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 Hormones

Date of Review: September 2016

Date of Last Review: September 2015
Literature Search: July 2016

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

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.

Recommendations:
- No further review or research needed at this time.
- 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.

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, GH) products and formulations.
- There is insufficient new evidence that further described efficacy outcomes associated with use of GH.
- 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:
- No change to the PDL recommended at this time. Update clinical PA criteria to reflect Guideline Note 74.

Author: Deanna Moretz, PharmD, BCPS

Date: September 2016

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. The Medline search strategy used for this literature scan is available in **Appendix 3**, 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 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:
In late 2015, CADTH updated a Rapid Response Report originally published in 2012. The focus of the report was to review of the efficacy and safety of human growth hormone (GH) treatment for PWS in adolescent and adult patients. The reviewers identified 189 citations from their search of published documents from January 1, 2012 through August 21, 2015. After screening the data they found 14 publications that met their inclusion criteria. The two research questions were:

1. What is the clinical effectiveness of human GH treatment for PWS in adolescent and adult patients?[1] The reviewers concluded studies were of low to moderate quality and suggested there is improvement in body composition such as body fat mass and lean body mass; however, results were not always significant and should be interpreted with caution.[1] Very few studies reviewed for the CADTH summary reported adverse events.
2. What are the evidence based guidelines for the use of human growth hormone treatment for PWS in adolescent and adult patients?[1] Patients with PWS should have a genetically confirmed diagnosis and multidisciplinary evaluation prior to starting GH therapy.[1] GH therapy should be continued as long as demonstrated benefits outweigh the risks.[1]

New Guidelines:
None identified.

New Formulations and Indications:
None identified.

New FDA Safety Alerts:
None identified.

References:
1. Human Growth Hormone Treatment for Prader-Willi Syndrome in Adolescent and Adult Patients: Clinical Evidence, Safety, and Guidelines | CADTH.ca. https://www.cadth.ca/human-growth-hormone-treatment-prader-willi-syndrome-adolescent-and-adult-patients-clinical-eviden-0. Accessed July 18, 2016.

Appendix 1: Current Status on Preferred Drug List

ROUTE	FORMULATION	BRAND	GENERIC	PDL
SUB-Q	CARTRIDGE	SAIZEN	SOMATROPIN	Y
SUB-Q	PEN INJCTR	NORDITROPIN FLEXPRO	SOMATROPIN	Y
SUB-Q	VIAL	SAIZEN	SOMATROPIN	Y
INJECTION	CARTRIDGE	HUMATROPE	SOMATROPIN	N
INJECTION	VIAL	HUMATROPE	SOMATROPIN	N
SUB-Q	CARTRIDGE	NUTROPIN AQ	SOMATROPIN	N
SUB-Q	PEN INJCTR	NUTROPIN AQ NUSPIN	SOMATROPIN	N
SUB-Q	VIAL	SEROSTIM	SOMATROPIN	N
SUB-Q	VIAL	ZOMACTON	SOMATROPIN	N
SUB-Q	VIAL	ZORBTIVE	SOMATROPIN	N
SUB-Q	CARTRIDGE	GENOTROPIN	SOMATROPIN	
SUB-Q	CARTRIDGE	OMNITROPE	SOMATROPIN	
SUB-Q	SYRINGE	GENOTROPIN	SOMATROPIN	
SUB-Q	VIAL	OMNITROPE	SOMATROPIN	

Appendix 2: New Clinical Trials

A total of 69 citations resulted from initial literature search. After further review, all studies were excluded due to the wrong study design (observational), comparator (placebo), or outcome (non-clinical).

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to July Week1 2016

1 exp Growth Hormone/ 22243
2 somatotropin.mp. 3271
3 somatropin.mp. 128
4 1 or 2 or 3 23442
5 limit 4 to (english language and yr="2015 -Current" and (clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or multicenter study or pragmatic clinical trial or randomized controlled trial)) 81
6 limit 5 to humans 69

Author: Moretz Date: September 2016

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 to not require a copay. • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the 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 do not require a copay. • Preferred products are evidence based reviewed for comparative effectiveness and safety by the 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: *9/16; 9/15; 9/14; 9/10; 5/10; 9/08; 2/06; 11/03; 9/03*
Implementation: *1/1/11, 7/1/10, 4/15/09, 10/1/03, 9/1/06; 10/1/03*