



*Preserving the integrity of competition. Inspiring true sport. Protecting the rights of athletes.*

## **ATHLETES & PRESCRIBING PHYSICIANS PLEASE READ**

USADA can grant a Therapeutic Use Exemption (TUE) in compliance with the World Anti-Doping Agency International Standard for TUEs. The TUE application process is thorough and designed to balance the need to provide athletes access to critical medication while protecting the rights of clean athletes to compete on a level playing field.

Included in this document is a checklist of items necessary for a complete TUE Application and the WADA Guidelines used to evaluate TUE Applications for your specific condition. (Please be aware that the TUE Committee may ask for additional information while evaluating TUE Applications). It is important that the TUE Application include all the documentation outlined in the checklist below. Please reference the included guidelines for details related to types of diagnoses, specific laboratory tests, and more.

### **TUE APPLICATION CHECKLIST – ADULT GROWTH HORMONE DEFICIENCY**

- Complete and legible TUE Application form
- Copies of all relevant examinations and clinical notes from the original diagnosis through present
  - The requirements for adults diagnosed with GHD as a child (entering the transition period) are different from those for adults with new onset GHD, please see the guidelines for what items are required in the diagnostic workup of each condition
- Copies of all laboratory results/reports related to the diagnosis (please see the guidelines for specific results to include)
- A statement from the physician explaining why the Prohibited Substance is needed
  - Please explain why permitted alternative treatments were not effective or not appropriate/indicated for treatment

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**U.S. Anti-Doping Agency**

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## **1. Medical Condition**

### **GROWTH HORMONE DEFICIENCY (ADULT)**

## **2. Diagnosis**

### **A. Medical History**

Growth hormone deficiency (GHD) is a result of dysfunction of the hypothalamic-pituitary axis either at the hypothalamic or pituitary levels. Adults who have GHD include individuals who have been diagnosed with GHD as a child and those who have acquired GHD as an adult due to hypothalamic-pituitary disease. For the individual who has been diagnosed with GHD as a child, the transition period can be defined as beginning in late puberty, the time when near adult height has been attained, and ending with full adult maturation (6-7 years after achievement of adult height). During this period ongoing growth hormone therapy may be necessary to attain somatic maturation, normal intermediary metabolism and appropriate quality of life. Adults who develop GHD de novo include individuals with hypothalamic-pituitary disease, e.g. pituitary tumors, subarachnoid hemorrhage, surgery or irradiation in these cranial areas or traumatic brain injury. Such individuals may have pituitary hormone deficiencies. In general, the diagnosis of GHD should be determined by an endocrinologist with expertise in pituitary disorders.

### **B. Diagnostic criteria**

The diagnosis of GHD requires an appropriate/plausible clinical setting and is confirmed through biochemical testing. Evaluation for GHD should be performed in patients with evidence of hypothalamic-pituitary disease (e.g. pituitary tumors), after cranial irradiation, after significant traumatic brain injury (TBI) and in some individuals who have been treated for GHD as a child.

The diagnosis of GHD rests on:

- Evidence for hypothalamic-pituitary disease;
- Subnormal serum IGF-1 levels;
- Abnormal GH stimulation test.

*Medical Information to Support the Decisions of TUE Committees  
Growth Hormone Deficiency (Adult)*

- 1) Re-evaluation for the adolescent/adult who is transitioning having been treated for childhood GHD is mandatory because some forms of childhood GHD may recover. For emerging adults who were diagnosed with GHD as children/adolescents an IGF-1 level should be measured after 2-4 weeks off rhGH therapy. However, in certain conditions a GH stimulation test is not required because GHD is almost certain on clinical or genetic grounds.

This applies to patients with:

- a) More than three additional pituitary hormone deficits and a low IGF-I level (strong evidence for hypopituitarism);
  - b) Transcription factor mutation known to result in pituitary maldevelopment and hypopituitarism (e.g. *POU1F1* (Pit-1), *PROP-1*, *LHX-3*, *LHX-4*);
  - c) Mutations in genes known to result in isolated GHD (e.g. *GH-1* or *GHRH-R*).
- 2) This re-evaluation should be performed when linear growth has ceased and includes:
    - a) Height, weight, BMI, anthropometric measurements;
    - b) Serum IGF-1 levels;
    - c) GH Stimulation tests (for threshold levels of these tests refer to Ho et al. Consensus Guidelines or Cook et al. AACE Medical Guidelines, both are listed below):
      - 1) Insulin Tolerance Test;
      - 2) GHRH+Arginine Test - with BMI adjustments for obesity;
      - 3) Glucagon Stimulation Test.

When evaluating individuals with traumatic brain injury, **the timing of the evaluation is critical**. The evaluation should be undertaken no sooner than 12 months after injury.

**In addition to the investigations above, the diagnostic workup of the adult with new onset GHD** requires the following additional assessment:

MRI of brain with specific attention to hypothalamus and pituitary.

C. Relevant medical information

- a) GH and IGF-1 results must be expressed in mass units;
- b) Low IGF-1 concentration below normal range is insufficient evidence for GHD. GH stimulation testing must be performed unless there is conclusive other evidence of hypothalamic-pituitary dysfunction (such as an organic lesion and hypopituitarism with more than 3 additional pituitary hormones being deficient or the presence of the genetic disorders listed above);
- c) Therapeutic use exemption (TUE) for the treatment of GHD should be granted for only those who have conclusive evidence of GHD;
- d) Subjects should be investigated for other pituitary hormone deficits and these should be adequately replaced before biochemical evaluation for GHD is performed.

### **3. Medical best practice treatment**

A. Name of prohibited substance

Recombinant growth hormone, e.g. Genotropin, Humatrope, Norditropin, Nutropin, Omnitrope, Saizen, Valtropin, TevTropin

B. Route

Subcutaneous injections

C. Dosage and Frequency

- a) Women – 0.3 mg/day (may need higher dosage if taking oral estrogens);
- b) Men – 0.2 mg/day.

Adjust dose dependent upon clinical assessment, adverse effects and IGF-1 levels maintained at 0 – +1 SD unless previous history of malignancy.

**D. Recommended duration of treatment**

- a) Adult onset GHD requires lifelong treatment (continuing treatment for the aging population is the decision of the treating endocrinologist);
- b) Childhood onset GHD requires re-evaluation within the transition period.

**4. Other non-prohibited alternative treatments**

No alternative for human growth hormone substitution.

**5. Consequences to health if treatment is withheld**

The following consequences to health for individuals with untreated GHD include:

- a) Decreased quality of life;
- b) Decreased bone mineral density;
- c) Increased fat mass;
- d) Increase in cardiovascular risk factors.

**6. Treatment monitoring**

Treatment should be periodically monitored using the following:

- a) BMI;
- b) IGF-1 levels;
- c) Blood glucose and Hemoglobin A1c (oral glucose tolerance test may be indicated based on results of Hgb A1c or strong family history of Diabetes Mellitus);
- d) Cardiovascular risk markers should be assessed and managed appropriately;
- e) Bone density may be affected negatively in those with GHD and should be monitored;

- f) As part of therapy, quality of life (QoL) may be monitored by use of GHD specific questionnaires, e.g. QoL-AGHDA.

## **7. TUE validity and recommended review process**

- 1) Eight years if genetic, congenital or hypothalamic-pituitary structural abnormality;
- 2) Four years if due to brain trauma or irradiation.

The results of regular monitoring should be submitted annually for review.

## **8. Any appropriate cautionary matters**

Due to the significant risk for abuse of growth hormone for performance enhancement, these requirements must be strictly followed. The diagnosis should be confirmed by an endocrinologist with expertise in hypothalamic-pituitary disorders.

Given the potential controversy associated with the approval of a TUE for Growth Hormone, the opinion of an independent endocrinologist with expertise in hypothalamic-pituitary disorders is strongly suggested.

Also, the TUE reviewers working on behalf of the national anti-doping agencies (NADOs) and international federations (IFs) should be endocrinologists with expertise in hypothalamic-pituitary disorders.

Most patients with GHD self administer GH. Although self administration may seemingly present difficulty with monitoring, a log book of growth hormone prescriptions and administration should be maintained by the athlete. The administration log book may be subject to review at any time including for the annual review. Quantities of growth hormone administered to the athlete must be strictly controlled and limited by prescription.

## **9. References**

- 1) Cook, DM et al. American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice for Growth Hormone Use in Growth Hormone Deficient Adults and Transition Patients – 2009 Update:

*Medical Information to Support the Decisions of TUE Committees  
Growth Hormone Deficiency (Adult)*

Executive Summary of Recommendations. *Endocrine Practice*, 15(6): 580-586. 2006.

2) Cook, DM and Rose, SR. A Review of Guidelines for Use of Growth Hormone in Pediatric and Transition Patients, *Pituitary*, 15: 301-310. 2012.

3) Glynn, N and Agha, A. Review Article: Diagnosing Growth Hormone Deficiency in Adults. *International Journal of Endocrinology*, Volume 2012: 1-7. 2012.

4) Ho, KKY et al. Consensus Guidelines for the Diagnosis and Treatment of Adults with GH Deficiency II: a statement of the GH Research Society in association with the European Society for Pediatric Endocrinology, Lawson Wilkins Society, European Society of Endocrinology, Japan Endocrine Society and Endocrine Society of Australia. *European Journal of Endocrinology*, 157: 695-700. 2007.

5) Inzaghi, E and Cianfarani, S. The Challenge of Growth Hormone Deficiency Diagnosis and Treatment during the Transition from Puberty into Adulthood, *Frontiers in Endocrinology*, 4 (34): 1-8. 2013.

6) Mauras, N. GH use in the transition of adolescence to adulthood, *Endocrine Development*, 18:109-25. 2010.

7) Molitch, ME et al. Evaluation and Treatment of Adult Growth Hormone Deficiency: An Endocrine Society Clinical Practice Guideline. *Journal of Clinical Endocrinology Metabolism*, 96 (6): 1587-1609. 2011.