

Title: Growth Hormone: Somatropin (all products except Serostim)

Origination: 09/27/96	Revised: 06/04/10	Annual Review: 12/15/11
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Purpose:

To provide guidelines and criteria for the review and decision determination of requests for medications that requires prior authorization.

Background Information:

Reference Statement

- Guidelines are compiled from available US Food and Drug Administration (FDA) approved indications, general practice guidelines, and/or evidence-based uses established through phase III clinical studies without published conflicting data. Only clinical studies published in their entirety in reputable peer-reviewed journals will be evaluated.

Eligibility Criteria

- Member must be eligible for benefit coverage (i.e., self-injectable rider) within the specified date(s) of service.
- Prior authorization requests that do not meet clinical criteria in this Procedure will be forwarded to a Clinical Pharmacist to review.

Exclusions

- Because of the potent anabolic effects, Growth Hormone (GH) therapy is contraindicated in children with active malignancies and is generally withheld for at least one (1) year after completion of successful therapy for a malignancy.
- Omnitrope Cartridge 5mg/1.5mL, 10mg/1.5ml, and Omnitrope for injection 5.8mg/vial must **NOT** be given to premature babies or neonates.
- The efficacy and safety of GH in idiopathic short stature or non-growth hormone deficient short stature, constitutional delay of growth or development, glucocorticoid-induced growth failure, renal transplantation, skeletal dysplasias, osteogenesis imperfecta, infertility, burn injuries, obesity, hypophosphatemia, muscular dystrophy, cystic fibrosis, spina bifida, juvenile rheumatoid arthritis, osteoporosis, post-traumatic stress disorder, depression, hypertension, precocious puberty, chronic fatigue syndrome, Crohn's disease, anti-aging, growth retardation secondary to amphetamine use, chronic catabolic state, Down syndrome and any other genetic and chromosomal disorders (except Prader-Willi Syndrome, Turners Syndrome, Noonan Syndrome, and SHOX) associated with short stature have not been established and thus, are not covered.
- While on growth hormone, growth rate decreases to less than 2.5 cm/year.
- Member achieves height consistent with midparental height, which is an average of Member's Mother's and Father's height.
- Continuation of growth hormone treatment once a Member's epiphyses have fused.
- Use in adults (greater than 18 years of age) with childhood-onset growth hormone deficiency.

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Additional Information

- Omnitrope is the preferred Somatropin agent.
- Members who are sensitive or have a contraindication to preservative may use Genotropin Miniquick, which is without preservative.

Procedure:

- 1.0 Request for initial therapy for **pediatric growth hormone deficiency (GHD)** requires documentation from the Member's medical records maintained by the requesting provider verifying **ALL** of the following:
 - 1.1 Provider is a pediatric endocrinologist; **AND**
 - 1.2 Member's height at initiation of therapy must be greater than or equal to two (2) standard deviations below normal means for age and sex (or less than the 3rd percentile on the growth chart); **AND**
 - 1.3 Growth rate is less than four (4)cm/year; **AND**
 - 1.4 Growth hormone deficiency is confirmed by failure of two (2) standard GH provocation tests (with insulin, propranolol, levodopa, arginine, clonidine, or glucagon) and excluding tests using growth hormone releasing hormone for stimulation. **A failure is defined as a measured GH level peak of less than 10ng/ml after stimulation. (NOTE: One standard GH provocation test is sufficient for children with defined central nervous system pathology, such as empty sella syndrome, interruption of pituitary stalk, hypoplasia of the pituitary gland, craniofacial developmental defects, pituitary or hypothalamic tumors, etc.); AND**
 - 1.5 Member has delayed bone age greater than or equal to two (2) years below actual age; **AND**
 - 1.6 Member does not meet any exclusion criteria;

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Procedure, continued:

- 1.0 Request for initial therapy for **pediatric growth hormone deficiency (GHD)** requires documentation from the Member's medical records maintained by the requesting provider verifying **ALL** of the following, continued:
 - 1.7 If all of the above criteria are met, may approve Omnitrope, dosed up to 0.3mg/kg/week, divided into 6-7 daily injections, for up to one (1) year;
OR
 - 1.7 If Member is in puberty (verifying **all** criteria below), approve Omnitrope, dosed up to 0.7mg/kg/week, divided into 6-7 daily injections, for up to one (1) year:
 - 1.7.1 For Males:
 - 1.7.1.1 Age between 10-18 years old;
 - 1.7.1.2 Tanner stage 2-5 or Testis volume of 4 ml or more;
 - 1.7.1.3 Bone age of 14 years or greater;
 - 1.7.2 For Females:
 - 1.7.2.1 Age between 8-16 years old;
 - 1.7.2.2 Tanner breast stage of two (2) or more;
 - 1.7.2.3 Bone age of 12 years or greater.
- 2.0 Request for continuation of therapy for **pediatric growth hormone deficiency (GHD)** requires documentation from the Member's medical records maintained by the requesting provider verifying the following:
 - 2.1 Pre-treatment growth rate has doubled while on GH therapy; **OR**
 - 2.1 Growth rate is at least 2.5cm/year in those children with extremely low pretreatment growth rates; **AND**
 - 2.2 Member's epiphyses have been confirmed as open (i.e., through wrist film evaluation); **AND**
 - 2.3 Member does not meet any exclusion criteria;

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Procedure, continued:

- 2.0 Request for continuation of therapy for **pediatric growth hormone deficiency (GHD)** requires documentation from the Member's medical records maintained by the requesting provider verifying the following, continued
 - 2.4 If all of the above criteria are met, may approve Omnitrope, dosed up to 0.3mg/kg/week, divided into 6-7 daily injections, for up to one (1) year;
OR
 - 2.4 If Member is in puberty (verifying **all** criteria below), approve Omnitrope, dosed up to 0.7mg/kg/week, divided into 6-7 daily injections, for up to one (1) year:
 - 2.4.1 For Males:
 - 2.4.1.1 Age between 10-18 years old;
 - 2.4.1.2 Tanner stage 2-5 or Testis volume of 4 ml or more;
 - 2.4.1.3 Bone age of 14 years or greater;
 - 2.4.2 For Females:
 - 2.4.2.1 Age between 8-16 years old;
 - 2.4.2.2 Tanner breast stage of 2 or more;
 - 2.4.2.3 Bone age of 12 years or greater.

- 3.0 Request for initial therapy due to growth failure associated with children with **chronic renal insufficiency (CRI) up to the time of renal transplantation** requires documentation from the Member's medical records maintained by the requesting provider verifying **ALL** of the following:
 - 3.1 Provider is a pediatric endocrinologist; **AND**
 - 3.2 Diagnosis of CRI as evidenced by GFR less than 60mL/min/1.73m² or Creatinine greater than 1.8mg/dL for at least three (3) months; **AND**
 - 3.3 Member's height at initiation of therapy must be greater than or equal to two (2) standard deviations below normal means for age and sex (or less than the 3rd percentile on the growth chart); **AND**
 - 3.4 Growth rate is less than four (4)cm/year; **AND**
 - 3.5 Member has delayed bone age greater than or equal to two (2) years below actual age; **AND**

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- 3.0 Request for initial therapy due to growth failure associated with children with **chronic renal insufficiency (CRI) up to the time of renal transplantation** requires documentation from the Member's medical records maintained by the requesting provider verifying **ALL** of the following, continued:
 - 3.6 Member does not meet any exclusion criteria;
 - 3.7 If all of the above criteria are met, may approve Omnitrope, dosed up to 0.35mg/kg/week, divided into 6-7 daily injections, for up to one (1) year.

- 4.0 Request for continuation of therapy due to growth failure associated with **chronic renal insufficiency (CRI) up to the time of renal transplantation** requires documentation from the Member's medical records maintained by the requesting provider verifying all of the following:
 - 4.1 Pre-treatment growth rate has doubled while on GH therapy; **OR**
 - 4.1 Growth rate is at least 2.5cm/year in those children with extremely low pretreatment growth rates; **AND**
 - 4.2 Member's epiphyses have been confirmed as open (i.e., through wrist film evaluation); **AND**
 - 4.3 Member does not meet any exclusion criteria;
 - 4.4 If all of the above criteria are met, may approve Omnitrope, dosed up to 0.35mg/kg/week, divided into 6-7 daily injections, for up to one (1) year.

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Procedure, continued:

- 5.0 Request for initial therapy for Growth failure associated with any established genetic disorders, to include **Turner Syndrome (TS), Prader-Willi Syndrome (PWS), Noonan Syndrome, and SHOX (short stature homeobox-containing gene)**, requires documentation from the Member’s medical records maintained by the requesting provider verifying **ALL** of the following:
 - 5.1 Provider is a pediatric endocrinologist; **AND**
 - 5.2 Diagnosis of **any of the above** must be confirmed by appropriate genetic testing; **AND**
 - 5.3 Member’s height at initiation of therapy must be greater than or equal to two (2) standard deviations below normal means for age and sex (or less than the 3rd percentile on the growth chart); **AND**
 - 5.4 Growth rate is less than four (4)cm/year; **AND**
 - 5.5 Member’s epiphyses have been confirmed as open (i.e., through wrist film evaluation); **AND**
 - 5.6 Member does not meet any exclusion criteria;
 - 5.7 If all of the above criteria are met, may approve Omnitrope up to one (1) year, dosing based on specific diagnoses:

Diagnosis:	Omnitrope Dosing (divided into 6-7 daily injections, for up to one (1) year):
Turner Syndrome (TS)	up to 0.375mg/kg/week
Prader-Willi Syndrome (PWS)	up to 0.24mg/kg/week
Noonan Syndrome	up to 0.066mg/kg/ day
SHOX (short stature homeobox-containing gene)	up to 0.35mg/kg/week

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Procedure, continued:

6.0 Request for continuation of therapy for Growth failure associated with any established genetic disorders, to include **Turner Syndrome (TS), Prader-Willi Syndrome (PWS), Noonan Syndrome, and SHOX (short stature homeobox-containing gene)** requires documentation from the Member’s medical records maintained by the requesting provider verifying all of the following:

- 6.1 Pre-treatment growth rate has doubled while on GH therapy; **OR**
- 6.1 Growth rate is at least 2.5cm/year in those children with extremely low pretreatment growth rates; **AND**
- 6.2 Member does not meet any exclusion criteria;
- 6.3 If all of the above criteria are met, may approve Omnitrope up to one (1) year, dosing based on specific diagnoses:

Diagnosis:	Omnitrope Dosing (divided into 6-7 daily injections, for up to 1 year):
Turner Syndrome (TS)	up to 0.375mg/kg/week
Prader-Willi Syndrome (PWS)	up to 0.24mg/kg/week
Noonan Syndrome	up to 0.066mg/kg/ day
SHOX (short stature homeobox-containing gene)	up to 0.35mg/kg/week

7.0 Request for initial therapy in adults with documented growth hormone deficiency **due to destructive lesions of the pituitary ONLY** requires documentation from the Member’s medical records maintained by the requesting provider verifying **ALL** of the following:

- 7.1 Provider is an endocrinologist; **AND**
- 7.2 Diagnosis of **GH deficiency as a result of hypothalamic or pituitary disease** (i.e., panhypopituitarism, pituitary adenoma, trauma, traumatic brain injury, aneurysmal subarachnoid hemorrhage, radiation therapy, cranial irradiation, pituitary surgery) and at least two (2) or more anterior pituitary hormone deficiencies (IGF-1, ACTH, cortisol, TSH and T4, FSH/LH, low testosterone in males, estrogen in females, etc.); **AND**

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- 7.0 Request for initial therapy in adults with documented growth hormone deficiency **due to destructive lesions of the pituitary ONLY** requires documentation from the Member's medical records maintained by the requesting provider verifying **ALL** of the following, continued:
- 7.3 Member is already receiving adequate replacement therapy for any other pituitary hormone deficiencies (i.e., levothyroxine, liothyronine, hydrocortisone, testosterone replacement therapy); **AND**
- 7.4 Growth hormone deficiency confirmed by failure of at least one (1) standard GH provocation tests (with insulin, propranolol, levodopa, arginine, clonidine, or glucagon). Not required for Members who have had surgical removal of pituitary and/or panhypopituitarism where it would not be expected to produce a clinical response (absence of all pituitary hormones). **A failure is defined as a measured GH level peak of less than 5ng/ml after stimulation; AND**
- 7.5 For members with irreversible hypothalamic-pituitary structural lesions and/or panhypopituitarism, serum IGF-I levels need to be below the age/sex appropriate reference ranges; **AND**
- 7.6 Member has a perceived impairment of quality of life (QoL), as demonstrated by a reported score of at least 11 in a disease-specific Quality of life assessment of growth hormone deficiency in adults (QoL-AGHDA) questionnaire (refer to Attachment A);
- 7.7 If all of the above criteria are met, may approve Omnitrope, dosed up to 0.08mg/kg/week, divided into 6-7 daily injections, OR up to 0.3mg/day for up to six (6) months.

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Procedure, continued:

- 8.0 Request for continuation of therapy in **adults** with documented growth hormone deficiency **due to destructive lesions of the pituitary ONLY** requires documentation from the Member's medical records maintained by the requesting provider verifying the following:
- 8.1 Serum IGF-1 levels should be improving from baseline with a target at the middle of the normal range for age and sex using appropriate reference range per lab standard; **AND**
 - 8.2 Noted improvement in symptoms (i.e., increase in total lean body mass, increased exercise capacity) and absence of adverse events, especially glucose intolerance; **AND**
 - 8.3 Repeat Quality of life assessment of growth hormone deficiency in adults (QoL-AGHDA) questionnaire (refer to Attachment A) shows an improvement of seven (7) or more points from baseline; **AND**
 - 8.4 If all of the above criteria are met, may approve Omnitrope, dosed up to 0.08mg/kg/week, divided into 6-7 daily injections OR up to 0.3mg/day for up to one (1) year.

- 9.0 Request for initial therapy for **Children Small for Gestational Age (SGA)** requires documentation from the Member's medical records maintained by the requesting provider verifying **ALL** of the following:
- 9.1 The child's birth weight, birth length, or both must be more than two (2) SD below the mean normal values following adjustment for age and gender; **AND**
 - 9.2 The child must be over two (2) years of age; **AND**
 - 9.3 The child's current height must be at least two (2) SD below the mean normal values following adjustment for age and gender (signifying that there was no sufficient catch-up growth before age 2);
 - 9.4 If all of the above criteria are met, may approve Omnitrope, dosed up to 0.3mg/kg/week, divided into 6-7 daily injections, for up to one (1) year;
OR

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9.0 Request for initial therapy for **Children Small for Gestational Age (SGA)** requires documentation from the Member's medical records maintained by the requesting provider verifying **ALL** of the following, continued:

9.4 If Member is in puberty (verifying **all** criteria below), approve Omnitrope, dosed up to 0.7mg/kg/week, divided into 6-7 daily injections, for up to one (1) year:

9.4.1 For Males:

9.4.1.1 Age between 10-18 years old;

9.4.1.2 Tanner stage 2-5 or Testis volume of 4 ml or more;

9.4.1.3 Bone age of 14 years or greater;

9.4.2 For Females:

9.4.2.1 Age between 8-16 years old;

9.4.2.2 Tanner breast stage of two (2) or more;

9.4.2.3 Bone age of 12 years or greater.

10.0 Request for continuation of therapy for **Children Small for Gestational Age (SGA)** requires documentation from the Member's medical records maintained by the requesting provider verifying **ALL** of the following:

10.1 Pre-treatment growth rate has doubled while on GH therapy; **OR**

10.1 Growth rate is at least 2.5cm/year in those children with extremely low pretreatment growth rates; **AND**

10.2 Member's epiphyses have been confirmed as open (i.e., through wrist film evaluation);

10.3 If all of the above criteria are met, may approve Omnitrope, dosed up to 0.3mg/kg/week, divided into 6-7 daily injections, for up to one (1) year;

OR

10.3 If Member is in puberty (verifying **all** criteria below), approve Omnitrope, dosed up to 0.7mg/kg/week, divided into 6-7 daily injections, for up to one (1) year:

10.3.1 For Males:

10.3.1.1 Age between 10-18 years old;

10.3.1.2. Tanner stage 2-5 or Testis volume of 4 ml or more;

10.3.1.3 Bone age of 14 years or greater;

10.3.2 For Females:

10.3.2.1 Age between 8-16 years old;

10.3.2.2 Tanner breast stage of two (2) or more;

10.3.2.3. Bone age of 12 years or greater.

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- 11.0 Request for Growth Hormone product other than Omnitrope requires:
- 11.1 Documented sensitivity to any excipients of Omnitrope; **OR**
 - 11.1 Documented sensitivity to phenol;
 - 11.2 If one (1) of the above criterion is met, may approve Genotropin Miniquick (same dosing as established for each indication in the above procedure) for up to one (1) year.

References:

1. Cook DM, Yuen KC, Biller BM, Kemp SF, Vance ML; American Association of Clinical Endocrinologists. American Association of Clinical Endocrinologists medical guidelines for clinical practice for growth hormone use in growth hormone-deficient adults and transition patients - 2009 update. *Endocrine Practice*. 2009 Sep-Oct; 15(Suppl 2):1-29.
2. Albertsson-Wikland K, Aronson AS, Gustafsson J, Hagenäs L, Ivarsson SA, Jonsson B, Kriström B, Marcus C, Nilsson KO, Ritzén EM, Tuvemo T, Westphal O, Aman J. Dose-dependent effect of growth hormone on final height in children with short stature without growth hormone deficiency. *J Clin Endocrinol Metab*. 2008 Nov; 93(11):4342-4350.
3. Romer T, Saenger P, Peter F, Walczak M, Le Bouc Y, Khan-Boluki J, Berghout A. Seven years of safety and efficacy of the recombinant human growth hormone Omnitrope in the treatment of growth hormone deficient children: results of a phase III study. *Horm Res*. 2009;72(6):359-369.
4. Growth Hormone 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. *J Clin Endocrinol Metab*. 2000 Nov;85(11):3990-3993.
5. Wilson TA, Rose SR, Cohen P, Rogol AD, Backeljauw P, Brown R, Hardin DS, Kemp SF, Lawson M, Radovick S, Rosenthal SM, Silverman L, Speiser P; Lawson Wilkins Pediatric Endocrinology Society Drug and Therapeutics Committee. Update of guidelines for the use of growth hormone in children: the Lawson Wilkins Pediatric Endocrinology Society Drug and Therapeutics Committee. *J Pediatr*. 2003 Oct;143(4):415-421.
6. McKenna SP, Doward LC, Alonso J, Kohlmann T, Niero M, Prieto L, Wíren L. The QoL-AGHDA: an instrument for the assessment of quality of life in adults with growth hormone deficiency. *Qual Life Res*. 1999 Jun;8(4):373-383.
7. Jung H, Land C, Nicolay C, De Schepper J, Blum WF, Schönau E. Growth response to an individualized versus fixed dose GH treatment in short children born small for gestational age: the OPTIMA study. *Eur J Endocrinol*. 2009 Feb;160(2):149-156.

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References, continued:

8. Mauras N, Attie KM, Reiter EO, Saenger P, Baptista J. High dose recombinant human growth hormone (GH) treatment of GH-deficient patients in puberty increases near-final height: a randomized, multicenter trial. Genentech, Inc., Cooperative Study Group. *J Clin Endocrinol Metab.* 2000 Oct;85(10):3653-3660.
9. Cohen P, Rogol AD, Howard CP, Bright GM, Kappelgaard AM, Rosenfeld RG; American Norditropin Study Group. Insulin growth factor-based dosing of growth hormone therapy in children: a randomized, controlled study. *J Clin Endocrinol Metab.* 2007 Jul;92(7):2480-2486. Epub 2007 Mar 13.
10. Cohen P, Bright GM, Rogol AD, Kappelgaard AM, Rosenfeld RG; American Norditropin Clinical Trials Group. Effects of dose and gender on the growth and growth factor response to GH in GH-deficient children: implications for efficacy and safety. *J Clin Endocrinol Metab.* 2002 Jan;87(1):90-98.
11. Wetterau L, Cohen P. New paradigms for growth hormone therapy in children. *Horm Res.* 2000;53 Suppl 3:31-6.
12. Lee KW, Cohen P. Individualizing growth hormone dosing in children. *Horm Res.* 2001;56 Suppl 1:29-34.
13. Vimalachandra D, Hodson EM, Willis NS, et al. Growth hormone for children with chronic kidney disease (Review). *The Cochrane Collaboration.* 2008.
14. Davenport ML, Crowe BJ, Travers SH, et al. Growth Hormone treatment of early growth failure in toddlers with Turner Syndrome: A randomized, controlled, multicenter trial. *Journal of Clinical Endocrinology & Metabolism.* 2007 June; 92(9):3406-16.
15. Lindgren AC, Hagenas L, Miller J, et al. Growth Hormone treatment of children with Prader-Willi syndrome affects linear growth and composition favorably. *Acta Paediatr* 1998; 87: 28-31.
16. Craig ME, Cowell CT, Larsson P, et al. Growth hormone treatment and adverse events in PWS: data from KIGS. *Clin Endocrinol (Oxf.)* 2006 Aug; 65 (2): 178-85.
17. Omnitrope [package insert]. Princeton, NJ: Sandoz Inc; 2008.
18. Genotropin [package insert]. New York, NY: Pfizer Inc.; 2009.
19. Humatrope [package insert]. Indianapolis, IN: Eli Lilly and Company; 2009.
20. Nutropin [package insert]. South San Francisco, CA: Genentech, Inc.; 2006.
21. *Clinical Pharmacology* . Tampa, FL: Gold Standard, Inc.; 2009. <http://cp.gsm.com>.



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Disclaimer Information:

Prior Authorization criteria are developed to determine coverage for AvMed Health Plans' benefits, and are published to provide a better understanding of the basis upon which coverage decisions are made. AvMed Health Plans makes coverage decisions based on the Member's benefit plan contract and these criteria. This guideline sets forth concise clinical coverage criteria which have been developed from a review of current literature, policies of the FDA and other government agencies, and other appropriate references, in consultation and with approval from practicing physicians who are members of AvMed's Pharmacy and Therapeutic committee. Treating providers are solely responsible for the medical advice and treatment of Members. This guideline may be updated and therefore is subject to change. The use of these criteria is neither a guarantee of payment nor a final prediction of how specific claim(s) will be adjudicated.