

Month/Year of Review: September 2013

PDL Classes: Growth Hormones

Date of Last Review: September 2012

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Current Status of PDL Class:

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

Previous Conclusions and Recommendation:

- Evidence does not support a difference in efficacy/effectiveness
- Evidence does not support a difference in harms/adverse events
- 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.

Conclusions and Recommendations:

- There is no comparative evidence that there is a difference in efficacy or safety between somatropin products.
- No further review or research needed at this time
- Based on comparative costs, make Norditropin preferred.

Methods:

A Medline OVID search was conducted with 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 English language articles of controlled trials conducted on humans published from September 2012 to August week one 2013. The Cochrane Collection, Dynamed and Medline OVID were searched for high quality systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts. Finally, a search for new or updated guidelines was conducted at the AHRQ National Guideline Clearinghouse (NGC).

New Systematic Reviews:

Wu et al evaluated the efficacy and safety in treating pediatric renal transplant patients with growth hormone (somatropin) to counter potential growth retardation.¹ Five randomized control trials were included in their meta-analysis with a total of 401 children aged 18 years or younger. The primary outcome measured was increase in the baseline height standard deviations score (HSDS); secondary safety outcomes examined allograft rejection rates and change in glomerular filtration rate (GFR). After one year, patients given growth hormone were significantly more likely to have an increase in baseline height standard deviation score (HSDS) than the control group, with a mean HSDS difference of 0.68 (95% CI 0.25 to 1.11) between the two groups. Growth hormone patients were more likely to experience an allograft rejection than placebo patients, although this difference was not significant (risk ratio 1.56; 95% CI 0.97 to 2.53). Placebo patients however were more likely to have a negative change in GFR: 3.27ml/min per 1.73m² (95% CI -3.54 to 10.09) which was also not statistically significant. No quality assessment was reported for the trials included in this analysis.¹

Sanchez et al performed a meta-analysis examining the effects of growth hormone therapy on adults with Prader-Willi syndrome (PWS).¹ Eight randomized control trials were included with 134 PWS adult subjects. Outcomes studied were the mean difference in body composition metrics (percent body fat, body mass index, and lean body mass) and metabolic changes (fasting glucose and insulin, insulin resistance, and lipids) after twelve months of growth hormone treatment and compared with placebo. Subjects on growth hormone therapy showed decreased body fat compared with placebo subjects: mean difference -2.9% (95% CI -3.9 to -1.91). They also had statistically significant increased lean body mass: mean difference from placebo 2.82 kg (95% CI 1.31 to 4.33). No difference was found between groups in body mass index (-0.48kg/m³; 95% CI -1.32 to 0.35). Growth hormone patients also had increased fasting glucose (0.27mmol/L; 95% CI 0.05 to 0.49mmol/L), and a nonsignificant increase in fasting insulin (20.24 pmol/L; 95% CI -0.55 to 41.02) and insulin resistance (0.60; 95% CI -0.04 to 1.24). No difference was found in mean difference in fasting lipids: total cholesterol -0.12mmol/L (-0.29 to 0.05) and LDL -0.11 mmol/L (-0.3 to 0.07). Individual trial quality assessment was not performed.²

The Cochrane Collaboration also looked at the effects of growth hormone treatment in children and young adults with cystic fibrosis. Thaker et al performed a systematic review to look for potential differences in height, weight, pulmonary function, blood glucose, and exacerbations.³ Four controlled trials were included with 161 subjects aged 25 years and younger, but only one study (n=67) was used for outcome analysis. After 24 weeks, subjects treated with growth hormone had a nonsignificant change in pulmonary function compared with placebo patients: percent change in baseline mean difference for FVC 3.8% (95% CI -4.72 to 12.32) and FEV1 2.5% (95% CI -8.6 to 13.60). Changes in weight (mean difference 1.00 kg; 95% CI -0.08 to 2.08) and height (2.5 cm; 95% CI -0.77 to 5.77) were also not significant. Growth hormone subjects did see a significant increase in fasting blood glucose levels (12.4 mg/dL; 95% CI 3.76 to 21.04). No difference was seen in exacerbation rate. Trial quality was evaluated as fair to poor. The authors felt the risk of bias in the four studies was high with most studies' allocation concealment, blinding and randomization not present or poorly explained.³

Finally, Breederveld et al examined the effect of growth hormone treatment on burn healing in adults and children. Thirteen randomized controlled trials (n=701) were included in the systematic review; the average total burn surface area was greater than 49%.⁴ Endpoints included time to heal and hyperglycemia. In two trials with adult subjects, growth hormone subjects healed significantly more quickly (9.07 days; 95% CI 4.39 to 13.76) than placebo subjects. Adult donor sites also had a significantly shorter healing time (3.15 days; 95% CI 1.54 to 4.75). Hyperglycemia was more likely to occur in growth hormone treated adults than placebo subjects (risk ratio 2.43; 95% CI 1.54 to 3.85). In two trials with children subjects, donor site healing time was also increased in growth hormone subjects than placebo patients (1.7days; 95% CI 1.54 to 3.85). No difference was seen in children for hyperglycemia. Trial quality was assessed as fair to poor. Allocation concealment was not performed in any study and randomization methods were not described for most.⁴

Guidelines:

The Growth Hormone Research Society Workshop created consensus guidelines for Recombinant Human Growth Hormone (rhGH) Therapy in Prader-Willi Syndrome.⁵ Forty-three experts participated in a workshop to review the available data from a literature search and review. The level of evidence was evaluated using the scoring procedure based on the Oxford Centre for Evidence-Based Medicine Level of Evidence scale. Most of the trials were performed in small populations, and durations were short compared to the length of rhGH treatment in the real-life setting. Most of the trials were graded of low quality. No specific preference to individual products was given. The workshop participants established the following recommendations:

- After genetic confirmation of the diagnosis of Prader-Willi, rhGH treatment should be considered and, if initiated, should be continued for as long as demonstrated benefits outweigh the risks (Recommendation level A; level of evidence 1).

- Before initiation of therapy, patients should have a genetically confirmed diagnosis and expert multidisciplinary evaluation (Recommendation level A; level of evidence 5).
- Exclusion criteria for starting patients on treatment include severe obesity, uncontrolled diabetes, untreated severe obstructive sleep apnea, active cancer, and active psychosis (Recommendation level A; level of evidence 4).
- Treatment with rhGH must be in the context of appropriate dietary, environmental, and lifestyle interventions necessary for care of all patients.

New drugs:

None

New Formulations/Indications:

None

New FDA safety alerts:

None

New Trials (Appendix 2):

A total of 214 citations resulted from the initial Medline search. Articles were excluded due to the wrong study design (observational), comparator (placebo), or outcome (non-clinical). After a review of titles and abstracts for inclusion, one relevant head-to-head clinical trials were identified and are discussed below. Please see Appendix 1 for the full abstracts.

Decker et al conducted a follow up study on children receiving growth hormone treatment to determine if dose changes would affect metabolic outcomes.⁶ Children with growth hormone deficiency or idiopathic short stature disorder were originally randomized to either individual growth hormone doses (17-1000 mg/kg/day) or a standard dose (43mg/kg/day) for a two year study. For this follow up, children in the individual treatment group were randomized to either an unchanged dose (n=28) or a 50% decrease in dose (n=37). Patients originally on a fixed dose regimen remained on that dose (n=33). The primary endpoint of the study was comparison in metabolic changes (fasting insulin, insulin sensitivity) and body composition changes (lean soft tissue, bone mineral content). After two years, subjects in the reduced dose group compared with the unchanged group had a significantly reduced level of fasting insulin (50%; $p < 0.05$) and insulin sensitivity (55.1%; $p < 0.05$), although no difference was seen when compared with the fixed dose group. No difference was seen in bone mineral composition and lean soft tissue between the three groups after two years. This was a poor quality study; randomization was not performed, and the study was essentially unblinded after its original trial.⁶

References:

1. Wu Y, Cheng W, Yang X, Xiang B. Growth hormone improves growth in pediatric renal transplant recipients—a systemic review and meta-analysis of randomized controlled trials. *Pediatric Nephrology*. 2012;28(1):129–133. doi:10.1007/s00467-012-2208-7.
2. Sanchez-Ortiga R, Klibanski A, Tritos NA. Effects of recombinant human growth hormone therapy in adults with Prader-Willi syndrome: a meta-analysis: Growth hormone therapy in Prader-Willi syndrome. *Clinical Endocrinology*. 2012;77(1):86–93. doi:10.1111/j.1365-2265.2011.04303.x.
3. Thaker V, Haagenen AL, Carter B, Fedorowicz Z, Houston BW. Recombinant growth hormone therapy for cystic fibrosis in children and young adults. In: The Cochrane Collaboration, Thaker V, eds. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 2013. Available at: <http://doi.wiley.com/10.1002/14651858.CD008901.pub2>. Accessed August 20, 2013.
4. Breederveld RS, Tuinebreijer WE. Recombinant human growth hormone for treating burns and donor sites. In: The Cochrane Collaboration, Tuinebreijer WE, eds. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 2012. Available at: <http://doi.wiley.com/10.1002/14651858.CD008990.pub2>. Accessed August 20, 2013.
5. Deal CL, Tony M, Hoybye C, et al. Growth Hormone Research Society workshop summary: consensus guidelines for recombinant human growth hormone therapy in Prader-Willi syndrome. *J Clin Endocrinol Metab*. 2013 Jun;98(6):E1072-87. Epub 2013 Mar 29.
6. Decker R, Albertsson-Wikland K, Krström B, Halldin M, Dahlgren J. Decreased GH dose after the catch-up growth period maintains metabolic outcome in short prepubertal children with and without classic GH deficiency. *Clinical Endocrinology*. 2012;77(3):407–415. doi:10.1111/j.1365-2265.2012.04386.x.

**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:
http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml

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

- New therapy
- Renewal therapy

Requires PA: All drugs in HIC3 = P1A

Pediatric Approval Criteria (<18 years old) - New Therapy		
1. Is the patient an adult (> 18 years old)?	Yes: Pass to RPH; Deny, (Not Covered by the OHP).	No: Go to #2.
2. Is this a request for initiation of growth hormone?	Yes: Go to question #3	No: Go to renewal therapy
3. Is the prescriber a pediatric endocrinologist or pediatric nephrologist?	Yes: Go to #4	No: Pass to RPH; Deny, (Medical Appropriateness)
4. Is the diagnosis promotion of growth delay in a child with 3 rd degree burns (ICD-9 codes 941.3-949.3)?	Yes: Document and send to DHS Medical Director for review and pending approval	No: Go to #5.
5. Is the diagnosis one of the following? • Turner's Syndrome (758.6)	Yes: Document and go to #6	No: Pass to RPH; Deny, (Not

<ul style="list-style-type: none"> • Noonan Syndrome (759.89) • Pre-transplant chronic renal insufficiency (CRI) (593.9) • Prader - Willi Syndrome(PWS) (759.81) • Neonatal Hypoglycemia associated with Growth Hormone Deficiency (775.6) • X-linked Hypophosphotemia • Pituitary Dwarfism (253.3) • SHOX (Short stature homeobox gene)(783.43) 		Covered by the OHP).
<p>6. If male, is bone age <16 years? If female, is bone age <14 years?</p>	Yes: Go to #7.	No: Pass to RPH; Deny, (Medical Appropriateness)
<p>7. Is there evidence of non-closure of epiphyseal plate?</p>	Yes: Go to #8.	No: Pass to RPH; Deny, (Medical Appropriateness)
<p>8. Is the product requested preferred?</p>	Yes: Approve for 1 year.	No: Go to #9.
<p>9. Will the prescriber consider a change to a preferred product?</p> <p>Message:</p> <ul style="list-style-type: none"> • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Health Resource Commission (HRC). Reports are available at: http://www.oregon.gov/OHPPR/HRC/Evidence_Based_Reports.shtml. 	<p>Yes: Inform provider of covered alternatives in class. http://www.oregon.gov/DHS/healthplan/tools_prov/dl.shtml. Approve for 1 year.</p>	No: Approve for 1 year.

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

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

3. Is male bone age <16 years and Is female bone age <14 years?	Yes: Approve for 1 year.	No: Pass to RPH; Deny, (Medical Appropriateness)
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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: Abstracts of Randomized Control Trials

Decker R, Albertsson-Wikland K, Kriström B, Halldin M, Dahlgren J. Decreased GH dose after the catch-up growth period maintains metabolic outcome in short prepubertal children with and without classic GH deficiency. *Clinical Endocrinology*. 2012;77(3):407–415. doi:10.1111/j.1365-2265.2012.04386.x.

Objective Few studies have evaluated metabolic outcomes following growth hormone (GH) treatment in short prepubertal children during different periods of growth. Previously, we found that individualized GH dosing in the catch-up period reduced the variation in fasting insulin levels by 34% compared with those receiving a standard GH dose. We hypothesized that the GH dose required to maintain beneficial metabolic effects is lower during the prepubertal growth phase after an earlier catch-up growth period.

Design Short prepubertal children with isolated GH deficiency or idiopathic short stature were randomized to individualized GH treatment (range, 17–100 lg/kg/day) or a standard dose in a preceding 2-year study. After achieving near mid-parental height SDS, children receiving an individualized dose were randomized to either a 50% reduced individualized dose (RID, n = 28) or an unchanged individualized dose (UID, n = 37) for 2 years. The dose remained unchanged in 33 children initially randomized to receive a standard dose (FIX, 43 lg/kg/day). We evaluated whether the variations in metabolic parameters measured during maintenance growth diminished in RID compared with UID or FIX.

Results We observed less variation in fasting insulin levels ($\sim 50\%$), insulin sensitivity as assessed by homoeostasis model assessment ($\sim 55\text{--}1\%$), lean soft tissue ($\sim 27\text{--}8\%$) and bone mineral content ($\sim 31\text{--}3\%$) in RID compared with UID (all $P < 0.05$), but no differences compared with FIX.

Conclusions Continued reduced individualized GH treatment after the catch-up growth period is safe and reduces hyperinsulinism. Individualized GH dose can be reduced once the desired height SDS is achieved to avoid overtreatment in terms of metabolic outcome.