



## Drug and Biologic Coverage Policy

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# Somatropin

## Table of Contents

Overview .....	1
Coverage Policy.....	1
FDA Approved Indications .....	8
FDA Recommended Dosing .....	9
General Background.....	12
Coding/Billing Information.....	15
References .....	15

## Related Coverage Resources

[Mecasermin](#)  
[Unassigned Drug or Biologic Code Medical Precertification](#)

### 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.

## Overview

This coverage policy addresses the following growth hormone (somatropin) products:

- **Genotropin®** (somatropin injection)
- **Humatrope®** (somatropin injection)
- **Norditropin Flexpro®** (somatropin injection)
- **Nutropin AQ®** (somatropin injection)
- **Omnitrope®** (somatropin injection)
- **Saizen®** (somatropin injection)
- **Serostim®** (somatropin injection)
- **Zomacton™** (somatropin injection)
- **Zorbtive®** (somatropin injection)

## Coverage Policy

**Somatropin (Genotropin®, Humatrope®, Norditropin Flexpro®, Nutropin AQ®, Omnitrope®, Saizen®, or Zomacton™) is considered medically necessary for the following uses (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)

**Somatropin is NOT considered medically necessary for the following uses (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

**Growth Hormone Use in Children:****Summary by Diagnosis of Stimulation Testing Requirements for Children\*\***

Diagnosis	Stimulation Testing Requirements
<b>Pediatric Uses:</b>	
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

**\*\*See individual subsections for additional specific coverage criteria requirements for each indication**

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), Adrenocorticotrophic Hormone (ACTH)], neither stimulation testing nor auxologic evaluation (stature and growth velocity data) is required.

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:
  - o Individual's height is more than two standards of deviation (SD) below average for the population mean height for age and sex, and EITHER of the following:
    - Child has a one-year height velocity more than one SD below the mean for chronological age
    - Child is 2 years of age or older, and there is a decrease in height of more than 0.5 SD over one year
  - o Individual's one-year height velocity is more than two SD below the mean for age and sex
  - o Individual's height velocity is more than 1.5 SD below the mean sustained over two years
- Diagnostic evaluation including **BOTH** of the following:
  - o Other pituitary hormone deficiencies (for example, thyroid, cortisol or sex steroids) have been ruled out and/or corrected prior to time of testing
  - o **EITHER** 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.
    - Growth hormone response of less than 10 ng/mL to **ONE** provocative stimuli of growth hormone release\*: clonidine, glucagon, insulin, L-arginine, levodopa, propranolol will be required for children with **ANY** of the following:
      - o Defined central nervous system pathology (for example, empty sella syndrome, interruption of pituitary stalk, hypoplasia of the pituitary gland, craniofacial developmental defects, pituitary or hypothalamic tumors)
      - o Multiple pituitary hormone deficiency (MPHD) (for example, deficiency of two or more pituitary hormones) or a proven genetic defect affecting the growth hormone axis

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

For 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

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  $60\text{ml/min/1.73m}^2$ )
- Auxologic evaluation (stature and growth velocity data) including **ONE** of the following:
  - o Individual's height is more than two standards of deviation (SD) below average for the population mean height for age and sex, and EITHER of the following:
    - Child has a one-year height velocity more than one SD below the mean for chronological age
    - Child is 2 years of age or older, and there is a decrease in height of more than 0.5 SD over one year

- o Individual's one-year height velocity is more than two SD below the mean for age and sex
- o Individual's height velocity is 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 demonstrates individual's pre-treatment height is less than the 5<sup>th</sup> percentile for age.

**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:
  - o Individual's height is more than two standards of deviation (SD) below average for the population mean height for age and sex, and EITHER of the following:
    - Child has a one-year height velocity more than one SD below the mean for chronological age
    - Child is 2 years of age or older, and there is a decrease in height of more than 0.5 SD over one year
  - o Individual's one-year height velocity is more than two SD below the mean for age and sex
  - o Individual's height velocity is 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:
  - o Individual's height is more than two standards of deviation (SD) below average for the population mean height for age and sex, and EITHER of the following:
    - Child has a one-year height velocity more than one SD below the mean for chronological age
    - Child is 2 years of age or older, and there is a decrease in height of more than 0.5 SD over one year
  - o Individual's one-year height velocity is more than two SD below the mean for age and sex
  - o Individual's height velocity is 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:
  - o Individual's height is more than two standards of deviation (SD) below average for the population mean height for age and sex, and EITHER of the following:
    - Child has a one-year height velocity more than one SD below the mean for chronological age
    - Child is 2 years of age or older, and there is a decrease in height of more than 0.5 SD over one year
  - o Individual's one-year height velocity is more than two SD below the mean for age and sex
  - o Individual's height velocity is more than 1.5 SD below the mean sustained over two years

**Initial authorization is up to 12 months**

**Somatropin (Genotropin®, Humatrope®, Norditropin Flexpro®, Nutropin AQ®, Omnitrope®, Saizen®, or Zomacton™) is considered medically necessary for continued use in children with a history of cranial or whole body irradiation or panhypopituitarism when the initial authorization criteria are met.**

**Somatropin (Genotropin®, Humatrope®, Norditropin Flexpro®, Nutropin AQ®, Omnitrope®, Saizen®, or Zomacton™) is considered medically necessary for continued use in children (excluding cranial or whole body irradiation and panhypopituitarism) when ALL of the following criteria are met:**

- Initial authorization criteria are met
- Documented beneficial clinical response as evidenced by growth curve chart
- Bony epiphyses remain open in order to continue coverage for growth promotion

Reauthorization is up to 12 months.

## Growth Hormone Use in Adults:

### Summary by Diagnosis of Stimulation Testing Requirements for Adults\*\*

Diagnosis	Stimulation Testing Requirements
<b>Adult Uses:</b>	
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 additional specific coverage criteria requirements for each indication**

**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), Adrenocorticotrophic Hormone (ACTH)], stimulation testing is NOT required.**

**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/m<sup>2</sup>
  - [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

\*Note: Macrilen® (macimorelin) may be subject to medical necessity review. *Please refer to the related coverage policy link ([Unassigned Drug or Biologic Code Medical Precertification](#))*

**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/m<sup>2</sup>
- [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)]

\*Note: Macilen® (macimorelin) may be subject to medical necessity review. *Please refer to the related coverage policy link ([Unassigned Drug or Biologic Code Medical Precertification](#))*

**Initial and reauthorization is up to 12 months**

**Somatropin (Genotropin®, Humatrope®, Norditropin Flexpro®, Nutropin AQ®, Omnitrope®, Saizen®, or Zomacton™) is considered medically necessary for continued use in adults when the initial authorization criteria are met:**

**Somatropin (Serostim®) is considered 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/m<sup>2</sup>
- Documented failure, intolerance, or contraindication to appetite stimulants and/or other anabolic agents
- Continuous use of antiviral therapy

**Initial authorization in an adult for the treatment of HIV with wasting or cachexia is limited to 12 weeks**

**Reauthorizations (if initial criteria are met) may 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.**

**Somatropin (Zorbtive®) is considered 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 for treatment of short bowel syndrome is to consist of ONE four-week course of therapy**

**Coverage for somatropin varies across plans. Refer to the customer's benefit plan document for coverage details. Where coverage requires the use of preferred products, the following will apply in addition to the applicable criteria listed above.**

**For Employer Group Plans:**

Documented contraindication per FDA label or intolerance to **BOTH** of the preferred products:

- **Humatrope®**
- **Norditropin Flexpro®**

**For Individual and Family Plans:**

Documented contraindication per FDA label or intolerance to the preferred product:

- **Humatrope®**

**There is a lack of reliable evidence that any one growth hormone product is superior to other products, coverage may depend on the applicable health benefit plan definition of medical necessity. Where that definition limits coverage to the most cost-effective equivalent treatment, the use of Genotropin®, Nutropin AQ®, Omnitrope®, Saizen®, or Zomacton™ is not considered medically necessary.**

**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 therapy.**

**Somatropin is considered experimental, investigational or unproven for ANY other use including the following (this list may not be all inclusive):**

- Anti-aging and somatopause
- Celiac disease
- Chromosomal anomalies unless otherwise specified as covered (for example, but not limited to; deletion of chromosome 18q)
- Combination use with any other medication for the purpose of pubertal suppression
- Congenital adrenal hyperplasia
- Crohn's disease or ulcerative colitis
- Cystic fibrosis
- Down Syndrome and other syndromes associated with short stature
- Enhancement of athletic performance
- Glucocorticoid-induced growth failure
- Hypophosphatemic rickets
- Infertility
- Juvenile rheumatoid arthritis
- Muscular dystrophy
- Obesity
- Osteoporosis
- Precocious puberty - to prolong the pre-pubertal state in combination with GnRH agonists (for example; Supprelin LA®, Lupron) or any other medication for the purpose of pubertal suppression
- Primary or idiopathic (i.e. of unknown origin) insulin-like growth factor-1 (IGF-1) deficiency
- Russell-Silver Syndrome (unless criteria are met for Small for Gestational Age)
- Short Bowel Syndrome repeat courses of therapy
- Skeletal dysplasias (for example, achondroplasia, hypochondroplasia, osteogenesis imperfecta)
- Spinal cord defects

**Note: Macrilen® (macimorelin) is considered experimental, investigational, or unproven for the confirmation of growth hormone deficiency in children.** Please refer to the Related Coverage Resources link ([Unassigned Drug or Biologic Code Medical Precertification](#))

**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.**

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

## FDA Approved Indications

Product	FDA Approved Indications
<b>Genotropin®</b> (somatropin)	Genotropin is a recombinant human growth hormone indicated for: <b>Pediatric:</b> 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 <b>Adult:</b> Treatment of adults with either adult onset or childhood onset GHD
<b>Humatrope®</b> (somatropin)	Humatrope is a recombinant human growth hormone (somatropin) indicated for: <b>Pediatric:</b> 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. <b>Adult:</b> Treatment of adults with either childhood-onset or adult-onset GH deficiency.
<b>Norditropin FlexPro®</b> (somatropin)	Norditropin is a recombinant human growth hormone indicated for: <b>Pediatric:</b> 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) <b>Adult:</b> Replacement of endogenous GH in adults with growth hormone deficiency (1.2)
<b>Nutropin AQ®</b> (somatropin)	Nutropin AQ is indicated for: <b>Pediatric:</b> 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 <b>Adult:</b> Treatment of adults with either childhood-onset or adult-onset GHD
<b>Omnitrope®</b> (somatropin)	Omnitrope is a recombinant human growth hormone indicated for: <b>Pediatric:</b> 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 <b>Adult:</b> Treatment of adults with either adult onset or childhood onset GHD
<b>Saizen®</b> (somatropin)	Saizen is a recombinant human growth hormone indicated for: <b>Pediatric:</b> Treatment of children with growth failure due to growth hormone deficiency (GHD) <b>Adult:</b> Treatment of adults with either adult onset or childhood onset GHD.
<b>Serostim®</b> (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.
<b>Zomacton™</b> (somatropin)	Zomacton is a recombinant human growth hormone indicated for: <b>Pediatric:</b> 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) <b>Adult:</b> Replacement of endogenous GH in adults with GH deficiency (1.2)



<b>Zorbtive®</b> (somatropin)	Zorbtive is a recombinant human growth hormone indicated for the treatment of short bowel syndrome in adult patients receiving specialized nutritional support.
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Somatropin products have different indications but these products are considered clinically equivalent. (Woodcock, 2007) Table 1 below summarizes the FDA-approved indications for somatropin.

**Table 1. FDA-Approved Indications for Somatropin.**

Indication	Genotropin	Humatrope	Norditropin	Nutropin AQ®	Omnitrope	Saizen	Serostim	Zomacton	Zorbtive
GHD in children	✓	✓	✓	✓	✓	✓		✓	
Turner syndrome	✓	✓	✓	✓	✓			✓	
Replacement in adults	✓	✓	✓	✓	✓	✓		✓	
Prader Willi syndrome	✓		✓		✓				
Idiopathic short stature in children	✓	✓	✓	✓	✓			✓	
Children with CKD				✓					
SHOX deficiency		✓						✓	
Children born SGA	✓	✓	✓		✓			✓	
Noonan syndrome			✓						
HIV wasting/cachexia							✓		
Short bowel syndrome									✓

## FDA Recommended Dosing

Product	FDA Recommended Dosing
<b>Genotropin</b> (somatropin)	<p>Genotropin should be administered subcutaneously.</p> <p><b>Pediatric GHD:</b> 0.16 to 0.24 mg/kg/week  <b>Prader-Willi Syndrome :</b> 0.24 mg/kg/week  <b>Small for Gestational Age:</b> Up to 0.48 mg/kg/week  <b>Turner Syndrome:</b> 0.33 mg/kg/week  <b>Idiopathic Short Stature :</b> up to 0.47 mg/kg/week</p> <p><b>Adult GHD:</b> 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.  <u>Non-weight based dosing:</u> 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.  <u>Weight based dosing:</u> 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.</p>
<b>Humatrope</b> (somatropin)	<p>Humatrope should be administered subcutaneously.</p> <p>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:  <b>Pediatric GH deficiency:</b> 0.18 to 0.30 mg/kg/week  <b>Turner syndrome:</b> Up to 0.375 mg/kg/week  <b>Idiopathic short stature:</b> Up to 0.37 mg/kg/week  <b>SHOX deficiency:</b> 0.35 mg/kg/week  <b>Small for gestational age:</b> Up to 0.47 mg/kg/week</p>

	<p><b>Adult GH deficiency:</b> 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.</p> <p><u>Non-weight based dosing:</u> 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.</p> <p><u>Weight-based dosing:</u> 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.</p>
<p><b>Norditropin FlexPro</b> (somatropin)</p>	<p><b><u>Pediatric Dosage</u></b></p> <ul style="list-style-type: none"> <li>Individualize dosage for each patient based on the growth response.</li> <li>Divide the calculated weekly NORDITROPIN dosage into equal doses given either 6, or 7 days per week.</li> </ul> <p>The recommended weekly dose in milligrams (mg) per kilogram (kg) of body weight for pediatric patients is:</p> <ul style="list-style-type: none"> <li><b>Pediatric GH Deficiency:</b> 0.17 mg/kg/week to 0.24 mg/kg/week (0.024 to 0.034 mg/kg/day)</li> <li><b>Noonan Syndrome:</b> Up to 0.46 mg/kg/week (up to 0.066 mg/kg/day)</li> <li><b>Turner Syndrome:</b> Up to 0.47 mg/kg/week (up to 0.067 mg/kg/day)</li> <li><b>Small for Gestational Age (SGA):</b> Up to 0.47 mg/kg/week (up to 0.067 mg/kg/day) <ul style="list-style-type: none"> <li>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.</li> </ul> </li> <li><b>Idiopathic Short Stature:</b> Up to 0.47 mg/kg/week (up to 0.067 mg/kg/day)</li> <li><b>Prader-Willi Syndrome:</b> 0.24 mg/kg/week (0.034 mg/kg/day)</li> </ul> <p><b><u>Adult Dosage</u></b></p> <p>Either of two NORDITROPIN dosing regimens may be used:</p> <ul style="list-style-type: none"> <li>Non-weight based <ul style="list-style-type: none"> <li>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.</li> <li>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.</li> <li>Maintenance dosages will vary considerably from person to person, and between male and female patients.</li> </ul> </li> <li>Weight-based <ul style="list-style-type: none"> <li>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.</li> <li>Use the patient's clinical response, adverse reactions, and determination of age-and gender-adjusted serum IGF-1 concentrations as guidance in dose titration.</li> </ul> </li> </ul>

	<ul style="list-style-type: none"> <li>○ Not recommended for obese patients as they are more likely to experience adverse reactions with this regimen</li> </ul>
<b>Nutropin AQ</b> (somatropin)	<p>Nutropin AQ should be administered subcutaneously.</p> <p><b>Pediatric GHD:</b> Up to 0.3 mg/kg/week</p> <p><b>Pubertal Patients:</b> Up to 0.7 mg/kg/week</p> <p><b>Idiopathic Short Stature:</b> Up to 0.3 mg/kg/week</p> <p><b>Chronic Kidney Disease:</b> Up to 0.35 mg/kg/week</p> <p><b>Turner Syndrome:</b> Up to 0.375 mg/kg/week</p> <p><b>Adult GHD:</b> Either a non-weight based or weight-based dosing regimen may be followed, with doses adjusted based on treatment response and IGF-I concentrations.</p> <p><u>Non-weight-based:</u> 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.</p> <p><u>Weight-based:</u> 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 &gt; 35 years old.</p>
<b>Omnitrope</b> (somatropin)	<p>Omnitrope should be administered subcutaneously.</p> <p><b>Pediatric GHD:</b> 0.16 to 0.24 mg/kg/week, divided into 6 to 7 daily injections.</p> <p><b>Prader-Willi Syndrome:</b> 0.24 mg/kg/week, divided into 6 to 7 daily injections.</p> <p><b>Small for Gestational Age:</b> Up to 0.48 mg/kg/week, divided into 6 to 7 daily injections.</p> <p><b>Turner Syndrome:</b> 0.33 mg/kg/week, divided into 6 to 7 daily injections.</p> <p><b>Idiopathic Short Stature:</b> Up to 0.47 mg/kg/week, divided into 6 to 7 daily injections</p> <p><b>Adult GHD:</b> 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.</p>
<b>Saizen</b> (somatropin)	<p><b>Pediatric GHD:</b> 0.18 mg/kg/week, divided into equal doses given either on 3 alternate days, 6 times per week or daily.</p> <p><b>Adult GHD:</b> 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.</p> <p><u>Non-weight-based dosing:</u> 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.</p> <p><u>Weight-based dosing:</u> 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.</p>
<b>Serostim</b> (somatropin)	<p>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.</p>
<b>Zomacton</b> (somatropin)	<p><b><u>Pediatric Dosage</u></b></p> <ul style="list-style-type: none"> <li>• Individualize dosage for each patient based on the growth response.</li> <li>• Divide the calculated weekly ZOMACTON dosage into equal doses given either 3, 6, or 7 days per week.</li> <li>• The recommended weekly dose in milligrams (mg) per kilogram (kg) of body weight for pediatric patients is:             <ul style="list-style-type: none"> <li>○ <b>Pediatric GH Deficiency:</b> 0.18 mg/kg/week to 0.3 mg/kg/week (0.026 mg/kg/day to 0.043 mg/kg/day)</li> <li>○ <b>Turner syndrome:</b> Up to 0.375 mg/kg/week (up to 0.054 mg/kg/day)</li> <li>○ <b>Idiopathic short stature:</b> Up to 0.37 mg/kg/week (up to 0.053 mg/kg/day)</li> <li>○ <b>SHOX Deficiency:</b> 0.35 mg/kg/week (0.05 mg/kg/day)</li> <li>○ <b>Small for Gestational Age (SGA):</b> Up to 0.47 mg/kg/week (up to 0.067 mg/kg/day)                 <ul style="list-style-type: none"> <li>▪ 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</li> </ul> </li> </ul> </li> </ul>

	<p>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.</p> <p><b><u>Adult Dosage</u></b>  Either of two ZOMACTON dosing regimens may be used:</p> <p><b><u>Non-weight based</u></b></p> <ul style="list-style-type: none"> <li>○ 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.</li> <li>○ 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.</li> <li>○ Maintenance dosages will vary considerably from person to person, and between male and female patients.</li> </ul> <p><b><u>Weight-based</u></b></p> <ul style="list-style-type: none"> <li>○ 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.</li> <li>○ Use the patient's clinical response, adverse reactions, and determination of age-and gender-adjusted serum IGF-1 concentrations as guidance in dose titration.</li> <li>○ Not recommended for obese patients as they are more likely to experience adverse reactions with this regimen.</li> </ul>
<b>Zorbtive</b> (somatropin)	The recommended dosage is 0.1 mg/kg subcutaneously once daily to a maximum daily dose of 8 mg for 4 weeks.

## 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 IGF-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 adrenocorticotrophic hormone deficiency in childhood cancer survivors. (Sklar, 2018)

### **The American Board of Internal Medicine's (ABIM) Foundation Choosing Wisely® Initiative:**

No recommendations are available for somatropin.

### **Other Uses with Supportive Evidence**

AHFS Drug Information 2020 Edition does not support any off-label uses of somatropin

### **Compendia and Other Published Clinical Studies**

Adult uses for which growth hormone have 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 (Myreliid, 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 hypoglycemia and increased height (Wakeling, 2017). SRS children have a similar height gain during treatment with growth hormones as subjects with non-SRS. (Smeets, 2017)

Compendia and other published clinical studies do not currently support any other use of somatropin. Coverage criteria will be updated as new published data are available.

## **Coding/Billing Information**

Note: Somatropin is 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.

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