Clinical Policy Title:	somatropin
Policy Number:	RxA.597
Drug(s) Applied:	Genotropin®, Genotropin Miniquick®, Humatrope®, Humatrope Combo Pack®, Norditropin FlexPro®, Nutropin AQ® NuSpin®, Omnitrope®, Saizen®, Serostim®, Zomacton™, Zorbtive™
Original Policy Date:	05/2018
Last Review Date:	12/07/2020
Line of Business Policy Applies to:	All lines of business

Background

The following are recombinant human growth hormones requiring prior authorization: somatropin (Genotropin®, Genotropin Miniquick®, Humatrope®, Humatrope Combo Pack®, Norditropin FlexPro®, Nutropin AQ® NuSpin®, Omnitrope®, Saizen®, Serostim®, Zomacton™, Zorbtive™).

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. Isolated growth hormone deficiency (GHD) is defined by growth failure in combination with retarded bone age, low serum insulin-like growth factor-1, and insufficient GH peaks in two independent GH stimulation tests.
- Adult Patients: Treatment of adults with either childhood-onset or adult-onset GHD. Isolated growth hormone deficiency (GHD) is defined by growth failure in combination with retarded bone age, low serum insulin-like growth factor-1, and insufficient GH peaks in two independent GH stimulation tests.

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. Isolated growth hormone deficiency (GHD) is defined by growth failure in combination with retarded bone age, low serum insulin-like growth factor-1, and insufficient GH peaks in two independent GH stimulation tests.

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. Isolated growth hormone deficiency (GHD) is defined by growth failure in combination with retarded bone age, low serum insulin-like growth factor-1, and insufficient GH peaks in two independent GH stimulation tests.
- Adult Patients: Treatment of adults with either childhood-onset or adult-onset GHD. Isolated growth hormone

deficiency (GHD) is defined by growth failure in combination with retarded bone age, low serum insulin-like growth factor-1, and insufficient GH peaks in two independent GH stimulation tests.

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. Isolated growth hormone deficiency (GHD) is defined by growth failure in combination with retarded bone age, low serum insulin-like growth factor-1, and insufficient GH peaks in two independent GH stimulation tests.
- Adult Patients: Treatment of adults with either childhood-onset or adult-onset GHD. Isolated growth hormone deficiency (GHD) is defined by growth failure in combination with retarded bone age, low serum insulin-like growth factor-1, and insufficient GH peaks in two independent GH stimulation tests.

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. Isolated growth hormone deficiency (GHD) is defined by growth failure in combination with retarded bone age, low serum insulin-like growth factor-1, and insufficient GH peaks in two independent GH stimulation tests.
- Adult Patients: Treatment of adults with either childhood-onset or adult-onset GHD. Isolated growth hormone deficiency (GHD) is defined by growth failure in combination with retarded bone age, low serum insulin-like growth factor-1, and insufficient GH peaks in two independent GH stimulation tests.

Saizen is indicated for:

- Pediatric Patients: Treatment of children with growth failure due to GHD. Isolated growth hormone deficiency (GHD) is defined by growth failure in combination with retarded bone age, low serum insulin-like growth factor-1, and insufficient GH peaks in two independent GH stimulation tests.
- Adult Patients: Treatment of adults with either childhood-onset or adult-onset GHD. Isolated growth hormone deficiency (GHD) is defined by growth failure in combination with retarded bone age, low serum insulin-like growth factor-1, and insufficient GH peaks in two independent GH stimulation tests.

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 (SBS) in patients receiving specialized nutritional support. Zorbtive therapy should be used in conjunction with optimal management of SBS.

Dosing Information			
Drug Name	**Indication**	**Dosing Regimen**	**Maximum Dose**

Somatropin (Genotropin, Genotropin Miniquick, Humatrope, Humatrope Combo Pack, Norditropin Flexpro, Nutropin Aq Nuspin, Omnitrope, Saizen, Zomacton, Zorbtive)	Children and adolescents with GHD, small for gestational age, Turner syndrome, Prader- Willi syndrome, Noonan syndrome, SHOX deficiency, growth failure secondary to CKD, idiopathic short stature, Adults with growth hormone deficiency, SBS	Refer to prescribing information (*Somatropin, rh-GH doses must be individualized and are highly variable depending on the nature and severity of the disease, the formulation being used, and on patient response*)	Refer to prescribing information
Serostim	Wasting or Cachexia in HIV patients	• < 35 kg = 0.1 mg/kg SC QHS • 35 to 45 kg = 4 mg SC QHS • 45 kg to 55 kg = 5 mg SC QHS • > 55 kg = 6 mg SC QHS	6 mg SC/day

Dosage Forms

Genotropin lyophilized powder- Dual-chamber syringe: 5 mg, 12 mg
Genotropin Miniquick (without preservative)- 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- Cartridge: 6 mg, 12 mg, 24 mg
Humatrope- Vial: 5mg
Norditropin Flexpro- Pen: 5 mg/1.5 mL, 10 mg/1.5 mL, 15 mg/1.5 mL, 30 mg/3 mL
Nutropin AQ NuSpin- Cartridge: 5 mg/2 mL
Nutropin AQ NuSpin- Pen: 10 mg/2 mL, 20 mg/2 mL
Omnitrope- Cartridge:5 mg/1.5 mL, 10 mg/1.5 mL
Omnitrope- Dual-chamber syringe: 5.8 mg
Saizen- Cartridge: 8.8 mg
Saizen- Vial: 5 mg, 8.8 mg
Serostim- Vial: 4 mg, 5 mg, 6 mg
Zomacton- Vial: 5 mg, 10 mg
Zorbtive- Vial: 8.8 mg

Clinical Policy

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

I. Initial Approval Criteria

A. Growth Hormone Use in Children (must meet all):

1. Diagnosis of one of the following (a, b, c, d, e, f, or g):
   a. GHD;
      i. Isolated growth hormone deficiency (GHD) is defined by growth failure in combination with retarded bone age, low serum insulin-like growth factor-1, and insufficient GH peaks in two independent GH stimulation tests.
   b. Idiopathic Short Stature as defined by > 2.25 standard deviations below the normal adult height for gender (5' 3" for a male and 4' 11" for a female);

   c. SHOX deficiency with Shoxdna Dx® genetic test that detects mutations and deletions in the SHOX gene;
   d. Growth failure secondary to chronic kidney disease in pre-transplantation;
   e. Prader-Willi syndrome, Turner syndrome, Noonan syndrome;
   f. Neonatal hypoglycemia;
   g. Central nervous system tumor treated with radiation;
   h. Small for gestational age;
2. Prescribed by or in consultation with an endocrinologist;
3. Age ≤ 18 years;
4. For Prader-Willi syndrome, Turner syndrome, Noonan syndrome, and SHOX deficiency: confirmation of diagnosis by genetic testing;
5. Documentation of baseline height at the time of request;
6. Member's bone age is ≤ 15 years if girl or ≤ 17 years if boy;
7. Failure of Humatrope and Norditropin if requesting non-preferred products, unless contraindicated or clinically significant adverse effects are experienced;
8. Dose does not exceed the maximum indicated in Background (Dosage and Administration).

Approval Duration
Commercial: 6 months
Medicaid: 6 months

B. Adult GHD or Short Bowel Syndrome (must meet all):
1. Diagnosis of one of the following (a or b):
   a. Adult GHD;
      i. Isolated growth hormone deficiency (GHD) is defined by growth failure in combination with retarded bone age, low serum insulin-like growth factor-1, and insufficient GH peaks in two independent GH stimulation tests.
   b. SBS;
2. Age ≥ 18 years;
3. Prescribed by or in consultation with an endocrinologist or gastroenterologist;
4. For Adult GHD only: member has multiple pituitary hormone deficiencies resulting from structural hypothalamic/pituitary disease, radiation, defined CNS pathology, cranial radiation, trauma, pituitary surgery, or genetic defect affecting the GH axis with low IGF-1 and low IGFBP-3;
5. Failure of Humatrope and Norditropin if requesting non-preferred products, unless contraindicated or clinically significant adverse effects are experienced;
6. Dose does not exceed the maximum indicated in Background (Dosage and Administration).

Approval Duration
Commercial:
Adult GHD: 6 months
SBS: 4 weeks (not renewable)
Medicaid:
Adult GHD: 6 months
SBS: 4 weeks (not renewable)

C. Wasting or Cachexia in HIV Patients (must meet all):
1. Diagnosis of HIV infection;
2. Age ≥ 18 years;
3. Member is on concomitant anti-viral therapy for the treatment of HIV;

4. Involuntary weight loss of >10% of body weight;
5. One of the following (a or b) unless contraindicated or clinically significant adverse effects are experienced:
   a. If inadequate appetite, failure of megestrol acetate or dronabinol to stimulate appetite;
   b. If inadequate intake due to nausea, failure of ≥ 1 preferred agent(s) for nausea (*see Appendix B*);
6. Failure of a therapeutic trial of testosterone in combination with an anabolic steroid in males unless contraindicated or clinically significant adverse effects are experienced;
7. Failure of Humatrope and Norditropin if requesting non-preferred products, unless contraindicated or clinically significant adverse effects are experienced;
8. Dose does not exceed the maximum indicated in Background (Dosage and Administration).

Approval Duration
Commercial: 6 months
Medicaid: 6 months

II. Continued Therapy Approval

A. Growth Hormone Use in Children (must meet all):

1. Currently receiving medication via RxAdvance benefit or member has previously met initial approval criteria;
2. Member is responding positively to therapy as evidenced by one of the following (a or b):
   a. Increased growth rate by 2 cm over baseline in first year or 1 cm over baseline in 6 months for those patients undergoing a 6-month trial;
   b. For ISS treatment, the child's height continues to be > 2.25 standard deviations below the normal adult height for gender (5' 3" for a male and 4' 11" for a female);
3. Member's bone age is ≤ 15 years if girl or ≤ 17 years if boy;
4. If request is for a does increase, new dose does not exceed the maximum indicated in Background (Dosage and Administration).

Approval Duration
Commercial: 6 months
Medicaid: 6 months

B. Adult GHD, HIV-Related Cachexia, or Short Bowel Syndrome (must meet all):

1. Currently receiving medication via Rxadvance benefit or member has previously met initial approval criteria;
2. Member is responding positively to therapy;
3. If request is for a dose increase, new dose does not exceed the maximum indicated in Background (Dosage and Administration).

Approval Duration
Commercial:
Adult GHD, HIV-Related Cachexia: 6 months
SBS: 4 weeks (not renewable)
Medicaid:
Adult GHD, HIV-Related Cachexia: 6 months
SBS: 4 weeks (not renewable)

III. Appendices

APPENDIX A: Abbreviation/Acronym Key

CKD: chronic kidney disease
CNS: central nervous system
FDA: Food and Drug Administration
GHD: growth hormone deficiency
GH: growth hormone
HIV: human immunodeficiency virus
IGF-1: insulin-like growth factor-1
IGFBP-3: insulin-like growth factor binding protein-3
ISS: idiopathic short stature
rhGH: recombinant human growth hormone
SGA: small for gestational age
SBS: short bowel syndrome
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 once daily	7.5 mg/day
Androgel® (testosterone gel)	5 - 10 gm gel (delivers 50 – 100 mg testosterone) applied topically once daily	10 gm/day gel (100 mg/day testosterone)
Testim® (testosterone gel)	5 - 10 gm gel (delivers 50 – 100 mg testosterone) applied topically once daily	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*		
chlorpormazine	10 to 25 mg PO q4 to 6 hours prn	2,000 mg/day
Nausea/vomiting treatments*		
perphenazine	8 to 16 mg/day PO in divided doses	64 mg/day
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

- Contraindication(s):
  - Genotropin, Genotropin Miniquick, Humatrope, Humatrope Combo Pack, Norditropin FlexPro, Nutropin AQ NuSpin, Omnitrope, Saizen, Zomacton: acute critical illness; children with Prader-Willi syndrome who are severely obese or have severe respiratory impairment (reports of sudden death); active malignancy; hypersensitivity; active proliferative or severe non-proliferative diabetic retinopathy; children with closed epiphyses
  - Zorbtive: acute critical illness; active malignancy; hypersensitivity; active proliferative or severe non-proliferative diabetic retinopathy
  - Serostim: acute critical illness; active malignancy; diabetic retinopathy; hypersensitivity

- Boxed Warning(s):
  - None reported.

APPENDIX D: General Information

- Preferred products, where applicable: Humatrope and Norditropin
- Non-preferred products: Genotropin, Nutropin AQ, Omnitrope, Saizen, Serostim, Zomacton, Zorbtive
- 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.

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Review/Revision History	Review/Revision Date	P&T Approval Date
Policy was established.	05/2018	02/07/2020
• Policy was reviewed. "Gastroenterologist" was added to I.B.3 for SBS. • This statement was added: "Isolated growth hormone deficiency (GHD) is defined by growth failure in combination with retarded bone age, low serum insulin-like growth factor-1, and insufficient GH peaks in two independent GH stimulation tests."	12/17/2020	12/22/2020