of **growth hormone deficiency (GHD)** for **PEDIATRIC** members listed in the 'Coverage Criteria' sections above when ALL appropriate criteria have been met.

All other uses of growth hormone that are not an FDA-approved indication or not included in the 'Coverage Criteria' section of this policy are considered experimental/investigational or not a covered benefit of this policy. This subject to change based on research and medical literature, or at the discretion of Molina Healthcare.

Growth hormone is not authorized for all other indications, including (but not limited to) the following indications due to a lack of medical literature to establish efficacy for these indications: [ANY]

- Amyotrophic lateral sclerosis
- Anabolic therapy to enhance body mass or strength for professional, recreational or social reasons
- Anti-aging
- Burn injuries
- Cerebral palsy
- CHARGE (Coloboma, Heart defect, Atresia choanae, Retarded growth and development, Genital hypoplasia, Ear anomalies/deafness) syndrome
- Chondrodystrophy
- Chronic catabolic states, including inflammatory bowel disease, pharmacologic glucocorticoid administration, and respiratory failure
- Chronic fatigue syndrome
- Congestive heart failure
- **Constitutional delay*** defined as lower than expected height percentiles compared with their target height percentiles and delayed skeletal maturation when growth velocities and rates of bone age advancement are normal (i.e., delayed skeletal maturation with normal growth velocities and rates of bone age advancement, members who are at the lowest 5% of the growth curve at age three)
- Corticosteroid-induced pituitary ablation
- Crohn's disease
- Cystic fibrosis
- Depression
- Down syndrome and other syndromes associated with short stature and increased susceptibility to neoplasms (e.g., Bloom syndrome, Fanconi syndrome)
- Fibromyalgia
- Fracture healing
- Glucocorticoid-induced growth failure
- Growth hormone insensitivity (partial or complete)
- Growth retardation due to amphetamines (e.g., Adderall, Ritalin)
- Hypochondroplasia
- Hypophosphatemia (e.g., hypophosphatemic rickets)
- Infertility/in-vitro fertilization
- HIV lipodystrophy
- Hypertension
- **Idiopathic Short Stature (ISS)** **Further information below**
- **Intra-Uterine Growth Restriction (IUGR)/Small for Gestational Age (SGA)** **Further information below**
- Ischemic heart disease
- Isochromosome Yp defect
- Juvenile rheumatoid arthritis

- Kabuki syndrome
- Muscular dystrophy
- Neurosecretory growth hormone dysfunction
- Non-classic congenital adrenal hyperplasia
- Obesity/morbid obesity
- Osteogenesis imperfect
- Osteoporosis
- Post bariatric surgery
- Post-traumatic stress disorder
- Precocious puberty
- Pseudohypoparathyroidism
- Russell-Silver syndrome (that does not result in small for gestational age)
- Skeletal dysplasias (e.g., achondroplasia, kyphomelic dysplasia)
- "Somatopause" in older adults
- Spina bifida
- Stem cell mobilization
- Wound healing

Idiopathic Short Stature (ISS)

ISS is also referred to as non-GHD short stature in children.

- ISS is a clinical description rather than a disease. ISS is defined as short stature in an otherwise healthy child, exclusion of other causes of short stature (endocrine, metabolic, or other disease), bone age within 2 standard deviations (SD) of chronological age, a height below the 3rd percentile for that age and gender in the same ethnic group, or normal growth hormone response on provocative testing (Lee, 2006; Manmohan, 2005). Cohen 2008

- ISS is not associated with a definable physical functional impairment (e.g., limiting ability to drive), is not due to growth hormone deficiency, and is not the result of accidental injury, disease, trauma, or treatment of a disease and is not a congenital defect. Even though the child may be below the 3rd percentile on the growth chart, he/she may only be on the low side of a scale. They are not considered as having a disease or disability by most standards.

- There are no well-designed trials to support that gains in adult height from growth hormone treatment significantly improve functional status or long-term health outcomes for these children. Although GH therapy has been around for decades, the safety and efficacy of long-term use of rhGH in children with ISS (non-GH deficient short stature) is unknown at this time. There are some concerns that long-term administration of growth hormone therapy in supraphysiological doses may lead to malignancy, slipped capital femoral epiphysis, carbohydrate metabolism and irreversible joint disturbances years after treatment therapy (Holden, 2000; Kemp et al., 2005; Quigley et al., 2005)

- A Cochrane review by Bryant et al. (2009) evaluated GH therapy for idiopathic short stature in children and adolescents. A total of 10 RCTs met eligibility criteria, which included being conducted in children who had normal GH secretion, normal size for gestational age at birth, and no evidence of chronic organic disease. In addition, studies needed to compare GH treatment with placebo or no treatment and provide GH treatment for at least 6 months. Three studies were placebo- controlled, and the other 7 compared GH therapy with no treatment. Unlike the Deodati and Cianfarani review previously described, studies were not required to report final adult height. Nine of 10 studies in the Cochrane review were short term and reported intermediate outcomes. A pooled analysis of 3 studies reporting growth velocity at 1 year found a statistically significantly greater growth velocity in treated than in untreated children. The WMD was 2.84 (95% CI, 2.06 to 2.90). Five studies reported height SDSs, but there was heterogeneity among studies and the findings were not pooled. These data suggest that GH has an effect on height in children with idiopathic short stature in the short term but that evidence on GH's effects on adult height is extremely limited.

- There is a lack of medical consensus within the pediatric endocrinology community, and the approved use of GH to increase height in ISS remains controversial.[Maheshwari N, et al 2012] Although GH therapy initially causes growth acceleration, it also accelerates pubertal development and advances bone age so that the duration of growth during puberty is shortened.

- **Molina Healthcare does not consider ISS a disease as coverage of treatment extends to disease or injury.** This basis of this policy is coverage of growth hormone therapy as a replacement for endogenous growth hormone in patients with evidence of a deficiency. Therefore, growth hormone treatment is not authorized when used for treatment of short stature in the absence of a growth hormone deficiency or for the majority of other conditions in which growth hormone has not been shown to provide clinical benefits or improvements in functional impairment or long-term health outcomes.

Small for Gestational Age (SGA)/Intrauterine Growth Retardation (IUGR)

- SGA with IUGR may or may not be associated with a growth hormone deficiency and occurs from a pathophysiologic process in utero that adversely affects fetal growth.[A] SGA has been defined as a birth weight < 2500 grams (g) at gestational age > 37 weeks or birth weight or length below the 3rd percentile for gestational age (AACE, 2003).[A]

- IUGR is diagnosed during pregnancy and is linked to an increase of 6 to 10 times in perinatal mortality (Creasy and Resnik, 1994; Bernstein and Gabbe, 1996). Children born SGA but with no comorbidities are often not diagnosed until they fail to achieve catch-up height by the age of 2 to 4 years or when they start school (Lee et al., 2003). Severe short stature may be physically debilitating in untreated children (Munns et al., 2003), with children being at greater risk of bullying at school and social isolation (Voss and Mulligan, 2000). Some children with short stature may also have difficulties with emotionally immature behavior, anxiety, and poor school performance (Tanaka et al., 2002). However, not all children who are shorter than their peers will experience problems. For example, the Royal College of Obstetricians and Gynecologists states that the majority of children born SGA do not have any appreciable morbidity or mortality (RCOG, 2002). However, others indicate that children born SGA who remain short may suffer from alienation, low self-esteem, impaired social dynamics, behavioral problems, lower educational achievement and professional success (Lee et al., 2003).

- Clinical trials show that growth hormone treatment results in a significant height gains compared to pre-treatment predictions and final adult height that is closer to their mid-parental target height.
    - *Wilton P et al. Growth hormone treatment induces a dose-dependent catch-up growth in short children born small for gestational age: A summary of four clinical trials. Horm Res 1997;48(suppl1):67-71.*
    - *Ranke MB et al. Growth hormone treatment of short children born small for gestational age or with Silver-Russell syndrome: results from KIGS (Kabi International Growth Study), including the first report on final height. Acta Paediatr 1996;47(suppl):18-26.*
    - *Coutant R et al. Response to growth hormone treatment and final height in children with short stature secondary to intrauterine growth retardation. J Clin Endocrinol Metab 1998;83:1070-74*
    - *Arends NJ et al. Growth Hormone treatment and its effect on bone mineral density, bone maturation and growth in short children born small for gestational age: 3-year results of a randomized, controlled Growth Hormone trial. Clin Endocrinol (Oxf). 2003;59:779-87.*
    - *Hokken-Koelega AC et al. Final height data, body composition and glucose metabolism in growth hormone treated short children born small for gestational age. Horm Res. 2003;60 (Suppl 3):113-4.*
    - *Boonstra V et al. Puberty in growth hormone treated children born small for gestational age (SGA). J Clin Endocrinol Metab. 2003 Dec;88:5753-8.*
    - *Bryant J et al. Recombinant growth hormone in idiopathic short stature in children and adolescents (Cochrane Review). In: The Cochrane Library, Issue 4, 2004. Chichester, UK: John Wiley & Sons, Ltd.*
    - *Carel JC et al. Improvement in adult height after growth hormone treatment in adolescents with short stature born small for gestational age: results of a randomized controlled study. J Clin Endocrinol Metab. 2003;88:1587-93.*

- Many studies have noted an association between intrauterine growth restriction and long-term health risks, including type 2 diabetes, the metabolic syndrome, and cardiovascular disease. However, the mechanisms underlying this association have not been established. It is still unclear whether growth hormone treatment exacerbates or improves these long-term risks.
  Reference: Rogol, Alan D. Growth hormone treatment for children born small for gestational age. In: UpToDate, Geffner, Mitchell E (Ed), UpToDate, Waltham, MA. Literature review current through: Jan 2017. (Accessed on February 2017) 2013.)

- **Hayes** assigned a *D2 rating 'for rhGH treatment for preterm infants with intrauterine growth retardation/restriction. This Rating reflects the very limited negative evidence (1 study) available for this population.'
  *D2: Insufficient evidence. There is insufficient published evidence to assess the safety and/or impact on health outcomes or patient management.
  Reference: A Hayes assessment addressing "Recombinant Human Growth Hormone Treatment in Children Under 2 Years of Age" (reviewed April 6, 2016) is available via a Medical Technology Directory.

- **Similar to ISS, there is inadequate data to support gains in final adult height in children with SGA/IUGR with growth hormone therapy make a substantial clinical difference in functional status or long-term outcomes.**

Drug Safety Communication

- In December 2010, the FDA issued a Drug Safety Communication to inform the public that it was reviewing the results from a study conducted in France, the Santé Adulte GH Enfant (SAGhE) study, and other available information of a possible increased risk of death of children treated with rhGH (Drug Safety Commumication). The study found that persons with certain kinds of short stature (idiopathic GHD, ISS, SGA), who were treated with rhGH during childhood and who were followed over a long period of time, were at a small increased risk of death when compared with individuals in the general population of France.

- In August 2011, the FDA issued another Drug Safety Communication updating the public about its ongoing safety review of rhGH, or somatropin, and the reported potential risk and recommended that patients continue their rhGH treatment as prescribed by their healthcare provider (Safety Review Update of Recombinant Human Growth Hormone). The FDA identified a number of study design weaknesses that limit the interpretability of the study results. Also, the FDA's review of the medical literature, as well as reports from the Agency's Adverse Event Reporting System, did not provide evidence suggestive of a link between rhGH and an increased risk of death. The FDA determined that the evidence regarding rhGH and increased risk of death was inconclusive and that healthcare professionals and patients should continue to prescribe and use rhGH according to the labeled recommendations.

*Pharmaceutical samples: The use of pharmaceutical samples (from the prescriber or manufacturer assistance program) will not be considered when evaluating the medical condition, prior prescription history, or as continuation of therapy.

SUMMARY OF EVIDENCE/POSITION

CLINICAL PRACTICE GUIDELINES

National Institute of Health and Clinical Excellence (NICE)
In 2010, NICE in the U.K. issued guidance on human growth hormone for growth failure in children.[E] NICE recommends GH as a possible treatment for children with growth failure who have any of the following conditions:[E]

- Growth hormone deficiency
- Turner syndrome
- Prader-Willi syndrome
- Chronic renal insufficiency
- Small for gestational age and have growth failure at 4 years
- Short stature homeobox (SHOX) gene deficiency

National Institute for Health and Clinical Excellence (NICE)
NICE produced a technology appraisal in 2010 updating its recommendations on the use of rhGH for the treatment of growth failure in children. NICE recommends human GH (somatropin) as a treatment option for children with growth failure if they have any of the following (NICE, 2010): GHD, TS, PWS, CRI, Growth failure at ≥ 4 years and born SGA, or SHOX-D.[E]

The assessment suggests the following criteria be used to define subnormal growth in children with GHD:[E]

- Decreasing growth rate combined with a predisposing condition such as previous cranial irradiation, OR
- Evidence of other pituitary hormone deficiencies or signs of congenital GHD (hypoglycemia, microphallus), OR
- Moderate growth retardation with height SDS for sex and chronological age between -2 and -3 SDS below the mean and decreased growth rate (growth velocity (GV) below 25th percentile for age and sex), OR
- Severe deceleration in growth rate (GV below 3rd percentile for age and sex), OR
- Severe growth retardation with height standard deviation score (SDS) for sex and chronological age less than 3 SDS below the mean.

❖ Pediatric Endocrine Society
The Pediatric Endocrine Society Drug and Therapeutics Committee published an evidence-based report (2015) on risk of neoplasia in patients receiving GH therapy.[B] The report concluded that GH therapy can be administered without concerns about impact on neoplasia in children without known risk factors for malignancy. For children with medical conditions associated with an increased risk of future malignancies, cases should be evaluated on an individual basis and decisions made about the tradeoff between a possible benefit of GH therapy and possible risks of neoplasm.

❖ Endocrine Society
An Endocrine Society clinical practice guideline on adult growth hormone deficiency (GHD), updated in 2011, includes the following recommendations:[D]

- GH therapy of GH-deficient adults offers significant clinical benefits in body composition and exercise capacity
- GH therapy of GH-deficient adults offers significant clinical benefits in skeletal integrity
- Documentation of persistent GHD that GH therapy be continued after completion of adult height to obtain full skeletal/muscle maturation during the transition period

❖ American Association of Clinical Endocrinologists (AACE)
In 2009, the American Association of Clinical Endocrinologists issued updated guidelines (2009) on growth hormone (GH) use in growth hormone-deficient adults and transition patients include the following: [F]

- GHD is a well-recognized clinical syndrome in adults that is associated with significant comorbidities if untreated
- GH should only be prescribed to patients with clinical features suggestive of adult GHD and biochemically proven evidence of adult growth hormone deficiency
- No data are available to suggest that GH has beneficial effects in treating aging and age-related conditions and the enhancement of sporting performance; therefore, the guideline developers do not recommend the prescription of GH to patients for any reason other than the well-defined approved uses of the drug.
- GH should only be prescribed to patients with clinical features suggestive of adult GHD and biochemically proven evidence of adult GHD.
- No data are available to suggest that GH has beneficial effects in treating aging and age-related conditions and the enhancement of sporting performance; therefore, we do not recommend the prescription of GH to patients for any reason other than the well-defined approved uses of the drug.
- For childhood GH treatment of conditions other than GHD, such as Turner's syndrome and idiopathic short stature, there is no proven benefit to continuing GH treatment in adulthood; hence, there is no indication to retest these patients when final height is achieved.
- On restarting GH therapy, the starting dose of GH in transition patients should be approximately 50% of the dose between the pediatric doses required for growth and the adult dose.
- **There is no evidence that one GH product is more advantageous over the other, apart from differences in pen devices, dose increments and decrements, and whether or not the product requires refrigeration; therefore, we do not recommend the use of one commercial GH preparation over another.**

DEFINITIONS

❖ **Growth Hormone (GH) Provocative Stimulation Test:** One of the procedures that may be performed to diagnose growth hormone deficiency (GHD). A provocative agent is used to stimulate the pituitary gland to secrete GH. The intent is to determine the maximum peak GH response from the provocative agent. This peak is the value used to determine whether the response is considered normal or abnormal for the purpose of supporting the diagnosis of GHD. Serum levels may be measured by radioimmunoassay (RIA) or immunoradiometric assay (IRMA). Baseline testing is performed prior to administration of the provocative agent and frequent blood sampling is done thereafter. Sampling occurs approximately 30, 60, 90, 120 and 180 minutes after provocative agent administration. Sampling defines the "curve" of the response (going from a lower GH value prior to provocation to the highest, or peak, GH value after provocation and then a drop from peak) and must provide sufficient information to determine a peak value.

❖ **Insulin-Like Growth Factor 1 (IGF-1):** A hormone created mainly by the liver that mediates most of the effects of growth hormone. IGF-1 blood tests may be used in the diagnosis of growth hormone deficiency.

❖ **Insulin-Like Growth Factor Binding Protein (IGFBP-3):** The transport protein for IGF-1 and IGF-2 in the circulation. It modulates IGF activity and inhibits cell growth. Its levels increase in the presence of IGF-I, insulin and other growth-stimulating factors such as growth hormone. IGFBP-3 blood tests may be used in the diagnosis of growth hormone deficiency.

❖ The pituitary gland produces a number of hormones, which are released into the blood to control other glands in the body (thyroid, adrenal, ovary or testicles). If the pituitary is not producing one or more of these hormones, the condition is called **hypopituitarism.** If all the hormones produced by the anterior pituitary are decreased, the condition is called **panhypopituitarism.**

APPENDIX

Appendix 1

Growth charts for infants, children and adolescents are available on the following internet sites:

National Center for Health Statistics:
http://www.humatrope.com/Documents/pdf/growth_chart_both.pdf
(This link includes growth charts with curves down to 2 standard deviations (approximately 3rd percentile)).

Centers for Disease Control and Prevention:
http://www.cdc.gov/nchs/about/major/nhanes/growthcharts/clinical_charts.htm#Clin%202

CODING INFORMATION: THE CODES LISTED IN THIS CLINICAL POLICY ARE FOR INFORMATIONAL 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. COVERAGE IS DETERMINED BY THE BENEFIT DOCUMENT. THIS LIST OF CODES MAY NOT BE ALL INCLUSIVE AND INCLUSION OR EXCLUSION OF ANY CODES DOES NOT GUARANTEE COVERAGE. PROVIDERS SHOULD REFERENCE THE MOST UP-TO-DATE SOURCES OF PROFESSIONAL CODING GUIDANCE PRIOR TO THE SUBMISSION OF CLAIMS FOR REIMBURSEMENT OF COVERED SERVICES.

CPT	Description
NA	

HCPCS	Description
J2941	Injection, somatropin, 1 mg
S9558	Home injectable therapy; growth hormone, including administrative services, professional pharmacy services, care coordination, and all necessary supplies and equipment (drugs and nursing visits coded separately), per diem

REFERENCES

Package Insert, FDA, Drug Compendia

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b. Humatrope (somatropin) [prescribing information]. Indianapolis, IN: Lilly USA LLC; July 2014.
c. Norditropin (somatropin) [prescribing information]. Plainsboro, NJ: Novo Nordisk; January 2015.
d. Nutropin® Nutropin® AQ prescribing information, Genentech, South San Francisco, CA. March 2014..
e. Omnitrope (somatropin) package insert. Princeton, NJ: Sandoz, Inc.; 2016 Dec.
f. Saizen (somatropin) [prescribing information]. Rockland, MA: Serono Inc; June 2014.
g. Serostim (somatropin) [prescribing information]. Rockland, MA: Serono Inc; April 2012.
h. Zorbtive (somatropin) [prescribing information]. Rockland, MA: Serono Inc; January 2012.
i. Drug Facts and Comparisons. Facts and Comparisons eAnswers [online]. Clinical Drug Information LLC, 2017. Available from Wolters Kluwer Health, Inc. [via subscription only] Accessed February 2017.
j. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2017. URL: http://www.clinicalpharmacology.com. [via subscription only] Accessed February 2017.
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l. Micromedex Healthcare Series. DrugDex. [Micromedex Web site]. Available at: http://www.thomsonhc.com/micromedex2/librarian [via subscription only].
m. Lexi-Drugs Compendium. Sebelipase alfa. [Lexicomp Online Web site via UpToDate subscription]. 2017. Available at: https://www.uptodate.com/contents/sebelipase-alfa-drug-information?source=search_result&search=kanuma&selectedTitle=1%7E4. Accessed February 2017.
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Clinical Trials, Definitions, Peer-Reviewed Publications

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3. Baxter L, Bryant J, Cave CB, et al. Recombinant growth hormone for children and adolescents with Turner syndrome. Cochrane Database Syst Rev. 2007(1):CD003887. PMID 17253498
4. The Canadian Growth Hormone Advisory Committee. Impact of growth hormone supplementation on adult height in turner syndrome: results of the Canadian randomized controlled trial. J Clin Endocrinol Metab 90:3360-6.
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9. Richmond, Erick J, et al. Diagnosis of growth hormone deficiency in children. UpToDate https://www.uptodate.com/contents/diagnosis-of-growth-hormone-deficiency-in-children#H10

Idiopathic Short Stature (ISS)

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Transition of gh-deficient patients from adolescence to adulthood

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