# Human Growth Hormone Therapy
# Policy Number: C6925-A

**CRITERIA EFFECTIVE DATES:**

| ORIGINAL EFFECTIVE DATE | LAST REVIEWED DATE | NEXT REVIEW DATE |
|---|---|---|
| 07/05/2007 | 03/13/2019 | 03/13/2020 |
| **J CODE** | **TYPE OF CRITERIA** | **LAST P&T APPROVAL** |
| J3490 | RxPA | Q3 |

**PRODUCTS AFFECTED:**
Genotropin; Genotropin MiniQuick; Humatrope; Norditropin FlexPro; Norditropin NordiFlex Pen [discontinued]; Nutropin AQ NuSpin 10; Nutropin AQ NuSpin 20; Nutropin AQ NuSpin 5; Nutropin AQ Pen [discontinued]; Omnitrope; Saizen; Saizen Click.Easy [discontinued]; Saizenprep; Serostim; Tev-Tropin [discontinued]; Zomacton; Zorbtive

**DRUG CLASS:**
Hormones and Hormone Modifiers; Pituitary Hormones; Growth hormone modifiers

**ROUTE OF ADMINISTRATION:**
Injectable (self-administration)

**PLACE OF SERVICE:**
Specialty Pharmacy

**AVAILABLE DOSAGE FORMS**:

**FDA-APPROVED USES:**
PEDIATRIC
Treatment of children with growth failure due to:

A. Growth Hormone Deficiency (GHD)
B. Idiopathic Short Stature (ISS)
C. Chronic Renal Insufficiency/Chronic Kidney Disease (CRI/CKD) up until the time of renal transplantation
D. Small for Gestational Age (SGA)
E. Turner Syndrome (TS)
F. Noonan Syndrome (NS)
G. Prader-Willi syndrome (PWS)
H. Short Stature Homeobox-Containing Gene (SHOX) Deficiency

ADULTS
Treatment of adults with either adult-onset or childhood-onset GHD

A. Growth hormone deficiency due to hypothalamic or pituitary condition
B. Child onset growth hormone deficiency continuing into adulthood
C. Short-bowel syndrome (SBS)
D. HIV Wasting

**COMPENDIAL APPROVED OFF-LABELED USES:** Neonatal Hypoglycemia related to GH Deficiency

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**COVERAGE CRITERIA: INITIAL AUTHORIZATION**

1. Members authorized for GH therapy *previously by Molina Healthcare criteria* may be authorized for continuation of therapy in accordance with 'continuation of therapy' criteria
2. Members *receiving GH therapy without previous authorization by Molina Healthcare* (i.e. new members) may be considered for continuation of therapy by meeting condition-specific initial authorization criteria or continuation criteria

**DIAGNOSIS:** Hormone Deficiency (GHD), Idiopathic Short Stature (ISS), Chronic Renal Insufficiency/Chronic Kidney Disease (CRI/CKD) up until the time of renal transplantation, Small for Gestational Age (SGA), Turner Syndrome (TS), Noonan Syndrome (NS), Prader-Willi syndrome (PWS), Short Stature Homeobox-Containing Gene (SHOX) Deficiency, Growth hormone deficiency due to hypothalamic or pituitary condition, Child onset growth hormone deficiency continuing into adulthood, Short-bowel syndrome (SBS), HIV Wasting AND Neonatal Hypoglycemia related to GH Deficiency

**REQUIRED MEDICAL INFORMATION:**
**FOR ALL PEDIATRIC INDICATIONS: Pediatric GHD, CRI/CKD, SGA, Turner syndrome (TS), Noonan syndrome (NS), Prader-Willis syndrome (PWS), SHOX deficiency**

1. Documentation of 1 of the following for pediatric indications with associated with growth failure:
   a. Severe growth retardation: height standard deviation score (SDS) more than 3 SDS below the mean for chronological age and gender
      OR
   b. Moderate growth retardation with height SDS between 2 SD to 3 SD below the mean for chronological age/gender and decreased growth rate (growth velocity less than the 25th percentile for age/gender) tracked over at *least 1 year* documented by 1 of the following:
      i. 2 heights measured by an endocrinologist at least 6 months apart (≥ 1 year),
         OR
      ii. 4 heights measured by a primary physician at least 6 months apart (≥ 2 years)

      NOTE: Growth velocity (GV) should be tracked over at least 1 year
      OR
   c. 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
   d. Decreasing growth rate combined with a predisposing condition such as previous cranial irradiation or tumor
      OR
   e. For diagnosis of 'Children/Adolescents with Classic GH Deficiency' only, #e is also an option:
      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

AND

2. Open epiphyses confirmed by bone age X-ray of the left hand and wrist (12 years of age and older only). Males: not to exceed 16 0/12 years of age; Females: not to exceed 14 0/12 years of age. X-ray must be taken within 6 months of request. NOTE: Turner Syndrome (females): Open epiphyses confirmed not to exceed 14 years of age

AND

3. Thyroid function (TSH) tests are within normal range (TSH 0.4 - 4.0 mIU/L). 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. Documentation of normal TSH required.

AND

4. Other causes of GHD or secondary medical illnesses that affect GH have been ruled out [e.g. 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]

AND

5. Other pituitary hormone deficiencies have been ruled out and/or corrected prior to time of testing [e.g. ACTH, TSH, gonadotropin deficiency (LH and/or FSH counted as 1 deficiency), prolactin, or AVP deficiency]

AND

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

AND

7. History of malignancy: Anti-malignancy treatment must be completed AND evidence of complete remission for at least 12 months free of recurrence

AND

8. Imaging Studies [RECOMMENDED but not required; submit if available]: 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

**AND**

**ANY DIAGNOSIS/INDICAITON SPECIFIC CRITERIA BELOW**

A. PEDIATRIC GROWTH HORMONE DEFICIENCY (GHD) (18 years of age or younger)

1. (a) Diagnosis confirmed by 2 provocative stimulation tests producing peak growth hormone concentrations <10 ng/mL (e.g., L-dopa, clonidine, glucagon, propranolol, arginine, or insulin)
   OR
   (b) Diagnosis confirmed by 1 abnormal GH stimulation test (serum peak level below 10 ng/mL) for members with a defined CNS pathology*, history of irradiation, multiple pituitary hormone deficiency** (MPHD) or a genetic defect affecting the GH axis

**CNS pathology: e.g. 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*

***MPHD: 3 or more pituitary deficiencies (e.g. TSH, LH, FSH, ACTH, ADH) defined by at least 2 pituitary hormone deficiencies in addition to GHD*

OR

(c) Member has panhypopituitarism (defined as at least 3 pituitary hormone deficiencies) or pituitary surgery: No stimulation tests are required

OR

(d) Insulin growth factor-1 (IGF-1) a.k.a. somatomedin C, or IGF binding protein-3 (IGFBP-3) levels below normal range

OR

(e) Radiographic documentation that bone age is > 2 standard deviations below the mean for chronological age

OR

(f) Member produces two normal stimulation tests but has a height > 2.25 standard deviations below the age related mean and a growth velocity below the 25th percentile for bone age
NOTE: When growth deficiency is significant (meeting the definition stated) results of stimulation tests may not be as clinically significant.

B. IDOIOPATHIC SHORT STATURE(ISS) (18 years of age or younger)

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

C. CHRONIC RENAL INSUFFIENCIENY/CHORNIC KIDNEY DISEASE (CRI/CKD) (18 years of age or younger)
   1. Diagnosis of CRI/CKD with creatinine clearance less than or equal to 75 mL/min per 1.73 $m^2$ or serum creatinine greater than 3.0 mg/dl, or dialysis dependent
      AND
   2. Member has not received a renal transplantation (GH is not approved post-transplant; and evaluation for GH therapy resumption should occur at least 1 year after the transplant to allow time to determine whether catch-up growth will occur)
      AND
   3. GH Provocative Stimulation Test: NOT required for CRI/CKD

D. SMALL OF GESTATIONAL AGE (SGA) (18 years of age or younger)
   1. Between 2 years of age and 8 years
      EXCEPTIONS for age > 8 years as determined by Molina Clinical Pharmacist or Medical Director on a case-by-case basis:
      a. Pre-pubertal [who meets ALL applicable criteria]: Authorization may be recommended for an initial 12-month trial basis. If growth increases by 3 cm/year with therapy, then authorization for continued therapy may be recommended. NOTE: Additional supporting documentation and peer-to-peer with Prescriber may be requested.
         OR
      b. Clearly pubertal: An exception is NOT recommended. Efficacy has not been established in pubertal adolescents born SGA.

      AND
   2. Member was born small for gestational age, defined as 1 of the following:
      - ❍ Birth weight of less than 2,500 g at a gestational age of more than 37 weeks, OR
      - ❍ Birth weight or length below the 3rd percentile or > 2 standard deviations below the mean for gestational age

      AND
   3. Failure to manifest catch up growth by age 2 (defined as baseline pre-treatment height SDS < -2.5 SD for age and gender)
      AND
   4. Baseline pre-treatment height SDS < -2.5 SD for age and gender
      AND
   5. Growth charts (plotting growth) from birth through age 2 required
      AND
   6. GH Provocative Stimulation Test: NOT required for SGA

E. TURNER SYNDROME (TS) (18 years of age or younger)
   1. Diagnosis of Turner's Syndrome confirmed by karyotyping (peripheral blood karyotype showing a 45, XO genotype). Documentation required.
      AND
   2. Females 18 years of age or younger
      AND
   3. GH Provocative Stimulation Test: NOT required for TS

F. NOONAN SYNDROME (NS) (18 years of age or younger)
   1. Diagnosis of NS confirmed by molecular or genetic testing. Documentation required.
      AND
   2. No significant cardiac disease
      AND
   3. GH Provocative Stimulation Test: NOT required for NS

G. PRADER-WILLI SYNDROME (PWS) (18 years of age or younger)
   1. Diagnosis of PWS confirmed by genetic testing. Documentation required.
      AND
   2. Member does not have the following conditions:
      a. Severely obese [defined as a body mass index (BMI) ≥97th percentile for age and gender OR a BMI ≥35], OR
      b. Upper airway obstruction, severe respiratory impairment, or sleep apnea
      AND
   3. 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
   4. GH Provocative Stimulation Test: NOT required for PWS

H. SHORT STATURE HOMEOBOX-CONTAINING GENE (SHOX) DEFICIENCY (18 years of age or younger)
   1. Diagnosis of pediatric growth failure with SHOX gene deficiency as confirmed by molecular or genetic testing. Documentation of lab result confirming SHOX mutation is required.
   2. GH Provocative Stimulation Test: NOT required for SHOX deficiency

**COMPENDIAL APPROVED OFF-LABELED USES**

I. NEONATAL HYPOGLYCEMIA RELATED TO GH DEFICIENCY:
   1. Prescribed and managed by a board-certified neonatologist (in the neonatal period)
      AND
   2. 30 days old or less at time of diagnosis
      AND
   3. All of the following documentation requested for the criteria below must be submitted for review:
      a. Presence of neonatal hypoglycemia in the absence of a metabolic disorder
         AND
      b. 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
         AND
      c. Randomly assessed GH level less than 20ng/mL as confirmed by polyclonal radioimmunoassay (RIA) **No stimulation test required for neonates**
         NOTE: A GH level should 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.
         AND

d. Thyroid function tests are within normal range (TSH 0.4 - 4.0 mIU/L). NOTE: Documentation of normal thyroid function (TSH) required. If TSH level is not within normal range, TSH deficiency should be corrected
AND
e. Other pituitary hormone deficiencies (e.g. ACTH, TSH, FSH, LH, prolactin) have been evaluated, ruled out, and/or corrected prior to time of testing
AND
f. 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/Discontinuations (Refer criteria)
5. Continuation of Therapy for GHD in children (Refer criteria)

**ADULT GROWTH HORMONE DEFICIENCY: Age 18 and older or any age with closed epiphyses**
**REQUIRED MEDICAL INFORMATION:**
FOR ALL INDICATIONS: Documentation required of the following

1. Significant clinical symptoms related to GHD [e.g. increased body fat, increased abdominal fat mass, insulin resistance (although hyperglycemia does not usually develop), decreased lean body mass, decreased muscle mass and strength, decreased exercise capacity, impaired sense of well-being, excessive fatigue, poor sense of well-being persist despite maximizing treatment of other hormonal disorders, mood disorders, and medical illness), decreased bone density, and cardiovascular risk factors (such as increased clotting factors, decreased cardiac function, increase LDL, decrease HDL)]
AND
1. Thyroid function (TSH) tests are within normal range (TSH 0.4 - 4.0 mIU/L). 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. Documentation of normal TSH required.
AND
2. Other causes of GHD or secondary medical illnesses that affect GH have been ruled out [e.g. 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]
AND
3. Other pituitary hormone deficiencies have been ruled out and/or corrected prior to time of testing [e.g. ACTH, TSH, gonadotropin deficiency (LH and/or FSH counted as 1 deficiency), prolactin, or AVP deficiency]
AND
4. Nutritional status has been optimized, metabolic abnormalities have been corrected, and steroid usage has been reduced to a minimum
AND
5. History of malignancy: Anti-malignancy treatment must be completed AND evidence of complete remission for at least 12 months free of recurrence
AND
6. Imaging Studies [RECOMMENDED but not required; submit if available]: 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

**AND**
**ANY DIAGNOSIS/INDICAITON SPECIFIC CRITERIA BELOW**

A. ADULT ONSET GROWTH HORMONE DEFICIENCY: (18 years of age or older)
   1. Diagnosis of childhood-onset GHD supported by member's clinical documentation (as a result of congenital, genetic, acquired, or idiopathic causes)
      AND
   2. 'Transition from Childhood to Adult Growth Hormone Therapy: Continuation of Therapy After Completion of Linear Growth' criteria has been met (refer to criteria): a) GH treatment has been discontinued for at least 3 months *after* completion of linear growth, AND b) member has persistent GH deficiency documented by at least ONE (1) failed GH stimulation test
      AND
   3. GH reassessment through stimulation testing is not required for members with a high likelihood of GHD (defined as having a serum IGF-I level < 84µg/L while not receiving GH therapy) AND documented by 1 of the following:
      a. Severe GHD in childhood due to a genetic cause
      b. Structural hypothalamic-pituitary disease
      c. Central nervous system tumors
      d. Severe GHD and the receipt of high-dose cranial radiation therapy
      e. 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.

B. ADULT ONSET GROWTH HORMONE DEFICIENCY: PITUITARY OR HYPOTHALAMIC DISEASE
   1. Adult GHD is due to or the result of 1 of the following:
      a. Pituitary-hypothalamic disease (e.g., Sheehan's syndrome, autoimmune hypophysitis, or hypophysitis associated with other inflammatory conditions, such as sarcoidosis), OR
      b. Cranial surgery, OR
      c. Cranial radiation therapy, OR
      d. Head trauma, OR
      e. Idiopathic adult-onset growth hormone deficiency
   2. An abnormal response to 1 provocative stimulation test (ng/mL = mcg/L)
      NOTE: ITT (5.1mcg/L); Arginine (4.1mcg/L); Glucagon (2.5-3mcg/L, 1mcg/L for obese patients and 3mcg/L in normal weight); Arginine/GHRH (4.1mcg/L OR cutoff value varies by waist circumference, BMI, and age: peak GH values ≤ 11 ng/mL if BMI < 25 kg/m$^2$; ≤ 8ng/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)
      NOTE: Levodopa and Clonidine are not adequate agents for adult testing.
   3. 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): Surgical removal of the pituitary, OR Panhypopituitarism (criteria below)

C. ADULT ONSET GROWTH HORMONE DEFICIENCY: PANHYPOPITUITARISM
   1. Diagnosis of panhypopituitarism defined by at least 3 pituitary hormone deficiencies (ACTH, TSH, FSH, LH, prolactin)
   2. 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.
3. Growth hormone stimulation testing is not required for panhypopituitarism

D. IDIOPATHIC GHD: Adult OR Childhood Onset (18 years of age or older)
1. An abnormal response to 2 provocative stimulation tests (ng/mL = mcg/L)
   NOTE: ITT (5.1mcg/L); Arginine (4.1mcg/L); Glucagon (2.5-3mcg/L, 1mcg/L for obese patients and 3mcg/L in normal weight); Arginine/GHRH (4.1mcg/L OR cutoff value varies by waist circumference, BMI, and age: peak GH values ≤ 11 ng/mL if BMI < 25 $kg/m^2$; ≤ 8ng/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)
2. For members with a low IGF-1 (a marker of GH response) concentrations (SDS less than -2): Failure to respond to only 1 standard GH stimulation test is required
3. 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): Surgical removal of the pituitary, OR Panhypopituitarism (refer to panhypopituitarism criteria below)

E. SHORT BOWEL SYNDROME (SBS) (18 years of age or older)
1. 18 years of age or older
2. Member has not previously received 4 weeks of treatment with growth hormone
3. Diagnosis of SBS by a gastroenterologist
4. Receiving specialized nutritional support (e.g. enteral feedings, fluids, micronutrient supplements) AND dependent on intravenous parenteral nutrition (IPN) for nutritional support
5. Stimulation testing requirements not applicable for diagnosis of SBS

Zorbtive may only be authorized one 4-week course. GH treatment of SBS for more than 4 weeks is will NOT be authorized since administration of GH for more than 4 weeks duration has not been adequately studied for SBS.

F. HIV/AIDS-ASSOCIATED WASTING AND CACHEXIA (18 years of age or older)
1. Diagnosis of HIV/AIDs-associated wasting syndrome/cachexia, defined by ONE (1) of the following, not attributable to other concurrent illness(es) or medical condition(s):
   a. Unintentional weight loss of at least 10% of baseline weight within the past 12 months, OR
   b. BMI < 20 $kg/m^2$, not attributable to other concurrent illness(es) or medical condition(s), OR
   c. Weighs less than 90% Ideal Body Weight
   OR
   d. Baseline bioelectrical impedance analysis (BIA) or total body DEXA showing body cell mass (BCM) below 40% in males and 35% in females
2. Currently receiving optimal antiretroviral therapy for > 30 days prior to beginning somatropin therapy and will continue antiretroviral therapy throughout the course of somatropin treatment
3. A trial of androgen for HIV-associated wasting. If a trial of androgen is omitted, statement and supporting documentation of the clinical decision to advance directly to Serostim therapy must be submitted for review
4. Continued weight loss despite adequate nutrition and other measures including:
   a. Inadequate response, intolerance or contraindication to appetite stimulants, anabolic medications (Oxandrin, Winstrol, Nandrolone) and appetite stimulants (Marinol or Megace)
   AND

   b. Nutritional evaluation by a registered dietician (RD): RD has assessed, intervened, and monitored the Member according to the American Dietetic Association (ADA) Nutrition Therapy Protocol for HIV/AIDS. Documentation required.
5. Other underlying treatable conditions that may potentially cause weight loss have been ruled out, including ALL of the following:
   a. Inadequate nutritional intake evidenced by written evaluation by a RD, AND
   b. Presence of significant anxiety and/or depression affecting food intake, AND
   c. Growth inhibiting medication, chronic disease or chronic infectious diarrhea or endocrine disorders, AND
   d. Opportunistic infections (i.e. Mycobacterium avium, Pneumocystis carinii, esophageal candidiasis, cryptosporidiosis, microsporidiosis, Salmonella, Shigella, cytomegalovirus, tuberculosis), AND
   e. Evidence of other causes of wasting and cachexia have been ruled out, such as: hypothyroidism, chronic systemic disease, nutritional/emotional deprivation, intracranial malignancy or tumor, growth-inhibiting medication(s), and endocrine disorders, AND
   f. Members with history of malignancy: At least the past 12 months should be free of recurrence prior to initiating GH therapy. Anti-malignancy treatment must be completed with evidence of remission, AND
   g. Members with thyroid deficiency: Results of GH secretion tests will only be accepted after thyroid deficiency has been adequately treated because GH secretion may be subnormal as a result of hypothyroidism
6. Male members only: Normal testosterone blood levels (lab result within the past 2 months). If serum testosterone level is low, a documented trial of testosterone replacement therapy is required.
7. Baseline measurements of the following:
   a. Height, weight, ideal body weight, body mass index (BMI)
      AND
   b. Body cell mass (BCM) by bioelectrical impedance analysis (BIA)
      AND
   c. Serial measurements, weekly
8. Stimulation testing requirements not applicable for diagnosis of HIV/AIDS-associated wasting and cachexia

**DURATION OF APPROVAL:**
<u>All Indications</u> (unless otherwise stated—SBS, HIV/AIDS-associated wasting and cachexia)
Initial authorization: 6 months

Continuation of therapy: 12 months, OR for pediatric indications: 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)

For adult indications: For continuation, yearly reassessment of serum levels of IGF-I is required with appropriate dosage adjustments as GH requirements in adults will decrease with age.

<u>SBS</u>
Only Zorbtive is FDA-approved and can be used for this indication. Authorization is limited to one 4-week course of therapy (28 days) for SBS as there are currently no studies showing that additional benefit is conferred by further treatment beyond four weeks.
Initial authorization: 4 weeks of therapy based on FDA-approved dosage
Continuation of therapy: No additional authorizations after 4 weeks of therapy

<u>HIV/AIDS-associated wasting and cachexia</u>

Only Serostim is FDA approved and can be used for this indication. Initial authorization is limited to 12 weeks duration in order to determine effectiveness. Therapy with somatropin for HIV/AIDS-associated wasting and cachexiashould be limited to 48 weeks.
Initial therapy authorization period: Limited to 12 weeks duration to determine effectiveness
Continuation of Therapy or Repeat Courses: May be authorized for an additional 12 weeks
Duration of therapy: 48 weeks total (no additional authorizations after 48 weeks of therapy)

**QUANTITY:** 30-day supply per fill based on FDA-approved dosage for indication

**PRESCRIBER REQUIREMENTS:** Prescribed by a specialist based on the condition treated: pediatric endocrinologist or pediatric nephrologist (for children diagnoses), endocrinologist (for adults diagnoses) or infectious disease specialist (for AID

**AGE RESTRICTIONS:** Under 18 years of age ('Pediatric' criteria), 18 years of age and older ('Adult' criteria)

**GENDER:**
Male and female

**CONTINUATION OF THERAPY:**
FOR ALL INDICATIONS/DIAGNOSIS:

1. Member meets current initial diagnosis criteria
   AND
2. Member's age appropriate for criteria applied: PEDIATRIC diagnosis/indications if 18 years or younger, and ADULT criteria for members older than 18 years or adolescents whose epiphyses have closed
   AND
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 if poor adherence to the treatment regimen for any reason
   AND
4. Thyroid function tests are within normal range (TSH 0.4 - 4.0 mIU/L)
   AND
5. Other pituitary hormone deficiencies have been evaluated, ruled out, and/or corrected prior to time of testing (e.g. ACTH, TSH, FSH, LH, prolactin)
   AND
6. Nutritional status has been optimized, metabolic abnormalities have been corrected, and steroid usage has been reduced to a minimum
   AND
7. History of malignancy: Anti-malignancy treatment must be completed AND evidence of complete remission for at least 12 months free of recurrence
   AND
8. Diagnosis-specific criteria respective to member's condition is met, if applicable (#C below)
   AND
9. <u>For pediatric indications/diagnosis:</u> Pediatric GH deficiency, CRI/CKD, SGA, Turner syndrome, Noonan syndrome SHOX deficiency
   a. Open epiphyses confirmed by bone age X-ray of the left hand and wrist (required for 12 years of age and older only) at least once annually. Males: not to exceed 16 0/12 years of age; Females: not to exceed 14 0/12 years of age. X-ray must be taken within 6 months of request.
      AND

b. Expected adult height has not been reached (calculated using mid-parental height); 5th percentile for adults (65 inches for men and 60 inches for women); 50th percentile for height based on age
AND
c. Positive response as documented by growth curve chart (a or b):
i. First year of therapy: A doubling of pre-treatment growth, OR Growth velocity while on therapy is ≥ 2.5cm/year
ii. After the first year of therapy: Growth velocity remains above 2.5 cm/year (Not applicable to children with prior documented hypopituitarism)
iii. For PWS only: Body composition: Increase in lean body mass and decreases in fat mass. Documentation required.

10. For adult indications/diagnosis:
a. IGF-1 is in normal range for age and gender based on specific lab reference values. (If above normal, dose reduction required) NOTE: For continuation, yearly reassessment of serum levels of IGF-I is required with appropriate dosage adjustments as GH requirements in adults will decrease with age
b. Continual clinical benefit from growth hormone therapy [e.g. normalization of IGF-1 levels, improvements in cardiovascular risk markers, improvement in body composition; weight loss; body mineral density; increase bone mass; Improvement on lipid profile; serum cholesterol; Increase in physical or muscle strength; Improvement in 'Quality of Life Assessment of Growth Hormone Deficiency in Adults' (QoL-AGHDA) score]
NOTE: Children on GH therapy who transitions into GH therapy into adulthood OR adults with hypopituitarism of recent onset will not exhibit the manifestations of adult GHD and will not show the improvements listed above.

AND DIAGNOSIS/INDICATION SPECIFIC CRITERIA

A. HIV/AIDS-associated wasting and cachexia
1. Members who received a 3-month (12-week) course of HIV/AIDs-associated wasting syndrome/cachexia must have been off somatropin for at least ONE (1) month
a. Diagnosis of HIV/AIDs-associated wasting syndrome/cachexia continues to be met [defined as: a) Unintentional weight loss of at least 10% of baseline weight within the past 12 months; b) BMI < 20 kg/m2, not attributable to other concurrent illness(es) or medical condition(s); c) Weighs less than 90% Ideal Body Weight, OR d) Baseline bioelectrical impedance analysis (BIA) or total body DEXA showing body cell mass (BCM) below 40% in males and 35% in females]
AND
b. Positive clinical response to therapy from ONE of the following baseline measures:
i. Body mass index (BMI), OR
ii. Body cell mass (BCM) by bioelectrical impedance analysis (BIA)
c. For members who experienced weight loss after the initial four (4) weeks of therapy ONLY: Continuation of treatment will be considered after re-evaluation and documentation ALL of the following: a) Intervention of a clinical event (e.g., opportunistic infection) and resolution/treatment of this clinical event, AND b) Current clinical status, AND c) Measured BMI and BCM
NOTE: Therapy with somatropin for AIDS related wasting should be limited to 24 weeks total.

B. TRANSITION FROM CHILDHOOD TO ADULT GROWTH HORMONE THERAPY: (Continuation of Therapy After Completion of Linear Growth): GHD, Prader-Will syndrome (PWS), hypopituitarism (either alone or associated with multiple hormone deficiencies)

At completion of linear growth (i.e., growth rate less than 2.5 cm/year), GH therapy should be stopped for at least 3 months, and GH status should be re-assessed to determine whether continued GH

treatment into adulthood is necessary. Molina Healthcare will re-evaluate after GH therapy has been discontinued for 3 or more months to determine if the member meets the criteria for GH treatment.

NOTE: For CRI/CKD, SGA, Turner syndrome, Noonan syndrome, SHOX mutations treatment may continue until epiphyseal closure OR 'Continuation of Therapy' criteria are not met for member's respective condition

1. Member has completed linear growth as defined by growth rate less than 2.5 cm per year
2. GH treatment has been discontinued for at least 3 months after completion of linear growth
3. Member meets 1 of following sets of criteria (a or b)
    a. GH treatment has been stopped for at least 3 months AND diagnosis of GHD has been reconfirmed as follows:
        i. Subnormal response to TWO (2) provocative GH stimulation tests (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); Arginine/GHRH (4.1mcg/L OR cutoff value varies by waist circumference, BMI, and age: peak GH values ≤ 11 ng/mL if 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); OR

    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): Surgical removal of the pituitary or panhypopituitarism

        ii. Subnormal response to 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 1 month AND the diagnosis of GHD has been reconfirmed with the documented presence of ANY of the following conditions:
        i. Multiple Pituitary Hormone Deficiencies: Subnormal response (similar to the stimulation tests and values above criterion) to 1 provocative GH test AND/OR low IGF-1/IGFBP-3 level based on specific laboratory reference range
        ii. GH reassessment through stimulation testing is not required for the following members: 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; CNS 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 GH therapy)
4. Contraindications/Exclusions: Hypersensitivity to somatropin or any component of the formulation; 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

NOTE: 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.

**CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:**

All other uses of GH are considered experimental/investigational and therefore, will follow Molina's Off-Label policy.

1. History of hypersensitivity to somatropin or any component of the formulation.
2. Progression or recurrence of any underlying intracranial lesion or actively growing intracranial tumor

3. Acute critical illness caused by complications following open-heart or abdominal surgery, multiple accidental trauma or acute respiratory failure
4. Active malignancy
5. Active proliferative or severe non-proliferative diabetic retinopathy
6. Prader-Willi Syndrome: Individuals who are severely obese or have severe respiratory impairment (reports of sudden death); Uncontrolled diabetes; History of upper airway obstruction or severe respiratory impairment; Untreated severe obstructive sleep apnea; Active cancer; Active psychosis
7. CRI: Renal transplantation (GH therapy must be discontinued at the time of renal transplantation)

DISCONTINUATION

For pediatric indications with associated with growth failure:

1. Epiphyseal closure (Bone age ≥ 16 years (male), or ≥ 14 years (female) is reached)
2. Attained any of the following height goals (at any age): [ANY]
    a. 5th percentile for adults (65 inches for men and 60 inches for women)
    b. 50th percentile for height based on age
    c. Expected adult height has not been reached [Mid-parental height = (father's height + mother's height) divided by 2, plus 2.5 inches (male) or minus 2.5 inches (female)]
3. Poor response to treatment, generally defined as an increase in growth velocity of less than 50% from baseline, in the 1st year of therapy
4. Prader-Willi syndrome: Evaluation of response to therapy should also take into account whether body composition (i.e., ratio of lean to fat mass) has significantly improved; or
5. Increase in height velocity is less than 2.5 cm total growth in 1 year of therapy; or
6. Persistent and uncorrectable problems with adherence to treatment
7. Adverse reactions or side effects

EXCLUSIONS

1. Short stature in the absence of a GH deficiency or for the majority of other conditions in which GH has not been shown to provide clinical benefits or improvements in functional impairment or long-term health outcomes

**OTHER SPECIAL CONSIDERATIONS:**

Equivalence of Products

GH 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 vial: Medicaid; Omnitrope pen: Marketplace**

Non-Preferred Requests

1. Member meets all criteria for specific diagnosis/indication

AND

2. Failure or inadequate clinical response to the PREFERRED agent as documented by 1 of the following:
    a. 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, OR
    b. Member's diagnosis is not an FDA-labeled indication of the PREFERRED product, OR
    c. Previous hypersensitivity/allergy, clinical intolerance or labeled contraindication to the PREFERRED product. Documentation required.
        NOTE: 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). Genotropin or Humatrope contains a different preservative
        NOTE: 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.

**BACKGROUND:**

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.

Growth hormone 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.

Patients with childhood-onset growth hormone deficiency (GHD) who are appropriate candidates for GH therapy should be re-tested for GHD as adults unless they have known mutations, embryopathic lesions, or irreversible structural lesions/damage (level of evidence, high).

Growth Hormone Deficiency (GHD) is the inadequate secretion of endogenous growth hormone.

- GHD may be idiopathic or organic and may occur in childhood or adulthood. Pathophysiology differs between childhood or adulthood onsets. GHD is diagnosed through a combination of clinical and biochemical examination, testing and analysis.
- Generally results from conditions affecting the hypothalamus or pituitary gland including surgery and radiation therapy. Adults frequently report symptoms such as unintentional weight gain or difficult losing weight, low energy, reduced physical performance, decreased libido, impaired psychological well-being and a feeling that things are not right. Physical findings may include increased fat mass, decreased lean body and muscle mass, decreased bone density as well as reduced muscle strength and exercise capacity. There is however no single symptom or sign that is pathognomonic for GHD in adults. In addition, some adults with GHD may be entirely asymptomatic.

Recombinant human growth hormone (rhGH, 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 GH replacement in adults is to minimize the symptoms of GHD (e.g., fatigue, poor endurance, and poor sense of well-being), improve the quality of life, and achieve serum insulin–like growth factor (IGF-1) concentration in the normal range for age and sex. The major endpoints of treatment are to improve blood lipid levels, improve the patient's waist-to-hip ratio, improve body composition, improve quality of life, and reduce cardiovascular risk factors.

A stimulation test is needed to confirm the diagnosis of GHD in adults. Numerous tests are available. (AACE 2009)

- There is a lack of universal agreement on cutoff points for GH levels. Most experts suggest a peak value of less than 5 nanograms per milliliter (ng/ml) after stimulation as an indication of GHD. Regardless of the stimulation test and GH assay used, 5 ng/ml is the suggested cutoff point for all provocative tests.
- Stimulation tests used to diagnose growth hormone deficiency in adults include insulin tolerance (ITT), arginine, growth hormone releasing hormone (GHRH), and glucagon.
- The ITT is currently considered the gold standard of the tests available and is the preferred stimulation test agent. ITT is contraindicated in patients with cardiovascular disease, cerebrovascular disease, or seizure disorders, or in patients older than 65 years.
- A provocation test using arginine and GHRH (ARG + GHRH) is also acceptable and is considered more stringent than tests using arginine alone or levodopa alone. In patients where the ITT is not desirable and when recombinant GHRH is not available, the glucagon test is a reliable alternative, but not the levodopa and clonidine tests.
- Twenty-four hour continuous measurements of GH, serum levels of IGF-I, or serum of levels IGFBP [insulin-like growth factor-binding protein] are considered inadequate to document GHD.
- AACE (2009) does not recommend GH stimulation testing in patients with three or more pituitary hormone deficiencies and low IGF1.

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.

**APPENDIX:**

**DEFINITIONS:**

Mid-parental height = (father's height + mother's height) divided by 2, plus 2.5 inches (male) or minus 2.5 inches (female)

Growth Hormone (GH) Provocative Stimulation Test: 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. Normal Results of a GH Stimulation Test: Normal peak value: at least 10 ng/ml; Indeterminate: 5 to 10 ng/ml; Subnormal: 5 ng/ml

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.

HIV/AIDS-associated wasting and cachexia: Unintentional and progressive weight loss (cachexia) often accompanied by weakness, fever, nutritional deficiencies and diarrhea. The wasting can be caused by opportunistic infections that interfere with the gut’s ability to absorb nutrients, altered metabolism of nutrients or by inadequate food intake due to nausea and vomiting. The syndrome reduces the quality of life, exacerbates the illness and increases the risk of death for people with HIV. The goal of therapy is to increase the person’s body weight and promote an increase in lean body mass (muscle).

Short Bowel Syndrome (SBS) is a result of extensive surgical resection of the bowel resulting in various degrees of malabsorption depending on the area and site of resection and persistence of damage to the remaining bowel.

**IGF-1 Ranges (ng/mL)**

Reference Interval (ng/mL)

| AGE | MALE | FEMALE | AGE | MALE | FEMALE |
|---|---|---|---|---|---|
| 0.25 | 12 -94.1 | 13.8-86.4 | 40 | 98.5-229 | 91.4-227 |
| 0.5 | 11.8-94.6 | 15.4-92 | 41 | 96.4-226 | 89.8-225 |
| 1 | 11.8-96.4 | 18.7-104 | 42 | 94.4-223 | 88.1-224 |
| 2 | 13.9-104 | 26.1-128 | 43 | 92.4-221 | 86.5-222 |
| 3 | 18.9-116 | 34.2-155 | 44 | 90.5-218 | 84.9-221 |
| 4 | 26.8-134 | 43.2-185 | 45 | 88.5-216 | 83.3-220 |
| 5 | 36.6-156 | 53-216 | 46 | 86.5-214 | 81.8-219 |
| 6 | 47.1-184 | 63.6-250 | 47 | 84.6-211 | 80.2-218 |
| 7 | 57.5-216 | 75-286 | 48 | 82.6-209 | 78.7-218 |
| 8 | 67.5-254 | 87.3-324 | 49 | 80.6-207 | 77.2-217 |
| 9 | 76.9-296 | 99.9-363 | 50 | 78.7-205 | 75.7-215 |
| 10 | 85.9-343 | 112-398 | 51 | 76.7-203 | 74.3-214 |
| 11 | 93.9-392 | 123-427 | 52 | 74.8-201 | 72.8-212 |
| 12 | 101-434 | 132-451 | 53 | 72.8-200 | 71.4-210 |
| 13 | 108-467 | 140-468 | 54 | 70.9-198 | 70-207 |
| 14 | 115-489 | 146-480 | 55 | 68.9-196 | 68.6-204 |
| 15 | 120-501 | 151-485 | 56 | 67-195 | 67.3-201 |
| 16 | 125-503 | 154-485 | 57 | 65.3-194 | 65.9-198 |
| 17 | 129-495 | 156-479 | 58 | 63.7-193 | 64.6-194 |
| 18 | 132-476 | 156-466 | 59 | 62.3-192 | 63.3-190 |
| 19 | 134-450 | 155-449 | 60 | 61.1-191 | 62-186 |
| 20 | 136-421 | 152-429 | 61 | 60-190 | 60.7-182 |
| 21 | 137-394 | 148-410 | 62 | 59.2-189 | 59.5-179 |
| 22 | 137-370 | 143-392 | 63 | 58.5-188 | 58.3-176 |
| 23 | 136-348 | 138-375 | 64 | 57.9-188 | 57.3-173 |
| 24 | 135-328 | 134-359 | 65 | 57.4-187 | 56.3-170 |
| 25 | 132-310 | 130-343 | 66 | 56.8-186 | 55.5-168 |
| 26 | 130-295 | 126-329 | 67 | 56.3-186 | 54.8-166 |
| 27 | 128-282 | 122-315 | 68 | 55.8-185 | 54.2-164 |
| 28 | 125-271 | 118-303 | 69 | 55.2-185 | 53.8-163 |
| 29 | 123-263 | 115-292 | 70 | 54.7-185 | 53.5-162 |
| 30 | 120-257 | 112-280 | 71 | 54.1-184 | 53.3-161 |
| 31 | 118-253 | 109-271 | 72 | 53.6-184 | 53.2-160 |
| 32 | 116-250 | 107-263 | 73 | 53-184 | 53.2-160 |
| 33 | 114-247 | 104-255 | 74 | 52.4-184 | 53.3-160 |
| 34 | 111-244 | 102-248 | 75 | 51.9-184 | 53.5-160 |
| 35 | 109-242 | 100-242 | 76 | 51.3-184 | 53.7-161 |
| 36 | 107-239 | 98.3-238 | 77 | 50.7-184 | 54-162 |
| 37 | 105-236 | 96.5-234 | 78 | 50.2-184 | 54.3-163 |
| 38 | 103-234 | 94.8-231 | 79 | 49.6-184 | 54.7-164 |
| 39 | 101-231 | 93.1-228 | 80 | | 55.1-166 |

Insulin-like growth factor I (IGF-1) serum/plasma concentrations are age- and sex-dependent and should be interpreted in conjunction with the appropriate reference range. In addition to the IGF-1 concentration and corresponding reference range, Z scores are provided for all results for patients younger than 80 years old. A Z score is the number of standard deviations a given result is above (positive score) or below (negative score) the age- and sex-adjusted population mean. Results that are within the IGF-1 reference interval will have a Z score between -2.0 and +2.0. Z scores are calculated using the IGF-1 concentration and parameters provided by the assay manufacturer.

IGF-1 concentrations can be used to assess growth hormone (GH) deficiency or excess. Serum IGF-1 concentrations below the 2.5th percentile (Z-score < -2) are consistent with GH deficiency or severe GH resistance. Definitive diagnosis of GH deficiency or resistance may require additional diagnostic testing such as GH stimulation tests. The aim of GH replacement therapy in children and adults with GH deficiency is to achieve IGF-1 concentrations within the age- and sex-appropriate reference range, ideally the middle-to-upper third of that range.

Elevated IGF-1 concentrations help support diagnosis of acromegaly in conjunction with compatible clinical signs and symptoms. Additional diagnostic tests and imaging studies may aid in diagnosis.

Persons with anorexia or malnutrition often have low IGF-1 concentrations.

Reference ranges in pregnancy have not been formally established. IGF-1 concentrations increase approximately 2-fold during normal uterine pregnancy compared to pre-pregnancy baseline.

Note: Both patient age and sex are required for Z score calculation

**Insulin Like Growth Factor Binding Protein III (IGFBP-3)**

| Age | Male | Female |
|---|---|---|
| 0-12 months | 1039-3169 ng/mL | 1039-3169 ng/mL |
| 1-3 years | 972-4123 ng/mL | 1590-4225 ng/mL |
| 4-5 years | 1843-4968 ng/mL | 2169-4790 ng/mL |
| 6-7 years | 1838-4968 ng/mL | 2188-4996 ng/mL |
| 8-9 years | 1932-5858 ng/mL | 2072-5504 ng/mL |
| 10-11 years | 1828-6592 ng/mL | 2456-6992 ng/mL |
| 12-13 years | 2134-6598 ng/mL | 2838-6846 ng/mL |
| 14-15 years | 2330-6550 ng/mL | 2654-6680 ng/mL |
| 16-17 years | 2380-6400 ng/mL | 2756-6908 ng/mL |
| 18-19 years | 2340-6632 ng/mL | 2700-6492 ng/mL |
| 20-24 years | 2404-5948 ng/mL | 3032-5992 ng/mL |
| 25-29 years | 2614-5792 ng/mL | 2926-5858 ng/mL |
| 30-34 years | 2500-5806 ng/mL | 2878-6650 ng/mL |
| 35-39 years | 2474-5208 ng/mL | 2786-6084 ng/mL |
| 40-44 years | 2360-5560 ng/mL | 2514-6014 ng/mL |
| 45-49 years | 2314-5700 ng/mL | 2838-4954 ng/mL |
| 50-54 years | 2528-5050 ng/mL | 2562-5596 ng/mL |
| 55-59 years | 2482-5460 ng/mL | 2574-5914 ng/mL |
| 60-64 years | 2592-4770 ng/mL | 2684-5130 ng/mL |
| 65 years and older | 2698-5688 ng/mL | 2462-5274 ng/mL |
| Tanner Stage I | 1878-6190 ng/mL | 2314-6086 ng/mL |
| Tanner Stage II | 2112-6208 ng/mL | 2732-6738 ng/mL |
| Tanner Stage III | 2372-6602 ng/mL | 2870-7068 ng/mL |
| Tanner Stage IV & V | 2336-6414 ng/mL | 2756-7232 ng/mL |

Insulin-like growth factor binding proteins binds IGF-I and IGF-II with high affinity but do not bind insulin. Of the 6 distinct IGF binding proteins structurally characterized at this time, IGFBP-3 has been shown to be the major carrier of the IGFs, transporting approximately 95% of the circulating IGF-I and IGF-II.

IGFBP-3 is growth hormone (GH) responsive. Thus, levels are high in acromegaly and low in hypopituitarism, and levels increase in GH- deficient children after GH administration.

Other causes of short stature that result in reduced IGFBP-3 levels include poorly controlled diabetes. The IGFBP-3 assay can be useful in assessing nutritional status, since IGFBP-3 decreases during both caloric and protein restriction.

**ABBREVIATIONS:**
Adrenocorticotropin hormone (ACTH)
Thyroid stimulating hormone (TSH)
Leutinizing hormone (LH)
Follicle stimulating hormone (FSH)
Arginine vasopressin (AVP)

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