Clinical Policy: Somatropin (Human Growth Hormone)

Reference Number: AZ.CP.PHAR.402
Effective Date: 09.12.18
Last Review Date: 09.12.18
Line of Business: Arizona Medicaid

Revision Log

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:

- Pediatric Patients: 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
- Adult Patients: Treatment of adults with either childhood-onset or adult-onset GHD

Humatrope is indicated for:

- Pediatric Patients: Treatment of children with short stature or growth failure associated with growth hormone (GH) deficiency, Turner syndrome, idiopathic short stature (ISS), short stature homeobox-containing gene (SHOX) deficiency, and failure to catch up in height after small for gestational age birth
- Adult Patients: Treatment of adults with either childhood-onset or adult-onset GHD

Norditropin FlexPro is indicated for:

- Pediatric Patients: 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, Idiopathic Short Stature (ISS), and growth failure due to Prader-Willi Syndrome
- Adult Patients: Treatment of adults with either childhood-onset or adult-onset GHD

Nutropin AQ NuSpin is indicated for:

- Pediatric Patients: Treatment of children with growth failure due to GHD, ISS, Turner syndrome (TS), and chronic kidney disease (CKD) up to the time of renal transplantation
- Adult Patients: Treatment of adults with either childhood-onset or adult-onset GHD

Omnitrope is indicated for:

- Pediatric Patients: Treatment of children with growth failure due to GHD, Prader-Willi Syndrome, Small for Gestational Age, TS, and ISS
- Adult Patients: Treatment of adults with either childhood-onset or adult-onset GHD

Saizen is indicated for:
- Pediatric Patients: Treatment of children with growth failure due to GHD
- Adult Patients: Treatment of adults with either childhood-onset or adult-onset GHD

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

Zomacton is indicated for:
- Pediatric Patients: Treatment of pediatric patients who have growth failure due to inadequate secretion of normal endogenous GH
- Adult Patients: For replacement of endogenous GH in adults with GH deficiency

Zorbtive is indicate for:
- For the treatment of Short Bowel Syndrome in patients receiving specialized nutritional support. Zorbtive therapy should be used in conjunction with optimal management of Short Bowel Syndrome.

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.

It is the policy of health plans affiliated with Centene Corporation® 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 C*);
      iii. History of surgery or irradiation in the hypothalamic-pituitary region;
      iv. Defined central nervous system pathology;
   b. SHOX deficiency 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, 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 (a and b):
      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. Preferred products are Norditropin and Genotropin. Both of these must be tried prior to consideration of a non-preferred GH product unless medically contraindicated;
7. 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, ii, iii, or iv):
      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/m^2;
            2) ≤ 8.0 µg/L in members with BMI ≥ 25 and < 30 kg/m^2;
            3) ≤ 4.0 µg/L in members with BMI ≥ 30 kg/m^2;
         f) Evidence of ≥ 3 pituitary hormone deficiencies (*see Appendix C*);
         g) Documented genetic cause of GHD;
   b. Short Bowel Syndrome;
2. Age ≥ 18 years;
3. Prescribed by or in consultation with an endocrinologist;
4. Preferred products are Norditropin and Genotropin. Both of these must be tried prior to consideration of a non-preferred GH product unless medically contraindicated;
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. Preferred products are Norditropin and Genotropin. Both of these must be tried prior to consideration of a non-preferred GH product unless medically contraindicated;
6. 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*);

7. Failure of a therapeutic trial of testosterone in combination with an anabolic steroid in males unless contraindicated or clinically significant adverse effects are experienced;
8. Dose does not exceed the maximum indicated in the prescribing information.

Approval duration: 3 months

D. Other diagnoses/indications

1. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): HIM.PHAR.21 for health insurance marketplace and CP.PMN.53 for Medicaid.

II. Continued Therapy

A. Growth Hormone Use in Children (must meet all)**:**

1. Currently receiving medication via Centene benefit 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 girl or ≤ 17 years if boy;
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 Centene benefit or member has previously met all 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 health plan benefit and documentation supports positive response to therapy.
   Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to CP.PMN.53 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized). Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): HIM.PHAR.21 for health insurance marketplace and CP.PMN.53 for Medicaid.

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 policies – CP.CPA.09 for commercial, HIM.PHAR.21 for health insurance marketplace, and CP.PMN.53 for Medicaid or evidence of coverage documents.
B. Idiopathic short stature (ISS);
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
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.

Drug	Dosing Regimen	Dose Limit/Maximum Dose
Appetite stimulants		
Megestrol (Megace®)	400 - 800 mg PO daily (10 – 20 ml/day)	800 mg/day
Dronabinol (Marinol®)	2.5 mg PO bid	20 mg/day
Testosterone replacement products		
Testosterone enanthate or cypionate (Various brands)	50 - 400 mg IM Q2 – 4 wks	400 mg Q 2 wks
Androderm® (testosterone transdermal)	2.5 – 7.5 mg patch applied topically QD	7.5 mg/day
Androgel® (testosterone gel)	5 - 10 gm gel (delivers 50 – 100 mg testosterone) applied topically QD	10 gm/day gel (100 mg/day testosterone)
Testim® (testosterone gel)	5 - 10 gm gel (delivers 50 – 100 mg testosterone) applied	10 gm/day gel (100 mg/day testosterone)

Drug	Dosing Regimen	Dose Limit/Maximum Dose
	topically QD	
Anabolic steroid		
Oxandrolone (Oxandrin®)	2.5 – 20 mg PO /day	20 mg/day
Nandrolone decanoate	100 mg IM Q week	100 mg Q wk
Nausea/vomiting treatments*		
chlorpormazine	10 to 25 mg PO q4 to 6 hours prn	2,000 mg/day
perphenazine	8 to 16 mg/day PO in divided doses	64 mg/day
prochlorperazine	5 to 10 mg PO TID or QID	40 mg/day
promethazine	12.5 to 25 mg PO q4 to 6 hours prn	50 mg/dose; 100 mg/day
trimethobenzamide	300 mg PO TID or QID prn	1,200 mg/day

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.
**preferred status may differ based on specific formulary used*

Appendix C: General Information

- Preferred products: Norditropin and Genotropin
- 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.
- 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
    a) Boys: (father's height + mother's height + 13 cm)/2 or (Father's Height + Mother's Height + 5 inches)/2
    b) Girls: (father's height + mother's height − 13 cm)/2 or Father's Height – 5 inches + Mother's Height) / 2
  - Height velocity > 2 SD below the mean over 1 year
  - Height velocity > 1.5 SD below the mean over 2 years
- Contraindications to GH Therapy
  - Hypersensitivity to somatropin or any diluents/excipients in the prescribed product, such as history of angioedema
  - Acute critical illness due to complications following open heart surgery, abdominal surgery or multiple accidental trauma
  - Acute respiratory failure
  - Active or suspected malignancy within the last 12 months

- Active proliferative or severe non-proliferative diabetic retinopathy
- Epiphyseal closure
- For Prader-Willi Syndrome: severe obesity

- 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.
  - Body cell mass (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: adrenocorticotropic hormone
  - TSH: thyroid stimulating hormone
  - FSH: follicle stimulating hormone
  - LH: lutenizing hormone
  - PrL: Prolactin
  - Melatnocyte-stimulating hormone (MSH)
  - Oxytocin
  - ADH: Antidiuretic hormone

V. Dosage and Administration

Drug Name	Indication	Dosing Regimen	Maximum Dose
Somatropin (Genotropin, Genotropin Miniquick, Humatrope, Humatrope Combo Pack, Norditropin Flexpro, Nutropin Aq Nuspin, Omnitrope, Saizen, Zomacton, Zorbtive)	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, Short	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*)	

	bowel syndrome		
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 SC/day

VI. Product Availability

Drug	Availability
Genotropin lyophilized powder	Dual-chamber syringe: 5.8 mg, 12 mg
Genotropin Miniquick (without preservative)	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
Humatrope	Cartridge: 6 mg, 12 mg, 24 mg Vial: 5mg
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/2 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

1. Genotropin Prescribing Information. Ravensburg, Germany: Pharmacia Upjohn; December, 2016. Available at www.genotropin.com. Accessed January 24, 2018.
2. Humatrope Prescribing Information. Indianapolis, IN: Eli Lilly; December 2016. Available at: www.humatrope.com. Accessed January 24, 2018.
3. Norditropin Prescribing Information. Plainsboro, NJ: Novo Nordisk; February 2018. Available at: www.norditropin.com. Accessed March 6, 2018.
4. Nutropin AQ. Prescribing Information. South San Francisco, CA: Genentech; December 2016. Available at: www.nutropin.com. Accessed January 24, 2018.
5. Omnitrope Prescribing Information. Princeton, NJ: Sandoz; December, 2016. Available at: www.omnitrope.com. Accessed January 24, 2018.
6. Saizen Prescribing Information. Rockland, MA: Serono; May 2017. Available at: www.saizenus.com. Accessed January 24, 2018.
7. Serostim Prescribing Information. Rockland, MA: EMD Serono Inc.; May 2017. Available at: https://serostim.com/. Accessed January 24, 2018.
8. Zorbtive Prescribing information. Rockland, MA: EDM Serono, January 2012. Available at: http://www.emdserono.com. Accessed January 24, 2018.
9. Zomacton Prescribing information. Parsippany, NJ: Ferring Pharmaceuticals Inc., January 2018. Available at: www.zomacton.com. Accessed February 15, 2018.
10. DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed January 24, 2018.

11. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2016. Available at http://clinicalpharmacology-ip.com/.
12. GH Research Society. Consensus guidelines for the diagnosis and treatment of growth hormone (GH) deficiency in childhood and adolescence: summary statement of the GH Research Society. JCEM. 2000; 85(11): 3990-3993.
13. Wilson TA, Rose SR, Cohen P, et al. Update of guidelines for the use of growth hormone in children: The Lawson Wilkins Pediatric Endocrinology Society Drug and Therapeutics Committee. J Pediatr. 2003; 143: 415-421.
14. Cook DM, Yuen KCJ, Biller BMK, et al. American Association of Clinical Endocrinologists. Medical guidelines for clinical practice for growth hormone use in growth hormone-deficient adults and transition patients - 2009 update. Endocr Pract. 2009; 15(2): 1-28.
15. Molitch ME, Clemmons DR, Malozowski S, et al. Evaluation and treatment of adult growth hormone deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2011; 96: 1587-1609.
16. Nemecheck PM, Polsky B, Gottlieb MS. Treatment Guidelines for HIV-Associated Wasting. Mayo Clin Proc. 2000; 75: 386-394.
17. Polsky B, Kotler D, Steinhart C. Treatment guidelines for HIV-associated wasting. HIV Clin Trials 2004;5(1):50-61
18. Grimberg A, DiVall SA, Polychronakos C, et al. Guidelines for growth hormone and insulin-like growth factor-I treatment in children and adolescents: growth hormone deficiency, idiopathic short stature, and primary insulin-like growth factor-I deficiency. Horm Res Paediatr 2016; 86:361-397.
19. National Institute for Health and Care Excellence. Human growth hormone (somatropin) for treatment of growth failure in children: technology appraisal guidance; May 2010. Available at: www.nice.org.uk/guidance/ta188. Accessed February 2018.
20. Romer T, Zabransky M, Walczak M, Szalecki M, and Balser S. Effect of switching recombinant human growth hormone: comparative analysis of phase 3 clinical data. Biol Ther 2011; 1(2):005. DOI 10.1007/s13554-011-0004-8
21. Clayton PE, Cianfarani S, Czernichow P, Johannsson G, Rapaport R, Rogol A. Concensus statement: management of the child born small for gestational age through adulthood: a concensus statement of the international societies of pediatric endocrinology and the growth hormone research society. J Clin Endocrinol Metab 2007; 92:804-810.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
New policy (based on CP.PHAR.55, last reviewed 05.15. No changes except for preferred drugs to include both Genotropin and Norditropin per AHCCCS Drug List).	09.12.18	

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. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. 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. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

For Health Insurance Marketplace members, when applicable, this policy applies only when the prescribed agent is on your health plan approved formulary. Request for non-formulary drugs must be reviewed using the formulary exception policy.