

Short stature (non-growth hormone deficient)

Prohibited Substances: Human Growth Hormone, Gonadotropin Releasing Hormone Analogues, Aromatase Inhibitors

1. Introduction

Short stature is characterized for an individual as being more than 2 standard deviations (SD) below average for their age and sex on the appropriate growth chart. Short stature is most often a variant of normal growth, but also encompasses many medical conditions that can result from genetic, environmental, hormonal, and medical factors.

Genetic factors play an important role in determining an individual's height. If parents are shorter than average, their children are likely to inherit shorter stature as well. Idiopathic short stature is defined when there is no identifiable disorder, but the individual is more than 2 SD below the mean for the appropriate population. That is not a specific diagnosis, but a description of a heterogeneous group of short stature children. In the United States and several other countries, federal drug agencies have approved growth hormone treatment for those who are below -2.25 SD for height and who are unlikely to reach the lowest centiles of the growth chart at adult height.

Certain medical conditions, such as growth hormone deficiency (GHD) or genetic disorders like Turner syndrome or Noonan syndrome, can contribute to short stature. In some cases, medical interventions, such as growth hormone therapy, may be recommended to stimulate growth in individuals with GHD. These indications for growth hormone therapy are not universal but are noted below in Section 2.

This Therapeutic Use Exemption (TUE) Physician Guidelines document includes a spectrum of short stature conditions, not due to GHD, and presents guidelines on how to produce a complete TUE application for children and adolescent athletes. Please see [WADA's TUE Physician Guidelines – Growth Hormone Deficiency \(children and adolescents\)](#) for guidelines related to athletes with GHD.

2. Diagnosis

For the purposes of this document, the United States Food and Drug Administration (FDA) approved indications serve as a reference, as they are expansive compared to other countries that have fewer approved indications for recombinant human growth hormone (hGH). The seven conditions associated with short stature for which hGH has been approved by the FDA, in addition to GHD, are:

- Chronic kidney disease
- Born small for gestational age with failure to catch up to the growth curve (SGA)
- Turner syndrome
- SHOX gene haploinsufficiency
- Prader-Willi syndrome

- Idiopathic short stature
- Noonan syndrome

When diagnosing any of these conditions, GHD and other medical causes of growth failure leading to short stature should be investigated and excluded.

a) Medical history

Athlete's personal medical history:

- Gestational period (in weeks)
- Birth and neonatal (include weight and length)
- Growth (appropriate growth chart*)
- Relevant developmental and other medical and/or surgical history

Family history:

- Parental height:
 - Both biological parents should be measured carefully
 - A mid-parental target height may be calculated for boys by adding 13 cm to the mother's height and then taking the mean of the father's and mother's adjusted height; for girls by subtracting 13 cm from the father's height and then take the mean of the mother's and father's adjusted height.
 - If known, the ethnicity of the parents should be included.

*Please note: The appropriate growth chart may pertain to a specific country or region, or another relevant chart to evaluate the athlete's growth.

b) Diagnostic criteria

Chronic kidney disease (CKD)

- Standard medical criteria for the diagnosis of CKD, including estimated glomerular filtration rate per body surface area.

SGA with failure to catch up to the appropriate neonatal and then infant growth charts

- SGA is typically diagnosed by low weight for gestational age but, in more severe instances, may also adversely affect length and head circumference growth. Initiation of hGH for SGA is approved when catch up in length on the appropriate growth chart has not occurred by, for example: 2 years of age by the FDA (USA), by 4 years of age by the EMA* (Europe), and 3 years of age by the PMDA** (Japan).

*European Medical Agency

**Pharmaceutical and Medical Devices Agency

Turner syndrome

- Female phenotype, short stature, physical stigmata, chromosomal karyotype as 45X or mosaic form

SHOX haploinsufficiency

- Haploinsufficiency may be suspected clinically, especially with the Madelung deformity and is then confirmed with a genetic test for the SHOX gene.

Prader-Willi syndrome (PWS)

- Diagnosis is made clinically, and it is mandatory to confirm by genetic testing.

Idiopathic short stature (ISS)

- ISS is a non-specific diagnosis of exclusion which depends upon how extensively other causes of genetic short stature and delayed growth are pursued. Treatment of children with ISS with hGH varies widely around the world from no treatment permitted to varying degrees below the 2.3 height centile on a country-by-country basis.

Noonan syndrome

- Diagnosis is made by a clinical scoring system at birth. It is confirmed by specific gene testing.

For the purposes of this document, all children will be compared to the appropriate charts for birth weight, weight, height, height velocity, and BMI.

c) Transition period (as defined above in Section 2a)

In PWS, children may also be growth hormone deficient; therefore, it is mandatory to test for growth hormone deficiency at near adult height as they transition to an emerging adult.

Not applicable for other SS conditions in this document.

3. Treatment

There are conditions of short stature, not due to GHD, which may be treated with hGH with or without other medications. The indications for hGH treatment for short stature vary globally, ranging from no approval to different inclusion criteria, and off-label use in some countries. This guidance document addresses criteria for which TUEs may be granted for initial or continued prescription of hGH.

Aromatase inhibitors (AI) can be prescribed individually or in combination with hGH to increase height gain potential by keeping the long-bone epiphysis open for a longer period. Notably, AIs increase testosterone levels in males with the potential to be performance enhancing, making a TUE more difficult to obtain (ISTUE Article 4.2b).

Gonadotropin Releasing Hormone Analogues (GnRHa) may be prescribed for the same purpose, as they may delay closure of the long bone epiphyses by diminishing sex steroid production in both boys and girls.

a) Dosing

- hGH is administered subcutaneously at 25-50 mcg/kg/day, with some variation depending on the specific condition and country.
- GnRHa is administered subcutaneously, by implantation or intramuscularly, with dosing as applicable for this pharmacological agent.
- AI is administered orally, with dosing as applicable for this pharmacological agent.

Doses are typically adjusted depending upon growth response (change in height SDs or change in height velocity), adverse effects and IGF-1 levels maintained at normal range, unless previous history of malignancy, in which case suggested IGF-1 levels < 0 SD.

Endpoints of treatment vary depending on dose and duration of hGH administration as an athlete progresses through puberty, reaches near adult height (height velocity slows to less than 2.0 cm/year), or ceases to grow when the growth plate of the long bones fuse. For athletes without GHD, given a diminishing effect of hGH on height gain as puberty progresses and high likelihood for continued growth even if hGH treatment is stopped, it is proposed that TUEs be granted only to a point when athletes reach the 5th centile of adult height on the appropriate growth curve (see Section 7. TUE duration).

4. Non-prohibited alternative treatments

Not applicable.

5. Consequences to health if treatment is withheld

It should be emphasized that, with the exception of some athletes with PWS, these individuals are not GHD and thus are not dependent on exogenous hGH for GH-dependent metabolic and bone health. There may be complex psycho-social elements associated with the decision to treat, which should be considered on an individual basis.

In the case of PWS, increased fat mass and decreased lean body mass may follow when withholding or discontinuing hGH administration.

6. Treatment monitoring

Treatment monitoring of short stature athletes ensures that physicians can adapt treatment plans based on individual needs, growth potential and to monitor overall health including potential side effects of medications.

Treatment should be monitored every 3 to 6 months using the following:

1. Linear growth (following local curves)
2. IGF-1 levels
3. Bone age (yearly)
 - There are several standard methods, for example, Greulich-Pyle, Tanner Whitehouse, Fels and Bone-Expert. The method should be stated, and the actual films made available to the TUE Committee.
4. Monitoring pubertal maturation in boys
 - Clinically using the Tanner stages for genital maturation
 - Testosterone, morning levels (appropriate for the degree of pubertal maturation)
 - Luteinizing hormone (LH), morning levels (appropriate for the degree of pubertal maturation)
5. Monitoring pubertal maturation in girls
 - Clinically using the Tanner stages for genital maturation
 - Estradiol levels (may be confounded by ovarian cycles)
 - LH, morning levels (appropriate for the degree of pubertal maturation, but may be confounded by ovarian cycles)

Athletes may be asked to provide information on prescriptions and/or timing of the administration of hGH and related medications.

7. TUE duration

1. For short stature, hGH may be approved for up to four years for all non-GHD conditions or until 5th centile for sex-appropriate adult height is reached (growth chart), with monitoring as noted above.
2. For PWS, hGH may be approved for up to 10 years.

The results of regular monitoring must be submitted annually for review. A TUE committee may request further information as the athlete reaches near adult height.

8. Appropriate precautionary matters

The diagnosis and treatment should be confirmed by a pediatric endocrinologist or an endocrinologist familiar with treating these conditions. Ideally, the TUE Committees should include a pediatric endocrinologist, or at least an endocrinologist, familiar with the athlete's condition.

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