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Literature Scan: Growth Hormone

Date of Review: September 2015

Date of Last Review: September 2014
Literature Search: August 2014 – August 2015

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 (ie, 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.

Recommendations:
- No change to the PDL recommended at this time. Update clinical PA criteria to reflect Guideline Note 74.

Previous Conclusions:
- There is no new evidence that there is any difference in efficacy/effectiveness or safety between the different somatropin products and formulations.

Previous Recommendations:
- No further review or research needed. Evaluated comparative drug costs in the executive session.

Methods:
Evidence in this literature scan is limited to conditions outlined in Guideline Note 74 of the Health Evidence Review Commission's (HERC) Prioritized List of Health Services, titled GROWTH HORMONE TREATMENT[1]: "*Treatment with growth hormone 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 growth hormone 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".* Growth hormone studied for conditions not funded by the Oregon Health Plan (OHP) will be otherwise noted in abstract form only in **Appendix 3**.

Author: Date:

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 clinical trial results of studied conditions funded by the OHP are available in **Appendix 2**. 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 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:
Only one new systematic review that evaluated use of GH in populations with possible conditions funded by the OHP was identified.[2] The review did not evaluate efficacy but rather examined the evidence whether use of GH treatment during childhood may be associated with a higher risk of all-cause, cancer-related and cardiovascular-related mortality and morbidity.[2] The primary efficacy outcome was the all-cause, cancer and cardiovascular mortality, using the standardized mortality ratio (SMR), defined as the number of observed deaths divided by the number of expected deaths.[2] The secondary efficacy outcomes were incidence of primary cancer or secondary cancer in cancer survivors.[2] The standardized incidence ratio (SIR), defined as the number of observed cancer cases divided by the number of expected cases and the risk of second cancers, was used to assess incidence of malignancy.[2] Second cancer incidence in cancer survivors was described by relative risk (RR), defined as the incidence of a second malignancy in patients exposed to GH divided by the incidence among patients not exposed to GH.[2]

Twelve studies were identified that included mortality data, but 8 studies were excluded because the studies only observed deaths (n=4) or used indices different than SMR (n=4).[2] Four studies (n=24,456 patients; mean age 32.6 years) that used SMR rates to evaluate mortality were included in the review.[2] The overall all-cause SMR in GH treated patients, which was evaluated in 3 studies and mostly in children, was significantly increased at 1.19 (95% Confidence Interval [CI], 1.08 to 1.32; $p<0.001$).[2] Four studies reported SMRs for cancer-related mortality in patients treated with GH.[2] The overall mean malignancy SMR was not significantly different at 0.95 (95% CI, 0.74 to 1.19; $p=0.61$).[2] Mortality due to cardiovascular events was analyzed in 3 studies.[2] The mean cardiovascular SMR derived from all these studies was also not significantly different at 1.39 (95% CI, 0.76 to 2.55; $p =0.28$).[2]

Seven studies were identified that included primary cancer incidence data, but 3 studies were excluded because the studies only observed cancer incidence (n=2) or used indices other than SIR (n=1).[2] The overall mean malignancy SIR from the remaining 4 studies was significantly increased at 1.36 (95% CI, 1.00 to 1.85; $p=0.05$).[2] The incidences of second malignancies were captured in 5 studies which used RR to evaluated incidence of secondary tumors.[2] The overall mean RR of second malignancy in cancer survivors was also significantly higher at 1.99 (95% CI, 1.28 to 3.08; $p=0.002$).[2]

The results of this systematic review are limited by the heterogeneous populations studied, which comprised of both adult and pediatric cohorts, and patients of different diagnoses.[2]

Author: A. Gibler, Pharm.D. Date: September 2015

New Guidelines:
None identified.

New FDA Drug Approvals:
None identified.

New Formulations/Indications:
None identified.

New FDA Safety Alerts:
New warnings and precautions for malignancies in patients treated with somatotropin products were applied to labeling in September 2014.[3] These warnings stem from evidence that shows an increased risk of second neoplasm in childhood cancer survivors who were treated with radiation to the brain/head for their first neoplasm and who developed subsequent Growth Hormone deficiency and were treated with somatropin.[3] It is unknown if there is any relationship between GH replacement therapy and brain tumor recurrence in adults.[3] Because children with certain rare genetic causes of short stature have an increased risk of developing cancer, the risks and benefits of starting GH should be carefully considered in these patients.[3]

References:

1. Prioritized List of Health Services, January 1, 2015. Health evidence Review Commission, Oregon Health Plan. Available at http://www.oregon.gov/oha/herc/PrioritizedList/1-1-2015%20Prioritized%20List%20of%20Health%20Services.pdf. Accessed 6 August 2015.

2. Deodati A, Ferroli B, Cianfarani S. Association between growth hormone therapy andmortality, cancer and cardiovascular risk: Systematic review and meta-analysis. *Growth Hormone & IGF Research*. 2014;24:105-111. doi:10.1016/j.ghir.2014.02.001.

3. MedWatch Safety Information. U.S. Food and Drug Administration. Available at http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm258783.htm. Accessed 12 August 2015.

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Appendix 1: Current Status on Preferred Drug List

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

Appendix 2: New Clinical Trials

A total of 110 citations were manually reviewed from the literature search. After further review, all studies were excluded because of wrong study design (observational), comparator (placebo, different doses, not FDA-approved drug), or outcome studied (non-clinical; not funded by the OHP).

Appendix 4: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to July Week 5 2015

1 exp Growth Hormone/ 21514
2 somatotropin.mp. 3175
3 somatropin.mp. 120
4 1 or 2 or 3 22671
5 limit 4 to (english language and yr="2014 -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) and last year) 110

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Growth Hormones

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

Guideline Note 74: 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:
- Non-preferred drugs

Covered Alternatives:
- All GH products require prior authorization for OHP coverage. GH treatment for adults is not funded by the OHP.
- Preferred alternatives are 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? Message: • 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 / DUR Review: *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*