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. DOCUMENTATION

Submission of 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. Growth chart
D. Pretreatment and/or current IGF-1 level (laboratory report or medical record documentation)*
E. 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
F. 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. CRITERIA FOR INITIAL 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:
   i. Member has EITHER:
      a. Two pretreatment pharmacologic provocative GH tests with both results demonstrating a peak GH level < 10 ng/mL, OR
      b. A documented pituitary or CNS disorder (refer to Appendix A) and a pretreatment IGF-1 level > 2 standard deviations (SD) below the mean
   ii. 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
   iii. 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
   iv. 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:
   i. Birth weight < 2500 g at gestational age > 37 weeks
   ii. Birth weight or length less than 3rd percentile for gestational age
   iii. 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:

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 (CKD), 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:
   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
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, translocations, or inversions 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 meets both of the following:
   i. Member has had 2 pretreatment pharmacologic provocative GH tests and both results demonstrated deficient GH responses defined as the following:
      a. Insulin tolerance test (ITT) with a peak GH level ≤ 5 ng/mL
      b. Macrilen with a peak GH level of less than 2.8 ng/mL
      c. Glucagon stimulation test with a peak GH level ≤ 3.0 ng/mL in patients with a body mass index (BMI) ≤ 30 kg/m^2 and a high pretest probability of GHD (e.g., acquired structural abnormalities) OR a BMI < 25 kg/m^2

d. Glucagon stimulation test with a peak GH level ≤ 1.0 ng/mL in patients with a BMI of ≥ 25 kg/m^2 and a low pretest probability of GHD (e.g., acquired structural abnormalities) OR a BMI > 30 kg/m^2

ii. Member has a low pre-treatment IGF-1 (between 0 to 2 SD below the mean for age and gender)

2. Member meets both of the following:
   i. Member has had 1 pretreatment pharmacologic provocative GH test that demonstrated deficient GH responses defined as one of the following:
      i. Insulin tolerance test (ITT) with a peak GH level ≤ 5 ng/mL
      ii. Macrilen with a peak GH level of less than 2.8 ng/mL
      iii. Glucagon stimulation test with a peak GH level ≤ 3.0 ng/mL in patients with a body mass index (BMI) ≤ 30 kg/m^2 and a high pretest probability of GHD (e.g., acquired structural abnormalities) OR a BMI < 25 kg/m^2
      iv. Glucagon stimulation test with a peak GH level ≤ 1.0 ng/mL in patients with a BMI of ≥ 25 kg/m^2 and a low pretest probability of GHD (e.g., acquired structural abnormalities) OR a BMI > 30 kg/m^2
   ii. Member has a pretreatment IGF-1 level that is more than 2 SD below the mean for age and gender
3. Member has organic hypothalamic-pituitary disease (e.g., suprasellar mass with previous surgery and cranial irradiation) with ≥ 3 documented pituitary hormone deficiencies (refer to Appendix B) and a low pre-treatment IGF-1 more than 2 standard deviations below the mean for age and gender
4. Member has genetic or structural hypothalamic-pituitary defects (refer to Appendix C)
5. Member has childhood-onset GH deficiency and a congenital abnormality of the CNS, hypothalamus or pituitary (refer to Appendix C)

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/m^2 prior to starting therapy with growth hormone (see Appendix D)

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 ANY of the following criteria is met:

1. Member meets all of the following:
   i. Member has had 2 pretreatment pharmacologic provocative GH tests and both results demonstrated deficient GH responses defined as the following:
      a. Insulin tolerance test (ITT) or another provocative GH test with a peak GH level ≤ 5 ng/mL
      b. Macrilen with a peak GH level of less than 2.8 ng/mL
      c. Glucagon stimulation test with a peak GH level ≤ 3.0 ng/mL in patients with a body mass index (BMI) ≤ 30 kg/m^2 and a high pretest probability of GHD (e.g., acquired structural abnormalities) OR a BMI < 25 kg/m^2
      d. Glucagon stimulation test with a peak GH level ≤ 1.0 ng/mL in patients with a BMI of ≥ 25 kg/m^2 and a low pretest probability of GHD (e.g., acquired structural abnormalities) OR a BMI > 30 kg/m^2
   ii. Member has a low pre-treatment IGF-1 (between 0 to 2 SD below the mean for age and gender)
   iii. Current IGF-1 level is not elevated for age and gender
2. Member meets all of the following:
   i. Member has had 1 pretreatment pharmacologic provocative GH test that demonstrated deficient GH responses defined as one of the following:
      a. Insulin tolerance test (ITT) or another provocative GH test with a peak GH level ≤ 5 ng/mL
      b. Macrilen with a peak GH level of less than 2.8 ng/mL
      c. Glucagon stimulation test with a peak GH level ≤ 3.0 ng/mL in patients with a body mass index (BMI) ≤ 30 kg/m^2 and a high pretest probability of GHD (e.g., acquired structural abnormalities) OR a BMI < 25 kg/m^2
      d. Glucagon stimulation test with a peak GH level ≤ 1.0 ng/mL in patients with a BMI of ≥ 25 kg/m^2 and a low pretest probability of GHD (e.g., acquired structural abnormalities) OR a BMI > 30 kg/m^2
   ii. Member has a pretreatment IGF-1 level that is more than 2 SD below the mean for age and gender
   iii. Current IGF-1 level is not elevated for age and gender
3. Member meets both of the following:
   i. Member has organic hypothalamic-pituitary disease (e.g., suprasellar mass with previous surgery and cranial irradiation) with ≥ 3 documented pituitary hormone deficiencies (refer to Appendix B) and a low pre-treatment IGF-1 more than 2 standard deviations below the mean for age and gender
   ii. Current IGF-1 level is not elevated for age and gender
4. Member has genetic or structural hypothalamic-pituitary defects (refer to Appendix C) and current IGF-1 level is not elevated for age and gender
5. Member has childhood-onset GH deficiency and a congenital abnormality of the CNS, hypothalamus or pituitary (refer to Appendix C) and current IGF-1 level is not elevated for age and gender

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/m^2 (see Appendix D).

V. APPENDICES

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

1. Congenital genetic abnormalities
    a. Transcription factor defects (PIT-1, PROP-1, LHX3/4, HESX-1, PITX-2)
    b. Growth hormone releasing hormone (GHRH) receptor gene defects
    c. GH secretagogue receptor gene defects
    d. GH gene defects
    e. GH receptor/post receptor defects
2. Congenital structural abnormalities
    a. Optic nerve hypoplasia/septo-optic dysplasia
    b. Agenesis of corpus callosum
    c. Empty sella syndrome
    d. Ectopic posterior pituitary
    e. Pituitary aplasia/hypoplasia
    f. Pituitary stalk defect
    g. Holoprosencephaly
    h. Encephalocele
    i. Hydrocephalus
    j. Anencephaly or prosencephaly
    k. Arachnoid cyst
    l. Other mid-line defects (e.g., single central incisor, cleft lip/palate)
    m. Vascular malformations
3. Acquired structural abnormalities (or causes of hypothalamic/pituitary damage)
    a. CNS tumors/neoplasms (e.g., craniopharyngioma, glioma/astrocytoma, pituitary adenoma, germinoma)
    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 processes (e.g., autoimmune hypophysitis)
    i. Infiltrative processes (e.g., sarcoidosis, histiocytosis, hemochromatosis)
    j. Head trauma/traumatic brain injury
    k. Aneurysmal subarachnoid hemorrhage
    l. Perinatal or postnatal trauma
    m. Surgery of the pituitary or hypothalamus

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

1. Adrenocorticotropic 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: Requirements for GH-Stimulation Testing in Adults

1. Testing for adult GHD is not required
    a. Three or more pituitary hormone deficiencies and low IGF-1
    b. Congenital structural abnormalities
        i. Transcription factor defects (PIT-1, PROP-1, LHX3/4, HESX-1, PITX-2)

ii. GHRH receptor-gene defects
iii. GH-receptor/post-receptor defects
iv. GH-gene defects associated with brain structural defects
v. Single central incisor
vi. Cleft lip/palate

c. Acquired causes such as perinatal insults

2. Testing for adult GHD is required
   a. Acquired
      i. Skull-base lesions
      ii. Pituitary adenoma
      iii. Craniopharyngioma
      iv. Rathke's cleft cyst
      v. Meningioma
      vi. Glioma/astrocytoma
      vii. Neoplastic sellar and parasellar lesions
      viii. Chordoma
      ix. Hamartoma
      x. Lymphoma
      xi. Metastases
      xii. Other brain injury
      xiii. Traumatic brain injury
      xiv. Sports-related head trauma
      xv. Blast injury
      xvi. Infiltrative/granulomatous disease
      xvii. Langerhans cell histiocytosis
      xviii. Autoimmune hypophysitis (primary or secondary)
      xix. Sarcoidosis
      xx. Tuberculosus
      xxi. Amyloidosis
   b. Surgery to the sella, suprasellar, and parasellar region
   c. Cranial irradiation
   d. Central nervous system infections (bacteria, viruses, fungi, parasites)
   e. Infarction/hemorrhage (e.g., apoplexy, Sheehan's syndrome, subarachnoid hemorrhage, ischemic stroke, snake bite)
   f. Empty sella
   g. Hydrocephalus
   h. Idiopathic

D. Appendix D: Calculation of BMI[42]

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

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 (class 3)	≥ 40 kg/m^2

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