



**Class Update:** Growth Hormones

**Month/Year of Review:** September 2014

**PDL Class:** Growth Hormones

**Literature Search End Date:** August 2014

**Date of Last Review:** September 2013

**Source Document:** OSU College of Pharmacy

**Current Status of PDL Class:**

- Preferred Agents: SOMATROPIN (OMNITROPE®) CARTRIDGE, SOMATROPIN (SAIZEN®) CARTRIDGE & VIAL, SOMATROPIN (NORDITROPIN®)
- Non-Preferred Agents: SOMATROPIN (GENOTROPIN® MINIQUICK) VIAL, SOMATROPIN (GENOTROPIN®) VIAL, SOMATROPIN (HUMATROPE®), SOMATROPIN (NUTROPIN® AQ NUSPIN), SOMATROPIN (OMNITROPE) VIAL, SOMATROPIN (TEV-TROPIN®)

**Previous Conclusions and Recommendations:**

- There is no comparative evidence that there is a difference in efficacy or safety between somatropin products.
- Evidence is insufficient to identify a clinically meaningful benefit in adults.
- Recommend inclusion of at least one product with pediatric indications.

**PA Criteria:** Prior authorization criteria are currently in place for growth hormone to cover only for covered diagnosis and for medically appropriate conditions (Appendix 1). Use for adults is not covered.

**Recommendations:**

- No further research or review needed at this time. There is no new evidence that there is any difference in efficacy/effectiveness or safety between the different somatropin products and formulations.
- Evaluate Comparative costs in executive session.

**Methods:**

A PubMed search was conducted using the following search terms: cachexia, deficiency, disorder, dwarfism, pituitary, growth disorders, human growth hormone, Noonan syndrome, Prader-Willi syndrome, short bowel syndrome, short stature disorder, SHOX, somatropin, stature, Turner syndrome. The search was limited to randomized controlled trials, systematic review and meta-analysis, English language, and conducted in humans since the date of the literature search conducted from the previous P & T review to first week of August 2014. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were searched for high quality systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

**New Systematic Reviews:**

Since last review there was one systematic review<sup>1</sup> and one meta-analysis<sup>2</sup> that investigated the role of growth hormones (GH) in adults. Neither suggests changes and need to the GH coverage policy. Abstracts are available in Appendix 2.

**Guidelines:**

None

**New drugs:**

None

**New FDA Indications:**

None

**New FDA safety alerts:**

None

There has been growing concern about an increased cardiac and cerebrovascular risk in children treated with growth hormone. A recently published cohort study evaluated for stroke in a population-based cohort of patients in France treated with GH for short stature in childhood.<sup>3</sup> There was a significantly higher risk of stroke among patients treated with GH in childhood, most prominently hemorrhagic stroke. Further RCTs are needed to assess this plausible relationship.

**New Trials:**

A total of 45 citations resulted from initial literature search. Articles were excluded due to the wrong study design (observational), comparator (placebo), or outcome (non-clinical). After inclusion for further review, 7 were evaluated further and 3 potentially relevant comparative randomized trials<sup>4,5</sup> were identified through abstract review for appropriate medication, indication, study design, and outcomes (**Appendix 2**). The abstracts for these trials are in Appendix 2.

## References:

1. Gazzaruso C, Gola M, Karamouzis I, Giubbini R, Giustina A. Cardiovascular risk in adult patients with growth hormone (GH) deficiency and following substitution with GH--an update. *J Clin Endocrinol Metab.* 2014;99(1):18-29. doi:10.1210/jc.2013-2394.
2. Barake M, Klibanski A, Tritos NA. Effects of recombinant human growth hormone therapy on bone mineral density in adults with growth hormone deficiency: a meta-analysis. *J Clin Endocrinol Metab.* 2014;99(3):852-860. doi:10.1210/jc.2013-3921.
3. Poidvin A, Touzé E, Ecosse E, et al. Growth hormone treatment for childhood short stature and risk of stroke in early adulthood. *Neurology.* 2014;10.1212/WNL.0000000000000737. doi:10.1212/WNL.0000000000000737.
4. Blum WF, Ross JL, Zimmermann AG, et al. GH treatment to final height produces similar height gains in patients with SHOX deficiency and Turner syndrome: results of a multicenter trial. *J Clin Endocrinol Metab.* 2013;98(8):E1383-1392. doi:10.1210/jc.2013-1222.
5. Reus L, Pelzer BJ, Otten BJ, et al. Growth hormone combined with child-specific motor training improves motor development in infants with Prader-Willi syndrome: a randomized controlled trial. *Res Dev Disabil.* 2013;34(10):3092-3103. doi:10.1016/j.ridd.2013.05.043.

**Appendix 1: Current PA Criteria**

**Hormones – Growth Hormone  
(Somatropin)**

**Goal(s):** Cover drugs only for covered diagnoses and those where there is medical evidence of effectiveness and safety.

**NOTE:** Growth Hormone treatment is no longer covered by OHP for adult diagnoses, including isolated deficiency of human growth hormone, AIDS wasting in adults or other conditions in adults.

**Length of Authorization: 1 year**

**Preferred Alternatives:** All medications require a PA for OHP Coverage. GH for adults is not covered by OHP. For preferred products for children see: [www.orpdl.org](http://www.orpdl.org)

**Note:** Criteria is divided by: **Pediatric (<18 years old)**

- New therapy
- Renewal therapy

**Requires PA:** All drugs in HIC3 = P1A

<b>Pediatric Approval Criteria (&lt;18 years old) - New Therapy</b>		
<b>1.</b> Is the patient an adult (> 18 years old)?	<b>Yes:</b> Pass to RPH; Deny, (Not Covered by the OHP).	<b>No:</b> Go to #2.
<b>2.</b> Is this a request for initiation of growth hormone?	<b>Yes:</b> Go to question #3	<b>No:</b> Go to renewal therapy
<b>3.</b> Is the prescriber a pediatric endocrinologist or pediatric nephrologist?	<b>Yes:</b> Go to #4	<b>No:</b> Pass to RPH; Deny, (Medical Appropriateness)
<b>4.</b> Is the diagnosis promotion of growth delay in a child with 3 <sup>rd</sup> degree burns (ICD-9 codes 941.3-949.3)?	<b>Yes:</b> Document and send to DHS Medical Director for review and pending approval	<b>No:</b> Go to #5.
<b>5.</b> Is the diagnosis one of the following? <ul style="list-style-type: none"><li>• Turner’s Syndrome (758.6)</li><li>• Noonan Syndrome (759.89)</li><li>• Pre-transplant chronic renal insufficiency (CRI) (593.9)</li><li>• Prader - Willi Syndrome(PWS) (759.81)</li></ul>	<b>Yes:</b> Document and go to #6	<b>No:</b> Pass to RPH; Deny, (Not Covered by the OHP).

<ul style="list-style-type: none"> <li>• Neonatal Hypoglycemia associated with Growth Hormone Deficiency (775.6)</li> <li>• X-linked Hypophosphotemia</li> <li>• Pituitary Dwarfism (253.3)</li> <li>• SHOX (Short stature homeobox gene)(783.43)</li> </ul>		
<b>6.</b> If male, is bone age <16 years? If female, is bone age <14 years?	<b>Yes:</b> Go to #7.	<b>No:</b> Pass to RPH; Deny, (Medical Appropriateness)
<b>7.</b> Is there evidence of non-closure of epiphyseal plate?	<b>Yes:</b> .Go to #8.	<b>No:</b> Pass to RPH; Deny, (Medical Appropriateness)
<b>8.</b> Is the product requested preferred?	<b>Yes:</b> Approve for 1 year.	<b>No:</b> Go to #9.
<b>9.</b> Will the prescriber consider a change to a preferred product?  <b>Message:</b> <ul style="list-style-type: none"> <li>• Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Health Resource Commission (HRC). Reports are available at:  <a href="http://www.oregon.gov/OHPPR/HRC/Evidence_Based_Reports.shtml">http://www.oregon.gov/OHPPR/HRC/Evidence_Based_Reports.shtml</a>. </li> </ul>	<b>Yes:</b> Inform provider of covered alternatives in class. <a href="http://www.oregon.gov/DHS/healthplan/tools_prov/dl.shtml">http://www.oregon.gov/DHS/healthplan/tools_prov/dl.shtml</a> . Approve for 1 year.	<b>No:</b> Approve for 1 year.

### Pediatric Approval Criteria (<18 years old) – Renewal Therapy

<b>1.</b> Document approximate date of initiation of therapy and diagnosis (if not already done).		
<b>2.</b> Is growth velocity greater than 2.5 cm per year?	<b>Yes:</b> Go to #3.	<b>No:</b> Pass to RPH; Deny, (Medical Appropriateness)
<b>3.</b> Is male bone age <16 years and Is female bone age <14 years?	<b>Yes:</b> Approve for 1 year.	<b>No:</b> Pass to RPH; Deny, (Medical Appropriateness)

DUR Board Action: 9/16/10(KS), 5-27-10(KS), 9-18-08ca, 2-23-06, 11-18-03, 9-9-03,  
Revision(s) 1/1/11, 7-1-10, 4-15-09, 10-1-03, 9/1/06  
Initiated: 10-1-03

## **Appendix 2: Abstract of Systematic Reviews and Randomized Clinical Trials**

1. **Gazzaruso C, Gola M, Karamouzis I, Giubbini R, Giustina A. Cardiovascular risk in adult patients with growth hormone (GH) deficiency and following substitution with GH--an update. *J Clin Endocrinol Metab.* 2014;99(1):18-29.**

### **Abstract**

**Context:** GH deficiency (GHD) of the adult is a clinical condition characterized by the presence of several traditional and emerging cardiovascular risk factors that can significantly increase cardiovascular morbidity and mortality. It is still an open issue whether GH replacement is able not only to improve cardiovascular risk factors but also to decrease cardiovascular morbidity and mortality.

**Evidence acquisition:** The major source of data acquisition included PubMed research strategies. Original articles, systematic reviews and meta-analyses, and included relevant citations were screened.

**Evidence synthesis:** In untreated GHD, cardiovascular risk is increased due to abnormal lipid profile (increased total and low-density lipoprotein cholesterol, increased triglycerides, and reduced high-density lipoprotein cholesterol) and impaired glucose metabolism. Emerging cardiovascular risk factors/markers such as proinflammatory cytokines, C-reactive protein, and adipokines are also increased in GHD patients. Increased cardiovascular morbidity and mortality have also been reported in GHD. GH treatment has been shown to improve both traditional and emerging cardiovascular risk factors and markers. However, evidence on the effects of GH replacement on cardiovascular events and mortality is limited.

**Conclusion:** The GHD population may be considered at high cardiovascular risk, and GH substitution may be expected to bring an added value to patients with hypopituitarism in terms of cardiovascular protection. However, there is too limited evidence (rarely coming from randomized and controlled studies) to recommend GH treatment based on the cardiovascular status of the patients.

2. **Barake M, Klibanski A, Tritos NA. Effects of recombinant human growth hormone therapy on bone mineral density in adults with growth hormone deficiency: a meta-analysis. *J Clin Endocrinol Metab.* 2014;99(3):852-860.**

### **Abstract**

**Objective:** GH deficiency is associated with decreased bone mineral density (BMD) and increased fracture risk. Because the effects of recombinant human GH (rhGH) therapy on BMD and bone mineral content have not been systematically investigated, we conducted a meta-analysis of pertinent studies.

**Design:** A thorough search of the literature (MEDLINE, EMBASE, and the Cochrane Register) was performed. Relevant studies were divided and analyzed according to their design (randomized/controlled or prospective/retrospective) and duration of rhGH therapy ( $\leq 12$  months and  $> 12$  months).

**Results:** Administration of rhGH led to a significant increase in lumbar spine (LS) and femoral neck (FN) BMD in randomized/controlled studies of more than 1 year [weighted mean difference (95% confidence interval)] of 0.038 g/cm<sup>2</sup> (0.011-0.065) and 0.021 g/cm<sup>2</sup> (0.006-0.037) at the LS and FN, respectively, and a nonsignificant drop at the same sites in studies of shorter duration. In prospective studies, a significant increase in the LS and FN BMD was obtained. On meta-regression, a negative association was observed between the change in LS and FN BMD and subjects' age and a positive association between the BMD change and treatment duration. In a subgroup analysis, the increase in LS and FN BMD was significant in men [0.048 g/cm<sup>2</sup> (0.033-0.064) and 0.051 g/cm<sup>2</sup> (0.003-0.098), respectively] but not in women.

**Conclusion:** This meta-analysis suggests a beneficial effect of rhGH replacement on BMD in adults with GH deficiency. This effect is affected by gender, age, and treatment duration. Larger studies are needed to evaluate the effect of rhGH on fracture risk.

3. **Reus L, Pelzer BJ, Otten BJ, et al. Growth hormone combined with child-specific motor training improves motor development in infants with Prader-Willi syndrome: a randomized controlled trial. *Res Dev Disabil.* 2013;34(10):3092-3103.**

## Abstract

Although severe motor problems in infants with Prader-Willi syndrome (PWS) are striking, motor development has never been studied longitudinally and the results of growth hormone (GH) treatment on motor development are contradictory. The authors studied whether GH treatment can enhance the effect of physical training on motor development in infants with PWS. Twenty-two infants were followed for two years during a randomized controlled trial. The treatment and control groups began GH after baseline or following a control period, respectively. Both groups followed a child-specific physical training program. Motor performance was measured every three months. Multi-level regression analysis revealed that motor development differed significantly between infants ( $p < .001$ ), and this could be partially explained by baseline motor developmental level ( $p < .01$ ). GH treatment enhanced the effects of child-specific physical training on both motor developmental rate and motor developmental potential. Moreover, this effect was more pronounced when GH treatment was initiated at a younger age.

4. Blum WF, Ross JL, Zimmermann AG, et al. GH treatment to final height produces similar height gains in patients with SHOX deficiency and Turner syndrome: results of a multicenter trial. *J Clin Endocrinol Metab.* 2013;98(8):E1383-1392.

## Abstract

**Context:** Growth impairment in short stature homeobox-containing gene (SHOX) deficiency and Turner syndrome share a similar etiology. Because of the established effect of GH treatment on height in patients with Turner syndrome, we hypothesized that GH therapy would also stimulate growth in patients with SHOX deficiency.

**Objective:** Our objectives were to evaluate long-term efficacy of GH treatment in short patients with SHOX deficiency and to compare the effect on final (adult) height (FH) in patients with SHOX deficiency and Turner syndrome.

**Design and setting:** A prospective, multinational, open-label, randomized 3-arm study consisting of a 2-year control period and a subsequent extension period to FH. The treatment groups were 1) SHOX-D-C/GH (untreated during the control period, GH-treated during the extension), 2) SHOX-D-GH/GH, and 3) Turner-GH/GH (GH-treated during both study periods).

**Patients:** Short-statured prepubertal patients with genetically confirmed SHOX deficiency ( $n = 49$ ) or Turner syndrome ( $n = 24$ ) who participated in the extension.

**Intervention:** Depending on the study arm, patients received a daily sc injection of 0.05 mg/kg recombinant human GH from start of the study or start of the extension until attainment of FH or study closure.

**Results:** Height SD score gain from start of GH treatment to FH was similar between the combined SHOX-deficient groups ( $n = 28$ ,  $1.34 \pm 0.18$  [least-squares mean  $\pm$  SE]) and the Turner group ( $n = 19$ ,  $1.32 \pm 0.22$ ). In this FH population, 57% of the patients with SHOX deficiency and 32% of the patients with Turner syndrome achieved a FH greater than  $-2$  SD score.

**Conclusions:** GH treatment in short children with SHOX deficiency showed similar long-term efficacy as seen in girls with Turner syndrome.