Subject: Recombinant Human Growth Hormone: PEDIATRIC GENETIC DISEASES with Primary Effects on Growth

- Turner syndrome
- Noonan syndrome
- Prader-Willi syndrome
- SHOX mutations

Policy Number: MCP-004-B
Revision Date(s): 4/28/2010, 4/27/2011, 2/2017


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/GH, somatropin) for the treatment of PEDIATRIC INDICATIONS 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/GH, somatropin)** is used to treat a variety of childhood diseases affecting growth, including children with growth hormone deficiency (GHD), children born small for gestational age, idiopathic short stature (ISS), Chronic Renal Insufficiency/Chronic Kidney Disease (CRI/CKD), Turner syndrome (TS), Prader-Willi syndrome (PWS), Noonan syndrome, and short stature homeobox-containing gene deficiency (SHOX-D).

- **Somatropin** is used as replacement therapy in adults with endogenous growth hormone deficiency (GHD), such as those with idiopathic or acquired GHD. 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 GHD include a variety of metabolic, structural, psychological, and quality-of-life problems.

- Growth hormone (GH) treatment is **not** 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 GH therapy if there is a significant physical functional impairment and treatment with GH 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

- Recombinant human growth hormone (rhGH/GH, somatropin) 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.

- The 2009 American Association of Clinical Endocrinologists (AACE) Guidelines for Clinical Practice indicates that no evidence exists to support any specific growth hormone product over another.\(^F\)

- **PREFERRED PRODUCT: Omnitrope (vial for Medicaid; pen for Marketplace)**
  Prescribers and Molina Healthcare members are encouraged to use the more cost-effective agent when possible before other non-preferred growth hormone products. 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).

  - Available as: Omnitrope: Cartridge 5, 10 mg; Vial 5.8mg
  - If the PREFERRED brand (Omnitrope) is unavailable for any reason, Molina Healthcare will select the most cost-effective brand of GH that has the required labeling indication.

- **EXCEPTIONS TO PREFERRED PRODUCTS**
  *The following indications/drugs are excluded from the preferred product initiative:*
  - Diagnosis of Chronic Renal Insufficiency
  - Zorbitive and Serostim

- NON-PREFERRED products will be evaluated if the prescriber indicates a history of a trial, documented intolerance of, FDA labeled contraindication to, or hypersensitivity to the preferred growth hormone product. Requests for non-preferred growth hormone products will be reviewed when patient-specific documentation has been provided.

**REFER TO NON-PREFERRED PRODUCT CRITERIA**
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.

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

### Genetic Diseases with Primary Effects on Growth

**TURNER’S SYNDROME and NOONAN SYNDROME associated with SHORT STATURE**

- Growth Hormone (GH) Provocative Stimulation Test: NOT required for Turner’s Syndrome and Noonan Syndrome

### COVERAGE CRITERIA

Recombinant GH (rhGH/GH, somatropin) may be authorized for pediatric members with *Turner’s or Noonan Syndrome* associated with short stature who meet ALL of the following: [ALL]

1. **Prescriber specialty**
   - Prescribed and managed by a board-certified endocrinologist, pediatric endocrinologist or pediatric nephrologist

2. **Age/Gender/Restrictions**
   - 18 years of age or younger

3. **Diagnosis/Indication [ONE]**
   - Diagnosis of Turner’s Syndrome: Females with short stature associated with TS confirmed by appropriate genetic testing
   - Diagnosis of Noonan Syndrome: Confirmed by molecular or genetic testing
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 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) is needed at the time of GH stimulation testing
   NOTE: If TSH level is not within normal range, TSH deficiency should be corrected before performing GH stimulation tests since GH secretion may be subnormal as a result of the hypothyroidism.
   - 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. adrenocorticotropic 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

☐ BIOCHEMICAL GH DEFICIENCY: NOT required for Turner’s nor Noonan Syndrome

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<th>Diagnosis</th>
<th>Stimulation Testing Requirements</th>
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<tbody>
<tr>
<td>Turner’s or Noonan Syndrome</td>
<td>None</td>
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</tbody>
</table>
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]

- Severe growth retardation: Standing height of more than 3 standard deviation below the mean for chronological age, gender, and ethnic background
  OR
- 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
- 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)

- Growth rate documented for a period of at least six (6) months immediately prior to the submission of this request (or initiation of growth hormone therapy)

Imaging Studies [RECOMMENDED; 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.

- Noonan Syndrome only: No significant cardiac disease

  ➢ Because children treated with recombinant human GH might also have or be at risk for hypertrophic cardiomyopathy or hematological malignancy, patients should be monitored for adverse complications.

  ➢ The safety of Norditropin® in children with NS and significant cardiac disease is not known since children who had baseline cardiac disease significant enough to potentially affect growth were excluded from the study.

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
    ➢ 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 Turner’s or Noonan Syndrome associated with Short Stature

Recombinant GH therapy (rhGH/GH, somatropin) may be authorized for continuation of therapy for pediatric members diagnosed with Turner’s or Noonan Syndrome associated with short stature who meet ALL of the following: [ALL]

1. Member meets current initial diagnosis criteria for Turner’s or Noonan Syndrome

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 will not be authorized when there is poor adherence to the treatment regimen

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 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†
       †Not applicable 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 GH should be discontinued if ANY of the following apply: [ANY]
  - Closed epiphyses
  - Bone age ≥ 16 years (male), or ≥ 14 years (female) is reached
  - Attained any of the following height goals (at any age): [ANY]
    - 5th percentile for adults (65 inches for men and 60 inches for women)
    - 50th percentile for height based on age
    - 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)]
  - 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 [ONE]

- Turner Syndrome: 0.375 mg/kg/week divided and given as 6 or 7 daily SC injections
- Noonan Syndrome: up to 0.066 mg/kg/day and given as 6 or 7 daily SC injections

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 are 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 required are figured by dividing total milligrams of GH required 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.
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 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.
PRADER-WILLI SYNDROME (PWS)

- Growth Hormone (GH) Provocative Stimulation Test: NOT required for PWS.

- Informational Note: Fatalities have been reported in pediatric patients with PWS following the use of GH. The reported fatalities occurred in patients with one or more risk factors, including severe obesity, history of upper airway obstruction or sleep apnea, respiratory impairment, or unidentified respiratory infection; male patients with one or more of these factors may be at greater risk. Monitor for sleep apnea, upper airway obstruction, and respiratory infections. Treatment interruption is recommended in patients who show signs of upper airway obstruction, including the onset of, or increased, snoring and/or new-onset sleep apnea.

COVERAGE CRITERIA

Recombinant GH therapy (rhGH/GH, somatropin) may be authorized for members with Prader-Willi syndrome (PWS) who meet ALL of the following criteria [ALL]

1. Prescriber specialty
   - Prescribed and managed by a board-certified endocrinologist or pediatric endocrinologist

2. Diagnosis/Indication
   - Diagnosis of PWS confirmed with DNA methylation testing. Laboratory documentation required.

3. Age/Gender/Restrictions [ALL]
   - 18 years of age or younger
   - Member does not have the following conditions: [ANY]
     - Severely obese [defined as a body mass index (BMI) ≥97th percentile for age and gender OR a BMI ≥35]
     - Upper airway obstruction, severe respiratory impairment, or sleep apnea

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 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)
       - 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.

NOTE: Documentation of normal thyroid function (TSH) is needed at the time of GH stimulation testing.
NOTE: If TSH level is not within normal range, TSH deficiency should be corrected before performing GH stimulation tests since GH secretion may be subnormal as a result of the hypothyroidism.
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

**BIOCHEMICAL GH DEFICIENCY: NOT required for PWS**

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<tr>
<td>Prader Willi Syndrome</td>
<td>None</td>
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</tbody>
</table>

**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]**

- Severe growth retardation: Standing height of more than 3 standard deviation below the mean for chronological age, gender, and ethnic background

- 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)

- 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)

- Growth rate documented for a period of at least six (6) months immediately prior to the submission of this request (or initiation of growth hormone therapy)

- 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.
Sleep study: Absence of obstructive sleep apnea by sleep study or treated obstructive sleep apnea

**NOTE:** Any sleep disorders or upper airway obstruction must be effectively treated prior to starting GH therapy

- The FDA recommends that patients with PWS be evaluated for signs of upper airway obstruction and sleep apnea prior to therapy initiation. Treatment should be interrupted in patients showing signs of upper airway obstruction (including onset of increased snoring) and/or sleep apnea.
- Individuals with PWS have a high incidence of both central and obstructive sleep apnea. Factors contributing to sleep-disordered breathing include obesity, restrictive lung disease due to muscle weakness or scoliosis, reduced ventilatory response to hypercapnia, and hypoxia during sleep and wakefulness.

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
  - Evidence of active malignancy
    - Due to the potent anabolic effects, GH therapy is contraindicated in children with active malignancies and is generally withheld for at least one (1) year after completion of successful therapy for a malignancy.
  - Active proliferative or severe non-proliferative diabetic retinopathy

Contraindications SPECIFIC to PWS patients with GHD

- Authorization to continue GH therapy will not be authorized if ANY of the following has occurred: [ANY]
  - Patients with PWS without growth hormone deficiency (except Genotropin)
  - Severe obesity
  - Uncontrolled diabetes
  - History of upper airway obstruction or severe respiratory impairment
  - Untreated severe obstructive sleep apnea
  - Active cancer
  - Active psychosis
CONTINUATION of Therapy for Prader-Willi Syndrome (PWS)

Recombinant GH therapy (rhGH/GH, somatropin) may be authorized for continuation of therapy for members with PWS who meet ALL of the following criteria: [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 will not be authorized when there is poor adherence to the treatment regimen

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 x-ray† once annually (children over 12 years of age only)
     †Bone age should be assessed through radiological examination of the left hand and wrist to determine that epiphyses have not yet closed (children over 12 years of age 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

   - Positive response as documented by growth curve chart: [ALL APPLICABLE]
     - First year of therapy: [ONE]
       - A doubling of pre-treatment growth rate
       - 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)
     - Body composition: Increase in lean body mass and decreases in fat mass. Documentation required.

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
     - Evidence of active malignancy
     - Active proliferative or severe non-proliferative diabetic retinopathy
6. Discontinuation

- Authorization to continue GH therapy will **not** be authorized if ANY of the following has occurred: [ANY]
  - Closed epiphyses
  - Bone age ≥ 16 years (male), or ≥ 14 years (female) is reached
  - Attained any of the following height goals (*at any age*): [ANY]
    - 5th percentile for adults (65 inches for men and 60 inches for women)
    - 50th percentile for height based on age
    - 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)]
  - 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

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**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**

- PWS: 0.24 mg/kg/week divided and given as 6 or 7 daily SC injections

**Authorization Limit** [ALL APPLICABLE]

- **Prior to Completion of Linear Growth: [ONE]**
  - Continuation of 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.
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 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.
Children with Short Stature Homeobox containing Gene (SHOX) Deficiency

- Growth Hormone (GH) Provocative Stimulation Test: NOT required for SHOX deficiency

Recombinant GH (rhGH/GH, somatropin) may be authorized for members with **Short Stature Homeobox-Containing Gene (SHOX) Deficiency** who meet **ALL** of the following criteria **[ALL]**

1. Prescriber specialty
   - ☐ Prescribed and managed by a board-certified endocrinologist or pediatric endocrinologist

2. Diagnosis/Indication **[ALL]**
   - ☐ Diagnosis of pediatric growth failure with SHOX gene deficiency as confirmed by molecular or genetic testing

3. Age/Gender/Restrictions
   - ☐ 18 years of age or younger

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 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) is needed at the time of GH stimulation testing
     **NOTE:** If TSH level is not within normal range, TSH deficiency should be corrected before performing GH stimulation tests since GH secretion may be subnormal as a result of the hypothyroidism.
     - 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

**BIOCHEMICAL GH DEFICIENCY: NOT required for SHOX deficiency**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Stimulation Testing Requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td>SHOX Deficiency</td>
<td>None</td>
</tr>
</tbody>
</table>

**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]

- Severe growth retardation: Standing height of more than 3 standard deviation below the mean for chronological age, gender, and ethnic background

- 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)

- 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)

Growth rate documented in centimeters for a period of at least six (6) months immediately prior to the submission of this request (or initiation of GH therapy)

**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.
6. **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
  - Evidence of active malignancy
    - Due to the potent anabolic effects, GH therapy is contraindicated in children with active malignancies and is generally withheld for at least one (1) year after completion of successful therapy for a malignancy.
  - Active proliferative or severe non-proliferative diabetic retinopathy

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**CONTINUATION of Therapy for Short Stature Homeobox-Containing Gene (SHOX) Deficiency**

Recombinant GH (rhGH/GH, somatropin) may be authorized for continuation of therapy for members with SHOX deficiency 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 will not be authorized when there is poor adherence to the treatment regimen
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 x-ray† once annually (children over 12 years of age only)
     - Bone age should be assessed through radiological examination of the left hand and wrist to determine that epiphyses have not yet closed (children over 12 years of age 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
   - Positive response as documented by growth curve chart: [ALL APPLICABLE]
     - First year of therapy: [ONE]
       - A doubling of pre-treatment growth rate
       - 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)

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
  - Evidence of active malignancy
  - Active proliferative or severe non-proliferative diabetic retinopathy
6. Discontinuation
   - Authorization to continue GH therapy will not be authorized if ANY of the following has occurred: [ANY]
     - Closed epiphyses
     - Bone age ≥ 16 years (male), or ≥ 14 years (female) is reached
     - Attained any of the following height goals (at any age): [ANY]
       - 5th percentile for adults (65 inches for men and 60 inches for women)
       - 50th percentile for height based on age
       - 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)]
     - 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
- SHOX: 0.35 mg/kg/week SC divided and 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)

- 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 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.
TRANSITION FROM AFTER CHILDHOOD TO ADULT GROWTH HORMONE THERAPY

Continuation of Therapy After Completion of Linear Growth

The transition period is the time 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, as detailed above.

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: Transition is required for Prader-Will syndrome (PWS) only.

Turner syndrome, Noonan syndrome, SHOX mutations may continue treatment until epiphyseal closure OR ‘Continuation of Therapy’ criteria are not met for member’s respective condition.

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

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\[\text{GHRS, J}\]
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: A OR B]

   ☐ Idiopathic isolated GHD [ONE: 1 OR 2]

   1) Subnormal response to TWO (2) provocative GH stimulation tests: [TWO]
   \[\text{ng/mL = mcg/L}\]
   ○ ITT [5.1 mcg/L]
   ○ Arginine: [4.1 mcg/L]
   ○ Glucagon [2.5-3 mcg/L, 1 mcg/L for obese patients and 3 mcg/L in normal weight\]
   ○ Arginine/GHRH [4.1 mcg/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/m²; ≤ 8 ng/mL if BMI ≥ 25 and < 30 kg/m²; ≤ 4 ng/L if BMI ≥ 30 kg/m²]
   ○ Arginine/L-Dopa [peak GH ≤ 1.5 ng/mL]

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O 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)

OR

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 the range of the specific laboratory

O 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 the range of the specific laboratory

B. Documented presence of ANY of the following conditions [ANY]
  O GH reassessment through stimulation testing is not required for the following members: [ANY]
    O 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)
    O Structural hypothalamic-pituitary disease
    O Central nervous system tumors
    O Multiple (≥ 3) Pituitary Hormone Deficiencies (MPHD): Deficiencies in at least 3 of the following pituitary hormones: 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
    O Severe GHD and the receipt of high-dose cranial radiation therapy

4. Contraindications/Exclusions
  O Authorization to continue GH therapy will not be authorized if ANY of the following has occurred: [ANY]
    O Hypersensitivity to somatropin or any component of the formulation
    O Growth promotion in pediatric patients with closed epiphyses
    O Progression or recurrence of any underlying intracranial lesion or actively growing intracranial tumor
    O Acute critical illness caused by complications following open-heart or abdominal surgery, multiple accidental trauma or acute respiratory failure
    O 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.
    O 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
- 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 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
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]
      - 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
      - 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.
This policy only addresses the indication of **recombinant GH (rhGH/GH, somatropin)** in the treatment of **PEDIATRIC** members for Growth Hormone Deficiency (GHD) as stated in the ‘Coverage Criteria’ section when all appropriate criteria are met.

All other uses of recombinant GH therapy 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.

**NOTE:** 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.

### CONDITIONS NOT COVERED

<table>
<thead>
<tr>
<th>Recombinant GH (GH, somatropin) 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]</th>
</tr>
</thead>
</table>
| - 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)**
Intra-uterine growth restriction (IUGR) not meeting diagnostic criteria for small for gestational age (SGA)*
- Ischemic heart disease
- Isochromosome Yp defect
- Juvenile rheumatoid arthritis
- Kabuki syndrome
- Muscular dystrophy
- Neurosecretory growth hormone dysfunction
- Non-classic congenital adrenal hyperplasia
- Noonan Syndrome without short stature [Noonan Syndrome with growth failure/short stature is covered for members meeting all condition-specific criteria]
- 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

*Rationale for non-coverage in the section below.

Constitutional Delay in Growth and Development
Constitutional delay of growth is characterized by normal prenatal growth followed by growth deceleration during infancy and childhood, which is reflected by declining height percentiles at this time. Children with constitutional delay have later timing of puberty than do their peers, allowing a longer period during which they are able to grow. Most commonly, these patients achieve normal adult height if no treatment is given. Although constitutional delay may be treated with GH, other effective and less costly treatments are available. In male patients, the literature shows testosterone or anabolic steroids are effective, and in female patients, low dose estrogens may be used.

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 sex 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 GH 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. 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. 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). 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 GH 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.

• 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.

Hayes assigned a *D2 rating for GH 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.

• Intra-uterine growth restriction An UpToDate review on ‘Fetal growth restriction: Evaluation and management’ (Resnik, 2013) does not mention the use of GH as a management tool.

• Small for Gestational Age An UpToDate review on ‘Growth hormone treatment for children born small for gestational age’ indicates that growth hormone treatment is likely to yield only modest gains in height compared with no treatment (an increase in adult height of approximately 6 cm, provided the treatment is begun early and continued for at least seven years). Adult height will usually be below average despite therapy.

There were only modest advantages of a higher-dose regimen as compared with a lower-dose regimen (67 mcg/kg/day versus 33 mcg/kg/day); higher doses yield greater short-term growth responses, but confer only modest advantages on long-term height outcomes.

• Similar to idiopathic short stature (ISS), there is inadequate data to support gains in final adult height in children with SGA/IUGR with GH therapy make a substantial clinical difference in functional status or long-term outcomes.

Drug Safety Communications

• 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 GH (Drug Safety Communication). The study found that persons with certain kinds of short stature (idiopathic GHD, ISS, SGA), who were treated with GH 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 GH, or somatropin, and the reported potential risk and recommended that patients continue their GH 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 GH and an increased risk of death. The FDA determined that the evidence regarding GH and increased risk of death was inconclusive and that healthcare professionals and patients should continue to prescribe and use GH according to the labeled recommendations.
**Summary of Evidence/Position**

**Clinical Practice Guidelines**

**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. 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**

Clinical practice guideline on adult GHD, updated in 2011, includes the following recommendations:

- 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 AACE issued updated guidelines (2009) on growth hormone (GH) use in growth hormone-deficient adults and transition patients include the following:

- 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 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, 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.**
**Turner’s Syndrome**

- TS is a chromosomal condition that describes girls and women with common features that are caused by complete or partial absence of the second sex chromosome. The most common feature of TS is short stature.\(^A\)
- TS, which occurs in 1 in every 2,000 live born girls, is due to abnormalities or absence of an X chromosome and is frequently associated with short stature, which may be ameliorated with GH treatment.
- Growth hormone deficiency is not seen in TS, unlike in Prader-Willi syndrome.
- Poor growth is evident in utero and further deceleration occurs during childhood and at adolescence.\(^A\) The mean adult height for those with TS is 58 inches (4 feet, 10 inches).
- The FDA approvals for GH were based on the results of randomized, controlled clinical trials that included final adult height as the outcome.\(^b,d\) Clinical trials reporting final adult height show children with TS treated with GH achieved final heights of approximately 146.0 cm – 147.5 cm (58.4 – 59.0 inches) compared to an untreated control group who achieved final height of 141.0 cm - 142.1 cm (56.4 – 56.8 inches).\(^b,d\)
- In 2007, a Cochrane review identified 4 RCTs (total n=365) evaluating GH for treating TS.\(^3\) Studies included children who had not yet achieved final height, treated children for at least 6 months, and compared GH to placebo or no treatment. Only one trial reported final height, so findings on this outcome could not be pooled. A pooled analysis of 2 trials found that short-term growth velocity was greater in treated than untreated children (MD: 3 cm per year, 95% CI: 2 to 4 cm/year).

**Noonan Syndrome (NS)**

**Noonan’s syndrome** (NS) is a genetic, multisystem disorder with variable phenotype. The main clinical characteristics of the syndrome consist of short stature, cardiovascular abnormalities (pulmonary valve stenosis, hypertrophic cardiomyopathy), cryptorchidism, and facial dysmorphology (hypertelorism, ptosis, low-set and posteriorly rotated ears, webbed neck).\(^5\) Short stature is a common manifestation of NS. Although birth weight and body length are usually normal in NS, pubertal growth is often delayed. At pubertal ages, short stature can be the most striking finding. Adult height in these patients is approximately 2 standard deviation (SD) below the mean for healthy adults. The causes of the growth disturbances in NS are multifactorial.\(^5\) Improved patient outcomes with GH treatment include an increased change in height SD and mean height gain, with the greatest increases in NS patients who are started early and then maintained on GH for an extended duration.\(^5\)

NS occurs in approximately 1 in 1,000 to 2,500 children.\(^5\) Defects in the KRAS and PTPN11 genes cause NS. About half of those affected by NS have a PTPN11 mutation. Persons with a defect in the KRAS gene have a severe or atypical form of NS. Problems with these genes cause certain proteins involved in growth and development to become overactive. Due to several shared characteristics, NS is sometimes called pseudo Turner syndrome. However, unlike Turner syndrome, there is no known chromosomal cause, and infertility and intrauterine growth retardation are not characteristic.

- Although up to 80% of individuals born with NS have short stature with normal birth weight and length, growth decelerates to a height at the third percentile or less.\(^5\) Therefore, routine measurements for changes in weight and length should be plotted 3 times per year for the child’s first 3 years and at least yearly thereafter. Improved patient outcomes with GH treatment include an increased change in height SD and mean height gain, with the greatest increases in patients who are started early and then maintained on GH for an extended duration.\(^5\)

- In 2007, the FDA approved use of GH (Norditropin) for treatment of short stature in children with NS. This approval was based on a comparative study of 21 children that showed improvement in height and growth velocity in those with short stature due to NS.\(^5\) The FDA approval was based upon the results of a 2-year long prospective, open label, randomized, parallel group trial of GH in 21 children with short stature associated with NS. An additional 6 children were not randomized, but did follow the protocol. After the initial 2-year trial, children continued on
Norditropin until final height. Retrospective final height and adverse event data were collected from 18 of the 21 subjects who were originally enrolled in the trial and the 6 who had followed the protocol without randomization. Historical reference materials of height velocity and adult height analyses of NS patients served as the controls. The 24 children (12 females and 12 males) aged 3 to 14 years received either 0.033 mg/kg/day or 0.066 mg/kg/day of GH subcutaneously which, after the first 2 years, was adjusted based on growth response. In addition to a diagnosis of NS, key inclusion criteria included bone age determination showing no significant acceleration, pre-pubertal status, height SDS less than or equal to 2, and height velocity SDS less than 1 during the 12 months pre-treatment. Exclusion criteria were previous or ongoing treatment with GH, anabolic steroids or corticosteroids, congenital heart disease or other serious disease perceived to possibly have major impact on growth, fasting plasma glucose greater than 120 mg/dL, or GHD. Patients obtained a final height gain from baseline of 1.5 and 1.6 SDS estimated according to the national and the Noonan reference, respectively. A height gain of 1.5 SDS (national) corresponds to a mean height gain of 9.9 cm in boys and 9.1 cm in girls at 18 years of age, while a height gain of 1.6 SDS (Noonan) corresponds to a mean height gain of 11.5 cm in boys and 11.0 cm in girls at 18 years of age. A comparison of height velocity between the 2 treatment groups during the first 2 years of treatment for the randomized subjects was 10.1 and 7.6 cm/year with 0.066 mg/kg/day versus 8.55 and 6.7 cm/year with 0.033 mg/kg/day, for year 1 and year 2, respectively. Age at start of treatment was a factor for change in height SDS (national reference). The younger the age at start of treatment, the larger the change in height SDS. Examination of gender subgroups did not identify differences in response to GH.

- The FDA-approved labeling for Norditropin brand of GH indicates that not all patients with NS 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 NS, establish that the patient does have short stature.** The FDA-approved labeling for Norditropin recommends a dosage of GH of up to 0.066 mg/kg/day for pediatric patients with short stature associated with NS.

In 2015, Giacomozzi et al published a systematic review of literature on the effect of GH therapy on adult height. Included in the review were studies treating individuals with a diagnosis of Noonan syndrome with no other causes of short stature and a normal karyotype in females. In addition, studies needed to follow patients for at least 3 years. A total of 23 studies met the inclusion criteria; none were RCTs and only 1 was controlled. Three of the studies were case reports and the remainder was prospective or retrospective cohort studies. In the 1 controlled study (MacFarlane et al, 2001), over the 3 year followup, the GH treated group gained a mean of 3.3 cm more than the untreated group. Among the uncontrolled studies, 2 reported adult height. Mean height SDS was -2.8 (SD=0.6) and mean adult height SDS was -1.4 (SD=0.9). Two uncontrolled studies reported near-adult height which was -2.1 (SD=0.9). In addition, 2 studies reported a change in height SDS corresponding to 8.6 cm (SD=5.9). The data are limited by the paucity of controlled studies and lack of RCTs.

Prader-Willi Syndrome (PWS)

Prader-Willi syndrome (PWS) is a genetic disorder characterized by a microdeletion in the long arm of chromosome 15. PWS is a complex genetic disorder caused by lack of expression of genes on the paternally inherited chromosome 15q11.2-q13. Approximately 70% are due to deletion of this region, 25% are due to maternal uniparental disomy (UPD) of chromosome 15, and most of the remaining 5% are due to an imprinting center defect. In infancy, PWS is characterized by general hypotonia, feeding difficulties, and low body weight resulting from poor suck and swallowing reflexes, with short stature becoming more obvious during the second year of life. The goals of GH treatment are to improve growth to achieve improved adult height and to positively alter body composition, thereby increasing the ratio of lean to fat body mass. Mean spontaneous adult height has been reported to be 152 to 162 cm for boys and 145 to 150 cm for girls.

In adulthood, clinical manifestations include hyperphagia, obesity if food intake is not strictly controlled, decreased basal metabolic rate; sleep disordered breathing, cognitive disability, short stature, and hypogonadism. The following are also characteristic of the syndrome: low muscle tone and abnormal body composition with decreased lean body mass and increased fat mass. Hypothalamic dysfunction has been implicated in many manifestations of this syndrome, including GH insufficiency. The benefits of recombinant GH therapy on body composition and motor function, in addition to linear growth, in children with PWS are well-established. Evidence is emerging on the benefits of GH therapy in adults with PWS as well.

Bakker (2013) describes a longitudinal study of 60 children with PWS treated with GH and followed for 8 years. The authors reported significant and sustained benefits from GH treatment with regard to lean body mass (p<0.001) and BMI standard deviation score (p<0.0001). Height and head circumference had completely normalized. IGF-1 standard deviation score increased +2.36 during the first year of treatment (p<0.0001) and remained stable through the rest of the study period. No adverse effects due to GH treatment on glucose homeostasis, serum lipids, blood pressure, and bone maturation were reported.

For adults with PWS, the benefits of GH treatment are less apparent, and treatment of adults with PWS is not an FDA-approved indication for GH (Genotropin). In 2012, Sode-Carlsen et al in Scandinavia published an RCT evaluating GH therapy in 46 adults with genetically verified PWS. Patients were randomized to receive 12 months of GH treatment or placebo. The authors reported a number of outcomes related to body composition and laboratory test results; they did not specify a primary outcome. In addition, the authors primarily reported within-group outcomes. For example, in the GH-treated group, after 1 year, lean body mass increased a mean of 2.25 kg (p=0.005 vs baseline), and fat mass decreased by a mean of 4.2 kg (p<0.001 vs baseline). In the same time period, there was no significant change in lean body mass in the placebo group and a significant increase (p<0.001) in fat mass (change in kg was not reported for the placebo group). During the 12-month treatment period, no significant changes were found in either group on other variables including in levels of high-density lipoprotein–cholesterol or triglycerides, peak expiratory flow, fasting glucose, fasting insulin and physical function. However, the level of low-density lipoprotein–cholesterol decreased significantly more in the GH-treated compared with control group (mean difference [MD], 0.27 mmol/L, p=0.047).

This study presents insufficient evidence that GH therapy is effective for improving health outcomes in adults with PWS.

Growth Hormone Research Society (GHRS)
In 2013, a GHRS issued consensus guidelines for use of recombinant GH (rhGH) for patients with PWS. They recommend consideration of rhGH therapy following genetic confirmation and continuation of therapy as long as benefits outweigh the risks. In addition, GHRS does not recommend stimulation testing for PWS. GHRS also states that clinical outcomes priorities should vary depending on age and on the presence of physical, mental, and social disability. The following were among GHRS recommendations:
- After genetic confirmation of the diagnosis of PWS, rhGH treatment should be considered and, if initiated, should be continued for as long as demonstrated benefits outweigh the risks.
- GH stimulation testing should not be required as part of the therapeutic decision-making process in infants and children with PWS.
- Exclusion criteria for starting rhGH in patients with PWS include severe obesity, uncontrolled diabetes, untreated severe obstructive sleep apnea, active cancer, and active psychosis.
- Scoliosis and cognitive impairment should not be considered exclusion criteria.

**Short Stature Homeobox-Containing Gene (SHOX) Deficiency**

**Short stature homeobox gene (SHOX)** is a gene on the X and Y chromosomes that controls the formation of many body structures, including the growth and maturation of bones in the arms and legs. Patients with SHOX deficiency (gene mutation or present in only one copy) may present with a broad phenotypic spectrum ranging from isolated short stature with no distinguishing clinical features to short stature with moderate to severe skeletal dysplasia.

- Treatment of children with short stature due to SHOX deficiency is an FDA-approved indication for GH therapy. Humatrope PI
- A 2010 Health Technology Assessment on GH treatment of growth disorders in children conducted a systematic review and identified 1 RCT evaluating GH therapy for children with short stature due to SHOX. Takeda
  - It included 52 prepubertal children age at least 3 years who had SHOX deficiency.
  - Height requirements were less than the 3rd percentile of the local reference range or less than 10th percentile with height velocity less than the 25th percentile.
  - Participants were randomized to receive 2 years of GH treatment (n=27) or usual care (n=25). The primary outcome was first-year height velocity.
  - Fifty-one of 52 patients completed the study.
  - Results: The first-year height velocity was 8.7 cm/y (SD=0.3) in the GH therapy group and 5.2 cm/y (SD=0.2) in the untreated group; the difference between groups was statistically significant (p<0.001).
    - Height gain over the 2-year treatment period was 16.4 (SD=0.4) cm in the treatment group and 10.5 (0.4) cm in the untreated group (p<0.001).
    - No SAEs were reported for either group.
  - The effectiveness of GH therapy in children with SHOX-D was equivalent to that observed in children with TS. It was concluded that GH is effective in improving the linear growth of patients with various forms of SHOX-D.
DEFINITIONS

الف – Abbreviations
  • Recombinant human growth hormone: GH, rhGH, or somatropin

الف – Human growth hormone 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 rhGH (a single polypeptide chain of 191 amino acids).

الف – Mid-parental height: Calculation of the sex-adjusted mid-parental height (or "target height) aids in evaluating a child's genetic potential. This sex-adjusted mid-parental height represents the statistically most probable adult height for the child, based on parental contribution.

\[
\text{Mid-parental height} = \frac{(\text{father's height} + \text{mother's height})}{2} \pm 2.5 \text{ inches (male) or minus 2.5 inches (female)}
\]
  • For boys, calculate the sex-adjusted mid-parental height by adding 2.5 in or 6.5 cm from the mean of the parents' heights.
  • For girls, subtract 2.5 in or 6.5 cm from the mean of the parents' heights.

الف – 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.

الف – 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.

الف – 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.

APPENDIX

Appendix 1: Growth Charts

http://www.cdc.gov/growthcharts/index.htm

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.

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**REFERENCES**

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**Clinical Trials, Definitions, Peer-Reviewed Publications**

**Idiopathic Short Stature (ISS)**


Noonan syndrome

Prader-Willi Syndrome (PWS)

Short stature homeobox gene (SHOX)

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

Government Agencies, Professional Societies, and Other Authoritative Publications


