Cigna Drug and Biologic Coverage Policy

Effective Date…….. 05/1/2019
Next Review Date……..01/1/2020
Coverage Policy Number……..4012

Subject: **Somatropin**

Table of Contents

Related Coverage Resources

Mecasermin

INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Coverage Policy

Employer Group Plans:
Humatrope® and Norditropin Flexpro® are the preferred somatropin brand products.

In addition to the criteria detailed below, Genotropin®, Nutropin®, Nutropin AQ®, Omnitrope®, Saizen® and Zomacton™ will only be covered when there is a contraindication per FDA label, or documented intolerance to Humatrope® and Norditropin Flexpro®.

Individual and Family Plans:
Humatrope® is the preferred somatropin brand product.

In addition to the criteria detailed below, Genotropin®, Norditropin Flexpro®, Nutropin®, Nutropin AQ®, Omnitrope®, Saizen® and Zomacton™ will only be covered when there is a contraindication per FDA label, or documented intolerance to Humatrope®.

Cigna covers somatropin (Humatrope, Genotropin, Norditropin Flexpro, Nutropin, Nutropin AQ, Omnitrope, Saizen, and Zomacton) as medically necessary for the following conditions (see individual subsections for specific coverage criteria requirements for each indication):

Growth Hormone Use in Children:
- Growth hormone use following cranial or whole body irradiation
- Growth hormone use in panhypopituitarism
- Growth hormone deficiency (GHD) in children
- Small for gestational age (SGA)
- Growth delay in children with chronic renal failure

- Turner Syndrome
- Prader-Willi Syndrome
- Noonan Syndrome
- SHOX (short stature homeobox-containing gene) gene deletion

Growth Hormone Use in Adults:
- Growth hormone deficiency (GHD) of defined etiology
- Growth hormone deficiency (GHD) of idiopathic etiology
- Continuation of therapy from GHD in childhood
- Treatment of HIV with wasting or cachexia (Serostim only)
- Treatment of Short Bowel Syndrome (Zorbtive only)

Summary of Diagnosis and Stimulation Testing Requirements

Diagnosis	Stimulation Testing Requirements
Pediatric Uses:	
Cranial irradiation history	None
Whole body irradiation history	None
Panhypopituitarism in children	None
GHD in children (including pituitary dwarfism)	2
• Defined CNS pathology such as empty sella syndrome, interruption of pituitary stalk, hypoplasia of the pituitary gland, craniofacial developmental defects, pituitary or hypothalamic tumors, etc.	1
• Multiple Pituitary Hormone Deficiency (MPHD)	1
• Genetic defect along GH axis	1
Small for Gestational Age (SGA)	None
Chronic Kidney Disease	None
Turner Syndrome	None
Prader-Willi Syndrome	None
Noonan Syndrome	None
SHOX Gene Deletion	None
Adult Uses:	
Panhypopituitarism in an adult	None
GHD of defined etiology in an adult	1
GHD of idiopathic etiology in an adult	2
HIV with wasting and cachexia (Serostim only)	None
Short Bowel Syndrome (Zorbtive only)	None

(See individual subsections for specific coverage criteria requirements for each indication)

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to somatropin (Genotropin®, Humatrope®, Norditropin FlexPro®, Nutropin®, Nutropin® AQ, Omnitrope®, Saizen®, Serostim®, Zomacton™, Zorbtive®) therapy.

Note: Receipt of sample product does not satisfy any criteria requirements for coverage

Growth Hormone Use in Children:

- **For a history of cranial or whole body irradiation it may be assumed that GH is absent and neither stimulation testing nor auxologic evaluation (stature and growth velocity data) is required.**

- **For documented panhypopituitarism in children, defined by the absence of all other anterior pituitary hormones [Luteinizing Hormone (LH), Follicle Stimulating Hormone (FSH), Thyroid Stimulating Hormone (TSH), Adrenocorticotropic Hormone (ACTH)], neither stimulation testing nor auxologic evaluation (stature and growth velocity data) is required.**

NOTE: Coverage for continuation of therapy of the above conditions requires meeting current initial use criteria.

- **For growth hormone deficiency (GHD) in children (including pituitary dwarfism), when BOTH of the following criteria are met:**
  - auxologic evaluation (stature and growth velocity data), including **ONE** of the following:
    - individual's height is more than two standards of deviation (SD) below average for the population mean height for age and sex, **AND** a height velocity measured over one year is more than one SD below the mean for chronological age, **OR** for children over two years of age, there is a decrease in height SD of more than 0.5 over one year
    - individual's height velocity measured over one year is more than two SD below the mean for age and sex **OR** more than 1.5 SD below the mean sustained over two years
  - diagnostic evaluation, including **BOTH** of the following:
    - growth hormone response of less than 10 ng/mL to two provocative stimuli of growth hormone release*: clonidine, glucagon, insulin, L-arginine, levodopa, propranolol. One abnormal growth hormone stimulation test is sufficient for children with defined central nervous system (CNS) pathology (for example, empty sella syndrome, interruption of pituitary stalk, hypoplasia of the pituitary gland, craniofacial developmental defects, pituitary or hypothalamic tumors, etc.); multiple pituitary hormone deficiency (MPHD) (i.e., deficiency of two or more pituitary hormones) or a proven genetic defect affecting the growth hormone axis.
    - other pituitary hormone deficiencies (for example, thyroid, cortisol or sex steroids) have been ruled out and/or corrected prior to time of testing

    *NOTE: Growth hormone response of greater than or equal to 10 ng/mL to any provocative stimulus of growth hormone release excludes GH deficiency

- **Small for Gestational Age (SGA) when ALL of the following criteria are met:**
  - child was born small for gestational age, defined as birth weight and/or length at least two standard deviations below the mean for gestational age
  - child fails to manifest catch-up growth by two years of age, defined as height at least two standard deviations below the mean for age and sex
  - absence of chromosomal anomalies unless otherwise specified as covered

- **For Growth Delay in children with Chronic Kidney Disease (CKD) when BOTH of the following criteria are met:**
  - renal function at stage 2 or more advanced CKD (or GFR equal to or less than 60ml/min/1.73m^2)
  - auxologic evaluation (stature and growth velocity data), including **ONE** of the following:
    - individual's height is more than two standards of deviation (SD) below average for the population mean height for age and sex, **AND** a height velocity measured over one year is more than one SD below the mean for chronological age, **OR** for children over two years of age, there is a decrease in height SD of more than 0.5 over one year
    - individual's height velocity measured over one year is more than two SD below the mean for age and sex **OR** more than 1.5 SD below the mean sustained over two years

- **For Turner Syndrome, when BOTH of the following criteria are met:**
  - documentation of diagnosis as established by genetic testing
  - auxologic evaluation (stature and growth velocity data), including **ONE** of the following:
    - individual's height is more than two standards of deviation (SD) below average for the population mean height for age and sex, **AND** a height velocity measured over one year is more than one SD below the mean for chronological age, **OR** for children over two years of age, there is a decrease in height SD of more than 0.5 over one year

        - individual's height velocity measured over one year is more than two SD below the mean for age and sex **OR** more than 1.5 SD below the mean sustained over two years

- **For Prader-Willi Syndrome, when BOTH of the following criteria are met:**
  - diagnosis of Prader-Willi Syndrome is confirmed by appropriate genetic testing
  - auxologic evaluation (stature and growth velocity data), including **ONE** of the following:
    - individual's height is more than two standards of deviation (SD) below average for the population mean height for age and sex, **AND** a height velocity measured over one year is more than one SD below the mean for chronological age, **OR** for children over two years of age, there is a decrease in height SD of more than 0.5 over one year
    - individual's height velocity measured over one year is more than two SD below the mean for age and sex **OR** more than 1.5 SD below the mean sustained over two years

- **For Noonan Syndrome, when BOTH of the following criteria are met:**
  - diagnosis of Noonan Syndrome is confirmed by appropriate genetic testing
  - auxologic evaluation (stature and growth velocity data), including **ONE** of the following:
    - individual's height is more than two standards of deviation (SD) below average for the population mean height for age and sex, **AND** a height velocity measured over one year is more than one SD below the mean for chronological age, **OR** for children over two years of age, there is a decrease in height SD of more than 0.5 over one year
    - individual's height velocity measured over one year is more than two SD below the mean for age and sex **OR** more than 1.5 SD below the mean sustained over two years

- **For SHOX (short stature homeobox-containing gene) gene deletion treatment when BOTH of the following criteria are met:**
  - diagnosis of SHOX gene deletion is confirmed by appropriate genetic testing
  - auxologic evaluation (stature and growth velocity data), including **ONE** of the following:
    - individual's height is more than two standards of deviation (SD) below average for the population mean height for age and sex, **AND** a height velocity measured over one year is more than one SD below the mean for chronological age, **OR** for children over two years of age, there is a decrease in height SD of more than 0.5 over one year
    - individual's height velocity measured over one year is more than two SD below the mean for age and sex **OR** more than 1.5 SD below the mean sustained over two years

NOTE: Standard reauthorization criteria apply to the above conditions (excluding cranial or whole body irradiation and panhypopituitarism):

- **Yearly reassessment for reauthorization of coverage is required.**
- **Coverage for continuation of therapy requires meeting current initial use criteria and evidence of a beneficial response as shown by growth curve chart.**
- **Coverage for growth promotion will cease when the bony epiphyses have closed.**

Growth Hormone Use in Adults:

- **For an adult with documented panhypopituitarism, defined by the absence of all other anterior pituitary hormones [Luteinizing Hormone (LH), Follicle Stimulating Hormone (FSH), Thyroid Stimulating Hormone (TSH), Adrenocorticotropic Hormone (ACTH)], stimulation testing is NOT required.**

NOTE: Coverage for continuation of therapy of the above condition requires meeting current initial use criteria.

- **For growth hormone deficiency (GHD) of defined etiology in an adult when ALL of the following conditions are met:**
  - etiology of GHD is a result of destructive hypothalamic or pituitary disease, radiation therapy, surgery or trauma **OR** is a result of documented GHD in childhood
  - confirmation of GHD by appropriate evaluation of stimulation testing by ONE of the following:

        - For insulin, levodopa, clonidine, arginine, or glucagon: growth hormone response of less than 5 ng/mL when measured by polyclonal antibody (RIA) or less than 2.5 ng/mL when measured by monoclonal antibody (IRMA) to one provocative stimuli of growth hormone release
        - For macimorelin*, **BOTH** of the following:
            - Maximum serum growth hormone level observed after stimulation of less than 2.8 ng/ml for the 4 blood draws
            - Body mass index (BMI) less than or equal to 40 kg/m2
        - [Test currently unavailable, however when historically used] GHD had been confirmed by arginine-GHRH testing resulting in plasma growth hormone concentrations of < 11ng/mL with a BMI of <25, < 8ng/mL with a BMI of 25-30, and < 4ng/mL with a BMI ≥30 when measured by monoclonal antibody (IRMA)
    - other pituitary hormone deficiencies, for example, thyroid, cortisol or sex steroids, have been ruled out and/or corrected

- **For growth hormone deficiency (GHD) of idiopathic etiology in an adult, when BOTH of the following conditions are met:**
    - IGF-1 level below the lower limits of normal
    - confirmation of GHD by appropriate evaluation of stimulation testing defined by TWO of the following tests:
        - For insulin: growth hormone response of less than 5 ng/mL when measured by polyclonal antibody (RIA) or less than 2.5 ng/mL when measured by monoclonal antibody (IRMA) to provocative stimulation of growth hormone release
        - For glucagon: growth hormone response of less than 5 ng/mL when measured by polyclonal antibody (RIA) or less than 2.5 ng/mL when measured by monoclonal antibody (IRMA) to provocative stimulation of growth hormone release
        - For macimorelin*, **BOTH** of the following:
            - Maximum serum growth hormone level observed after stimulation of less than 2.8 ng/ml for the 4 blood draws
            - Body mass index (BMI) less than or equal to 40 kg/m2
        - [Test currently unavailable, however when historically used] arginine-GHRH testing resulting in plasma growth hormone concentrations of < 11ng/mL with a BMI of <25, <8ng/mL with a BMI of 25-30, and <4ng/mL with a BMI ≥30 when measured by monoclonal antibody (IRMA)]

**May be subject to medical necessity review*

NOTE: Standard reauthorization criteria apply to the above conditions (excluding panhypopituitarism):

- **Yearly reassessment for reauthorization of coverage is required**
- **Coverage for continuation of therapy requires meeting current initial use criteria**

Cigna covers Serostim as medically necessary in an adult for the treatment of HIV with wasting or cachexia when ALL of the following conditions are met:

- Weight loss greater than 10% of pre-illness baseline body weight or body mass index (BMI) less than 20 kg/m2
- Documented failure, intolerance, or contraindication to appetite stimulants and/or other anabolic agents
- Continuous use of antiviral therapy

Initial authorization is limited to 12 weeks. Reauthorizations (if initial criteria are met) will be provided for an additional 12 weeks if baseline body weight and BMI are not achieved at the end of prior authorization period for a total duration of 48 weeks.

Cigna covers Zorbtive as medically necessary in an adult for treatment of short bowel syndrome when BOTH of the following conditions are met:

- Use with special diets and glutamine supplementation
- Current dependence upon intravenous (IV) parenteral nutrition

Authorization to consist of ONE four-week course of therapy

Cigna does NOT cover somatropin for the diagnosis/treatment/management of the following conditions because they are considered not medically necessary (this list may not be all-inclusive):

- idiopathic (i.e. of unknown origin) short stature, also called non-growth hormone deficient short stature in children
- increased athletic performance in adults
- idiopathic (i.e. of unknown origin) IGF-1 deficiency

Cigna does NOT cover somatropin in combination with GnRH (Supprelin® LA, Lupron®) to prolong the pre-pubertal state because this is considered not medically necessary.

Cigna does not cover the use of somatropin for any other indication including the following because it is considered experimental, investigational or unproven (this list may not be all-inclusive):

Growth Hormone Use in Children:
- Celiac disease
- Chromosomal anomalies unless otherwise specified as covered
- Combination use with gonadotropin-releasing hormones (GnRH) for precocious puberty
- Combination use with any other medication for the purpose of pubertal suppression
- Congenital adrenal hyperplasia
- Continuation of growth hormone treatment for growth promotion once epiphyses are closed
- Crohn's disease or ulcerative colitis
- Cystic fibrosis
- Deletion of chromosome 18q
- Down Syndrome and other syndromes associated with short stature and malignant diathesis
- Duchenne muscular dystrophy
- Glucocorticoid-induced growth failure
- Hypochondroplasia
- Hypophosphatemic rickets
- Intrauterine growth restriction (IUGR)
- Juvenile rheumatoid arthritis
- Osteogenesis imperfecta
- Precocious puberty
- Primary insulin-like growth factor-1 (IGF-1) deficiency
- Repeat courses of therapy in Short Bowel Syndrome
- Silver-Russell Syndrome (unless they meet criteria for Small for Gestational Age)
- Skeletal dysplasias, for example, achondroplasia
- Spinal cord defects

Note: Macimorelin is considered experimental, investigational, or unproven for confirmation of GHD in children.

Note: An individual diagnosed with a co-morbid condition found on the experimental, investigational, or unproven list may still be eligible for growth hormone therapy if the applicable medical necessity criteria established in the coverage policy are met.

Growth Hormone Use in Adults:
- continuation of growth hormone treatment from childhood use once epiphyses are closed
- Crohn's disease or ulcerative colitis
- infertility
- muscular dystrophy
- obesity
- osteoporosis
- repeat courses of therapy in Short Bowel Syndrome
- somatopause

Note: An individual diagnosed with a co-morbid condition found on the experimental, investigational, or unproven list may still be eligible for growth hormone therapy if the applicable medical necessity criteria established in the coverage policy are met.

FDA Approved Indications

Product	FDA Approved Indications
Genotropin (somatropin)	Genotropin is a recombinant human growth hormone indicated for: **Pediatric:** 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:** Treatment of adults with either adult onset or childhood onset GHD
Humatrope (somatropin)	Humatrope is a recombinant human growth hormone (somatropin) indicated for: **Pediatric:** Treatment of children with short stature or growth failure associated with growth hormone (GH) deficiency, Turner syndrome, idiopathic short stature, SHOX deficiency, and failure to catch up in height after small for gestational age birth. **Adult:** Treatment of adults with either childhood-onset or adult-onset GH deficiency.
Norditropin FlexPro (somatropin)	Norditropin is a recombinant human growth hormone indicated for: **Pediatric:** Treatment of pediatric patients with growth failure due to inadequate secretion of endogenous growth hormone (GH), short stature associated with Noonan syndrome, short stature associated with Turner syndrome, short stature born small for gestational age (SGA) with no catchup growth by age 2 to 4 years, Idiopathic Short Stature (ISS), and growth failure due to Prader-Willi Syndrome (1.1) **Adult:** Replacement of endogenous GH in adults with growth hormone deficiency (1.2)
Nutropin and **Nutropin AQ** (somatropin)	Nutropin and Nutropin AQ are indicated for: **Pediatric:** Treatment of children with growth failure due to growth hormone deficiency (GHD), idiopathic short stature (ISS), Turner syndrome (TS), and chronic kidney disease (CKD) up to the time of renal transplantation **Adult:** Treatment of adults with either childhood-onset or adult-onset GHD
Omnitrope (somatropin)	Omnitrope is a recombinant human growth hormone indicated for: **Pediatric:** 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:** Treatment of adults with either adult onset or childhood onset GHD
Saizen (somatropin)	Saizen is a recombinant human growth hormone indicated for: **Pediatric:** Treatment of children with growth failure due to growth hormone deficiency (GHD) **Adult:** Treatment of adults with either adult onset or childhood onset GHD.
Serostim (somatropin)	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 (somatropin)	Zomacton is a recombinant human growth hormone indicated for: **Pediatric:** Treatment of pediatric patients with growth failure due to inadequate secretion of endogenous growth hormone (GH), short stature associated with Turner syndrome, idiopathic short stature (ISS), short stature or growth failure in short stature homeobox-containing gene (SHOX) deficiency, and short stature born small for gestational age (SGA) with no catch-up growth by 2 years to 4 years. (1.1) **Adult:** Replacement of endogenous GH in adults with GH deficiency (1.2)
Zorbtive (somatropin)	Zorbtive is a recombinant human growth hormone indicated for the treatment of short bowel syndrome in adult patients receiving specialized nutritional support.

FDA Recommended Dosing

Product	FDA Recommended Dosing
Genotropin (somatropin)	Genotropin should be administered subcutaneously. **Pediatric GHD*:*** 0.16 to 0.24 mg/kg/week

	Prader-Willi Syndrome *:* 0.24 mg/kg/week **Small for Gestational Age*:*** Up to 0.48 mg/kg/week **Turner Syndrome*:*** 0.33 mg/kg/week **Idiopathic Short Stature *:*** up to 0.47 mg/kg/week **Adult GHD*:*** Either a non-weight based or a weight based dosing regimen may be followed, with doses adjusted based on treatment response and IGF-I concentrations. Non-weight based dosing: A starting dose of approximately 0.2mg/day (range, 0.15-0.30 mg/day) may be used without consideration of body weight, and increased gradually every 1-2 months by increments of approximately 0.1-0.2 mg/day. Weight based dosing: The recommended initial dose is not more than 0.04 mg/kg/week; the dose may be increased as tolerated to not more than 0.08 mg/kg/week at 4–8 week intervals.
Humatrope (somatropin)	Humatrope should be administered subcutaneously. For pediatric patients, the recommended weekly dosages in milligrams (mg) per kilogram (kg) of body weight (given in divided doses 6 to 7 times per week) are: **Pediatric GH deficiency:** 0.18 to 0.30 mg/kg/week **Turner syndrome:** Up to 0.375 mg/kg/week **Idiopathic short stature:** Up to 0.37 mg/kg/week **SHOX deficiency:** 0.35 mg/kg/week **Small for gestational age:** Up to 0.47 mg/kg/week **Adult GH deficiency*:*** Either a non-weight based or a weight-based dosing regimen may be followed, with doses adjusted based on treatment response and IGF-I concentrations. Non-weight based dosing*:* A starting dose of approximately 0.2 mg/day (range, 0.15-0.30 mg/day) may be used without consideration of body weight, and increased gradually every 1-2 months by increments of approximately 0.1-0.2 mg/day. Weight-based dosing*:* The recommended initial daily dose is not more than 0.006 mg/kg (6 µg/kg); the dose may be increased to a maximum of 0.0125 mg/kg (12.5 µg/kg) daily.
Norditropin FlexPro (somatropin)	**Pediatric Dosage** • Individualize dosage for each patient based on the growth response. • Divide the calculated weekly NORDITROPIN dosage into equal doses given either 6, or 7 days per week. The recommended weekly dose in milligrams (mg) per kilogram (kg) of body weight for pediatric patients is: • **Pediatric GH Deficiency:** 0.17 mg/kg/week to 0.24 mg/kg/week (0.024 to 0.034 mg/kg/day) • **Noonan Syndrome:** Up to 0.46 mg/kg/week (up to 0.066 mg/kg/day) • **Turner Syndrome:** Up to 0.47 mg/kg/week (up to 0.067 mg/kg/day) • **Small for Gestational Age (SGA):** Up to 0.47 mg/kg/week (up to 0.067 mg/kg/day) o In very short pediatric patients, HSDS less than -3, and older pubertal pediatric patients consider initiating treatment with a larger dose of NORDITROPIN (up to 0.067 mg/kg/day). Consider a gradual reduction in dosage if substantial catch-up growth is observed during the first few years of therapy. In pediatric patients less than 4 years of age with less severe short stature, baseline HSDS values between -2 and -3, consider initiating treatment at 0.033 mg/kg/day and titrate the dose as needed. • **Idiopathic Short Stature:** Up to 0.47 mg/kg/week (up to 0.067 mg/kg/day) • **Prader-Willi Syndrome:** 0.24 mg/kg/week (0.034 mg/kg/day) **Adult Dosage** Either of two NORDITROPIN dosing regimens may be used: • Non-weight based

	○ Initiate NORDITROPIN with a dose of approximately 0.2 mg/day (range, 0.15 mg/day to 0.3 mg/day) and increase the dose every 1-2 months by increments of approximately 0.1 mg/day to 0.2 mg/day, according to individual patient requirements based on the clinical response and serum insulin-like growth factor 1 (IGF1) concentrations. ○ Decrease the dose as necessary on the basis of adverse reactions and/or serum IGF-1 concentrations above the age-and gender-specific normal range. ○ Maintenance dosages will vary considerably from person to person, and between male and female patients. • Weight-based ○ Initiate NORDITROPIN at 0.004 mg/kg daily and increase the dose according to individual patient requirements to a maximum of 0.016 mg/kg daily. ○ Use the patient's clinical response, adverse reactions, and determination of age-and gender-adjusted serum IGF-1 concentrations as guidance in dose titration. ○ Not recommended for obese patients as they are more likely to experience adverse reactions with this regimen
Nutropin and **Nutropin AQ** (somatropin)	Nutropin should be administered subcutaneously. **Pediatric GHD:** Up to 0.3 mg/kg/week **Pubertal Patients:** Up to 0.7 mg/kg/week **Idiopathic Short Stature:** Up to 0.3 mg/kg/week **Chronic Kidney Disease:** Up to 0.35 mg/kg/week **Turner Syndrome:** Up to 0.375 mg/kg/week **Adult GHD:** Either a non-weight based or weight-based dosing regimen may be followed, with doses adjusted based on treatment response and IGF-I concentrations. Non-weight-based: A starting dose of approximately 0.2 mg/day (range 0.15-0.3 mg/day) increased gradually every 1-2 months by increments of approximately 0.1-0.2 mg/day. Weight-based: Initiate from not more than 0.006 mg/kg/day; the dose may be increased up to a maximum of 0.025 mg/kg/day in patients ≤ 35 years old or 0.0125 mg/kg/day in patients > 35 years old.
Omnitrope (somatropin)	Omnitrope should be administered subcutaneously. **Pediatric GHD:** 0.16 to 0.24 mg/kg/week, divided into 6 to 7 daily injections. **Prader-Willi Syndrome:** 0.24 mg/kg/week, divided into 6 to 7 daily injections. **Small for Gestational Age:** Up to 0.48 mg/kg/week, divided into 6 to 7 daily injections. **Turner Syndrome:** 0.33 mg/kg/week, divided into 6 to 7 daily injections. Idiopathic Short Stature: Up to 0.47 mg/kg/week, divided into 6 to 7 daily injections **Adult GHD:** not more than 0.04 mg/kg/week (divided into daily injections) to be increased as tolerated to not more than 0.08 mg/kg/week); to be increased gradually every 1 to 2 months.
Saizen (somatropin)	**Pediatric GHD:** 0.18 mg/kg/week, divided into equal doses given either on 3 alternate days, 6 times per week or daily. **Adult GHD:** Either a non-weight based or a weight based dosing regimen may be followed, with doses adjusted based on treatment response and IGF-1 concentrations. Non-weight-based dosing: A starting dose of approximately 0.2 mg/day (range, 0.15-0.30 mg/day) may be used without consideration of body weight, and increased gradually every 1 to 2 months by increments of approximately 0.1 to 0.2 mg/day. Weight-based dosing: The recommended initial dose is not more than 0.005 mg/kg/day; the dose may be increased as tolerated to not more than 0.01 mg/kg/day after 4 weeks.
Serostim (somatropin)	The recommended dose of Serostim is 0.1 mg/kg subcutaneously (SC) daily (up to 6 mg) at bedtime for HIV patients with wasting or cachexia.
Zomacton (somatropin)	**Pediatric Dosage** • Individualize dosage for each patient based on the growth response.

	• Divide the calculated weekly ZOMACTON dosage into equal doses given either 3, 6, or 7 days per week. • The recommended weekly dose in milligrams (mg) per kilogram (kg) of body weight for pediatric patients is: o ***Pediatric GH Deficiency:*** 0.18 mg/kg/week to 0.3 mg/kg/week (0.026 mg/kg/day to 0.043 mg/kg/day) o ***Turner syndrome:*** Up to 0.375 mg/kg/week (up to 0.054 mg/kg/day) o ***Idiopathic short stature:*** Up to 0.37 mg/kg/week (up to 0.053 mg/kg/day) o ***SHOX Deficiency:*** 0.35 mg/kg/week (0.05 mg/kg/day) o ***Small for Gestational Age (SGA):*** Up to 0.47 mg/kg/week (up to 0.067 mg/kg/day) ▪ In very short pediatric patients, HSDS less than -3, and older pubertal pediatric patients consider initiating treatment with a larger dose of ZOMACTON (up to 0.067 mg/kg/day). Consider a gradual reduction in dosage if substantial catch-up growth is observed during the first few years of therapy. In pediatric patients less than 4 years of age with less severe short stature, baseline HSDS values between -2 and -3, consider initiating treatment at 0.033 mg/kg/day and titrate the dose as needed. **Adult Dosage** Either of two ZOMACTON dosing regimens may be used: Non-weight based o Initiate ZOMACTON with a dose of approximately 0.2 mg/day (range, 0.15 mg/day to 0.3 mg/day) and increase the dose every 1 to 2 months by increments of approximately 0.1 mg/day to 0.2 mg/day, according to individual patient requirements based on the clinical response and serum insulin-like growth factor 1 (IGF-1) concentrations. o Decrease the dose as necessary on the basis of adverse reactions and/or serum IGF-1 concentrations above the age-and gender-specific normal range. o Maintenance dosages will vary considerably from person to person, and between male and female patients. Weight-based o Initiate ZOMACTON at 0.006 mg/kg daily and increase the dose according to individual patient requirements to a maximum of 0.0125 mg/kg daily. o Use the patient's clinical response, adverse reactions, and determination of age- and gender-adjusted serum IGF-1 concentrations as guidance in dose titration. o Not recommended for obese patients as they are more likely to experience adverse reactions with this regimen.
Zorbtive (somatropin)	The recommended dosage is 0.1 mg/kg subcutaneously once daily to a maximum daily dose of 8 mg for 4 weeks.

Drug Availability

Product	Drug Availability
Genotropin (somatropin)	**Genotropin** lyophilized powder in a two-chamber color-coded cartridge (3): • 5 mg (green tip) and 12 mg (purple tip) (with preservative) **Genotropin Miniquick** Growth Hormone Delivery Device containing a two chamber cartridge (without preservative): • 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 (somatropin)	Humatrope is a sterile, white lyophilized powder available in the following vial and cartridge sizes: • 5 mg vial and a 5-mL vial of Diluent for Humatrope • 6 mg cartridge (gold) and a prefilled syringe of Diluent for Humatrope • 12 mg cartridge (teal) and a prefilled syringe of Diluent for Humatrope

	• 24 mg cartridge (purple) and a prefilled syringe of Diluent for Humatrope Humatrope cartridges should be used only with the appropriate corresponding pen device.
Norditropin FlexPro (somatropin)	NORDITROPIN injection is a clear and colorless solution available as follows: • 5 mg in 1.5 mL (orange): NORDITROPIN FlexPro pen • 10 mg in 1.5 mL (blue): NORDITROPIN FlexPro pen • 15 mg in 1.5 mL (green): NORDITROPIN FlexPro pen • 30 mg in 3 mL (purple): NORDITROPIN FlexPro pen
Nutropin and **Nutropin AQ** (somatropin)	**Nutropin** 10 mg vial and 10 mL diluent **Nutropin AQ** is a sterile liquid available in the following pen cartridge and NuSpin forms: • Pen Cartridge: 10 mg/2 mL (yellow color band), and 20 mg/2 mL (purple color band). • NuSpin: 5 mg/2 mL (clear device), 10 mg/2 mL (green device), and 20 mg/2 mL (blue device).
Omnitrope (somatropin)	• Omnitrope Cartridge 5 mg/1.5 mL is a prefilled sterile solution in a glass cartridge ready to be administered with the Omnitrope® Pen 5. • Omnitrope Cartridge 10 mg/1.5 mL is a prefilled sterile solution in a glass cartridge ready to be administered with the Omnitrope® Pen 10. • Omnitrope for injection 5.8 mg/vial is supplied with two vials, one containing somatropin as a powder and the other vial containing diluent.
Saizen (somatropin)	• Saizen lyophilized powder in vial: 5 mg and 8.8 mg • Saizen click.easy reconstitution device: One vial Saizen containing 8.8 mg somatropin and one cartridge diluent containing 1.51 mL 0.3% (w/v) metacresol in Sterile Water for Injection • Saizenprep reconstitution device: One vial Saizen containing 8.8 mg somatropin and one cartridge diluent containing 1.51 mL 0.3% (w/v) metacresol in Sterile Water for Injection
Serostim (somatropin)	• Single-dose administration (to be administered with Sterile Water for Injection): Serostim 5 mg/ vial Serostim 6 mg/ vial • Multi-dose administration (to be administered with Bacteriostatic Water for Injection): Serostim 4 mg/ vial
Zomacton (somatropin)	ZOMACTON for injection is a white, lyophilized powder available as: o 5 mg vial with a 5 mL vial of bacteriostatic 0.9% sodium chloride [preserved with benzyl alcohol] o 10 mg vial with a syringe of 1 mL of bacteriostatic water [preserved with metacresol] with a 25G reconstitution needle o 10 mg vial with a syringe of 1 mL of bacteriostatic water [preserved with metacresol] with a vial adapter
Zorbtive (somatropin)	For injection: 8.8 mg, lyophilized powder in a single-patient use vial for reconstitution.

General Background

Pharmacology
Somatropin is identical to endogenous growth hormone (GH). Endogenous growth hormone is produced in the anterior pituitary gland. It stimulates the production of insulin-like growth factor-I (IGF-I), resulting in decreased insulin use by peripheral tissues, increased breakdown of lipids, and increased muscle mass. This “anti-insulin” effect promotes linear growth in children and development of normal muscle mass, reduced adiposity, and improved exercise tolerance in children and adults. Recombinant human growth hormone functions in an identical way to endogenous growth hormone. For most indications, it is replacing a natural deficiency of endogenous hormone, and in a few indications it is used to overcome resistance to the effects of growth hormone. When given by intravenous (IV) administration, the elimination half-life of somatropin is approximately

20 to 30 minutes. When given by subcutaneous (SC) or intramuscular (IM) administration, the elimination half-life of somatropin is three to five hours. Somatropin is metabolized via classical protein catabolism in both the liver and kidneys. In renal cells, at least a portion of the breakdown products are returned to the systemic circulation.

Interpretation of Macrilen Test Results

Macimorelin is an oral growth hormone (GH) secretagogue receptor agonist labeled to diagnose growth hormone deficiency (GHD) in adults. It is the first drug labeled for this indication. Provocative tests for diagnosing adult growth hormone deficiency (AGHD) recommended by the Endocrine Society the American Academy of Clinical Endocrinologists include the insulin tolerance test (ITT), a combination of the growth hormone releasing hormone (GHRH) and arginine tests, or the glucagon test. Growth hormone releasing hormone is not currently available in the US.

The FDA Prescriber Information states that clinical studies have established that a maximally stimulated serum GH level of less than 2.8 ng/mL (i.e., at the 30, 45, 60 and 90 minute timepoints) following Macrilen administration confirms the presence of adult growth hormone deficiency.

Guidelines

Consensus guidelines are available for several childhood disorders affecting stature and body composition. The diagnosis of GHD is confirmed by measurements of growth hormone secretion, commonly following stimulation by a provocative agent(s). The American Association of Clinical Endocrinologists (AACE) and the Growth Hormone Research Society (GHRS) all consider a growth hormone response of less than 10 ng/mL supportive of the diagnosis of GHD. The Endocrine Society's clinical guidelines (2011) now recommend GH for use in idiopathic adult GHD although this diagnosis is rare. Guidelines are also available from American Academy of Pediatrics (AAP), National Kidney Foundation (NKF), and the Turner Syndrome Study Group. Guidelines for Prader-Willi syndrome are issued by several organizations.

American Academy of Pediatrics (AAP)

The AAP states that there is no evidence that growth hormone insufficiency improves with age and continuation of growth hormone therapy into adulthood is an acceptable consideration. Because obstructive sleep apnea may occur during growth hormone therapy, the group suggests a drug holiday until polysomnography results improve. The organization advises periodic monitoring polysomnographies, dosing based on IGF-1 results and keeping IGF-1 levels within normal limits and head circumference measurements to check for abnormal growth.

American Association of Clinical Endocrinologists (AACE)

The AACE recommends that GH should only be prescribed to patients with clinical features suggestive of adult GHD and biochemically proven evidence of adult GHD. The organization does not recommend the administration of GH to patients for improvement of athletic performance, to treat aging or age-related conditions, or for any reason other than the well-defined approved uses of the drug. The goal is to keep IGF-1 levels in the middle of the normal age and sex appropriate range, taking into consideration side effects. Once at a maintenance dose, an individual should be monitored every six months- including a clinical evaluation, including side effects, and appropriate labs. An annual lipid profile is suggested. If there was an abnormal baseline DEXA scan, follow up scans should be performed every 2 to 3 years. Re-testing is advised for individuals transitioning from pediatric to adult care, particularly those who had isolated GHD. (AACE, 2009)

Citing a lack of evidence that one GH product is more beneficial than other, AACE does not recommend a particular marketed product. AACE provides no guidance regarding length of GH therapy, but states that treatment should continue so long as benefits are seen. Discontinuation of GH treatment should be considered when no apparent benefits are achieved after at least two years of treatment. (AACE, 2009)

Traumatic brain injury and aneurysmal subarachnoid hemorrhage are known causes of GHD and GHD in these conditions may be temporary. The AACE suggests GH stimulation testing be performed at a minimum of 12 months after the occurrence. (AACE, 2009)

.

National Kidney Foundation

In the 2009 Kidney Disease Outcomes Quality Initiative Clinical Practice Guidelines for Nutrition in Children with Chronic Kidney Disease (KDOQI), the NKF advises addressing any nutritional deficits and metabolic issues in children prior to initiating recombinant human growth hormone treatment. Once these concerns are addressed,

the group suggests there is a role for human growth hormone therapy in children with certain parameters of kidney disease and growth if growth failure continues beyond three months. (KDOQI, 2009)

Growth Hormone Research Society (GHRS)
The pediatric recommendations of GHRS are endorsed by five international organizations. GHRS guidelines include recommendations for diagnosis of GHD, as well as rhGH treatment and safety monitoring for children and adolescents.

Prior to initiation of GH treatment in adults, the GHRS recommends a comprehensive examination, and documentation of the baseline height, weight and BMI. The GHRS affirms that GH therapy has beneficial results throughout life, and recommends GH treatment continue in young adults who have continued GHD once final height is reached. The goal of continued treatment once linear growth has stopped is to achieve appropriate bone and muscle mass. Dosing of GH replacement should be individualized based on IGF-1 levels, which should be maintained below the upper limit of normal for the individual's age and gender, as well as taking adverse events into consideration. Monitoring appropriate biochemistries, height, weight and body composition via DEXA scan, if available, are necessary to assess response to treatment. (GHRS, 2007)

In 2013 guidelines for use of rhGH for patients with Prader-Willi Syndrome (PWS) were published by GHRS. They recommend consideration of rhGH therapy following genetic confirmation and continuation of therapy as long as benefits outweigh the risks. In addition, GHRS does not recommend stimulation testing for PWS. GHRS also states that clinical outcome priorities should vary depending on age and on the presence of physical, mental, and social disability. (Deal, 2013)

The Endocrine Society
Idiopathic GHD in adults is very rare, and stringent criteria are necessary to make this diagnosis. Because in the absence of suggestive clinical circumstances there is a significant false-positive error rate in the response to a single GH stimulation test, the use of two tests is recommended before making a diagnosis. The presence of a low I GF-I also increases the likelihood that this diagnosis is correct. (Endocrine Society, 2011)

Biochemical criteria for the diagnosis of idiopathic adult GHD are complicated by the lack of normative data that are age-, sex-, and BMI-adjusted; by assay variability; and by the stimulus used. With polyclonal RIA, the cutoff values for stimulated GH levels for diagnosing adult GHD were established at levels between 3 and 5 µg/liter. Whether lower cutoffs should be used with the newer, more sensitive, two-site assays has not been definitively determined. Still, according to a multicenter study, which used a sensitive, immunochemiluminescent two-site assay, the values of 5.1 µg/liter for the ITT and 4.1 µg/liter for GHRH arginine test had sufficient specificity and sensitivity for the diagnosis of adult GHD.

Turner Syndrome Study Group
In the Care of Girls and Women with Turner Syndrome guideline, the study group advises initiating treatment with growth hormone when growth failure is detected and dosing adjustments should be based on growth and IGF-1 levels. Treatment should be directed by a pediatric endocrinologist and the patient monitored for orthopedic issues and growth velocity. (Bondy, 2007)

Consensus Statement on the Diagnosis and Treatment of Children with Idiopathic Short Stature (ISS)
In 2008 this statement was crafted in collaboration by the Growth Hormone Research Society, Lawson Wilkins Pediatric Endocrine Society, and the European Society for Pediatric Endocrinology. The group states that although there are no biochemical markers to guide starting growth hormone therapy, appropriate patient selection should be based on standard deviation scores for height, age and ruling out other causes of ISS. Therapy should be discontinued whenever the patient is near adult height or in the normal adult height range for the particular sex. (Cohen, 2008)

Expert Meeting of the Comprehensive Care of Patients with Prader-Willi Syndrome
This study group suggests appropriate patient selection by genetic confirmation and growth hormone treatment should be initiated in childhood. Patient monitoring is important and growth hormone therapy should be discontinued if the benefits outweigh the risks or when the patient achieves final height.

Pediatric Endocrine Society
The Pediatric Endocrine Society recommends a trial of GH therapy before initiating IGF-1 for patients with unexplained IGF-1 deficiency. This recommendation, however, is not supported by clinical trial evidence. (Grimberg, 2016)

Endocrine Society - Hypothalamic–Pituitary and Growth Disorders in Survivors of Childhood Cancer
The objective of the Endocrine Society was **to** formulate clinical practice guidelines for the endocrine treatment of hypothalamic–pituitary and growth disorders in survivors of childhood cancer. The recommendations are as follows:

For the treatment of short stature/impaired linear growth in childhood cancer survivors, the society recommends against using growth hormone treatment in survivors of cancer who do not have growth hormone deficiency to treat for short stature or poor linear growth following spinal irradiation. In addition, the society recommends against growth hormone treatment in children with short stature or impaired linear growth in those being treated with tyrosine kinase inhibitors.

For the treatment of growth hormone deficiency in childhood cancer survivors, the society recommends treatment with a growth hormone be offered in childhood cancer survivors with confirmed growth hormone deficiency which is based on the efficacy and safety demonstrated in this patient population.

The society suggests following similar recommends as the noncancer population in the following: (1) treatment of central precocious puberty in childhood cancer survivors, (2) treatment of luteinizing hormone/follicle-stimulating hormone deficiency in childhood cancer survivors, (3) treatment of thyroid-stimulating hormone deficiency in childhood cancer survivors, (4) Treating adrenocorticotropic hormone deficiency in childhood cancer survivors. (Sklar, 2018)

Experimental, Investigational, Unproven Uses
Adult uses for which growth hormone has been studied without conclusive benefit include obesity (Hong, 2011), osteoporosis (Van der Sluis, 2000), muscular dystrophy (Cittadini, 2003), infertility (Bassiouny, 2016), and increased athletic performance (Meinhardt, 2010). Growth hormone has also been used in children with the following conditions, although there are no prospective studies that assess linear growth until final height is achieved: hypochondroplasia (Pinto, 2014), Down syndrome (Myrelid, 2010), hypophosphatemic rickets (Zivicnjak, 2011), juvenile rheumatoid arthritis (Bechtold, 2005), Duchenne muscular dystrophy (Cittadini, 2003), cystic fibrosis (Stalvey, 2012). There is insufficient evidence in the peer-reviewed published scientific literature to support the safety and efficacy of growth hormone therapy in these conditions.

There is no data to support the use of growth hormone for the treatment of somatopause in the elderly or spinal cord defects.

Combination Use with Recombinant Human Growth Hormone (GH)
The literature on the final effect of the addition of GnRH agonists to GH in GH-deficient (GHD) children is limited. Studies did show positive results when leuprolide was given in combination with GH for precocious puberty, however, the need for further studies with larger groups of patients is warranted before safety and efficacy of use can be confirmed. (Pucarelli, 2000; Pucarelli, 2003)

Silver-Russell Syndrome will be covered if the criteria for SGA are met. The Nature Reviews consensus statement summarizes the management of patients with Silver–Russell syndrome (SRS). SRS is an imprinting disorder which causes both prenatal and postnatal growth retardation. There is a large overlap between the treatment for those born small for gestational age and those with SRS. The benefits of treating patients with SRS with growth hormone includes the following: improved body composition, motor development and appetite, reduced risk of hypoglycaemia and increased height (Wakeling, 2017). SRS children have a similar height gain during treatment with growth hormones as subjects with non-SRS. (Smeets, 2017)

Coding/Billing Information

Note: Somatropin products are typically covered under pharmacy benefit plans. Certain prescription drugs require an authorization for coverage to ensure that appropriate treatment regimens are followed. Medical drug coding and diagnosis codes, however, are generally not required for pharmacy claims submissions, therefore, this section is not in use.

References

1. American Association of Clinical Endocrinologists. AACE medical guidelines for clinical practice for growth hormone use in adults and children - 2009 update. Accessed 11/20/2017. Available at https://www.aace.com/files/growth-hormone-guidelines.pdf
2. Bassiouny YA, Dakhly D, Bayoumi, YA et al. Does the addition of growth hormone to the in vitro fertilization/intracytoplasmic sperm injection antagonist protocol improve outcomes in poor responders? A randomized, controlled trial. Fertil Steril. 2016 Mar;105(3):697-702.
3. Bechtold S, Ripperger P, Bonfig W, et al. Growth hormone changes bone geometry and body composition in patients with juvenile idiopathic arthritis requiring glucocorticoid treatment: a controlled study using peripheral quantitative computed tomography. J Clin Endocrinol Metab. 2005 Jun;90(6):3168-73.
4. Blackman MR, Sorkin JD, Munzer T, et al. Growth hormone and sex steroid administration in healthy aged women and men: a randomized controlled trial. JAMA. 2002;288(18):2282-2292.
5. Bondy CA. Care of Girls and Women with Turner Syndrome: A Guideline of the Turner Syndrome Study Group. J Clin Endocrinol Metab. 2007 Jan;92(1):10-25. Available at https://academic.oup.com/jcem/article/92/1/10/2597828
6. Cittadini A, Ines C, Longobardi S, et al. A preliminary randomized study of growth hormone administration in Becker and Duchenne muscular dystrophies. Eur Heart J. 2003 Apr;24(7):664-72.
7. Cohen P, Rogol AD, Deal CL, et al. Consensus statement on the diagnosis and treatment of children with idiopathic short stature: a summary of the Growth Hormone Research Society, the Lawson Wilkins Pediatric Endocrine Society, and the European Society for Paediatric Endocrinology Workshop. J Clin Endocrinol Metab. 2008 Nov;93(11):4210-7. Available at https://academic.oup.com/jcem/article/93/11/4210/2627229
8. Deal CL, Tony M, Höybye C, Allen DB, Tauber M, Christiansen JS, and the 2011 Growth Hormone in Prader-Willi Syndrome Clinical Care Guidelines Workshop Participants. Growth Hormone Research Society Workshop Summary: Consensus Guidelines for Recombinant Human Growth Hormone Therapy in Prader-Willi Syndrome. J Clin Endocrinol Metab 2013 June; 98: E1072–E1087.
9. Eli Lilly and Company. Somatropin (rDNA origin) for injection (Humatrope®) package insert. Indianapolis, IN: Eli Lilly and Company. December 2016.
10. EMD Serono Inc. Saizen® [somatropin (rDNA origin) for injection] package insert. Rockland, MA: Serono Inc. May 2017.
11. EMD Serono Inc. Serostim® [somatropin (rDNA origin) for injection] package insert. Rockland, MA: EMD Serono Inc. May 2017.
12. EMD Serono. Inc. Zorbtive® [somatropin (rDNA origin) for injection] package insert. Rockland, MA: EMD Serono Inc. May 2017.
13. Evaluation and Treatment of Adult Growth Hormone Deficiency: An Endocrine Society Clinical Practice Guideline. 2011. Journal of Clinical Endocrinology & Metabolism, 96(6):1587–1609. Accessed 12/5/2017. Available at https://academic.oup.com/jcem/article/96/6/1587/2833853
14. Genentech Inc. Nutropin® [somatropin (rDNA origin) for injection] package insert. South San Francisco, CA: Genentech Inc. August 2016.
15. Genentech Inc. Nutropin AQ® [somatropin (rDNA origin) injection] package insert. South San Francisco, CA: Genentech Inc. August 2016.
16. Grimberg A, DiVall S, Polychronakos C, et al. On behalf of the Drug and Therapeutics Committee and Ethics Committee of the Pediatric Endocrine Society. 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 Nov 2016; 86: 361–397
17. Growth Hormone Research Society. Consensus guidelines for the diagnosis and treatment of adults with GH deficiency II: a statement of the GH Research Society in association with the European Society for Pediatric Endocrinology, Lawson Wilkins Society, European Society of Endocrinology, Japan Endocrine Society, and Endocrine Society of Australia. European Journal of Endocrinology (2007) 157 695–700. Available at http://www.ghresearchsociety.org/files/2007_Consensus_AGHD.pdf
18. Hong JW, Park JK, Lim CY, et al. A weekly administered sustained-release growth hormone reduces visceral fat and waist circumference in abdominal obesity. Horm Metab Res. 2011 Dec;43(13):956-61
19. Isley WL. Growth hormone therapy for adults: not ready for prime time? Ann Intern Med. Aug 6 2002;137(3):190-196.
20. KDOQI Clinical Practice Guideline for Nutrition in Children with CKD: 2008 update. Executive summary. Am J Kidney Dis. 2009 Mar;53(3 Suppl 2):S11-104. Available at http://www2.kidney.org/professionals/KDOQI/guidelines_ped_ckd/

21. Lee PDK, Allen DB, Angulo MA, et al. Consensus statement-Prader-Willi syndrome: Growth hormone (GH)/insulin-like growth factor axis deficiency and GH treatment. Endocrinologist. 2000;10(4 supp 1):71s-74s.
22. Meinhardt U, Nelson AE, Hansen JL, et al. The effects of growth hormone on body composition and physical performance in recreational athletes: a randomized trial. Ann Intern Med. 2010 May 4;152(9):568-77.
23. Mericq MV, Eggers M, Avila A, Cutler GB, Jr., Cassorla F. Near final height in pubertal growth hormone (GH)-deficient patients treated with GH alone or in combination with luteinizing hormone-releasing hormone analog: results of a prospective, randomized trial. J Clin Endocrinol Metab. Feb 2000;85(2):569-573.
24. Myrelid Å, Bergman S, Elfvik Strömberg M, et al. Late effects of early growth hormone treatment in Down syndrome. Acta Paediatr. 2010 May;99(5):763-769
25. Nielsen S, Moller N, Pedersen SB, Christiansen JS, Jorgensen JO. The effect of long-term pharmacological antilipolysis of substrate metabolism in growth hormone (GH)-substituted GH-deficient adults. J Clin Endocrinol Metab. 2002;87(7):3274-3278.
26. Novo Nordisk Inc. Somatropin (rDNA origin) injection (Norditropin FlexPro®) package insert. Princeton, NJ: Novo Nordisk Inc. August 2017.
27. Pharmacia and Upjohn Company. Somatropin [rDNA origin] for injection (Genotropin®) package insert. New York, NY: Pfizer Inc. December 2016.
28. Pinto G, Cormier-Daire V, Le Merrer M, et al. Efficacy and safety of growth hormone treatment in children with hypochondroplasia: comparison with an historical cohort. Horm Res Paediatr. 2014;82(6):355-63.
29. Pucarelli, I. et.al. Combined therapy with GnRH analog plus growth hormone in central precocious puberty. J Pediatric Endocrinology Metabolism. 2000 Jul;13 Suppl 1:811-20.
30. Pucarelli, I. et.al. Effects of combined gonadotropin-releasing hormone agonist and growth hormone therapy on adult height in precocious puberty: a further contribution. J Pediatric Endocrinology Metabolism. 2003 Sep;16(7):1005-10.
31. Quigley CA, Crowe BJ, Anglin DG, Chipman JJ. Growth hormone and low dose estrogen in Turner syndrome: results of a United States multi-center trial to near-final height. J Clin Endocrinol Metab. May 2002;87(5):2033-2041.
32. Reiter EO, Attie KM, Moshang T, Jr., et al. A multicenter study of the efficacy and safety of sustained release GH in the treatment of naive pediatric patients with GH deficiency. J Clin Endocrinol Metab. Oct 2001;86(10):4700-4706.
33. Rondanelli M, Caselli D, Arico M, et al. Insulin-like growth factor I (IGF-I) and IFG-binding protein 3 response to growth hormone is impaired in HIV-infected children. AIDS Research and Human Retroviruses. 2002;18(5):331-339.
34. Sandoz Inc. Omnitrope® [somatropin (rDNA origin) for injection] package insert. Princeton, NJ: Sandoz Inc. February 2017.
35. Sklar et al. Endocrine Society - Hypothalamic–Pituitary and Growth Disorders in Survivors of Childhood Cancer. Journal of Clinical Endocrinology and Metabolism. June 2018
36. Smeets, et al. Long-Term Results of GH Treatment in Silver-Russell Syndrome (SRS): Do They Benefit the Same as Non-SRS Short-SGA. J Clin Endocrinol Metab 101: 2105–2112, 2016.
37. Stalvey MS, Anbar RD, Konstan MW, et al. A multi-center controlled trial of growth hormone treatment in children with cystic fibrosis. Pediatr Pulmonol. 2012 Mar;47(3):252-63.
38. Teva Pharmaceuticals. Zomacton® [somatropin (rDNA origin) for injection] package insert. Horsham, PA: Teva Pharmaceuticals USA, Inc. January 2017.
39. Van der Sluis I, Boot AM, Nauta J, et al. Bone density and body composition in chronic renal failure: effects of growth hormone treatment. Pediatr Nephrol. 2000;15:221-228.
40. Wakeling, et al. Expert Consensus Document: Diagnosis and management of Silver–Russell syndrome: first international consensus statement. Nature reviews Endocrinology. Volume 13; February 2017
41. Zivičnjak M, Schnabel D, Staude H, et al. Three-year growth hormone treatment in short children with X-linked hypophosphatemic rickets: effects on linear growth and body disproportion. J Clin Endocrinol Metab. 2011 Dec;96(12):E2097-105.

"Cigna Companies" refers to operating subsidiaries of Cigna Corporation. All products and services are provided exclusively by or through such operating subsidiaries, including Cigna Health and Life Insurance Company, Connecticut General Life Insurance Company, Cigna Behavioral Health, Inc., Cigna Health Management, Inc., QualCare, Inc., and HMO or service company subsidiaries of Cigna Health Corporation. The Cigna name, logo, and other Cigna marks are owned by Cigna Intellectual Property, Inc. © 2018 Cigna.