Growth Hormone, Human

EOCCO POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: EOCCO126

Description

Somatropin and somapacitan are purified polypeptide hormones of recombinant DNA origin. Somatropin is comprised of amino acids in a sequence identical to that of human growth hormone. Somapacitan includes a single substitution in the amino acid backbone to which an albumin-binding moiety is attached; it is otherwise an identical amino acid sequence to human growth hormone. Human growth hormone stimulates growth of linear bone, skeletal muscle, and organs, and stimulates erythropoietin which increases red blood cell mass, exerts both insulin-like and diabetogenic effects, and enhances the transmucosal transport of water, electrolytes, and nutrients across the gut. In short-bowel syndrome, growth hormone may directly stimulate receptors in the intestinal mucosa or indirectly stimulate the production of insulin-like growth factor-I which is known to mediate many of the cellular actions of growth hormone.

Length of Authorization

- Initial: Six months
  - i. AIDS wasting syndrome: three months only
  - ii. Short bowel syndrome: 1 month only
  - iii. All others: Six months
- Renewal: 12 months
  - i. AIDS wasting syndrome: three months only
  - ii. Short bowel syndrome: no renewal allowed
  - iii. All others: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
somatropin (Genotropin)	5 mg/mL cartridge	• Prader-Willi syndrome • Turner syndrome • Growth failure in children • Growth hormone deficiency, adults • Idiopathic short stature	0.08 mg/kg/week
	12 mg/mL cartridge		
somatropin (Genotropin MiniQuick)	0.2 mg/0.25 mL syringe		
	0.4 mg/0.25 mL syringe		
	0.6 mg/0.25 mL syringe		
	0.8 mg/0.25 mL syringe		
	1 mg/0.25 mL syringe		
	1.2 mg/0.25 mL syringe		
	1.4 mg/0.25 mL syringe		
	1.6 mg/0.25 mL syringe		
	1.8 mg/0.25 mL syringe		
	2 mg/0.25 mL syringe		
	5 mg vial		0.0875 mg/kg/week

somatropin (Humatrope)	6 mg cartridge 12 mg cartridge 24 mg cartridge	• Turner syndrome • Growth failure in children • Growth hormone deficiency, adults • Idiopathic short stature • Short stature homeobox-containing gene (SHOX) deficiency	
somatropin (Norditropin FlexPro)	5 mg/1.5 mL pen injector 10 mg/1.5 mL pen injector 15 mg/1.5 mL pen injector 30 mg/3 mL pen injector	• Noonan syndrome • Prader-Willi syndrome • Turner syndrome • Growth failure in children • Growth hormone deficiency, adults • Idiopathic short stature	0.112 mg/kg/week
somatropin (Nutropin AQ)	5 mg/2 mL pen injector 10 mg/2 mL pen injector 20 mg/2 mL pen injector	• Growth failure associated with chronic renal insufficiency (CRI) • Turner syndrome • Growth failure in children • Growth hormone deficiency, adults • Idiopathic short stature	**<u>35 years and younger:</u>** 0.175 mg/kg/week **<u>36 years or older:</u>** 0.0875 mg/kg/week
somatropin (Omnitrope)	5.8 mg vial 5 mg/1.5 mL cartridge 10 mg/1.5 mL cartridge	• Prader-Willi syndrome • Turner syndrome • Growth failure in children • Growth hormone deficiency, adults • Idiopathic short stature	0.08 mg/kg/week
somatropin (Saizen) somatropin (Saizen Click Easy) somatropin (Saizenprep)	5 mg vial 8.8 mg vial 8.8 mg/1.51 mL cartridge 8.8 mg cartridge	• Growth failure in children • Growth hormone deficiency, adults	0.07 mg/kg/week
somatropin (Serostim)	4 mg vial 5 mg vial		168 mg/28 days

	6 mg vial	• Wasting or cachexia associated with HIV	
somapacitan (Sogroya)	10 mg/1.5 mL pen	• Growth hormone deficiency, adults	6 mL/28 days
somatropin (Zomacton)	5 mg vial	• Turner syndrome • Growth failure in children • Growth hormone deficiency, adults • Idiopathic short stature • Short stature homeobox-containing gene (SHOX) deficiency	0.0875 mg/kg/week
	10 mg vial		
somatropin (Zorbtive)	8.8 mg vial	• Short bowel syndrome	224 mg/28 days
lonapegsomatropin (Skytrofa)	3.0 mg cartridge	• Growth failure in children	4 cartridges/28 days
	3.6 mg cartridge		
	4.3 mg cartridge		
	5.2 mg cartridge		
	6.3 mg cartridge		
	7.6 mg cartridge		
	9.1 mg cartridge		
	11.0 mg cartridge		
	13.3 mg cartridge		

Growth Hormone Therapy in Children and Adolescents

Initial Evaluation

I. **Growth hormone replacement** may be considered medically necessary for **children and adolescents** when the following criteria below are met:
   A. Medication is prescribed by, or in consultation with, an endocrinologist; **AND**
   B. Member's epiphyses are not closed (as confirmed by radiograph of the wrist and hand); **AND**
   C. Member has not reached final height; **AND**
   D. A diagnosis of one of the following:

1. **Short stature associated with Turner Syndrome, Prader-Willi` Syndrome, Noonan Syndrome, SHOX gene deficiency, or Chronic renal insufficiency; AND**
    i. The member has short stature as confirmed by <u>one</u> of the following:
        a. <u>Current height</u>: more than two standard deviations (SD) (less than 3rd percentile) below the mean for age and gender; **OR**
        b. <u>Growth velocity</u>: more than two SD below the mean for age and gender over one year; **OR**
        c. <u>Growth velocity</u>: more than 1.5 SD sustained over two years; **OR**
        d. <u>Delayed skeletal maturation (delayed bone age):</u> bone age compared to chronological age is equal to, or greater than, two SD below the mean for age and gender; **AND**
    ii. Diagnosis aligns with FDA-approved indication for the requested medication as documented within the table above; **OR**
2. **Growth Hormone Deficiency; OR**
3. **Growth failure in children born small for gestational age (SGA); AND**
    i. Member failed to manifest catch-up growth by two years of age; **AND**
    ii. Birth weight and/or length is less than two SD below the mean for gestational age; **AND**
    iii. Height remains less than two SD below the mean age and gender at two years of age; **AND**
    iv. Diagnosis aligns with FDA-approved indication for the requested medication as documented within the table above

<u>Growth Hormone Therapy in Adults</u>

Initial Evaluation

II. **Growth hormone replacement** may be considered medically necessary in **<u>adults</u>** when the following criteria below are met:
    A. Medication is prescribed by, or in consultation with, an endocrinologist or gastroenterologist; **AND**
    B. A diagnosis of one of the following:
        1. **Short bowel syndrome; AND**
            i. Member is currently on specialized nutritional support that has been protein, calorie, and fluid intake-optimized for at least two weeks; **AND**
            ii. The request is for somatropin (Zorbtive); **OR**
        2. **HIV/AIDS associated wasting or cachexia; AND**

i. Treatment with an appetite stimulant (dronabinol or megestrol) has been ineffective, contraindicated, or not tolerated; **AND**
ii. The request is for somatropin (Serostim); **OR**

3. **Adult Growth Hormone Deficiency (GHD); AND**
    i. Diagnosis of GHD that is one of the following:
        a. Adult onset from one of the following: hypopituitarism due to pituitary disease, hypothalamic disease, pituitary surgery, cranial radiation therapy, or traumatic brain injury; **AND**
            i. A subnormal response (less than 10 ng/ml) to any TWO of the following provocative growth hormone (GH) stimulation tests:
                1. Arginine
                2. Clonidine
                3. Glucagon
                4. Insulin induced hypoglycemia
                5. L-dopa
                6. Propranolol; **OR**
        b. Childhood-onset growth hormone deficiency; **AND**
            i. Serum insulin-like growth factor-1 (IGF-1) concentration lower than the age- and gender appropriate reference range; **OR**
        c. Idiopathic GH deficiency diagnosis; **AND**
            i. Diagnosis been confirmed by BOTH of the following:
                1. A subnormal response (less than 10 ng/ml) to any TWO of the following provocative growth hormone (GH) stimulation tests:
                    a. Arginine
                    b. Clonidine
                    c. Glucagon
                    d. Insulin induced hypoglycemia
                    e. L-dopa
                    f. Propranolol; **AND**
                2. Serum insulin-like growth factor-1 (IGF-1) concentration lower than the age- and gender appropriate reference range; **AND**
    ii. Diagnosis aligns with FDA-approved indication for the requested medication as documented within the table above

II. Growth hormone is considered not medically necessary when used for all other conditions, including but not limited to:
   A. Idiopathic (i.e. of unknown origin) short stature, also called non-growth hormone deficient short stature in children
   B. Increased athletic performance in adults

III. Growth hormone is considered investigational when used for all other conditions, including but not limited to:
   A. Growth hormone insensitivity (Laron Syndrome)
   B. Constitutional growth delay
   C. Children with growth failure caused by glucocorticoids
   D. Children who are not growth hormone deficient but have short stature associated with chronic disease
   E. Children with chromosomal and genetic disorders (except Turner's and Prader Willi Syndromes) or familial short stature
   F. Russell Silver syndrome
   G. Altered body habitus or lipodystrophy associated with antiviral therapy
   H. Precocious puberty
   I. Obesity
   J. Cystic fibrosis
   K. Idiopathic dilated cardiomyopathy
   L. Juvenile idiopathic arthritis

Renewal Evaluation

I. Member has not been established on therapy by the use of free samples, manufacturer coupons, or otherwise; **AND**

II. Member has received a previous prior authorization approval for this agent through this health plan; **AND**

III. A diagnosis of one of the following:
   A. Children with short stature associated with Turner Syndrome, Prader-Willi Syndrome, Noonan Syndrome, SHOX Gene Deficiency, Chronic Renal Insufficiency, Children with Growth Hormone Deficiency, or Growth failure in children born small for gestational age (SGA); AND
      a. Member's epiphyses are not closed (as confirmed by radiograph of the wrist and hand); **AND**
      b. Member has not reached final height; **AND**
      c. Member has shown a response to growth hormone therapy (i.e. increase in height, increase in height velocity); **OR**

B. **HIV/AIDS associated wasting or cachexia; AND**
   a. Member has shown clinical benefits by an increase in muscle mass and weight from growth hormone replacement; **AND**
   b. Member has not received more than six months of therapy; **OR**

C. Adult Growth Hormone Deficiency; AND
   a. Member has shown clinical benefits from growth hormone replacement as assessed by one of the following:
      i. Normalization of insulin-like growth factor I (IGF-I)
      ii. Improvement in body composition (i.e. bone density increase, lipolysis changes)
      iii. Clinical assessment of patient focusing on improvement in quality of life issues

Supporting Evidence

I. All recombinant human growth hormone (GH) products that are administered via daily injections are somatropin. Other than device and FDA approved indications, there is little to no differentiation between these products. Sogroya (somapacitan), provides the option of weekly administration; however, efficacy results were based on a single trial in which numerical values compared to open-label Norditropin showed lower results. Sogroya (somapacitan) was evaluated statistically only against placebo in a space with several established treatment options and patients in the trial were treatment naïve, thus place in therapy and clinical efficacy compared to other available agents is unknown.

II. The agents listed above with weight based dosing quantity limits also have an alternative dosing regimen available (0.2mg/day, increasing by 0.1 to 0.2mg/daily every 1 to 2 months according to response); however, this dosing would still be approvable as it would fall below the maximum weight based dose.

III. The diagnosis of GH deficiency is confirmed by measurement of GH secretion, commonly following stimulation by a provocative agent. 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.

IV. Due to a lack of evidence that one GH product is more beneficial than other, AACE does not recommend a particular 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.

V. Somatropin and somapacitan should not be used for growth promotion in pediatric patients with closed epiphyses.

VI. Zorbtive is indicated for the treatment of SBS in patients receiving specialized nutritional support. Administration for more than 4 weeks has not been adequately studied.

VII. Payment consideration for growth hormone used to treat HIV/AIDS wasting syndrome or cachexia is reserved for members that have had an inadequate response to appetite stimulants. Per package insert, there is no safety or efficacy data available from controlled studies in which patients were treated with Serostim continuously for more than 48 weeks. There is also no safety or efficacy data available from trials in which patients with HIV wasting or cachexia were treated intermittently with Serostim. A search in the medical literature as of September 2020 revealed two prospective controlled trials which are the pivotal trials in the Serostim package insert. The search did not identify any clinical studies or reports evaluating the use of human GH longer than 48 weeks in this treatment setting.

VIII. Guidelines for Use of Growth Hormone in Clinical Practice: Patients with childhood-onset GH deficiency previously treated with GH replacement in childhood should be retested after final height is achieved and GH therapy discontinued for at least 1 month to ascertain their GH status before considering restarting GH therapy. Exceptions include those with known mutations, those with embryopathic/congenital defects, those with irreversible hypothalamic-pituitary structural lesions, and those with evidence of panhypopituitarism (at least 3 pituitary hormone deficiencies) and serum IGF-I levels below the age- and sex-appropriate reference range off GH therapy.

- For childhood GH treatment of conditions other than GHD, such as Turner's syndrome and idiopathic short stature, there is no proven benefit to continuing GH treatment in adulthood; hence, there is no indication to retest these patients when final height is achieved.

IX. The Endocrine Society's clinical guidelines now recommend GH for use in idiopathic adult GH deficiency although this diagnosis is rare. Significant false-positive error rates occur in response to a single GH stimulation test, therefore, 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.

FDA Approved Indications for Growth Hormone Products

Brand	GHD		TS	ISS	SGA	PWS	CKD	NS	SHOX	HIV	SBS
	Ch	Ad									
Genotropin	x	x	x	x	x	x					
Humatrope	x	x	x	x	x				x		
Norditropin	x	x	x		x			x			
Nutropin AQ	x	x	x	x			x				
Omnitrope	x	x	x	x	x	x					
Saizen	x	x									
Zomacton	x	x	x	x	x				x		
Skytrofa	x										
Sogroya		x									
Serostim										x	
Zorbtive											x

GHD = Growth Hormone Deficiency (Ch = Children, Ad = Adult)
TS = Turner Syndrome
ISS = Idiopathic Short Stature
SGA = Growth failure in children born Small for Gestational Age
PWS = Prader-Willi Syndrome in children
CKD = Growth failure due to chronic kidney disease
NS = Noonan Syndrome
SHOX = Short stature homeobox-containing gene deficiency
HIV = HIV-associated Wasting or Cachexia
SBS = Short Bowel Syndrome

Investigational or Not Medically Necessary Uses

I. Idiopathic short stature
   A. Growth hormone therapy for certain conditions may not be approved when use is not expected to correct a significant functional deficit or when reduced growth is not due to an underlying medical condition. Idiopathic short stature is a term used to define height of children who are short, for unknown or hereditary reasons, compared to others in their age- and gender appropriate reference range. Idiopathic short stature is not associated with a definable physical functional impairment, is not due to growth hormone deficiency, and is not the result of accidental injury, disease, trauma, or treatment of a disease, and is not a congenital defect. Additionally, the efficacy of growth hormone therapy for idiopathic short stature is highly variable and those that respond may only have modest additional growth. Growth hormone therapy may be prescribed to circumvent psychosocial burden associated with idiopathic short stature; however, treatment has not been proven effective in producing those intended effects on health outcomes, such as morbidity and quality of life. The potential for modest improvement in growth and unknown impact to psychosocial burden should be balanced with safety concerns associated with treatment including increased risk of cancer, cerebrovascular disease, and metabolic side effects. Given highly variable response rate, modest potential height gain, lack of underlying medical condition, unproven impact on psychosocial burden, and risk for adverse effects, treatment with growth hormone therapy is not medically necessary.
II. Increased athletic performance in adults
   A. The AACE recommends that GH should only be prescribed to patients with clinical features suggestive of adult GHD. Administration of GH to patients for improvement of athletic performance or for any reason other than its approved medical uses is not recommended.
III. There is insufficient or inconclusive medical and scientific evidence to support the safety and efficacy of growth hormone therapy in the listed conditions:
   A. Growth hormone insensitivity (Laron Syndrome)
   B. Constitutional growth delay
   C. Children with growth failure caused by glucocorticoids

D. Children who are not growth hormone deficient but have short stature associated with chronic disease
E. Children with chromosomal and genetic disorders (except Turner's and Prader Willi Syndromes) or familial short stature
F. Russell Silver syndrome
G. Altered body habitus or lipodystrophy associated with antiviral therapy
H. Precocious puberty
I. Obesity
J. Cystic fibrosis
K. Idiopathic dilated cardiomyopathy
L. Juvenile idiopathic arthritis

References

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Policy Implementation/Update:

Action and Summary of Changes	Date
Removal of confirmatory diagnostic criteria in setting of pediatric growth hormone deficiency setting. Update to not medically necessary supporting evidence for idiopathic short stature.	08/2022

Addition of new product lonapegsomatropin in non-preferred position	08/2021
Addition of new product Sogroya in non-preferred position	02/2021
Added further supporting evidence to duration of therapy with Serostim in the setting of HIV/AIDS associated wasting or cachexia	11/2020
Updated to policy format. Updated growth hormone stimulation requirements to align with guideline recommendations (Molitch 2011 and Grimberg 2016). Added requirement of treatment to be prescribed by specialist. Removed route for coverage in the setting of idiopathic short stature as growth hormone therapy for certain conditions may not be approved when growth hormone use is not expected to correct a significant functional deficit OR when reduced growth is not due to an underlying medical condition.	11/2019
Criteria update: updated criteria to new format, deleted question defining HIV wasting, added routing questions for growth failure in children born small for gestational age added clinical notes to questions.	03/2018
Criteria Created	08/2014