Clinical Policy: Human Growth Hormone (Norditropin, Genotropin, Humatrope, Nutropin, NuSpin, Omnitrope, Saizen, Serostim, Sogroya, Zomacton, Zorbtive)

Reference Number: AZ.CP.PHAR.517
Effective Date: 02.01.21
Last Review Date: 02.21
Line of Business: Arizona Medicaid (AzCH-CCP and Care1st) Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description

The following human growth hormone (hGH) formulations require prior authorization:

- hGH analogs: somapacitan-beco (Sogroya®)
- Recombinant hGH (rhGH) formulations: somatropin (Genotropin®, Humatrope®, Norditropin®, Nutropin AQ®, Omnitrope®, Saizen®, Serostim®, Zomacton®, Zorbtive®)

AHCCCS preferred drugs in this class include- Norditropin (brand only) and Genotropin (brand only).

AHCCCS non-preferred drugs in this class include- Humatope, Nutropin AQ NuSpin, Omintrope, Saizen, Serostim, Sogroya, Zomacton and Zorbtive.

Drugs	Children								Adults		
	GHD	PWS	TS	NS	SHOX	CKD	SGA	ISS	GHD	HIV	SBS
Sogroya									X		
Genotropin	GF	GF	GF				GF	GF	X		
Humatrope	SS/GF		SS/GF		SS/GF		SS/GF	SS/GF	X		
Norditropin	GF	GF	SS	SS			SS	SS	X		
NutropinAQ	GF		GF			GF		GF	X		
Omnitrope	GF	GF	GF				GF	GF	X		
Saizen	GF								X		
Serostim										X	
Zomacton	GF		SS		SS		SS	SS	X		
Zorbtive											X

Abbreviations: CKD: chronic kidney disease, GF: growth failure, GHD: growth hormone deficiency, HIV: human immunodeficiency virus, ISS: idiopathic short stature, NS: Noonan syndrome, PWS: Prader-Willi syndrome, SBS: short bowel syndrome, SGA: small for gestational age, SHOX: short stature homeobox-containing gene, SS: short stature, TS: Turner syndrome

FDA Approved Indication(s)

hGH Analogs:

Sogroya is indicated for:

- Replacement of endogenous GH in adults with GHD

rhGH Formulations:
Genotropin is indicated for:
- Pediatric Patients: 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 Patients: Treatment of adults with either childhood-onset or adult-onset GHD

Humatrope is indicated for:
- Pediatric Patients: Treatment of children with short stature or growth failure associated with growth hormone (GH) deficiency, Turner syndrome, idiopathic short stature (ISS), short stature homeobox-containing gene (SHOX) deficiency, and failure to catch up in height after small for gestational age birth
- Adult Patients: Treatment of adults with either childhood-onset or adult-onset GHD

Norditropin FlexPro is indicated for:
- Pediatric Patients: Treatment of children with growth failure due to GHD, short stature associated with Noonan syndrome, short stature associated with Turner syndrome, and short stature born small for gestational age with no catch-up growth by age 2 to 4 years, Idiopathic Short Stature (ISS), and growth failure due to Prader-Willi Syndrome
- Adult Patients: Treatment of adults with either childhood-onset or adult-onset GHD

Nutropin AQ NuSpin is indicated for:
- Pediatric Patients: Treatment of children with growth failure due to GHD, ISS, Turner syndrome (TS), and chronic kidney disease (CKD) up to the time of renal transplantation
- Adult Patients: Treatment of adults with either childhood-onset or adult-onset GHD

Omnitrope is indicated for:
- Pediatric Patients: Treatment of children with growth failure due to GHD, Prader-Willi Syndrome, Small for Gestational Age, TS, and ISS
- Adult Patients: Treatment of adults with either childhood-onset or adult-onset GHD

Saizen is indicated for:
- Pediatric Patients: Treatment of children with growth failure due to GHD
- Adult Patients: Treatment of adults with either childhood-onset or adult-onset GHD

Serostim is indicated for:
- Treatment of HIV patients with wasting or cachexia to increase lean body mass and body weight, and improve physical endurance

Zomacton is indicated for:
- Pediatric Patients: Treatment of pediatric patients who have growth failure due to inadequate secretion of normal endogenous GH, short stature associated with TS, ISS, SHOX

deficiency, and short stature born small for gestational age (SGA) with no catch-up growth by 2 years to 4 years
- Adult Patients: For replacement of endogenous GH in adults with GH deficiency

Zorbtive is indicate for:
- For the treatment of Short Bowel Syndrome in patients receiving specialized nutritional support. Zorbtive therapy should be used in conjunction with optimal management of Short Bowel Syndrome.

Policy/Criteria
Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

Index

I. Initial Approval Criteria
A. Growth Hormone Deficiency with Neonatal Hypoglycemia (off-label)
B. Growth Hormone Deficiency with Short Stature/Growth Failure - Children *(open epiphyses)*
C. Genetic Disorders with Short Stature/Growth Failure - Children
D. Chronic Kidney Disease with Growth Failure - Children
E. Born Small for Gestational Age with Short Stature/Growth Failure - Children
F. Growth Hormone Deficiency - Adults and Transition Patients *(closed epiphyses)*
G. Short Bowel Syndrome - Adults
H. HIV-Associated Wasting/Cachexia - Adults
I. Other diagnoses/indications
II. Continuing Approval Criteria
A. All Pediatric Indications *(open epiphyses)*
B. Growth Hormone Deficiency - Adults and Transition Patients *(closed epiphyses)*
C. Short Bowel Syndrome - Adults
D. HIV-Associated Wasting/Cachexia - Adults
E. Other diagnoses/indications
III. Diagnoses/Indications for which coverage is NOT authorized:
IV. Appendices
V. Dosage and Administration
VI. Product Availability
VII. References

It is the policy of Arizona Complete Health-Complete Care Plan that somatropin (recombinant human growth hormone (rhGH)) is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Growth Hormone Deficiency with Neonatal Hypoglycemia (off-label) (must meet all)**:**

1. Diagnosis of neonatal hypoglycemia due to GHD;
2. Request is for a somatropin formulation;
3. Prescribed by or in consultation with a pediatric endocrinologist;
4. Age ≤ 1 month;
5. Serum GH concentration ≤ 5 µg/L;
6. Member meets (a or b):
   a. Imaging shows hypothalamic-pituitary abnormality;
   b. Deficiency of ≥ 1 anterior pituitary hormone other than GH (e.g., ACTH, TSH, LH, FSH, prolactin);
7. The requested product is not prescribed concurrently with Increlex® (mecasermin);
8. If request is NOT for Norditropin or Genotropin but another somatropin formulation (a or b):
   a. The requested product dose is < 0.025 mg per injection;
   b. Norditropin and Genotropin product excipients are contraindicated or member has experienced a clinically significant adverse effect to Norditropin and Genotropin;
9. Dose does not exceed 0.30 mg/kg per week.

Approval duration: 12 months

B. Growth Hormone Deficiency with Short Stature/Growth Failure - Children *(open epiphyses)* (must meet all)**:**

1. Diagnosis of GHD;
2. Request is for a somatropin formulation;
3. Prescribed by or in consultation with a pediatric endocrinologist;
4. Age < 18 years;
5. If age > 10 years, open epiphysis on x-ray;
6. Member meets (a or b):
   a. Low insulin-like growth factor (IGF)-I serum level;
   b. Low insulin-like growth factor binding protein (IGFBP)-3 serum level;
7. Member meets (a, b, c, d, or e):
   a. Two GH stimulation tests with peak serum levels ≤ 10 µg/mL (e.g., stimulants: arginine, clonidine, glucagon);
   b. Deficiency of ≥ 3 pituitary hormones (i.e., ACTH, TSH, LH, FSH, prolactin);
   c. Surgery or radiotherapy to the hypothalamic-pituitary region;
   d. Imaging shows hypothalamic-pituitary abnormality;
   e. GHD-specific mutation (e.g., POU1F1, PROP1, LHX3, LHX4, HESX1, OTX2, TBX19, SOX2, SOX3, GLI2, GHRHR, GH1);
8. Member meets (a or b):
   a. SS: height < 2 SD below the mean for age and gender (SD, height, date, and age in months within the last 90 days required);
   b. GF: one of the following (i, ii, or iii):

i. Height deceleration across two growth chart percentiles representing > 1 SD below the mean for age and sex (SD and 2 heights, dates, and ages in months at least 6 months apart within the last year are required);
ii. Growth velocity > 2 SD below the mean for age and sex over 1 year (SD and 2 heights, dates, and ages in months at least 1 year apart within the last year are required);
iii. Growth velocity > 1.5 SD below the mean for age and sex sustained over 2 years (SD and 2 heights, dates, and ages in months at least 2 years apart within the last two years are required);

9. The requested product is not prescribed concurrently with Increlex (mecasermin);
10. If request is NOT for Norditropin or Genotropin but another somatropin formulation (a or b):
    a. The requested product dose is < 0.025 mg per injection;
    b. Norditropin and Genotropin product excipients are contraindicated or member has experienced a clinically significant adverse effect to Norditropin and Genotropin;
11. Dose does not exceed 0.30 mg/kg per week.

Approval duration: 12 months

C. Genetic Disorders with Short Stature/Growth Failure - Children (must meet all)**:**

1. Diagnosis of PWS, TS, NS, or SHOX deficiency confirmed by a genetic test;
2. Request is for a somatropin formulation;
3. Prescribed by or in consultation with a pediatric endocrinologist;
4. Age < 18 years;
5. If age > 10 years, open epiphysis on x-ray;
6. Member meets (a or b):
    a. SS: height < 2 SD (< 1.5 SD if TS) below the mean for age and gender (SD, height, date, and age in months within the last 90 days required);
    b. GF: one of the following (i, ii, or iii):
        i. Height deceleration across two growth chart percentiles representing > 1 SD below the mean for age and sex (SD and 2 heights, dates, and ages in months at least 6 months apart within the last year are required);
        ii. Growth velocity > 2 SD below the mean for age and sex over 1 year (SD and 2 heights, dates, and ages in months at least 1 year apart within the last year are required);
        iii. Growth velocity > 1.5 SD below the mean for age and sex sustained over 2 years (SD and 2 heights, dates, and ages in months at least 2 years apart within the last two years are required);
7. The requested product is not prescribed concurrently with Increlex (mecasermin);
8. If request is NOT for Norditropin or Genotropin but another somatropin formulation (a or b):
    a. The requested product dose is < 0.025 mg per injection;
    b. Norditropin and Genotropin product excipients are contraindicated or member has experienced a clinically significant adverse effect to Norditropin and Genotropin;

9. Request meets one of the following (a, b, or c):
   a. PWS: Dose does not exceed 0.24 mg/kg per week;
   b. TS, NS: Dose does not exceed 0.5 mg/kg per week;
   c. SHOX deficiency: Dose does not exceed 0.35 mg/kg per week.

Approval duration: 12 months

D. Chronic Kidney Disease with Growth Failure – Children (must meet all)**:**

1. Diagnosis of CKD;
2. Request is for a somatropin formulation;
3. Prescribed by or in consultation with a pediatric endocrinologist or nephrologist;
4. Age < 18 years;
5. If age > 10 years, open epiphysis on x-ray;
6. Member meets (a, b, c, or d):
   a. GFR < 60 mL/min per 1.73 m^2 for ≥ 3 months;
   b. Dialysis dependent;
   c. Diagnosis of nephropathic cystinosis;
   d. History of kidney transplant ≥ 1 year ago;
7. Member meets (a or b):
   a. SS: height < 2 SD below the mean for age and gender (SD, height, date, and age within the last 90 days required);
   b. GF: one of the following (i, ii, or iii):
      i. Height deceleration across two growth chart percentiles representing > 1 SD below the mean for age and sex (SD and 2 heights, dates, and ages in months at least 6 months apart within the last year are required);
      ii. Growth velocity > 2 SD below the mean for age and sex over 1 year (SD and 2 heights, dates, and ages in months at least 1 year apart within the last year are required);
      iii. Growth velocity > 1.5 SD below the mean for age and sex sustained over 2 years (SD and 2 heights, dates, and ages in months at least 2 years apart within the last two years are required);
8. The requested product is not prescribed concurrently with Increlex (mecasermin);
9. If request is NOT for Norditropin or Genotropin but another somatropin formulation (a or b):
   a. The requested product dose is < 0.025 mg per injection;
   b. Norditropin and Genotropin product excipients are contraindicated or member has experienced a clinically significant adverse effect to Norditropin and Genotropin;
10. Dose does not exceed 0.35 mg/kg per week.

Approval duration: 12 months

E. Born Small for Gestational Age with Short Stature/Growth Failure - Children (must meet all)**:**

1. Diagnosis of SGA:
2. Request is for a somatropin formulation;

3. Prescribed by or in consultation with a pediatric endocrinologist;
4. Age ≥ 2 years and < 18 years;
5. If age > 10 years, open epiphysis on x-ray;
6. Member meets (a and b):
   a. Birth weight or length < 2 SD below the mean for gestational age (SD, birth weight, length, and gestational age are required);
   b. Current height > 2 SD below the mean for age and sex measured within the last year at ≥ 2 years of age (SD, height, date, and age in months are required);
7. The requested product is not prescribed concurrently with Increlex (mecasermin);
8. If request is NOT for Norditropin or Genotropin but another somatropin formulation (a or b):
   a. The requested product dose is < 0.025 mg per injection;
   b. Norditropin and Genotropin product excipients are contraindicated or member has experienced a clinically significant adverse effect to Norditropin and Genotropin;
9. Dose does not exceed 0.48 mg/kg per week.

Approval duration: 12 months

F. Growth Hormone Deficiency – Adults and Transition Patients *(closed epiphyses)* (must meet all):

1. Diagnosis of GHD;
2. Prescribed by or in consultation with an endocrinologist;
3. Age ≥ 18 years OR closed epiphysis on x-ray;
4. Member has NOT received somatropin therapy for ≥ 1 month prior to GH/IGF-I testing as outlined below;
5. Member meets (a, b, or c):
   a. Two fasting a.m. GH stimulation tests with peak serum levels ≤ 5 µg/mL (accepted stimulants: Macrilen™ [macimorelin] or combination of 2 stimulants such as arginine + glucagon);
   b. Both of the following (i and ii):
      i. One fasting a.m. GH stimulation test with peak serum level ≤ 5 µg/ml (accepted stimulants: Macrilen [macimorelin] or combination of 2 stimulants such as arginine + glucagon);
      ii. One low IGF-I serum level;
   c. One low IGF-I serum level and (i, ii, or iii):
      i. Imaging shows hypothalamic-pituitary abnormality;
      ii. Deficiency of ≥ 3 pituitary hormones (i.e., ACTH, TSH, LH, FSH, prolactin);
      iii. GHD-specific mutation (e.g., POU1F1, PROP1, LHX3, LHX4, HESX1, OTX2, TBX19, SOX2, SOX3, GLI2, GHRHR, GH1);
6. The requested product is not prescribed concurrently with Increlex (mecasermin);
7. If request is for Sogroya, member has previous trial and failure, intolerance or contraindication to Norditropin and Genotropin;
8. If request is NOT for Norditropin or Genotropin but another somatropin formulation (a or b):

a. The requested product dose is < 0.025 mg per injection;
b. Norditropin and Genotropin product excipients are contraindicated or member has experienced a clinically significant adverse effect to Norditropin and Genotropin;

9. Dose does not exceed one of the following (a or b):
   a. For Sogroya: 8 mg once weekly;
   b. For somatropin formulations: 0.4 mg/day (may adjust by up to 0.2 mg/day every 4 weeks to maintain normal IGF-1 serum levels; doses > 1.6 mg/day would be uncommon).

Approval duration: 6 months

G. Short Bowel Syndrome (must meet all):
1. Diagnosis of SBS;
2. Request is for a somatropin formulation;
3. Prescribed by or in consultation with a gastroenterologist;
4. Age ≥ 18 years;
5. Patient is dependent upon and receiving intravenous nutrition;
6. If request is NOT for Norditropin or Genotropin but another somatropin formulation (a or b):
   a. The requested product dose is < 0.025 mg per injection;
   b. Norditropin and Genotropin product excipients are contraindicated or member has experienced a clinically significant adverse effect to Norditropin and Genotropin;
7. Dose does not exceed 8 mg per day.

Approval duration: up to 4 weeks total

H. HIV-Associated Wasting or Cachexia (must meet all):
1. Diagnosis of HIV;
2. Request is for a somatropin formulation;
3. Prescribed by or in consultation with a physician specializing in HIV management;
4. Age ≥ 18 years;
5. Unintentional weight loss of ≥ 10% in the last 12 months occurring while on antiretroviral therapy;
6. Failure of at least 2 pharmacologic therapies from two separate drug classes *(Appendix B)* unless contraindicated or clinically adverse effects are experienced;
7. If request is NOT for Norditropin or Genotropin but another somatropin formulation (a or b):
   a. The requested product dose is < 0.025 mg per injection;
   b. Norditropin and Genotropin product excipients are contraindicated or member has experienced a clinically significant adverse effect to Norditropin and Genotropin;
8. Prescribed dose does not exceed 6 mg per day.

Approval duration: 6 months

I. Other diagnoses/indications

1. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): AZ.CP.PMN.53 for Arizona Medicaid.

II. Continued Therapy

A. All Pediatric Indications *(open epiphyses)* (must meet all)**:**

1. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
2. Age < 18 years OR open epiphysis on x-ray;
3. Member meets (a or b):
   a. For diagnosis of neonatal hypoglycemia, when member has received somatropin therapy for ≥ 2 years, member's height has increased ≥ 2 cm in the last year as documented by 2 height measurements taken no more than 1 year apart (dates and height measurements required);
   b. For all other pediatric diagnoses, member's height has increased ≥ 2 cm in the last year as documented by 2 height measurements taken no more than 1 year apart (dates and height measurements required);
4. If request is for a dose increase, request meets the one of the following (a, b, c, d, or e):
   a. GHD with or without neonatal hypoglycemia: New dose does not exceed 0.30 mg/kg per week;
   b. PWS: New dose does not exceed 0.24 mg/kg per week;
   c. TS, NS: New dose does not exceed 0.5 mg/kg per week;
   d. SHOX deficiency, CKD: New dose does not exceed 0.35 mg/kg per week;
   e. Born SGA: New dose does not exceed 0.48 mg/kg per week.

Approval duration: 12 months

B. Growth Hormone Deficiency - Adults and Transition Patients *(closed epiphyses)* (must meet all)**:**

1. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
2. For IGF-1 test results and dosing (test conducted within the last 90 days) (a, b, or c):
   a. Low IGF-1 serum level (i or ii):
      i. For Sogroya: 8 mg once weekly;
      ii. For somatropin formulations: If request is for a dose increase, new dose does not exceed an incremental increase of more than 0.2 mg/day and a total dose of 1.6 mg/day;
   b. Normal IGF-1 serum level: Requested dose is for the same or lower dose;
   c. Elevated IGF-1 serum level: Requested dose has been titrated downward.

Approval duration: 12 months

C. Short Bowel Syndrome - Adults (must meet all)**:**
1. Currently receiving medication via Centene benefit or member has previously met all initial approval criteria;
2. Member is responding positively to therapy;
3. Member has not received the requested product for ≥ 4 weeks;
4. If request is for a dose increase, new dose does not exceed 8 mg per day.

Approval duration: up to 4 weeks total

D. HIV-Associated Wasting/Cachexia - Adults (must meet all)**:**
1. Currently receiving medication via Centene benefit or member has previously met all initial approval criteria;
2. Member is responding positively to therapy;
3. Member has not received ≥ 12 months of therapy;
4. If request is for a dose increase, new dose does not exceed 6 mg per day.

Approval duration: up to 12 months total

E. Other diagnoses/indications (must meet 1 or 2)**:**
1. Currently receiving medication via health plan benefit and documentation supports positive response to therapy.
   Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to AZ.CP.PMN.53 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized). Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): AZ.CP.PMN.53 for Arizona Medicaid.

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – AZ.CP.PMN.53 for Arizona Medicaid.
B. Idiopathic short stature (ISS);
C. Constitutional delay of growth and puberty (i.e., constitutional growth delay; the member's growth rate is delayed compared to chronological age but appropriate for bone age as determined by x-ray);
D. Familial (genetic) short stature (i.e., height velocity and bone age, as determined by x-ray, are within the normal range and one or both parents are short);
E. Adult short stature or altered body habitus associated with antiviral therapy (other than HIV-associated wasting or cachexia);
F. Obesity treatment or enhancement of body mass/strength for non-medical reasons (e.g., athletic gains).

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

CKD: chronic kidney disease
FDA: Food and Drug Administration
GFR: glomerular filtration rate
GH: growth hormone
GHD: growth hormone deficiency
HIV: human immunodeficiency virus
IGF-1: insulin-like growth factor-1
IGFBP-3: insulin-like growth factor binding protein-3
ISS: idiopathic short stature
NS: Noonan syndrome
PWS: Prader-Willi syndrome
rhGH: recombinant human growth hormone
SBS: short bowel syndrome
SD: standard deviation
SGA: small for gestational age
SHOX: short stature homeobox-containing gene
TS: Turner syndrome

Appendix B: Therapeutic Alternatives

This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent for all relevant lines of business and may require prior authorization.

Drug	Dosing Regimen	Dose Limit/Maximum Dose
Appetite stimulants		
Megestrol (Megace®)	400 - 800 mg PO daily (10 – 20 ml/day)	800 mg/day
Dronabinol (Marinol®)	2.5 mg PO bid	20 mg/day
Testosterone replacement products		
Testosterone enanthate or cypionate (Various brands)	50 - 400 mg IM Q2 – 4 wks	400 mg Q 2 wks
Androderm® (testosterone transdermal)	2.5 – 7.5 mg patch applied topically QD	7.5 mg/day
Androgel® (testosterone gel)	5 - 10 gm gel (delivers 50 – 100 mg testosterone) applied topically QD	10 gm/day gel (100 mg/day testosterone)
Testim® (testosterone gel)	5 - 10 gm gel (delivers 50 – 100 mg testosterone) applied topically QD	10 gm/day gel (100 mg/day testosterone)
Anabolic steroid		
Oxandrolone (Oxandrin®)	2.5 – 20 mg PO /day	20 mg/day
Nandrolone decanoate	100 mg IM Q week	100 mg Q wk
Nausea/vomiting treatments*		
chlorpromazine	10 to 25 mg PO q4 to 6 hours prn	2,000 mg/day
perphenazine	8 to 16 mg/day PO in divided doses	64 mg/day

Drug	Dosing Regimen	Dose Limit/Maximum Dose
prochlorperazine	5 to 10 mg PO TID or QID	40 mg/day
promethazine	12.5 to 25 mg PO q4 to 6 hours prn	50 mg/dose; 100 mg/day
trimethobenzamide	300 mg PO TID or QID prn	1,200 mg/day

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.
**preferred status may differ based on specific formulary used*

Appendix C: Contraindications/Boxed Warnings

- Somatropin contraindications:
  - Acute critical illness
  - Children with PWS who are severely obese or have severe respiratory impairment (reports of sudden death)
  - Active malignancy
  - Product hypersensitivity
  - Active proliferative or severe non-proliferative diabetic retinopathy
  - Children with closed epiphyses
- Sogroya contraindications:
  - Acute critical illness
  - Active malignancy
  - Hypersensitivity to somapacitan-beco or excipients
  - Active proliferative or severe non-proliferative diabetic retinopathy
- Boxed warning(s): none reported

Appendix D:Short Stature and Growth Failure

- For SS, the policy follows the World Health Organization (WHO) definition of > 2 SD below the mean for age and sex.[1]
- For GF, the policy follows
  - Haymond et al (2013) and Rogol et al (2014) for height deceleration across two major percentiles representing a change of > 1 SD corrected for age and sex[2,3] and
  - the Growth Hormone Research Society (2000) for height velocity in the absence of SS that would prompt further investigation, namely, a height velocity > 2 SD below the mean over 1 year or > 1.5 SD below the mean sustained over 2 years for age and sex.[4]
- The Centers for Disease Control and Prevention (CDC) recommend WHO growth charts for infants and children age 0 to < 2 years and CDC growth charts for children age 2 years to < 20 years in the U.S.[5]
  - Based on CDC recommended growth chart data, SD approximations of major height percentiles falling below the mean are listed below:
    - 2nd percentile: 2 SD below the mean

- 5th percentile: 1.5 SD below the mean
- 15th percentile: 1 SD below the mean
- 30th percentile: 0.5 SD below the mean
- 50th percentile: 0 SD mean

- CDC recommended growth charts, data tables, and related information that may be helpful in assessing length, height and growth are available at the following link: https://www.cdc.gov/growthcharts/index.htm.

1. WHO Child Growth Standards: Length/Height-for-Age, Weight-for-Age, Weight-for-Length, Weight-for-Height and Body Mass Index-for-Age: Methods and Development. Geneva, Switzerland: World Health Organization; 2006. As cited in CDC. Division of Nutrition, Physical Activity, and Obesity. Growth Chart Training: Using the WHO Growth Charts. Page last reviewed April 15, 2015. Available at https://www.cdc.gov/nccdphp/dnpao/growthcharts/who/using/assessing_growth.htm. Accessed May 1, 2020.
2. Haymond M, Kappelgaard AM, Czernichow P, et al. Early recognition of growth abnormalities permitting early intervention. Acta Pædiatrica ISSN 0803-5253. April 2013. DOI:10.1111/apa.12266.
3. Rogol AD, Hayden GF. Etiologies ad early diagnosis of short stature and growth failure in children and adolescents. J Pediatr. 2014 May;164(5 Suppl):S1-14.e6. doi: 10.1016/j.jpeds.2014.02.027.
4. Consensus guidelines for the diagnosis and treatment of growth hormone (GH) deficiency in childhood and adolescence: summary statement of the GH Research Society. JCEM. 2000; 85(11): 3990-3993.
5. Centers for Disease Control and Prevention, National Center for Health Statistics. CDC growth charts: United States. http://www.cdc.gov/growthcharts/. Accessed April 22, 2020.

Appendix E: General Information

- Preferred products: Norditropin and Genotropin
- In childhood cancer survivors who were treated with radiation to the brain/head for their first neoplasm and who developed subsequent GHD and were treated with somatropin, an increased risk of a second neoplasm has been reported. Intracranial tumors, in particular meningiomas, were the most common of these second neoplasms. In adults, it is unknown whether there is any relationship between somatropin replacement therapy and CNS tumor recurrence.
- Short stature/growth failure prior to rhGH therapy is evidenced by one of the following:
  - Height > 3 SD below the mean
  - Height > 2 SD below the mean and (a or b)
    a) Height velocity > 1 SD below the mean for chronological age over 1 year
    b) Decrease in height SD > 0.5 over 1 year in children > 2 years of age
  - Height > 1.5 SD below midparental height

a) Boys: (father's height + mother's height + 13 cm)/2 or (Father's Height + Mother's Height + 5 inches)/2

b) Girls: (father's height + mother's height − 13 cm)/2 or Father's Height – 5 inches + Mother's Height) / 2

  - Height velocity > 2 SD below the mean over 1 year
  - Height velocity > 1.5 SD below the mean over 2 years
- The 2009 American Association of Clinical Endocrinologists (AACE) guidelines for clinical practice for growth hormone use in growth hormone-deficient adults and transition patients state that "there is no evidence that one GH product is more

advantageous over the other, apart from differences in pen devices, dose increments and decrements, and whether or not the product requires refrigeration; therefore, we do not recommend the use of one commercial GH preparation over another."

- Examples of positive response to therapy for cachexia in HIV patients include a 2% increase in body weight and/or body cell mass (BCM). Once BCM is normalized, therapy may be stopped and the patient may be monitored for wasting to reoccur.
  - Body cell mass (BCM): The total mass of all the cellular elements in the body which constitute all the metabolically active tissue of the body. The preferred method for assessing BCM depletion is bioelectrical impedance analysis (BIA) which can be performed with portable equipment in the office setting.
- GF-1 and IGFBP-3 levels should be interpreted against reference ranges that are standardized for sex and age (or better, by stage of sexual development, such as Tanner Stage if available). The range varies with the assay used, and results should be interpreted against standards provided by the laboratory performing the test.
- Other than growth hormone (GH), pituitary hormones include the following:
  - ACTH: adrenocorticotropic hormone
  - TSH: thyroid stimulating hormone
  - FSH: follicle stimulating hormone
  - LH: luteinizing hormone
  - PrL: Prolactin
  - Melanocyte-stimulating hormone (MSH)
  - Oxytocin
    ADH: Antidiuretic hormone
- Growth Hormone Stimulation Test Agents
  - Glucagon
  - Clonidine
  - Insulin
  - Arginine (L-Arginine)
- Given the substantial number of healthy, normally growing children who test below accepted limits, inadequate response to two different provocative tests is required for diagnosis of GHD. While it is possible that combining tests might yield different results from tests performed on separate days, there is no evidence against performing both tests sequentially on the same day.
- Defined central nervous system pathology
  - Pituitary Hypoplasia
  - Craniofacial Developmental Defects
  - Empty Sella Syndrome
  - Septo-optic dysplasia
  - Pituitary Stalk Interruption Syndrome
    a) Absent/hypoplastic anterior pituitary gland
    b) Thin or absent pituitary stalk
    c) Ectopic posterior pituitary

V. Dosage and Administration

Drug Name	Indication	Dosing Regimen	Maximum Dose
Pediatric Indications (Subcutaneous administration; weekly doses should be divided)			
Genotropin, Humatrope, Norditropin, Nutropin, Omnitrope, Saizen, Zomacton	GHD	G, O: 0.16 to 0.24 mg/kg/week H, Z: 0.18 to 0.30 mg/kg/week N: 0.17 to 0.24 mg/kg/week Nu: to 0.30 mg/kg/week S: 0.18 mg/kg/week	See dosing regimens
Genotropin, Norditropin, Omnitrope	PWS	G, N, O: 0.24 mg/kg/week	0.24 mg/kg/week
Genotropin, Humatrope, Norditropin, Omnitrope, Zomacton	SGA	G, O: to 0.48 mg/kg/week H, N, Z: to 0.47 mg/kg/week	0.48 mg/kg/week
Genotropin, Humatrope, Norditropin, Nutropin, Omnitrope, Zomacton	TS	G, O: 0.33 mg/kg/week H, Nu, Z: to 0.375 mg/kg/week N: to 0.47 mg/kg/week	See dosing regimens
Genotropin, Humatrope, Norditropin, Nutropin, Omnitrope, Zomacton	ISS	G, O, No: to 0.47 mg/kg/week H, Z: to 0.37 mg/kg/week Nu: to 0.30 mg/kg/week	See dosing regimens
Humatrope, Zomacton	SHOX	H, Z: 0.35 mg/kg/week	0.35 mg/kg/week
Norditropin	NS	0.46 mg/kg/week	0.46 mg/kg/week
Nutropin	CKD	0.35 mg/kg/week	0.35 mg/kg/week
Adult Indications (Subcutaneous administration)			
Genotropin, Humatrope, Norditropin, Nutropin, Omnitrope, Saizen, Zomacton	GHD	0.4 mg/day - may adjust by increments up to 0.2 mg/day every 6 weeks to maintain normal IGF-1 serum levels.* _____ **Dosing regimen from Endocrine Society guidelines (Fleseriu, et al., 2016).* Adult GHD dosing should be substantially lower than that prescribed for children. Adult doses beyond 1.6 mg/day would be uncommon.	See dosing regimen

Drug Name	Indication	Dosing Regimen	Maximum Dose
Serostim	HIV-associated wasting	0.1 mg/kg QOD or QD to 6 mg QD	6 mg/day up to 24 weeks
Sogroya	GHD	0.5 mg once weekly – increase by increments of 0.5-1.5 mg every 2-4 weeks based on clinical response and serum IGF-1 concentrations	8 mg/week
Zorbtive	SBS	0.1 mg/kg QD to 8 mg QD	8 mg/day up to 4 weeks

Abbreviations: G: genotropin, H: humatrope, N: norditropin, Nu: nutropin, O: omnitrope, S: saizen, Z: zomacton

VI. Product Availability

Drug	Availability*
hGH Analogs	
Sogroya	MD pen: 10 mg/1.5 mL
rhGH Formulations	
Genotropin lyophilized powder	MD dual-chamber syringe: 5 mg, 12 mg
Genotropin Miniquick	SD pen cartridge: 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	MD pen cartridge: 6 mg, 12 mg, 24 mg MD vial: 5mg
Norditropin Flexpro	MD pen: 5 mg/1.5 mL, 10 mg/1.5 mL, 15 mg/1.5 mL, 30 mg/3 mL
Nutropin AQ	MD: NuSpin: 5 mg/2 mL, 10 mg/2 mL, 20 mg/2 mL MD pen cartridge: 10 mg/2 mL, 20 mg/2 mL
Omnitrope	MD pen cartridge: 5 mg/1.5 mL, 10 mg/1.5 mL MD vial: 5.8 mg
Saizen	MD pen cartridge: 8.8 mg MD vial: 5 mg, 8.8 mg
Serostim	MD vial: 4 mg SD vial: 5 mg, 6 mg
Zomacton	MD vial: 5 mg, 10 mg
Zorbtive	MD vial: 8.8 mg

SD: single-dose, MD: multidose

VII. References

FDA Labels

1. Genotropin Prescribing Information. NY, NY: Pfizer, Inc.; April 2019. Available at www.genotropin.com. Accessed October 20, 2020.
2. Humatrope Prescribing Information. Indianapolis, IN: Eli Lilly; October 2019. Available at: www.humatrope.com. Accessed October 20, 2020.
3. Norditropin Prescribing Information. Plainsboro, NJ: Novo Nordisk; March 2020. Available at: www.norditropin.com. Accessed October 20, 2019.
4. Nutropin AQ. Prescribing Information. South San Francisco, CA: Genentech; December 2016. Available at: www.nutropin.com. Accessed October 20, 2020.
5. Omnitrope Prescribing Information. Princeton, NJ: Sandoz; June 2019. Available at: www.omnitrope.com. Accessed October 20, 2020.
6. Saizen Prescribing Information. Rockland, MA: Serono; February 2020. Available at: www.saizenus.com. Accessed October 20, 2020.
7. Serostim Prescribing Information. Rockland, MA: EMD Serono Inc.; June 2019. Available at: https://serostim.com/. Accessed October 20, 2020.
8. Sogroya Prescribing Information. Plainsboro, NJ: NovoNordisk Health Care AG; August 2020. Available at: https://www.novo-pi.com/sogroya.pdf. Accessed October 20, 2020.
9. Zorbtive Prescribing information. Rockland, MA: EDM Serono, September 2019. Available at: http://www.emdserono.com. Accessed October 20, 2020.
10. Zomacton Prescribing information. Parsippany, NJ: Ferring Pharmaceuticals Inc., July 2018. Available at: www.zomacton.com. Accessed October 20, 2020.

Compendia

11. DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically.
12. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2020. Available at http://clinicalpharmacology-ip.com/.

Somatropin Therapy - Children

13. Grimberg A, DiVall SA, Polychronakos C, et al. Guidelines for growth hormone and insulin-like growth factor-I treatment in children and adolescents: growth hormone deficiency, idiopathic short stature, and primary insulin-like growth factor-I deficiency. Horm Res Paediatr 2016; 86:361-397.
14. Rose SR, Cook DM, Fine MJ. Growth hormone therapy guidelines: Clinical and managed care perspectives. Am J Pharm Benefits. 2014;6(5):e134-e146.
15. Drube J, Wan M, Bonthuis M. Consensus statement: Clinical practice recommendations for growth hormone treatment in children with chronic kidney disease. Nephrology. September 2019; (15):S77-89.
16. National Kidney Foundation. KDOQI Clinical Practice Guideline for Nutrition in Children with CKD: 2008 Update. Am J Kidney Dis 53: S1-S124, 2009 (suppl 2).

GHD - Adults and Transition Patients

17. Yuen Keven CJ, Biller BMK, Radovick S, et al. American Association of Clinical Endocrinologists and American College of Endocrinology (AACE) guidelines for management of growth hormone deficiency in adults and patients transitioning from pediatric to adult care: 2019 AACE Growth Hormone Task Force. Endocrine Practice, November 2019; 25(11):1191-1232.

18. Fleseriu M, Hashim IA, Karavitaki N, et al. Hormonal replacement in hypopituitarism in adults: An Endocrine Society clinical practice guideline. J Clin Endocrinol Metab, November 2016, 101(11):3888 –3921 doi: 10.1210/jc.2016-2118.
19. Cook DM, Rose SR. A review of guidelines for use of growth hormone in pediatric and transition patients. Pituitary. September 2012, Volume 15, Issue 3, pp 301–310.
20. Molitch ME, Clemmons DR, Malozowski S, et al. Evaluation and treatment of adult growth hormone deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2011; 96: 1587-1609.

Short Bowel Syndrome

21. Pironi L, Arends J, Bozzetti F. ESPEN guidelines on chronic intestinal failure in adults. Clinical Nutrition. 2016; 35:247-307.

HIV-Associated Wasting

22. Badowski ME, Perez SE. Clinical utility of dronabinol in the treatment of weight loss associated with HIV and AIDS. HIV AIDS (Auckl). 2016 Feb 10;8:37-45. doi: 10.2147/HIV.S81420. eCollection 2016.

Somatropin Product Comparative Data

23. Romer T, Zabransky M, Walczak M, Szalecki M, and Balser S. Effect of switching recombinant human growth hormone: comparative analysis of phase 3 clinical data. Biol Ther 2011; 1(2):005. DOI 10.1007/s13554-011-0004-8

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created: adapted from previously approved policy AZ.CP.PHAR.55 Somatropin (Human Growth Hormones); retired AZ.CP.PHAR.55 Somatropin (Human Growth Hormones); no significant changes from previously approved policy; 1Q 2021 annual review: no significant changes; references reviewed and updated.	10.22.20	02.21
Added Care1st logo. Added verbiage to specify that criteria also applies to Care1st.	5.10.21	04.21

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. “Health Plan” means a health

plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.