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Month/Year of Review: September 2012
Date of Last Review: April 2010
PDL Classes: Growth Hormone (GH)
Source Document: Provider Synergies

Current Status of PDL Class:

- Preferred Agents: SOMATROPIN (GENOTROPIN®, NUTROPIN®, SAIZEN®)
- Non-preferred Agents: SOMATROPIN (HUMATROPE®, NORDITROPIN®, NUTROPIN AQ®, OMNITROPE®, TEV-TROPIN®, ZORBTIVE®, SEROSTIM®)

Previous Recommendations:

1. There is no evidence to support a difference in efficacy or effectiveness.
2. Evidence does not support a difference in adverse events or harm.
3. There is insufficient evidence to show a clinically significant benefit in HIV patients with respect to wasting.
4. Evidence is insufficient to identify a clinically meaningful benefit in adults.
5. It is recommended that at least one product be included with pediatric indications. There is insufficient evidence to determine a recommendation for coverage for adult patients.

PA Criteria/QL:

All medications require a prior authorization (PA) for OHP coverage (Appendix 1). GH for adults is not covered by OHP. Approval for new therapy in patients <18 years old requires the prescriber be a pediatric endocrinologist or pediatric nephrologist, have one approvable diagnosis including: Turner's syndrome (TS), Noonan syndrome, pre-transplant chronic renal insufficiency, Prader-Willi syndrome (PWS), neonatal hypoglycemia associated with growth hormone deficiency, x-linked hypophosphotemia, pituitary dwarfism, and short stature homeobox (SHOX), and bone age is <16 years in males and <14 years in females. Criteria for renewal requires a growth velocity greater than 2.5 cm per year and it is continued only until adult height as determine by bone age is achieved.

Methods:

A MEDLINE OVID search was conducted using all included drugs in children with either growth hormone deficiency (GHD), turner syndrome, chronic renal insufficiency (CRI), PWS, SHOX, Noonan syndrome, neonatal hypoglycemia, pituitary dwarfism, or x-linked hypophosphotemia and limits for humans, English language, and controlled clinical trials or randomized controlled trials from 2010 to current. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, Clinical Evidence, Up To Date, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. A search for any new evidence demonstrating a benefit in adult indications was also done. 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. The primary focus of the evidence is on high quality systematic reviews and evidence based guidelines for this class update. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Indications of Included Agents:

	Genotropin®	Humatrope®	Norditropin®	Nutropin®	Omnitrope®	Saizen®	Serostim®	Tev-Tropin®
Pediatric Indications								
Growth failure associated with chronic renal insufficiency before renal transplant				X				
Growth failure associated with Noonan syndrome			X					
Growth failure associated with Prader-Willi syndrome	X				X			
Growth failure associated with short-stature homeobox-containing gene deficiency		X						
Growth failure associated with Turner syndrome	X	X	X	X	X			
Growth failure in children born small for gestational age	X	X	X		X			
Growth hormone deficiency	X	X	X	X	X	X		X
Idiopathic short stature	X	X		X	X			
Adult Indications								
Growth hormone deficiency	X	X	X	X	X	X		
Human immunodeficiency virus-associated wasting or cachexia							X	

New Systematic Reviews:

Cochrane Collaboration

1) A recent review was conducted to determine whether the use of recombinant growth hormone (rhGH) therapy in children with x-linked hypophosphatemia (XLH) is associated with outcomes associated with changes in longitudinal growth.[1] A literature search through May 2011 resulted in only one small study that met inclusion criteria. This was a randomized, double-blind cross-over study over 24-months in five children with XLH.[1] RhGH only or combined with conventional treatment (calcitriol and oral phosphate) was compared with either placebo or conventional treatment alone. The primary outcome was longitudinal growth measured by growth velocity z score and height z score. Growth hormone therapy improved the height standard deviation score from a mean baseline of -2.66 to -2.02 and to -1.46 after 3 and 12 months. After 12 months of placebo administration, the height z score changed from -2.27 to -2.22. The growth velocity standard deviation score was -1.90 during the 12 months of placebo administration and 4.04 during the 12 months of growth hormone therapy. No significant side effects were observed during the study. Due to the limited data and that the study only included five children; the results reported should be interpreted with caution. Although allocation concealment and the method of blinding were adequate, generation of

randomization sequence was not described.[1] Authors concluded that the data are too few and of insufficient quality to provide recommendations for practice

2) Another systematic review from the Cochrane Collaboration was performed to look at the long term benefits and harms of rhGH use in children ≤18 years old with chronic kidney disease (CKD).[2] A literature search through December 2011 identified sixteen studies (809 children) with mostly poor study quality or poorly reported. The primary outcome was the end of treatment height standard deviation score (HSDS) and the end of treatment height velocity. The effect of growth hormone compared to placebo on HSDS was reported in eight studies (331 participants). There was moderate quality evidence that over a one year period, children treated with growth hormone showed an increase in HSDS of 0.82 compared to placebo (95%CI 0.56 to 1.07). This translates to approximately 5 cm of growth in one year. There were nine studies that compared growth hormone with placebo and presented data on height velocity. Two studies showed an increase in height velocity of 2.85 cm (95%CI 2.22 to 3.48) over six months (low quality evidence) and seven studies showed an increase in height velocity of 3.88cm/year (95%CI3.32 to 4.44) over 1 year (moderate quality evidence) with growth hormone therapy. Seven studies presented data on bone age in growth hormone versus placebo and found no significant difference between the two groups. [2] Data also suggested that children should be treated with 28 IU/m2/week of rhGH due to significant increases in height compared to 14 IU/m2/week but no differences compared to 56 IU/m2/week. Included data was based on relatively short duration, with maximum being two years. The most important height outcome is adult height. No RCT's have been published reporting final adult height as an outcome.

3) An additional systematic review was done to evaluate the efficacy of growth hormone with or without glutamine supplementation for adult patients with short bowel syndrome.[3] A literature search identified five trials that met inclusion criteria to evaluate the primary outcome of change in body weight. Data pooled from three of the studies demonstrated a statistically significant increase in body weight with rhGH compared to placebo (MD 1.66 kg, 95% CI 0.69 to 2.63, p=0.0008). [3] An increase in lean body mass and absorptive capacities was also seen, although these effects only lasted with treatment and the benefit disappeared after therapy was stopped. Authors concluded that the evidence demonstrated a possible short term benefit in weight gain and fat absorption, but the small number of patients, unsustainable benefits seen, and unknown long term safety demand these results be interpreted with caution. [3] Therefore, the available literature does not support the routine use of rhGH in short bowel syndrome in adults.

<u>Agency for Healthcare Research and Quality (AHRQ)</u>

1) A comparative effectiveness review was prepared to analyze the benefits and harms associated with rhGH in patients with cystic fibrosis (CF) to include a literature search through April 2010 which resulted in ten unique randomized controlled trials (nine fair quality and one good quality).[4] Although not indicated for use in CF, because of decreased growth measures associated with poorer outcomes in CF, rhGH has been investigated for this use. There was insufficient evidence to determine the effects of rhGH on most final health outcomes, including frequency of required intravenous antibiotic treatments, quality of life, bone fracture, or mortality. [4] There was moderate evidence to suggest that rhGH reduces the rate of hospitalizations (1.6 fewer hospitalizations per year; 95% CI 1.26 to 1.98)). Treatment with rhGH did improve certain intermediate outcomes including pulmonary function measures (significantly greater improvement in FVC, WMD 0.67L; 95% CI 0.24 to 1.09L; three trials, I^2=55%, moderate strength of evidence), change in height (WMD 3.13 cm; 95% CI 0.88 to 5.38 cm; three trials, I^2=77.3%, low strength of evidence), and change in weight (WMD 1.48kg, 95% CI 0.62 to 2.33 kg; five trials, I^2=49%, moderate strength of evidence). There were no significant effects on predicted FEV1 (moderate strength of evidence) and FEV1 Z score (insufficient evidence) from pooled results of trials from 6-12 months duration. [4] Authors noted that since predicted values of FEV1 are dependent upon a patient's height, simultaneous clinical improvements in both absolute FEV1 and height may attenuate or invalidate improved in predicted FEV1.
This review also looked at the strength of the evidence that links the intermediate outcomes affected by rhGH to final health outcomes including quality of life, bone consequences, and mortality. [4] The relationship between

absolute change in FVC and percent predicted FVC to mortality was weak. The evidence to support a relationship between percent predicted FEV1 and mortality was stronger with many trials finding an association with higher percent predicted FEV1 and improved survival. However, data pooled in the review did not demonstrate that rhGH significantly increased percent predicted FEV1. There was also no strong link seen between measures of height or weight and mortality. [4]

Guidelines:

National Institute for Health and Clinical Excellence

Nice guidelines on the use of somatropin for the treatment of growth failure in children was updated in May 2010.[5] Somatropin is recommended as treatment option for children with growth failure associated with GHD, Turner syndrome, Prader-Willi syndrome, chronic renal insufficiency, and those born small for gestational age with subsequent growth failure at four years of age or later, and short stature homeobox-containing gene deficiency. [5] The NICE guidelines continue to recommend that somatropin be initiated and monitored by a pediatrician and that the choice of brand name product should be made on an individual basis after consideration of likelihood of adherence to treatment and cost. The treatment of somatropin should be discontinued if growth velocity increases less than 50% from baseline in the first year of treatment, final height is approached and growth velocity is less than 2 cm total growth in 1 year, adherence issues, or if final height is attained. [5] Clinical guidelines do not prefer one growth hormone product over another.

Endocrine Society

Guidelines for the evaluation and treatment of adult growth hormone deficiency were updated in 2011, guided by systematic reviews of evidence and consensus discussions.[6] The Grading for Recommendations, Assessment, Development, and Evaluation (GRADE) system was used to describe the strength of the recommendations and quality of evidence. The following recommendations were included in the updated guidelines[6] :

- A strong recommendation based on moderate quality evidence that therapy GH therapy offers significant clinical benefits in body composition and exercise capacity.
- A weak recommendation based on low quality evidence that GH therapy offers significant clinical benefits in skeletal integrity.
- A weak recommendation based on low quality evidence that GH therapy improves several cardiovascular surrogate outcomes, but increases insulin resistance.
- A weak recommendation based on very low quality evidence that GH therapy has not been shown to improve mortality and low quality evidence that GH therapy does improve the quality of life of most patients.
- A strong recommendation based on low quality evidence that after documentation of persistent GHD that GH therapy be continued after reaching adult height to obtain full skeletal and muscle maturation during the transition period (new recommendation in update) [6]

New Trials:

A total of 12 citations resulted from the initial MEDLINE search and after review for inclusion, 3 potentially relevant clinical trials were identified. The other clinical trials were excluded due to lack of relevant outcomes. These trials are briefly described in Table 1.

Table 1: Study details

Study	Comparison	Population	Primary Outcome	Results
Davenport, et al.[7] Prospective, randomized, controlled, open-label clinical trial	GH (50ug/kg/day) vs. placebo	Girls aged 9 months to 4 years with TS	Occurrence rates of otitis media (OM), middle ear (ME) dysfunction	Annual occurrence of OM episodes GH: 1.5±1.6 Placebo: 1.9±1.4 p=0.17 Occurrence of ME dysfunction GH: 39±8%

			and hearing loss.	Placebo: 34±5% NS Prevalence of hearing loss from baseline to endpoint GH: 35% to 17% Placebo: 15% o 21% NS
Pfutzner, et al.[8] Noninterventional, randomized, open-label, crossover study	FlexPro containing 10 mg GH in 1.5 mL vs. Genotropin pen containing 12mg in 1.0 mL vs. easypod device containing 8.8 mg in 1.5 mL (in the intuitiveness group vs. instruction group)	Patients age >10 to <18 years who were diagnosed with growth hormone deficiency (GHD) or Turner syndrome or who were born small for gestational age	Mean injection time in patients provided with no instruction in the use of the device (intuitiveness group) and in patients instructed (instruction group)	Mean time to administer GH injection Intuitiveness group / Instruction group *FlexPro* 47 seconds / 30.7 seconds *Genotropin* 95.1 seconds / 40.7 seconds *Easypod* 219.2 seconds / 59.6 seconds *P-value* <0.01 / <0.001
Tanaka, et al.[9] 156-week extension study of an initial 104-week multicenter, randomized, double-blind, parallel-group trial	GH 33ug/kg/day vs. 67ug/kg/day vs. untreated (for 52 weeks) then treated with either 33ug or 67ug/kg/day GH	Japanese children born small for gestation age (age 3 to <8 years)	To evaluate long-term efficacy of two doses of GH by change in height velocity standard deviation scores (SDS) from baseline	Change in Height Velocity SDS from baseline at 4 years Untreated (then GH 33ug): 0.54 Untreated (then GH 57ug): 2.19 p<0.042 Change in Height Velocity SDS from baseline 4 years / 5 years 33ug/kg/day 0.40 / 0.46 67ug/kg/day 1.47 / 0.80 p<0.0001

New drugs:
None

New Formulations/Indications:
Flexpro® (somatropin recombinant 5mg/1.5mL; 10mg/1.5mL; 15mg/1.5mL) was approved by the US Food and Drug Administration (FDA) in March 2010 and is the most recent pen device developed to deliver Norditropin®. Norditropin Flexpro® is a multidose, disposable pen device designed to replace Norditropin Nordiflex pens, which are no longer manufactured. [10] One study by Pfutzner et al compared injection time, ease of use, usability, overall preference, and dose accuracy of the Norditropin® Flexpro® with two other injection devices in 56 pediatric patients. No efficacy or safety outcomes were evaluated.[8] Results showed that Flexpro® was associated with shorter injection times and greater intuitiveness than the other devices.

New Indications:
Omnitrope® – Treatment of children with growth failure due to Turner Syndrome (7/2011) and treatment of children with growth failure due to Idiopathic Short Stature (8/2010) were added to indications.

New FDA safety alerts:
In December 2010, the FDA issued a MedWatch to inform the public that results from a study conducted in France; the Sante Adulte GH Engant (SAGhE) study, found that persons with certain kinds of short stature (idiopathic growth

hormone deficiency and idiopathic or gestational short stature) treated with rhGH during childhood and who were followed over a long period of time, were at a small increased risk of death when compared to individuals in the general population of France.[11] In August 2011, the FDA determined that the evidence found in the SAGhE study is inconclusive due to a number of study design weaknesses that limit the interpretability of the study results. The FDA states that healthcare professionals and patients should continue to prescribe and use recombinant human growth according to the labeled recommendations.[11]

Recommendations:

1. No further research or review needed at this time.
2. Further evaluate comparative costs due to no difference in efficacy or safety between agents and include at least one agent with pediatric indications as preferred.

References:

1. Yang HM, Mao M, Yang F, Wan C. Recombinant growth hormone therapy for X-linked hypophosphatemia in children. In: *Cochrane Database of Systematic Reviews*. John Wiley & Sons, Ltd; 2011. Available at: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD004447.pub2/abstract. Accessed August 1, 2012.

2. Hodson EM, Willis NS, Craig JC. Growth hormone for children with chronic kidney disease. In: *Cochrane Database of Systematic Reviews*. John Wiley & Sons, Ltd; 2012. Available at: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003264.pub3/abstract. Accessed August 1, 2012.

3. Wales PW, Nasr A, de Silva N, Yamada J. Human growth hormone and glutamine for patients with short bowel syndrome. *Cochrane Database Syst Rev*. 2010;(6):CD006321.

4. Phung OJOJ, Coleman CICI, Baker ELEL, et al. Effectiveness of Recombinant Human Growth Hormone (rhGH) in the Treatment of Patients With Cystic Fibrosis. 2010. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21938797. Accessed August 6, 2012.

5. NICE. Human growth hormone (somatropin) for the treatment of growth failure in children: guidance. 2010. Available at: http://publications.nice.org.uk/human-growth-hormone-somatropin-for-the-treatment-of-growth-failure-in-children-ta188. Accessed July 31, 2012.

6. Molitch ME, Clemmons DR, Malozowski S, Merriam GR, Vance ML. Evaluation and treatment of adult growth hormone deficiency: an Endocrine Society clinical practice guideline. *J. Clin. Endocrinol. Metab.* 2011;96(6):1587–1609.

7. Davenport ML, Roush J, Liu C, et al. Growth Hormone Treatment Does Not Affect Incidences of Middle Ear Disease or Hearing Loss in Infants and Toddlers with Turner Syndrome. *Hormone Research in Paediatrics*. 2010;74(1):23–32.

8. Pfutzner A, Hartmann K, Winter F, et al. Intuitiveness, ease of use, and preference of a prefilled growth hormone injection pen: a noninterventional, randomized, open-label, crossover, comparative usability study of three delivery devices in growth hormone-treated pediatric patients. *Clinical Therapeutics*. 2010;32(11):1918–34.

9. Tanaka T, Yokoya S, Seino Y, et al. Long-Term Efficacy and Safety of Two Doses of Growth Hormone in Short Japanese Children Born Small for Gestational Age. *Hormone Research in Paediatrics*. 2011;76(6):411–418.

10. Yuen KCJ, Amin R. Developments in administration of growth hormone treatment: focus on Norditropin® Flexpro®. *Patient Prefer Adherence*. 2011;5:117–124.

11. Commissioner O of the. Safety Alerts for Human Medical Products - Recombinant Human Growth Hormone (somatropin): Ongoing Safety Review - Possible Increased Risk of Death. Available at: http://www.fda.gov/safety/medwatch/safetyinformation/safetyalertsforhumanmedicalproducts/ucm237969.htm. Accessed July 31, 2012.

Appendix 1: Prior Authorization 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: http://cms.oregon.gov/oha/healthplan/pages/tools_prov/pdl.aspx

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 3rd 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) • 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)	**Yes:** Document and go to #6	**No:** Pass to RPH; Deny (Not covered by the OHP)

• SHOX (Short stature homeobox gene)(783.43)		
6. If male, is bone age < 16 years? If female, is bone age < 14 years?	**Yes:** Go to #7	**No:** Pass to RPH; Deny (medical appropriateness)
7. Is there evidence of non-closure of epiphyseal plate?	**Yes:** Go to #8	**No:** Pass to RPH; Deny (medical appropriateness)
8. Is the product requested preferred?	**Yes:** Approve for 1 year	**No:** Go to #9
9. Will the prescriber consider a change to a preferred product? **Message:** • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Pharmacy and Therapeutics (P&T) Committee. Reports are available at: http://pharmacy.oregonstate.edu/drug_policy/reviews	**Yes**: Inform provider of covered alternatives in class. http://cms.oregon.gov/oha/healthplan/pages/tools_prov/pdl.aspx Approve for 1 year.	**No**: Approve for 1 year.
Pediatric Approval Criteria (<18 years old) – Renewal Therapy		
1. Document approximate date of initiation of therapy and diagnosis (if not already done).		
2. Is growth velocity greater than 2.5 cm per year?	**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)