

Reference number(s)
1742-A

SPECIALTY GUIDELINE MANAGEMENT

GENOTROPIN (somatropin)
HUMATROPE (somatropin)
NORDITROPIN (somatropin)
NUTROPIN AQ (somatropin)
OMNITROPE (somatropin)
SAIZEN (somatropin)
ZOMACTON (somatropin)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no contraindications or exclusions to the prescribed therapy.

A. FDA-Approved Indications

1. Pediatric patients with growth failure due to any of the following:
 - a. Growth hormone (GH) deficiency
 - b. Turner syndrome
 - c. Noonan syndrome
 - d. Small for gestational age (SGA)
 - e. Prader-Willi syndrome
 - f. Chronic kidney disease (CKD)
 - g. Short stature homeobox-containing gene (SHOX) deficiency
2. Adults with childhood-onset or adult-onset GH deficiency

B. Compendial Uses

1. Human immunodeficiency virus (HIV)-associated wasting/cachexia
2. Short bowel syndrome (SBS)
3. Growth failure associated with any of the following:
 - a. Cerebral palsy
 - b. Congenital adrenal hyperplasia
 - c. Cystic fibrosis
 - d. Russell-Silver syndrome

All other indications are considered experimental/investigational and not medically necessary.

II. REQUIRED DOCUMENTATION

The following information is necessary to initiate the prior authorization review for both initial and continuation of therapy requests (where applicable):

- A. Medical records supporting the diagnosis of neonatal GH deficiency
- B. Pretreatment growth hormone provocative test result(s) (laboratory report or medical record documentation)
- C. Pretreatment and/or current IGF-1 level (laboratory report or medical record documentation)*

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- D. The following laboratory test reports must be provided:
1. Diagnostic karyotype results in Turner syndrome
 2. Diagnostic genetic test results in Prader-Willi syndrome
 3. Diagnostic molecular or genetic test results in SHOX deficiency
- E. The following information must be provided for all continuation of therapy requests:
1. Total duration of treatment (approximate duration is acceptable)
 2. Date of last dose administered
 3. Approving health plan/pharmacy benefit manager
 4. Date of prior authorization/approval
 5. Prior authorization approval letter

* IGF-1 levels vary based on the laboratory performing the analysis. Laboratory-specific values must be provided to determine whether the value is within the normal range.

III. INITIAL CRITERIA FOR APPROVAL

A. Pediatric GH Deficiency

Authorization of 12 months may be granted to members with pediatric GH deficiency when EITHER criteria 1. or 2. below is met:

1. Member is a neonate or was diagnosed with GH deficiency as a neonate. Medical records must be available to support the diagnosis of neonatal GH deficiency (e.g., hypoglycemia with random GH level, evidence of multiple pituitary hormone deficiency, chart notes, or magnetic resonance imaging [MRI] results).
2. Member meets ALL of the following:
 - a. Member has EITHER:
 - i. Two pretreatment pharmacologic provocative GH tests with both results demonstrating a peak GH level < 10 ng/mL, OR
 - ii. A documented pituitary or CNS disorder (refer to Appendix A) and a pretreatment IGF-1 level > 2 standard deviations (SD) below the mean
 - b. For members < 2.5 years of age at initiation of treatment, the pretreatment height is > 2 SD below the mean and growth velocity is slow
 - c. For members ≥ 2.5 years of age at initiation of treatment:
 - i. Pretreatment height is > 2 SD below the mean and 1-year height velocity is > 1 SD below the mean, OR
 - ii. Pretreatment 1-year height velocity is > 2 SD below the mean
 - d. Epiphyses are open

B. Small for Gestational Age

Authorization of 12 months may be granted to members born SGA when ALL of the following criteria are met:

1. Member meets at least one of the following:
 - a. Birth weight < 2500 g at gestational age > 37 weeks
 - b. Birth weight or length less than 3rd percentile for gestational age
 - c. Birth weight or length ≥ 2 SD below the mean for gestational age
2. Pretreatment age is ≥ 2 years
3. Member failed to manifest catch-up growth by age 2 (i.e., pretreatment height > 2 SD below the mean)
4. Epiphyses are open

C. Turner Syndrome

Authorization of 12 months may be granted to members with Turner syndrome when ALL of the following criteria are met:

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1. Diagnosis was confirmed by karyotyping
2. Patient's pretreatment height is less than the 5th percentile for age
3. Epiphyses are open

D. Growth Failure Associated with Chronic Kidney Disease, Cerebral Palsy, Congenital Adrenal Hyperplasia, Cystic Fibrosis, and Russell-Silver Syndrome

Authorization of 12 months may be granted to members with CKD, cerebral palsy, congenital adrenal hyperplasia, cystic fibrosis, or Russell-Silver syndrome when ALL of the following criteria are met:

1. For members < 2.5 years of age at initiation of treatment, the pretreatment height is > 2 SD below the mean and growth velocity is slow
2. For members ≥ 2.5 years of age at initiation of treatment:
 - a. Pretreatment height is > 2 SD below the mean and 1-year height velocity is > 1 SD below the mean, OR
 - b. Pretreatment 1-year height velocity is > 2 SD below the mean
3. Epiphyses are open

E. Prader-Willi Syndrome

Authorization of 12 months may be granted to members with Prader-Willi syndrome when the diagnosis was confirmed by genetic testing demonstrating any of the following:

1. Deletion in the chromosomal 15q11.2-q13 region
2. Maternal uniparental disomy in chromosome 15
3. Imprinting defects or translocations involving chromosome 15

F. Noonan Syndrome

Authorization of 12 months may be granted to members with Noonan syndrome when ALL of the following criteria are met:

1. Pretreatment height is > 2 SD below the mean and 1-year height velocity is > 1 SD below the mean OR pretreatment 1-year height velocity is > 2 SD below the mean
2. Epiphyses are open

G. Short Stature Homeobox-Containing Gene Deficiency

Authorization of 12 months may be granted to members with SHOX deficiency when ALL of the following criteria are met:

1. The diagnosis of SHOX deficiency was confirmed by molecular or genetic analyses
2. Pretreatment height is > 2 SD below the mean and 1-year height velocity is > 1 SD below the mean OR pretreatment 1-year height velocity is > 2 SD below the mean
3. Epiphyses are open

H. Adult GH Deficiency

Authorization of 12 months may be granted to members with adult GH deficiency when ANY of the following criteria is met:

1. Member has had 2 pretreatment pharmacologic provocative GH tests and both results demonstrated GH levels < 5 ng/mL, unless the agent is Macrilen in which case a GH level of less than 2.8 ng/ml confirms the presence of adult GHD
2. Member has had 1 pretreatment pharmacologic provocative GH test that demonstrated a GH level < 5 ng/mL AND has a pretreatment IGF-1 level that is low for age and gender, unless the agent is Macrilen in which case a GH level of less than 2.8 ng/ml confirms the presence of adult GHD
3. Member has a structural abnormality of the hypothalamus or pituitary (refer to Appendix A) and ≥ 3 documented pituitary hormone deficiencies (refer to Appendix B)
4. Member has childhood-onset GH deficiency and a congenital abnormality of the hypothalamus or pituitary (refer to Appendix A)

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I. HIV-Associated Wasting/Cachexia

Authorization of 12 weeks may be granted to members with HIV-associated wasting or cachexia when ALL of the following criteria are met:

1. Member has trialed and experienced a suboptimal response to alternative therapies (e.g., cyproheptadine, dronabinol, megestrol acetate or testosterone if hypogonadal) or contraindication or intolerance to alternative therapies
2. Member is currently on antiretroviral therapy
3. BMI is less than 18.5 kg/m² prior to starting therapy with growth hormone (see Appendix C)

J. Short Bowel Syndrome

Authorization of a lifetime total of 8 weeks may be granted to members with short bowel syndrome who depend on intravenous parenteral nutrition when

GH will be used in conjunction with optimal management of SBS.

IV. CONTINUATION OF THERAPY

A. Pediatric GH Deficiency, Turner Syndrome, Noonan Syndrome, CKD, SGA, SHOX deficiency, Congenital Adrenal Hyperplasia, Cerebral Palsy, Cystic Fibrosis, and Russell-Silver Syndrome

Authorization of 12 months may be granted for continuation of therapy when ALL of the following criteria are met:

1. Epiphyses are open (confirmed by X-ray or X-ray is not available)
2. Member's growth rate is > 2 cm/year unless there is a documented clinical reason for lack of efficacy (e.g., on treatment less than 1 year, nearing final adult height/late stages of puberty)

B. Prader-Willi Syndrome

Authorization of 12 months may be granted for continuation of therapy when the member's body composition and psychomotor function have improved or stabilized in response to GH therapy.

C. Adult GH Deficiency

Authorization of 12 months may be granted for continuation of therapy when all criteria for initial authorization are met (refer to Section III.H. above).

D. HIV-Associated Wasting/Cachexia

Authorization of 12 weeks may be granted for continuation of therapy when ALL of the following criteria are met:

1. Member is diagnosed with HIV-associated wasting/cachexia
2. Member is currently on antiretroviral therapy.
3. Member is currently receiving treatment with growth hormone excluding obtainment as samples or via manufacturer's patient assistance programs
4. Current BMI is less than 27 kg/m² (see Appendix C).

V. APPENDICES

A. Appendix A: Examples of Hypothalamic/Pituitary/CNS Disorders

1. Congenital genetic abnormalities
 - a. Known mutations in growth-hormone-releasing hormone (GHRH) receptor, GH gene, GH receptor, or pituitary transcription factors
2. Congenital structural abnormalities
 - a. Optic nerve hypoplasia/septo-optic dysplasia
 - b. Agenesis of corpus callosum

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- c. Empty sella syndrome
 - d. Ectopic posterior pituitary
 - e. Pituitary aplasia/hypoplasia
 - f. Pituitary stalk defect
 - g. Anencephaly or prosencephaly
 - h. Other mid-line defects
 - i. Vascular malformations
3. Acquired structural abnormalities (or causes of hypothalamic/pituitary damage)
- a. CNS tumors/neoplasms (e.g., craniopharyngioma, glioma, pituitary adenoma)
 - b. Cysts (Rathke cleft cyst or arachnoid cleft cyst)
 - c. Surgery
 - d. Radiation
 - e. Chemotherapy
 - f. CNS infections
 - g. CNS infarction (e.g., Sheehan's syndrome)
 - h. Inflammatory lesions (e.g., autoimmune hypophysitis)
 - i. Infiltrative lesions (e.g., sarcoidosis, histiocytosis)
 - j. Head trauma/traumatic brain injury
 - k. Aneurysmal subarachnoid hemorrhage

B. Appendix B: Pituitary Hormones (Other than Growth Hormone)

- 1. Adrenocorticotrophic hormone (ACTH)
- 2. Antidiuretic hormone (ADH)
- 3. Follicle stimulating hormone (FSH)
- 4. Luteinizing hormone (LH)
- 5. Thyroid stimulating hormone (TSH)
- 6. Prolactin

C. Appendix C: Calculation of BMI

$$\text{BMI} = \frac{\text{Weight (pounds)} \times 703}{[\text{Height (inches)}]^2} \quad \text{OR} \quad \frac{\text{Weight (kg)}}{[\text{Height (m)}]^2}$$

BMI classification:	Underweight	< 18.5 kg/m ²
	Normal weight	18.5 – 24.9 kg/m ²
	Overweight	25 – 29.9 kg/m ²
	Obesity (class 1)	30 – 34.9 kg/m ²
	Obesity (class 2)	35 – 39.9 kg/m ²
	Extreme obesity	≥ 40 kg/m ²

VI. REFERENCES

- 1. Genotropin [package insert]. New York, NY: Pfizer Inc.; April 2019.
- 2. Humatrope [package insert]. Indianapolis, IN: Eli Lilly and Company; October 2019.
- 3. Norditropin [package insert]. Plainsboro, NJ: Novo Nordisk Inc.; February 2018.
- 4. Nutropin AQ [package insert]. South San Francisco, CA: Genentech, Inc.; December 2016.
- 5. Saizen [package insert]. Rockland, MA: EMD Serono Inc.; May 2018.
- 6. Zomacton [package insert]. Parsippany, NJ: Ferring Pharmaceuticals Inc.; July 2018.
- 7. Omnitrope [package insert]. Princeton, NJ: Sandoz Inc.; June 2019.

Reference number(s)
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8. Micromedex Solutions [database online]. Ann Arbor, MI: Truven Health Analytics Inc. Updated periodically. www.micromedexsolutions.com [available with subscription]. Accessed January 7, 2019.
9. Nemechek PM, Polsky B, Gottlieb MS. Treatment Guidelines for HIV-Associated Wasting. *Mayo Clin Proc.* 2000;75:386-394.
10. Grinspoon S, Mulligan K for the Department of Health and Human Services Working Group on the Prevention and Treatment of Wasting and Weight Loss. Weight loss and wasting in patients infected with human immunodeficiency virus. *Clin Infect Dis.* 2003;36(Suppl 2):S69-78.
11. Polsky B, Kotler D, Steinhart C. HIV-associated wasting in the HAART era: guidelines for assessment, diagnosis, and treatment. *AIDS Patient Care STDS.* 2001;15(8):411-23.
12. Parekh NR, Steiger E. Criteria for the use of recombinant human growth hormone in short bowel syndrome. *Nutrition Clin Pract.* 2005;20:503-508.
13. Caremark Clinical Programs Review: Focus on growth hormones, growth hormone releasing hormone, Increlex, Somavert. December 18, 2006.
14. Congilio SJ, Stevenson RD, Rogol AD. Apparent growth hormone deficiency in children with cerebral palsy. *Dev Med Child Neurol.* 1996;38(9):797-804.
15. Shim ML, Moshang T, Oppenheim WL, et al. Is treatment with growth hormone effective in children with cerebral palsy? *Dev Med Child Neurol.* 2004;46(8):569-71.
16. Gallagher MP, Levine LS, Oberfield SE. A review of the effects of therapy on growth and bone mineralization in children with congenital adrenal hyperplasia. *Growth Horm IGF Res.* 2005;15 Suppl A:S26-30.
17. Lin-Su K, Vogiatzi MG, Marshall I, et al. Treatment with growth hormone and luteinizing hormone releasing hormone analog improves final adult height in children with congenital adrenal hyperplasia. *J Clin Endocrinol Metab.* 2005;90:3318-3325.
18. Quintos JB, Vogiatzi MG, Harbison MD, et al. Growth hormone therapy alone or in combination with gonadotropin-releasing hormone analog therapy to improve the height deficit in children with congenital adrenal hyperplasia. *J Clin Endocrinol Metab.* 2001;86(4):1511-1517.
19. Hardin DS, Adams-Huet B, Brown D, et al. Growth hormone treatment improves growth and clinical status in prepubertal children with cystic fibrosis: results of a multicenter randomized controlled trial. *J Clin Endocrinol Metab.* 2006; 91(12):4925-9.
20. Hardin DS, Ellis KJ, Dyson M, et al. Growth hormone improves clinical status in prepubertal children with cystic fibrosis: Results of a randomized controlled clinical trial. *J Pediatr.* 2001;139:636-42.
21. Hardin DS, Rice J, Ahn C, et al. Growth hormone treatment enhances nutrition and growth in children with cystic fibrosis receiving enteral nutrition. *J Pediatr.* 2005;146:324-8.
22. Ranke MB, Lindberg A. Growth hormone treatment of short children born small for gestational age or with Silver-Russell syndrome: Results from KIGS (Kabi International Growth Study), including the first report on final height. *Acta Paediatr Suppl.* 1996;417:18-26.
23. American Association of Clinical Endocrinologists Growth Hormone Task Force. Medical guidelines for clinical practice for growth hormone use in adults and children 2003 Update. *Endocr Pract.* 2003;9(1):64-76.
24. Caremark Clinical Programs Review: Focus on pediatric endocrinology. April 23, 2014.
25. Caremark Clinical Programs Review: Focus on pediatric endocrinology. April 16, 2012.
26. National Institute for Clinical Excellence: Guidance on the use of human growth hormone (somatropin) for the treatment of growth failure in children. May 2010. <http://www.nice.org.uk/nicemedia/live/12992/48715/48715.pdf>. Accessed January 28, 2019.
27. 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.
28. Franklin SL, Geffner ME. Growth hormone: the expansion of available products and indications. *Pediatr Clin North Am.* 2011;58:1141-1165.
29. 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.

Reference number(s)
1742-A

30. Growth Hormone Usage in Short Children: American Association of Clinical Endocrinologists Position Statement. <https://www.aace.com/files/position-statements/shortchildren.pdf>. Accessed January 28, 2019.
31. Caremark Clinical Programs Review: Focus on pediatric endocrinology. December 8, 2009.
32. Deal CL, Tony M, Hoybye C, et al. Growth Hormone Research Society workshop summary: consensus guidelines for recombinant human growth hormone therapy in Prader-Willi syndrome. *J Clin Endocrinol Metab.* 2013;98:E1072-E1087.
33. Blum WF, Crowe BJ, Quigley CA, et al. Growth hormone is effective in treatment of short stature associated with short stature homeobox-containing gene deficiency: two-year results of a randomized, controlled, multicenter trial. *J Clin Endocrinol Metab.* 2007;92:219-228.
34. Blum WF, Ross JL, Zimmermann AG, et al. GH treatment to final height produces similar height gains in patients with SHOX deficiency and Turner syndrome: results of a multicenter trial. *J Clin Endocrinol Metab.* 2013;98(8):E1383-92.
35. 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.
36. Caremark Clinical Programs Review: Focus on pediatric endocrinology. March 30, 2011.
37. 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.
38. National Institute for Clinical Excellence: Human growth hormone (somatropin) in adults with growth hormone deficiency. August 2003.
39. Caremark Clinical Programs Review: Focus on pediatric endocrinology. May 15, 2013.
40. Caremark Clinical Programs Review: Focus on pediatric endocrinology. September 10, 2007.
41. Deal C, Hasselmann C, Pfaffle RW, et al. Associations between pituitary imaging abnormalities and clinical and biochemical phenotypes in children with congenital growth hormone deficiency: data from an international observational study. *Horm Res Paediatr.* 2013;79:283-292.
42. National Heart, Lung, and Blood Institute. Obesity Education Initiative: The practical guide: identification, evaluation, and treatment of overweight and obesity in adults. Bethesda, MD: US Dept of Health and Human Services, National Heart, Lung, and Blood Institute; 2000. NIH Publication No. 00-4084.
43. Macrilen [package insert]. Goettingen, Germany: Allphamed Pharbil Arzneimittel GmbH; January 2018.