Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Literature Scan: Growth Hormone

Date of Review: September 2017

Date of Last Review: September 2016
Literature Search: July 19, 2017

Current Status of PDL Class:
See **Appendix 1**.

Conclusions:
- No new evidence regarding the safety or efficacy of growth hormone (GH) has been published since the last literature scan.
- One guideline was updated by the Pediatric Endocrine Society to assist in guidance of GH treatment for 3 specific indications including idiopathic short stature, growth hormone deficiency (GHD), and primary IGF-1 deficiency in children and adolescents.[1]

Recommendations:
- No further review or research needed at this time.
- Review comparative costs in executive session.

Previous Conclusions:
- There is no new evidence that there is any difference in efficacy/effectiveness or safety between the different somatropin (i.e., Growth Hormone) products and formulations.
- There is no new evidence that further describes efficacy outcomes associated with use of GH.
- The updated Rapid Response Report from the Canadian Agency for Drugs and Technologies in Health (CADTH) found low to moderate quality evidence that suggest improvement in body composition for patients with Prader-Willi Syndrome (PWS) that received growth hormone treatment. Furthermore, growth hormone therapy should be continued for as long as the demonstrated benefits outweigh the risks.
- There is insufficient evidence to show a clinically significant benefit in HIV patients with respect to wasting.
- Evidence is insufficient to identify a clinically meaningful benefit in adults.
- There is low quality evidence that use of GH in childhood may increase all-cause mortality as an adult but has no significant effect on malignancy-related mortality or cardiovascular-related mortality.
- There is low quality evidence that use of GH in childhood may increase incidence of cancer as an adult and increase secondary malignancies in cancer survivors.

Previous Recommendations:

- After evaluation of comparative drug costs in the executive session, add Genotropin (somatropin) to the OHP fee-for-service Preferred Drug List (PDL) and remove Saizen (somatropin) from the PDL.
- It is recommended that at least one growth hormone product be included with pediatric indications. There is insufficient evidence to determine a recommendation for coverage for adult patients.
- Update clinical PA criteria to reflect HERC Guideline Note 74.

Background:

Growth hormone products are Food and Drug Administration (FDA) approved to treat syndromes associated with growth hormone deficiency (GHD). GHD is the result of impaired production of growth hormone (GH) and may be congenital or acquired. Children most at risk for GHD include those with short stature or a family history of short stature, short stature homeobox-containing gene (SHOX), chronic kidney disease (CKD), Turner's syndrome, Noonan's Syndrome, or Prader-Willi Syndrome. The diagnosis of GH deficiency in childhood is a multistep process involving clinical history, physical examination with detailed growth pattern assessment, biochemical testing, and pituitary imaging.[2] Most GH products are approved for use in pediatrics. Treatment with GH is indicated for children who need GH therapy and who have open epiphyses. Only 3 indications are approved for use in adults: cachexia associated with AIDS (Serostim®), short bowel syndrome (Zorbtive®) and GH deficiency. FDA approved indications for GH vary by brand name product and are presented in **Table 1**.

Table 1. Pediatric and Adults FDA Approved Indications for Growth Hormone[3,4]

	Accretropin®	Genotropin®	Humatrope®	Norditropin®	Nutropin AQ®	Omnitrope®	Saizen®	Serostim®	Zomacton®	Zorbtive®
Pediatric Indications										
GHD	X	X	X	X	X	X	X		X	
Prader-Willi Syndrome		X				X				
Noonan Syndrome				X						
Turner Syndrome	X	X	X	X	X	X				
Idiopathic Short Stature		X	X		X	X				
SHOX deficiency			X							
CKD with Growth Failure				X	X					

Small for gestational age		X	X	X		X				
Adult Indications										
GHD		X	X	X	X	X	X			
HIV Associated Cachexia								X		
Short Bowel Syndrome										X

Abbreviations: CKD = chronic kidney disease; FDA = Food and Drug Administration; GHD = growth hormone deficiency; HIV = Human immunodeficiency virus; SHOX = Short stature homeobox-containing gene

The NICE guidelines published in 2010 recommend that GH 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.[5] The treatment of GH 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 arise, or if final height is attained.[5] Clinical guidelines do not prefer one growth hormone product over another. The safety of recombinant human GH is currently the subject of much debate and research, and long-term controlled studies are needed to clarify the consequences of childhood growth hormone administration on cancer risk and the long-term safety of its treatment.[2]

Adult GHD (AGHD) is most often due to hypopituitarism secondary to head trauma, tumor of the hypothalamus or pituitary gland, or the consequences of cancer treatment such as surgery or radiation. Growth hormone deficiency is characterized by decreased lean body mass and bone mineral density, increased visceral adiposity, abnormal lipid profile, decreased muscle strength and decreased exercise endurance.[6] The diagnosis of GH deficiency is confirmed if other pituitary hormones such as thyroid stimulating hormone (TSH), corticotropin (ACTH), and gonadotropins are also diminished. A subnormal serum insulin-like growth factor-1 (IGF-1) concentration or subnormal serum GH response to a stimulation test also assists in confirming AGHD. The insulin tolerance test (ITT) and GHRH-arginine test are two tests recommended by the Endocrine Society to establish diagnosis of AGHD.[7] However, GH stimulation testing is invasive, time consuming, and can have increased risks in patients with seizure disorders or cardiovascular disease.[8]

Per the Health Evidence Review Commission (HERC) guideline note 74, treatment with growth hormone is included only for children with: pituitary dwarfism, Turner's syndrome, Prader-Willi-syndrome, Noonan's syndrome, SHOX, CKD (stages 3, 4, 5 or 6) and those with renal transplant.[9] Treatment with growth hormone should continue only until adult height as determined by bone age is achieved.[9] Treatment is not included for isolated deficiency of human growth hormone or other conditions in adults.[9]

In the second quarter of 2017 a total of 53 claims were received for growth hormone in the fee for service Oregon Medicaid population. Twenty-five (47%) claims were for preferred agents: Norditropin, Omnitrope, and Genotropin. Twenty-eight (53%) percent of claims were for non-preferred agents including Saizen, Humatrope, and Nutropin.

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. A summary of the clinical trials is available in **Appendix 2** with abstracts presented in **Appendix 3**. The Medline search strategy used for this literature scan is available in **Appendix 4**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The Food and Drug Administration (FDA) website was searched for new drug approvals, indications, and pertinent safety alerts. Finally, 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. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews: No new systematic reviews have been published since the last review.

New Guidelines:
Pediatric Endocrine Society
The 2016 publication by the Pediatric Endocrine Society (PES) updated 2003 guidance for the use of growth hormone in children and adolescents.[1] The guidelines were developed using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach.[10] Due to the numerous indications for growth hormone, the report focused on 3 indications including idiopathic short stature (ISS), GHD, and primary IGF-1 deficiency (PIGFD). GHD is defined by PES as the patients who have growth failure due to inadequate secretion of endogenous GH.[1] Idiopathic short stature is defined by a height standard deviation score of less than or equal to 2.25.[1] Severe PIGFD is defined as both height and serum IGF-I concentration below 3 standard deviations despite normal or elevated GH levels or patients with GH gene deletion who developed neutralizing antibodies to GH after a trial of GH therapy.[1] One of the major challenges for the task force was a lack of long term outcomes to evaluate GH therapy because most of the published studies are short term (less than 3 years).[1] No recommendations are made for particular growth hormone products, and only strong recommendations that are based on moderate to high quality evidence are presented below:

- The use of GH is recommended to normalize adult height and avoid extreme shortness in children and adolescents with GHD. (Strong recommendation, high quality evidence)[1]
- Reliance on GH provocative test results is not recommended as the sole diagnostic criterion of GHD. (Strong recommendation, high quality evidence)[1]
- Use of weight-based or body surface area (BSA)-based GH dosing is recommended in children with GHD. (Strong recommendation, moderate quality evidence)[1]
- Guidelines recommend monitoring of GH recipients for potential development of intracranial hypertension, slipped capital femoral epiphysis, and scoliosis progression by soliciting pertinent history and performing a physical examination at every follow-up clinic visit; further testing should be pursued if indicated. (Strong recommendation, high quality evidence)[1]
- Use of IGF-I therapy is recommended to increase height in patients with severe PIGFD. (Strong recommendation, high quality evidence)[1]

New FDA Drug Approvals: No new drug approvals were identified since the last review.

New Formulations/Indications: No new formulations or indications were identified since the last review.

New FDA Safety Alerts:
The FDA issued an import alert April 18, 2017 due an increased volume of unapproved GH products being imported into the United States (U.S.). In their alert the FDA noted that human growth hormone (HGH) has important benefits, but also serious, known risks. Possible long-term side effects which have been associated with use of HGH include an increased risk of cancer, nerve pain, and elevated cholesterol and glucose levels. For this reason, HGH is carefully regulated in the U.S. The cost of approved HGH products is high, averaging several hundred dollars per dose. Because of this high cost, HGH drugs have been counterfeited and unapproved HGH products are offered for sale to U.S. consumers. For example, the FDA reports HGH products have been imported as a lyophilized powder for use as an active pharmaceutical ingredient for pharmacy compounding. Some pharmacies promote compounded HGH for anti-aging purposes. It is sold as a "fountain of youth" in longevity clinics and to build body mass, decrease weight loss, increase libido, and gain stamina. None of these indications are in the labeling of the FDA approved products. The FDA is aware of unapproved HGH products being imported into the U.S. and recently noted a large increase of HGH imported for pharmacy compounding. If the drug is bought from foreign sources or over the Internet, safeguards built into the U.S. drug distribution system may be bypassed, placing consumers who use HGH at higher risk.[11]

Product labeling revisions:
Hypersensitivity
Serious systemic hypersensitivity reactions including anaphylactic reactions and angioedema have been reported with post-marketing use of somatropin products. Patients and caregivers should be informed that such reactions are possible and that prompt medical attention should be sought if an allergic reaction occurs.[12-14]

Acute Critical Illness Treatment
Acute critical illness treatment with pharmacologic amounts of somatropin is contraindicated in patients with acute critical illness due to complications following open heart surgery, abdominal surgery or multiple accidental trauma, or those with acute respiratory failure.[12] Two placebo-controlled clinical trials in non-growth hormone deficient adult patients (n=522) with these conditions in intensive care units revealed a significant increase in mortality (42% vs. 19%) among somatropin-treated patients (doses 5.3–8 mg/day) compared to those receiving placebo.[12] The safety of continuing somatropin treatment in patients receiving replacement doses for approved indications who concurrently develop these illnesses has not been established. Therefore, the potential benefit of treatment continuation with somatropin in patients having acute critical illnesses should be weighed against the potential risk.[12]

Hypoadrenalism
Patients receiving somatropin therapy who have or are at risk for pituitary hormone deficiency(s) may be at risk for reduced serum cortisol levels and/or unmasking of central (secondary) hypoadrenalism. In addition, patients treated with glucocorticoid replacement for previously diagnosed hypoadrenalism may require an increase in their maintenance or stress doses following initiation of somatropin treatment.[12-14]

References:

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8. Hartman ML, Crowe BJ, Biller BM, Ho KK, Clemmons DR, Chipman JJ. Which patients do not require a GH stimulation test for the diagnosis of adult GH deficiency? *J Clin Endocrinol Metab.* 2002;87(2):477-485.
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13. Norditropin (somatropin) Prescribing Information. Plainsboro, New Jersey. Novo Nordisk A/S. December 2016. https://www.norditropin.com/. Accessed July 21, 2017.
14. Nutropin (somatropin) Prescribing Information. South San Francisco, CA. Genentech. December 2016. https://www.gene.com/download/pdf/nutropin_aq_prescribing.pdf. Accessed July 21, 2017.
15. Kuppens RJ, Bakker NE, Siemensma EPC, et al. Beneficial Effects of GH in Young Adults With Prader-Willi Syndrome: A 2-Year Crossover Trial. *The Journal of Clinical Endocrinology & Metabolism.* 2016;101(11):4110-4116.

Appendix 1: Current Status on Preferred Drug List

Brand	Generic	Route	Formulation	PDL
GENOTROPIN	SOMATROPIN	SUB-Q	CARTRIDGE	Y
GENOTROPIN	SOMATROPIN	SUB-Q	SYRINGE	Y
OMNITROPE	SOMATROPIN	SUB-Q	CARTRIDGE	Y
NORDITROPIN FLEXPRO	SOMATROPIN	SUB-Q	PEN INJCTR	Y
HUMATROPE	SOMATROPIN	INJECTION	VIAL	N
HUMATROPE	SOMATROPIN	INJECTION	CARTRIDGE	N
SEROSTIM	SOMATROPIN	SUB-Q	VIAL	N
SAIZEN	SOMATROPIN	SUB-Q	VIAL	N
SAIZEN	SOMATROPIN	SUB-Q	CARTRIDGE	N
ZOMACTON	SOMATROPIN	SUB-Q	VIAL	N
OMNITROPE	SOMATROPIN	SUB-Q	VIAL	N
ZORBTIVE	SOMATROPIN	SUB-Q	VIAL	N
NUTROPIN AQ NUSPIN	SOMATROPIN	SUB-Q	PEN INJCTR	N

Appendix 2: New Clinical Trials

A total of 24 citations were manually reviewed from the literature search. After further review, 23 trials were excluded because of wrong study design (observational), comparator (placebo), or outcome studied (non-clinical). The remaining 1 trial is briefly described in the table below. Full abstracts are included in **Appendix 3.**

Table 1: Description of Clinical Trials

Study	Comparison	Population	Primary Outcome	Results
Kuppens et al[15] RCT, DB, PC, Crossover study	1. GH 0.67mg/m^2 SC once daily x 1 year Vs. 2. PBO SC once daily x 1 year	Young adults (mean age = 17.2 years) with Prader Willi syndrome treated with GH during childhood for at least 2 years who had attained adult height n=27	Body composition, including lean body mass and fat mass as measured by dual-energy x-ray absorptiometry	<table><tr><th>Metric</th><th>Relative Change PBO</th><th>Relative Change GH vs. PBO</th><th>Mean Difference between PBO and GH</th></tr><tr><td>FM</td><td>+21.5%</td><td>-17.3%</td><td>-2.9 kg (p = 0.004)</td></tr><tr><td>LBM</td><td>-2.0%</td><td>+3.5%</td><td>1.5 kg (p = 0.005)</td></tr></table>

Abbreviations: DB = double blind**;** FM = fat mass; GH= growth hormone**;** LBM = lean body mass**;** MC = multi-center; OL = open label; PC = placebo controlled; PBO = placebo; RCT = randomized controlled trial; SC = subcutaneous; SGA = small for gestational age

Appendix 3: Abstract of Clinical Trial

1. Beneficial Effects of GH in Young Adults with Prader-Willi Syndrome: A 2-Year Crossover Trial.

Kuppens RJ, Bakker NE, Siemensma EP, Tummers-de Lind van Wijngaarden RF, Donze SH, Festen DA, van Alfen-van der Velden JA, Stijnen T, Hokken-Koelega AC.

J Clin Endocrinol Metab. 2016 Nov; 101(11):4110-4116. Epub 2016 Aug 23

Abstract: Patients with Prader-Willi syndrome (PWS) are severely at risk to develop morbid obesity, diabetes mellitus type 2, and cardiovascular disease, leading to high mortality. They have an increased fat mass (FM) and decreased lean body mass (LBM). During childhood, GH treatment counteracts the natural course of increasing obesity. Discontinuation of GH treatment at attainment of adult height (AH) might deteriorate their improved clinical condition, whereas continuation might benefit them.

OBJECTIVE: To investigate the effects of GH versus placebo on body composition in young adults with PWS who were GH treated for many years during childhood and had attained AH.

DESIGN: Two-year, randomized, double-blind, placebo-controlled crossover study with stratification for gender and body mass index in 27 young adults with PWS.

SETTING: PWS Reference Center in The Netherlands.

INTERVENTION: Crossover intervention with GH (0.67 mg/m^2 · d) and placebo, both during 1 year.

MAIN OUTCOME MEASURES: Body composition, measured by dual-energy x-ray absorptiometry.

RESULTS: During placebo, FM increased (relative change +21.5%; P < .001). Compared with placebo, GH treatment resulted in lower FM (-2.9 kg; P = .004) and higher LBM (+1.5 kg; P = .005), representing relative changes of -17.3% FM and +3.5% LBM. Both limb and trunk FM percentage were lower during GH versus placebo (relative change +17.3% and +15.6%; P < .001 and P = .007, respectively). No GH-related adverse events occurred.

CONCLUSIONS: GH-treated young adults with PWS who have attained AH benefit from continuation of GH treatment. FM increases during placebo, whereas GH versus placebo results in lower FM and higher LBM. Thus, GH treatment maintains the improved body composition without safety concerns.

PMID: 27552545 DOI: 10.1210/jc.2016-2594

Appendix 4: Medline Search Strategy

[Example]
Ovid MEDLINE(R) without Revisions 1946 to July Week 2 2017; Ovid Medline In-Process and Other Non-Indexed Citations July 19, 2017

1	exp Growth Hormone/	22834
2	somatotropin.mp.	3416
3	somatropin.mp.	163
4	humatrope.mp.	16
5	nutropin.mp.	20
6	serostim.mp.	33
7	zomacton.mp.	2
8	saizen.mp.	23
9	norditropin.mp.	53
10	zorbtive.mp.	2
11	genotropin.mp.	81
12	omnitrope.mp.	36
13	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12	24186
14	limit 13 to (full text and humans and yr="2016 -Current" and (clinical study or clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or guideline or meta-analysis or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews))	24

Author: Moretz

Date: September 2017

Growth Hormones

Goal(s):
- Restrict use of growth hormone (GH) for funded diagnoses where there is medical evidence of effectiveness and safety.

NOTE: Treatment with growth hormone (GH) is included only for children with: pituitary dwarfism, Turner's syndrome, Prader-Willi-syndrome, Noonan's syndrome, short stature homeobox-containing gene (SHOX), chronic kidney disease (stage 3 or higher) and those with renal transplant. Treatment with GH should continue only until adult height as determined by bone age is achieved. Treatment is not included for isolated deficiency of human growth hormone or other conditions in adults.

Length of Authorization:
- Up to 12 months

Requires PA:
- All GH products require prior authorization for OHP coverage. GH treatment for adults is not funded by the OHP.

Covered Alternatives:
- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Initial Approval Criteria		
1. What is the diagnosis being treated?	Record ICD10 code	
2. Is the patient an adult (>18 years of age)?	**Yes:** Pass to RPh. Deny; not funded by the OHP	**No:** Go to #3
3. Is this a request for initiation of growth hormone?	**Yes:** Go to #4	**No:** Go to **Renewal Criteria**
4. Is the prescriber a pediatric endocrinologist or pediatric nephrologist?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness

Initial Approval Criteria		
5. Is the diagnosis promotion of growth delay in a child with 3rd degree burns?	**Yes:** Document and send to DHS Medical Director for review and pending approval	**No:** Go to #6
6. Is the diagnosis one of the following? • Turner's syndrome (ICD10 Q969) • Noonan's syndrome (ICD10 E7871-7872, Q872-873, Q875, Q8781, Q8789, Q898) • Prader-Willi syndrome (PWS) (ICD10 Q871) • Pituitary dwarfism (ICD10 E230) • Short stature homeobox-containing gene (SHOX) (ICD10 R6252) • Chronic kidney disease (CKD, Stage ≥3) (ICD10 N183-N185) • Renal transplant (ICD10 Z940)	**Yes:** Document and go to #7	**No:** Pass to RPh. Deny; not funded by the OHP.
7. If male, is bone age <16 years? If female, is bone age <14 years?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness
8. Is there evidence of non-closure of epiphyseal plate?	**Yes:** Go to #9	**No:** Pass to RPh. Deny; medical appropriateness
9. Is the product requested preferred?	**Yes:** Approve for up to 12 months	**No:** Go to #10
10. Will the prescriber consider a change to a preferred product? <u>Message</u>: • Preferred products are reviewed for comparative effectiveness and safety by the Oregon Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of covered alternatives in class and approve for up to 12 months.	**No:** Approve for up to 12 months

Renewal Criteria		
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 or female bone age <14 years?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Is the product requested preferred?	**Yes:** Approve for up to 12 months	**No:** Go to #5
5. Will the prescriber consider a change to a preferred product? Message: • Preferred products are reviewed for comparative effectiveness and safety by the Oregon Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of covered alternatives in class and approve for up to 12 months	**No:** Approve for up to 12 months

P&T Review: 09/17 (DM); 9/16; 9/15; 9/14; 9/10; 5/10; 9/08; 2/06; 11/03; 9/03
Implementation: 10/13/16; 1/1/11, 7/1/10, 4/15/09, 10/1/03, 9/1/06