Clinical Policy: Somatropin (Recombinant Human Growth Hormone)
Reference Number: ERX.SPA.14
Effective Date: 07.01.16
Last Review Date: 05.19

See Important Reminder at the end of this policy for important regulatory and legal information.

Description
The following are recombinant human growth hormones requiring prior authorization: somatropin (Genotropin®, Genotropin Miniquick®, Humatrope®, Humatrope Combo Pack®, Norditropin FlexPro®, Nutropin AQ NuSpin®, Omnitrope®, Saizen®, Serostim®, Zomacton™, Zorbtive™).

FDA Approved Indication(s)
Genotropin is indicated:
- For the treatment of children with growth failure due to growth hormone deficiency (GHD), Prader-Willi syndrome, small for gestational age, Turner syndrome, and idiopathic short stature
- For the treatment of adults with either childhood-onset or adult-onset GHD

Humatrope is indicated:
- For the treatment of children with short stature or growth failure associated with growth hormone (GH) deficiency, Turner syndrome, idiopathic short stature, short stature homeobox-containing gene (SHOX) deficiency, and failure to catch up in height after small for gestational age birth
- For the treatment of adults with either childhood-onset or adult-onset GHD

Norditropin FlexPro is indicated:
- For the treatment of children with growth failure due to GHD, short stature associated with Noonan syndrome, short stature associated with Turner syndrome, and short stature born small for gestational age with no catch-up growth by age 2 to 4 years
- For the treatment of adults with either childhood-onset or adult-onset GHD

Nutropin AQ NuSpin is indicated:
- For the treatment of children with growth failure due to GHD, idiopathic short stature (ISS), Turner syndrome (TS), and chronic kidney disease (CKD) up to the time of renal transplantation
- For the treatment of adults with either childhood-onset or adult-onset GHD

Omnitrope is indicated:
- For the treatment of children with growth failure due to GHD, Prader-Willi syndrome, small for gestational age, Turner syndrome, and idiopathic short stature
- For the treatment of adults with either childhood-onset or adult-onset GHD

Saizen is indicated:
- For the treatment of children with growth failure due to GHD
- For the treatment of adults with either childhood-onset or adult-onset GHD

Serostim is indicated:
- For the treatment of HIV patients with wasting or cachexia to increase lean body mass and body weight, and improve physical endurance

Zomacton is indicated:
- For the treatment of children who have growth failure due to inadequate secretion of normal endogenous GH, short stature associated with TS, ISS, SHOX deficiency, and short stature born small for gestational age (SGA) with no catch-up growth by 2 years to 4 years
- For replacement of endogenous GH in adults with GH deficiency
Zorbtive is indicated:
- For the treatment of short bowel syndrome (SBS) in patients receiving specialized nutritional support. Zorbtive therapy should be used in conjunction with optimal management of SBS.

**Policy/Criteria**
*Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.*

*Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.*

It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ that somatropin (recombinant human growth hormone [rhGH]) is **medically necessary** when the following criteria are met:

I. **Initial Approval Criteria**
   A. **Growth Hormone Use in Children** (must meet all):
      1. Diagnosis of one of the following (a, b, c, d, e, f, or g):
         a. GHD as evidenced by low or low normal insulin-like growth factor (IGF)-I or insulin-like growth factor binding protein (IGFBP)-3 level and one of the following (i, ii, iii, or iv):
            i. Two GH stimulation tests with peak levels ≤ 10 µg/L;
            ii. Evidence of ≥ 3 pituitary hormone deficiencies (see Appendix D);
            iii. History of surgery or irradiation in the hypothalamic-pituitary region;
            iv. Defined central nervous system pathology;
         b. SHOX deficiency in children with Shoxdna Dx® genetic test that detects mutations and deletions in the SHOX gene;
         c. Growth failure secondary to chronic kidney disease in pre-transplantation;
         d. Prader-Willi syndrome, Turner syndrome, or Noonan syndrome;
         e. Neonatal hypoglycemia;
         f. Central nervous system tumor treated with radiation;
         g. Small for gestational age as defined by both of the following (i and ii):
            i. Birth weight or length > 2 standard deviations (SD) below the mean for gestational age;
            ii. Failure to manifest catch-up growth to reach normal height range by age 2;
      2. Prescribed by or in consultation with an endocrinologist;
      3. Age ≤ 18 years;
      4. For Prader-Willi syndrome, Turner syndrome, Noonan syndrome, and SHOX deficiency: confirmation of diagnosis by genetic testing;
      5. Documentation of baseline height at the time of request;
      6. Member’s bone age is ≤ 15 years if female or ≤ 17 years if male;
      7. If request is for an rhGH product other than Norditropin or Humatrope, the Norditropin and Humatrope formulations are inappropriate (e.g., due to preservatives or dosing increment limitations) or member has a contraindication or experienced clinically significant adverse effects to Norditropin and Humatrope;
      8. Dose does not exceed the maximum indicated in the prescribing information.
   
   **Approval duration: 12 months**

   B. **Adult GHD or Short Bowel Syndrome** (must meet all):
      1. Diagnosis of one of the following (a or b):
         a. Adult GHD as evidenced by one of the following (i or ii):
            i. Two insulin tolerance test (ITT) GH stimulation tests with peak levels ≤ 5 µg/L;
            ii. One low IGF-I level and one of the following (a, b, c, d, e, f, or g):
               a) One ITT GH stimulation test with a peak level levels ≤ 5 µg/L;
               b) One glucagon GH stimulation test with peak level ≤ 3 µg/L;
               c) One arginine GH stimulation test with peak level ≤ 0.4 µg/L;
d) Hypothalamic-pituitary structural lesions;

e) Growth hormone releasing hormone/Arginine test with peak GH levels:
   1) ≤ 11.0 μg/L in members with BMI < 25 kg/m²;
   2) ≤ 8.0 μg/L in members with BMI ≥ 25 and < 30 kg/m²;
   3) ≤ 4.0 μg/L in members with BMI ≥ 30 kg/m²;

f) Evidence of ≥ 3 pituitary hormone deficiencies (see Appendix D);

b) SBS;

2. Age ≥ 18 years;

3. Prescribed by or in consultation with an endocrinologist;

4. If request is for an rhGH product other than Norditropin or Humatrope, the Norditropin and Humatrope formulations are inappropriate (e.g., due to preservatives or dosing increment limitations) or member has a contraindication or experienced clinically significant adverse effects to Norditropin and Humatrope;

5. Dose does not exceed the maximum indicated in the prescribing information.

Approval duration:
   Adult GHD – 12 months
   SBS – 4 weeks

C. Wasting or Cachexia in HIV Patients (must meet all):
   1. Diagnosis of HIV infection;
   2. Age ≥ 18 years;
   3. Member is on concomitant anti-viral therapy for the treatment of HIV;
   4. Involuntary weight loss of > 10% of body weight;
   5. One of the following (a or b) unless contraindicated or clinically significant adverse effects are experienced:
      a. If inadequate appetite, failure of megestrol acetate or dronabinol to stimulate appetite;
      b. If inadequate intake due to nausea, failure of ≥ 1 preferred agent(s) for nausea (see Appendix B);
   6. Failure of a therapeutic trial of testosterone in combination with an anabolic steroid in males unless contraindicated or clinically significant adverse effects are experienced;
   7. If request is for an rhGH product other than Norditropin or Humatrope, the Norditropin and Humatrope formulations are inappropriate (e.g., due to preservatives or dosing increment limitations) or member has a contraindication or experienced clinically significant adverse effects to Norditropin and Humatrope;
   8. Dose does not exceed the maximum indicated in the prescribing information.

Approval duration: 3 months

D. Other diagnoses/indications
   1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

II. Continued Therapy
   A. Growth Hormone Use in Children (must meet all):
      1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
      2. Member is responding positively to therapy as evidenced by increased growth rate by 2 cm over baseline in first year;
      3. Member’s bone age is ≤ 15 years if female or ≤ 17 years if male;
      4. If request is for a dose increase, new dose does not exceed the maximum indicated in the prescribing information.

Approval duration: 12 months
B. Adult GHD, HIV-Related Cachexia, or Short Bowel Syndrome (must meet all):
   1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
   2. Member is responding positively to therapy;
   3. If request is for a dose increase, new dose does not exceed the maximum indicated in the prescribing information.
   Approval duration: 12 months

C. Other diagnoses/indications (must meet 1 or 2):
   1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions and documentation supports positive response to therapy.
   2. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).
   Approval duration: Duration of request or 6 months (whichever is less); or

III. Diagnoses/Indications for which coverage is NOT authorized:
A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off-label use policy – ERX.PA.01 or evidence of coverage documents;
B. Idiopathic short stature;
C. Constitutional growth delay;
D. Obesity;
E. Adult short stature or altered body habitus associated with antiviral therapy;
F. Anabolic therapy to enhance body mass or strength for non-medical reasons (e.g., athletic gains).

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key
CKD: chronic kidney disease
FDA: Food and Drug Administration
GFR: glomerular filtration rate
GH: growth hormone
GHD: growth hormone deficiency
HIV: human immunodeficiency virus
IGF-1: insulin-like growth factor-1
IGFBP-3: insulin-like growth factor binding protein-3
ISS: idiopathic short stature
PWS: Prader-Willi syndrome
rhGH: recombinant human growth hormone
SBS: short bowel syndrome
SD: standard deviation
SGA: small for gestational age
SHOX: short stature homeobox-containing gene
TS: Turner syndrome

Appendix B: Therapeutic Alternatives
This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent for all relevant lines of business and may require prior authorization.

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dosing Regimen</th>
<th>Dose Limit/Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Appetite stimulants</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>megestrol (Megace&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>400 - 800 mg PO daily (10 – 20 ml/day)</td>
<td>800 mg/day</td>
</tr>
<tr>
<td>dronabinol (Marinol&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>2.5 mg PO BID</td>
<td>20 mg/day</td>
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<tr>
<td><strong>Testosterone replacement products</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>testosterone enanthate or cypionate (Various brands)</td>
<td>50 - 400 mg IM Q2 – 4 wks</td>
<td>400 mg Q 2 wks</td>
</tr>
<tr>
<td>Androderm&lt;sup&gt;®&lt;/sup&gt; (testosterone transdermal)</td>
<td>2.5 – 7.5 mg patch applied topically QD</td>
<td>7.5 mg/day</td>
</tr>
<tr>
<td>Androgel&lt;sup&gt;®&lt;/sup&gt; (testosterone gel)</td>
<td>5 - 10 gm gel (delivers 50 – 100 mg testosterone) applied topically QD</td>
<td>10 gm/day gel (100 mg/day testosterone)</td>
</tr>
</tbody>
</table>
### Clinical Policy

**Somatropin**

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dosing Regimen</th>
<th>Dose Limit/Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Testim® (testosterone gel)</strong></td>
<td>5 - 10 gm gel (delivers 50 – 100 mg testosterone) applied topically QD</td>
<td>10 gm/day gel (100 mg/day testosterone)</td>
</tr>
<tr>
<td><strong>Anabolic steroid</strong></td>
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<td></td>
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<tr>
<td>oxandrolone (Oxandrin®)</td>
<td>2.5 – 20 mg PO /day</td>
<td>20 mg/day</td>
</tr>
<tr>
<td>nandrolone decanoate</td>
<td>100 mg IM Q week</td>
<td>100 mg Q wk</td>
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<tr>
<td><strong>Nausea/vomiting treatments</strong></td>
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<td></td>
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<tr>
<td>chlorpromazine</td>
<td>10 to 25 mg PO q4 to 6 hours prn</td>
<td>2,000 mg/day</td>
</tr>
<tr>
<td>perphenazine</td>
<td>8 to 16 mg/day PO in divided doses</td>
<td>64 mg/day</td>
</tr>
<tr>
<td>prochlorperazine</td>
<td>5 to 10 mg PO TID or QID</td>
<td>40 mg/day</td>
</tr>
<tr>
<td>promethazine</td>
<td>12.5 to 25 mg PO q4 to 6 hours prn</td>
<td>50 mg/dose; 100 mg/day</td>
</tr>
<tr>
<td>trimethobenzamide</td>
<td>300 mg PO TID or QID prn</td>
<td>1,200 mg/day</td>
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</tbody>
</table>

*Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.*

**Appendix C: Contraindications/Boxed Warnings**

- **Contraindication(s):**
  - Genotropin, Genotropin Miniquick, Humatropo, Humatrope Combo Pack, Norditropin FlexPro, Nutropin AQ NuSpin, Omnitrope, Saizen, Zomacton: acute critical illness; children with Prader-Willi syndrome who are severely obese or have severe respiratory impairment (reports of sudden death); active malignancy; hypersensitivity; active proliferative or severe non-proliferative diabetic retinopathy; children with closed epiphyses
  - Zorbtive: acute critical illness; active malignancy; hypersensitivity; active proliferative or severe non-proliferative diabetic retinopathy
  - Serostim: acute critical illness; active malignancy; diabetic retinopathy; hypersensitivity
- **Boxed warning(s):** none reported

**Appendix D: General Information**

- **Preferred products:** Norditropin and Humatropo
- **In childhood cancer survivors who were treated with radiation to the brain/head for their first neoplasm and who developed subsequent GHD and were treated with somatropin, an increased risk of a second neoplasm has been reported. Intracranial tumors, in particular meningiomas, were the most common of these second neoplasms. In adults, it is unknown whether there is any relationship between somatropin replacement therapy and CNS tumor recurrence.**
- **Human growth hormones are contraindicated in patients with:** acute critical illness; for children with Prader-Willi Syndrome who are severely obese or have severe respiratory impairment reports of sudden death; active malignancy; active proliferative or severe non-proliferative diabetic retinopathy; and for children with closed epiphyses.
- **Short stature/growth failure prior to rhGH therapy is evidenced by one of the following:**
  - Height > 3 SD below the mean
  - Height > 2 SD below the mean and (a or b)
    a) Height velocity > 1 SD below the mean for chronological age over 1 year
    b) Decrease in height SD > 0.5 over 1 year in children > 2 years of age
  - Height > 1.5 SD below midparental height
  - Height velocity > 2 SD below the mean over 1 year
  - Height velocity > 1.5 SD below the mean over 2 years
- **The 2009 American Association of Clinical Endocrinologists (AACE) guidelines for clinical practice for growth hormone use in growth hormone-deficient adults and transition patients state that “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.”**
- **Examples of positive response to therapy for cachexia in HIV patients include a 2% increase in body weight and/or body cell mass (BCM). Once BCM is normalized, therapy may be stopped and the patient may be monitored for wasting to reoccur.**
**BCM:** The total mass of all the cellular elements in the body which constitute all the metabolically active tissue of the body. The preferred method for assessing BCM depletion is bioelectrical impedance analysis (BIA) which can be performed with portable equipment in the office setting.

- GF-1 and IGFBP-3 levels should be interpreted against reference ranges that are standardized for sex and age (or better, by stage of sexual development, if available). The range varies with the assay used, and results should be interpreted against standards provided by the laboratory performing the test.
- Other than growth hormone (GH), pituitary hormones include the following:
  - ACTH: adrenocorticotropin hormone
  - TSH: thyroid stimulating hormone
  - FSH: follicle stimulating hormone
  - LH: lutenizing hormone
  - PrL: prolactin
  - MSH: melanocyte-stimulating hormone
  - Oxytocin
  - ADH: antidiuretic hormone

### V. Dosage and Administration

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Indication</th>
<th>Dosing Regimen</th>
<th>Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somatropin (Genotropin, Genotropin Miniquick, Humatrope, Humatrope Combo Pack, Norditropin Flexpro, Nutropin AQ NuSpin, Omnitrope, Saizen, Zomacton, Zorbtive)</td>
<td>Children and adolescents with GHD, small for gestational age, Turner syndrome, Prader-Willi syndrome, Noonan syndrome, SHOX deficiency, growth failure secondary to CKD, adults with growth hormone deficiency, SBS</td>
<td>Refer to prescribing information (Somatropin, rh-GH doses must be individualized and are highly variable depending on the nature and severity of the disease, the formulation being used, and on patient response)</td>
<td>Refer to prescribing information</td>
</tr>
</tbody>
</table>
| Serostim                      | Wasting or cachexia in HIV patients             | • < 35 kg = 0.1 mg/kg SC QHS  
• 35 to 45 kg = 4 mg SC QHS  
• 45 kg to 55 kg = 5 mg SC QHS  
• > 55 kg = 6 mg SC QHS | 6 mg/day               |

### VI. Product Availability

<table>
<thead>
<tr>
<th>Drug</th>
<th>Availability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotropin lyophilized powder</td>
<td>Dual-chamber syringe: 5 mg, 12 mg</td>
</tr>
<tr>
<td>Genotropin Miniquick (without preservative)</td>
<td>Cartridge: 0.2 mg, 0.4 mg, 0.6 mg, 0.8 mg, 1.0 mg, 1.2 mg, 1.4 mg, 1.6 mg, 1.8 mg, and 2.0 mg</td>
</tr>
</tbody>
</table>
| Humatrope                 | Cartridge: 6 mg, 12 mg, 24 mg  
Vial: 5 mg               |
| Norditropin Flexpro       | Pen: 5 mg/1.5 mL, 10 mg/1.5 mL, 15 mg/1.5 mL, 30 mg/3 mL |
| Nutropin AQ NuSpin        | Cartridge: 5 mg/1 mL  
Pen: 10 mg/2 mL, 20 mg/2 mL |
| Omnitrope                 | Cartridge: 5 mg/1.5 mL, 10 mg/1.5 mL  
Dual-chamber syringe: 5.8 mg |
| Saizen                    | Cartridge: 8.8 mg  
Vial: 5 mg, 8.8 mg |
| Serostim                  | Vial: 4 mg, 5 mg, 6 mg                           |
| Zomacton                  | Vial: 5 mg, 10 mg                                |
| Zorbtive                  | Vial: 8.8 mg                                    |
VII. References


**Important Reminder**

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members.