## Drug Therapy Guidelines

Applicable

<table>
<thead>
<tr>
<th>Medical Benefit</th>
<th>Effective: 6/21/17</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacy- Formulary 1</td>
<td>x</td>
</tr>
<tr>
<td>Pharmacy- Formulary 2</td>
<td>x</td>
</tr>
<tr>
<td>Pharmacy- Formulary 3/Exclusive</td>
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</tr>
</tbody>
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### I. Medication Description

Endogenous growth hormone (GH) is responsible for stimulating normal skeletal, connective tissue, muscle, and organ growth in children and adolescents. It also plays an important role in adult metabolism. Recombinant products mimic all of these actions. Somatropin (recombinant growth hormone) is typically administered subcutaneously or intramuscularly once daily.

While all growth hormone products are variations of somatropin, some products are approved by the U.S. Food and Drug Administration for different pediatric and adult indications.

### Growth Hormone Products

<table>
<thead>
<tr>
<th>Growth Hormone Products</th>
<th>Indication</th>
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<tbody>
<tr>
<td></td>
<td>Adult GHD*</td>
</tr>
<tr>
<td>Genotropin®</td>
<td>✓</td>
</tr>
<tr>
<td>Humatrope®</td>
<td>✓</td>
</tr>
<tr>
<td>Norditropin®</td>
<td>✓</td>
</tr>
<tr>
<td>Nutropin®</td>
<td>✓</td>
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<tr>
<td>Nutropin AQ®</td>
<td>✓</td>
</tr>
<tr>
<td>Omnitrope®</td>
<td>✓</td>
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<tr>
<td>Saizen®</td>
<td>✓</td>
</tr>
<tr>
<td>Serostim®</td>
<td>✓</td>
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<tr>
<td>Zomacton™</td>
<td>✓</td>
</tr>
<tr>
<td>Zorbtive®</td>
<td>✓</td>
</tr>
</tbody>
</table>

*GHD = growth hormone deficiency/insufficiency  **CRD = growth failure due to chronic renal disease  +ISS = idiopathic short stature  ++SGA = small for gestational age  +++SHOX = treatment of short stature / growth failure in children with homeobox-containing gene deficiency

### II. Position Statement

Coverage is determined through a prior authorization process with supporting clinical documentation for every request.
III. Policy

Formulary 1: See Sections A, B
Formulary 2: See Sections A, B
Formulary 3/Exclusive: See Sections A, B
Formulary 4/AON: See Sections A, B

A. Prior authorization criteria:
   • Prescriber Requirements:
     o Pediatric members are under the care of a pediatric endocrinologist or a pediatric nephrologist with expertise in growth hormone.
     o Adult therapy must be ordered or recommended by an appropriate specialist for diagnosis.
   • Coverage is provided for the following diagnoses:
     o Pediatric growth hormone deficiency:
       ▪ Epiphyses must be confirmed as open in members ≥ 10 years of age AND
       ▪ GH deficiency established by:
         • Growth hormone deficiency confirmed by any 2 provocative test results below 10 ng/ml (i.e., L-Dopa, insulin-induced hypoglycemia, arginine, glucagon, clonidine) OR
         • One provocative stimulation test less than 15 ng/ml, combined with a low insulin-like growth factor-1 (IGF-1) level and low IGFBP-3 (insulin-like growth factor binding protein-3) both IGF values defined for age, gender, and pubertal status AND
       ▪ Growth failure established by:
         • Member’s height must be below the third percentile for their age and gender related height AND / OR
         • Growth velocity subnormal ≥ 2 standard deviations (SD) from the age-related mean measured over 1 year AND
         • Delayed skeletal maturation ≥ 2 SD below the age/gender related mean
     o Pediatric growth failure due to chronic kidney disease:
       ▪ Member has not received a renal transplant AND
       ▪ Member’s height must be below the third percentile for their age and gender related height as demonstrated on updated growth chart
     o Growth failure in children born small for gestational age (SGA):
       ▪ Member is born SGA, defined as growth charts showing birth weight, birth length, or both that are more than 2 standard deviations below mean normal values following adjustment for age and gender AND
       ▪ Failed to manifest catch-up growth by age 2
     o Turner’s syndrome in girls:
       ▪ Karyotype analysis confirms diagnosis (45, XO genotype) AND
       ▪ Member height falls below the fifth percentile for age (which usually occurs between two and five years of age) demonstrated on updated growth chart with baseline height and weight
- Prader-Willi syndrome:
  - Assessment for any underlying airway obstruction including sleep study is provided AND
  - Diagnosis confirmed by appropriate genetic testing (loss of gene function associated with chromosome 15 such as translocation or maternal uniparental disomy) AND
  - Contraindicated for use in members with severe obesity (e.g., weight >225 percent of ideal body weight), respiratory compromise, or severe sleep apnea AND
  - Baseline height and weight is provided

- Noonan Syndrome:
  - Chart documentation is provided confirming diagnosis AND
  - Updated growth chart is provided

- Short stature or growth failure in children with short stature homeobox (SHOX)–deficiency:
  - Diagnosis demonstrated by chromosome analysis AND
  - Updated growth chart is provided

- Adult growth hormone deficiency:
  - Adult-onset growth hormone deficiency isolated growth hormone or multiple hormone deficiencies (hypopituitarism), as a result of pituitary disease, hypothalamic disease, surgery, radiation therapy, or trauma with one of the following:
    - Serum IGF-1 concentration is lower than the age-specific lower limit of normal in a member who has organic pituitary disease OR
    - If IGF-1 is not subnormal, a subnormal GH response to insulin-induced hypoglycemia (<5.1 ng/ml) or arginine-GHRH (<4.1ng/ml) is necessary to confirm diagnosis
  - Childhood onset growth hormone deficiency as a result of congenital, genetic, acquired, or idiopathic causes:
    - A period of at least one month should pass before re-evaluating GH status after therapy has been discontinued at final height AND one of the following:
      - Retesting has been performed using Insulin tolerance test (ITT) as a first-line unless contraindicated (examples: members at high risk for coronary artery disease or with a history of seizures) OR
      - Alternative testing when ITT contraindicated:
        - growth hormone releasing hormone (GHRH)+arginine (ARG) test
        - glucagon test
        - ARG test alone OR
      - Retesting is waived due to:
        - known mutations, embryopathic/congenital defects, irreversible hypothalamic-pituitary structural lesions AND
        - evidence of panhypopituitarism (at least 3 pituitary hormone deficiencies) AND
• IGF-I levels below the age- and sex-appropriate reference range off GH therapy

• Coverage of Zorbtive® (or Norditropin®, if requested) is provided for the treatment of short bowel syndrome when:
  o Diagnosis is documented as a result of resected or damaged bowel with chronic diarrhea, weight loss, electrolyte imbalances, malnutrition, dehydration, and malabsorption of fats, vitamins and minerals AND
  o There is dependence on specialized nutritional support needs including dietary adjustments such as a high carbohydrate, low fat diet, enteral feedings, parenteral nutrition, fluid, and micronutrient supplements demonstrated through nutritionist consultation, dietary interventions, pertinent labs

• Coverage of Serostim® is provided for the treatment of HIV members with wasting or cachexia when:
  o Member is ≥ 18 years of age AND
  o Comparative weights and heights are documented AND
  o Wasting syndrome is not attributable to other causes such as; depression, MAC, chronic infectious diarrhea, or malignancy (Kaposi’s sarcoma limited to the skin or mucous membranes is covered) AND
  o Confirmation of wasting syndrome has been documented (e.g., unintentional weight loss of at least 10% of body weight) AND
  o Optimal antiretroviral therapy has been attempted AND
  o Failure of non-invasive forms of nutritional therapy (such as appetite stimulants like megestrol acetate and dronabinol).

B. Step therapy: A step edit is in place whereby non-preferred medications (Genotropin, Humatrope, Omnitrope, Nutropin, Saizen, ZomactonTM) will only be covered for members who have failed a trial with the plan-preferred medication (Norditropin):

• Member must have attempted and failed an adequate (3 month) trial with the plan-preferred medication somatropin (Norditropin) before any other growth hormone medication will be covered OR the following criteria must be met:
  o When requesting coverage of a brand medication for which an A/B rated generic is available, there is sufficient evidence that the use of the A/B rated generic equivalent has resulted in inadequate results AND
  o At least one of the following is met:
    ▪ The plan-preferred medications are contraindicated or will likely cause an adverse reaction by or physical or mental harm to the member.
    ▪ The plan-preferred medications are expected to be ineffective based on the known clinical history and conditions of the member and the member’s prescription drug regimen.
    ▪ The member has tried the plan-preferred medications or another prescription drug in the same pharmacologic class or with the same mechanism of action and such prescription drug was discontinued due to lack of efficacy or effectiveness, diminished effect, or an adverse event.
    ▪ The member is stable on the medication selected by their healthcare professional for the medical condition under consideration (where “stable” is defined as receiving the medication for an adequate period of time, have achieved optimal
response, and continued favorable outcomes are expected UNLESS the medication was initially selected due to the availability of a drug sample or a coupon card).

- The plan-preferred medication is not in the best interest of the member because it will likely cause a significant barrier to the member’s adherence or to compliance with the member’s plan of care, will likely worsen a comorbid condition of the member, or will likely decrease the member’s ability to achieve or maintain reasonable functional ability in performing daily activities.
  
- Exceptions: Norditropin® trial will NOT be required when:
  - Zorbtive® is used for treatment of short bowel syndrome OR
  - Serostim® is used in HIV related cachexia or wasting.

IV. Quantity Limits

- Adults
  - Genotropin® and Omnitrope®: 0.08 mg/kg/week
  - Humatrope®: 0.0125 mg/kg/day
  - Norditropin®: 0.016 mg/kg/day
  - Nutropin® and Nutropin AQ®: 0.025 mg/kg/day in members younger than 35 years of age; 0.0125 mg/kg/day in members 35 years of age and older
  - Saizen®: 0.01 mg/kg/day
  - Serostim®: 6 mg/day (weight dependent)
  - Zorbtive®: 8 mg/day

- Children- Dosing adjustments in children are dependent upon maintaining IGF-1 levels within a targeted range; therefore, maximum units are individualized.

V. Coverage Duration

- Pediatric human growth hormone deficiency, growth failure in children SGA, growth failure due to Turner’s syndrome, Noonan Syndrome, SHOX, chronic renal failure, or Prader-Willi Syndrome:
  - Norditropin®: coverage provided for 12 months and may be renewed
  - All other growth hormone products: coverage provided for 3 months with follow-up authorizations of up to 12 months depending on comparative response (see Step-Therapy requirements)

- Adult growth hormone deficiency
  - Norditropin®: coverage provided for 12 months and may be renewed
  - All other growth hormone products: coverage provided for 3 months with follow-up authorizations of up to 12 months depending on comparative response (see Step-Therapy requirements)

- Short bowel syndrome:
  - Zorbtive®: 1 month and may be renewed
  - Norditropin®: coverage is provided for 6 months and may be renewed

- HIV-related wasting or cachexia: 3 months and may be renewed
VI. Coverage Renewal Criteria

Coverage may be renewed according to the following criteria in the absence of unacceptable toxicity from the drug:

- Pediatric human growth hormone deficiency, growth failure in children SGA, growth failure due to Turner’s syndrome, Noonan Syndrome, SHOX, or chronic renal failure:
  - open epiphyses documented (bone age of 16 years for boys, 14 years for girls) AND
  - growth response of at least 4.5 cm/yr (prepubertal growth rate) or at least 2.5 cm/yr (post-pubertal growth rate) documented with updated growth chart and recent height and weight with date measured

- Prader-Willi Syndrome:
  - Updated growth chart and recent height and weight with date measured AND
  - Documented increase in lean body mass (or decrease in fat) OR
  - Maintenance of benefit in males up to 16 years of age and in females up to 14 years of age

- Adult growth hormone deficiency:
  - Clinical benefit documented (e.g., increase in total lean body mass, increase in IGF-1 and IGFBP-3 levels, or increase in exercise capacity) AND
  - Benefit seen from comparative weight to baseline with height

- Short bowel syndrome:
  - Progress notes showing benefit AND
  - Applicable labs/testing showing benefit AND
  - Renewable in situations where the member is deriving clinical benefit (e.g., the member is experiencing a decrease in intravenous nutrition requirements)

- HIV-related wasting or cachexia:
  - Renewable in the presence of weight stabilization or increase documented with height and comparable weights

VII. Billing/Coding Information

Pertinent diagnoses:

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>B20</td>
<td>Human immunodeficiency virus (HIV) disease</td>
</tr>
<tr>
<td>C75.1, C75.2</td>
<td>Malignant neoplasm of pituitary gland and craniopharyngeal duct</td>
</tr>
<tr>
<td>C79.31</td>
<td>Secondary malignant neoplasm of brain and spinal cord</td>
</tr>
<tr>
<td>D35.2, D35.3</td>
<td>Benign neoplasm of pituitary gland and craniopharyngeal duct</td>
</tr>
<tr>
<td>D44.3, D44.4</td>
<td>Neoplasm of uncertain behavior of pituitary gland and craniopharyngeal duct</td>
</tr>
<tr>
<td>E23.0</td>
<td>Panhypopituitarism</td>
</tr>
<tr>
<td>E23.0</td>
<td>Pituitary dwarfism</td>
</tr>
<tr>
<td>E23.6</td>
<td>Unspecified anterior pituitary disorders</td>
</tr>
<tr>
<td>E22.2</td>
<td>Other disorders of neurohypophysis</td>
</tr>
<tr>
<td>E23.1, E89.3</td>
<td>Iatrogenic pituitary disorders</td>
</tr>
</tbody>
</table>
E23.6    Other disorders of the pituitary and other syndromes of diencephalohypophyseal origin

E23.3, E23.7    Unspecified endocrine disorder

K91.2    Other and unspecified postsurgical nonabsorption

N18.2    Chronic kidney disease, stage ii (mild)

N18.3    Chronic kidney disease, stage iii (moderate)

N18.4    Chronic kidney disease, stage iv (severe)

N18.5    Chronic kidney disease, stage v

N18.6    End stage renal disease

N18.9    Chronic kidney disease, unspecified

Q96.9    Gonadal dysgenesis (i.e., Turner's syndrome)

Q87.1    Prader-Willi syndrome

Q87.1    Russell-Silver syndrome

R62.50    Lack of physiological development

R64    Cachexia

Z92.3    Personal history of irradiation presenting hazards to health

VIII. Summary of Policy Changes

- 3/1/11:
  - Increlex® policy moved to separate guideline
  - Removal of Idiopathic Short Stature from covered indications
  - Step-Therapy Modified to one plan-preferred product (Norditropin®)
- 6/15/12:
  - Additional indications added to Omnitrope®
  - Pancreatitis and benzyl alcohol warnings added
  - Required documentation added to criteria
- 3/15/13: clarified which plans have step therapy requirements
- 7/1/13: Commercial Rx and Medicaid/Family Health Plus criteria differentiated
- 3/15/14: no policy changes
- 3/15/15: no policy changes
- 7/1/15:
  - Formulary distinctions made
  - Zomacton added to policy
- 9/15/15: no policy changes
- 2/3/16: clarification made that Norditropin® would be considered for coverage in the treatment of short bowel syndrome
- 7/19/16: no policy changes
- 5/1/17: step therapy criteria added
- 6/21/17: no policy changes
IX. References

1. UpToDate Online, retrieved May 2016.


The Plan fully expects that only appropriate and medically necessary services will be rendered. The Plan reserves the right to conduct pre-payment and post-payment reviews to assess the medical appropriateness of the above-referenced therapies.

The preceding policy applies only to members for whom the above named pharmacy benefit medications are included on their covered formulary. Members with closed formulary benefits are subject to trying all appropriate formulary alternatives before a coverage exception for a non-formulary medication will be considered.

The preceding policy is a guideline to allow for coverage of the pertinent medication/product, and is not meant to serve as a clinical practice guideline.