



U.S. Anti-Doping Agency

TUE applications for Testosterone-Physician Worksheet

Attention Physicians- USADA will not process any Therapeutic Use Exemption for an athlete for the use of Testosterone unless we receive all of the requested documents in the checklist below. As you prepare the medical file, please keep the following points in mind:

- The Therapeutic Use Exemption Committee (TUEC) must review the entire work-up for hypogonadism. They need enough medical information, clinic notes and laboratory testing notes *to make the same diagnosis, and arrive at the same treatment plan as you without ever seeing the patient.*
- It is extremely unlikely that a Therapeutic Use Exemption will be approved for "functional" hypogonadism (a diagnosis of hypogonadism based on low testosterone levels but without a defined etiology).
- The International Standard for Therapeutic Use Exemptions specifically states that "low-normal" levels of any hormone will not justify the granting of a TUE.
- USADA will not grant TUEs for testosterone to females, including Hormone Replacement Therapies that contain testosterone, because there are permitted therapeutic alternatives available.
- The use of testosterone as an anti-aging medication for men is not justification for a TUE. Similarly, generalized fatigue, slow recovery from exercise and a decreased libido are not, in isolation, justification for the granting of a TUE for testosterone.

Required Documentation for a TUE application (please check these items as you add them to the application- if any items are unchecked, the application is incomplete and will be returned to the athlete):

- A completed TUE application form. Note, there are sections of the TUE application form that should be filled out by the physician.
- The tables on the next page completely filled out. You must provide *at least two baseline T measurements* (i.e measurements of T without any T therapy). If the athlete has been on T therapy, it should be discontinued for 1-2 months and then two baseline T measurements should be taken in the morning on two separate visits)
- A letter from the doctor clearly stating:
 - The diagnosis and the pertinent medical history
 - The conclusions made by the doctor based on the physical exams
 - The conclusions made by the doctor based on these lab tests.
- An appendix with copies of ALL PERTINENT LAB TESTS IN CHRONOLOGICAL ORDER.
 - A cover sheet for this appendix is provided in this packet. Please place this cover sheet on top of the lab tests before you scan, mail, or fax the packet to USADA so that we can clearly identify them.
- An appendix with copies of ALL RELEVANT CLINICAL NOTES IN CHRONOLOGICAL ORDER
 - A cover sheet for this appendix is provided in this packet. Please place this cover sheet on top of the lab tests before you scan, mail, or fax the packet to USADA so that we can clearly identify them.

Office Use Only: Assigned # _____ Case # _____



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Diagnosis

(please select one). If "other" please write here:

Primary Hypogonadism	Secondary Hypogonadism
<input type="checkbox"/> Klinefelter Syndrome <input type="checkbox"/> Bilateral Anorchia <input type="checkbox"/> Cryptorchidism <input type="checkbox"/> Leydig Cell Aplasia <input type="checkbox"/> Male Turner Syndrome <input type="checkbox"/> Noonan's Syndrome <input type="checkbox"/> Congenital adrenal hyperplasia	<input type="checkbox"/> Panhypopituitarism <input type="checkbox"/> Idiopathic hypogonadotropic hypogonadism <input type="checkbox"/> Kallmann's syndrome <input type="checkbox"/> Constitutional delay of puberty <input type="checkbox"/> LH deficiency <input type="checkbox"/> Prader Willi syndrome

Hormone Measurements Spreadsheet

Please summarize, in chronological order, the laboratory test results that you are supplying in this application. Make sure to attach copies the lab result using the coversheets below for each section.

Date and time of sample collection	Prl	T	LH	FSH	If the patient has been using T, how long since the last dose?	Method Used (please check) (USADA will not accept T measurements made using other methods)
Date: Time:					(you must provide a minimum of 2 baseline T measurements)	<input type="checkbox"/> Calculated Free T <input type="checkbox"/> Equilibrium Dialysis
Date: Time:					(you must provide a minimum of 2 baseline T measurements)	<input type="checkbox"/> Calculated Free T <input type="checkbox"/> Equilibrium Dialysis
Date: Time:						<input type="checkbox"/> Calculated Free T <input type="checkbox"/> Equilibrium Dialysis
Date: Time:						<input type="checkbox"/> Calculated Free T <input type="checkbox"/> Equilibrium Dialysis
Date: Time:						<input type="checkbox"/> Calculated Free T <input type="checkbox"/> Equilibrium Dialysis



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Attachment 1: Laboratory Tests organized in

Chronological order.

Please place this coversheet on top of the copies of the laboratory tests that you have noted in the Hormone Measurements table, and that you are using as the basis of your diagnosis.

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**Attachment 2: Clinical and Exam Notes organized in
Chronological order.**

Please place this coversheet on top of the copies of the relevant clinical exam notes that you used as the basis of your diagnosis.

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ANDROGEN DEFICIENCY/MALE HYPOGONADISM

1. Medical Condition

Hypogonadism in men is a clinical syndrome that results from failure of the testes to produce physiological levels of testosterone (androgen deficiency) and in some instances normal number of spermatozoa (infertility) due to disruption of one or more levels of the hypothalamic-pituitary-testicular axis. The two distinct yet interdependent testicular functions, spermatogenesis and steroidogenesis (androgen production), operate and can fail independently. Androgen deficiency is the focus of this document.

2. Diagnosis

A. Etiology

Androgen deficiency may be primary, due to a problem with the testes, or secondary, due to a problem with the hypothalamic-pituitary-gonadal axis or combined primary and secondary. The etiology of androgen deficiency may be organic, in which there is a pathological physical change in the structure of an organ or within the hypothalamic-pituitary-testicular axis. Androgen deficiency may be functional in which there is no observable pathological change in the structure of an organ or within the hypothalamic-pituitary-testicular axis. Organic defects are usually long lasting or permanent while functional defects are potentially reversible.

Organic causes of androgen deficiency *

Organic primary androgen deficiency may be due to:

1. Genetic abnormalities – Klinefelter’s Syndrome and variants (i.e. 47,XYY/46XY, 46,XX testicular DSD, 45,X/46,XY), dysgenetic testes, myotonic dystrophy
2. Developmental abnormalities – cryptorchidism, congenital anorchia
3. Metabolic abnormalities – hemochromatosis (usually consistent with secondary hypogonadism)
4. Direct testicular trauma, surgical bilateral orchidectomy, testicular torsion
5. Orchitis – severe bilateral with subsequent testicular atrophy due to mumps or other infections.
6. Radiation treatment or chemotherapy

Medical Information to Support the Decisions of TUECs
ANDROGEN DEFICIENCY/MALE HYPOGONADISM

Organic secondary androgen deficiency may be due to:

1. Genetic abnormalities – Isolated hypogonadotropic hypogonadism (IHH) and variants
2. Pituitary disorders – hypopituitarism, tumor, infection, hemochromatosis, hyperprolactinemia due to prolactin-secreting pituitary tumor
3. Structural and infiltrative effects of systemic diseases – CNS developmental abnormalities, infection, β -thalassemia/hemoglobinopathies, granulomatous diseases, lymphocytic hypophysitis hemochromatosis, sickle cell disease
4. Anatomical problems - pituitary stalk section, hypophysectomy, pituitary-hypothalamic disease, traumatic brain injury

Functional Causes of androgen deficiency*

Functional androgen deficiency may be due to:

1. Severe emotional stress
2. Morbid Obesity, untreated obstructive sleep apnea
3. Overtraining, malnutrition/nutritional deficiency, eating disorders
4. Medication – opioids, androgens, selective androgen receptor modulators (SARMs), glucocorticosteroids, progestins, estrogens, medication-induced hyperprolactinemia
5. Chronic systemic illness (chronic organ failure, diabetes mellitus, malignancy, rheumatic disease, HIV infection, Crohn's disease, inherited metabolic storage diseases)
6. Constitutional delayed puberty**
7. Aging/Late onset hypogonadism (LOH)
8. Alcohol excess

Defects in androgen action include:

1. Androgen receptor defects of which there is a full spectrum from testicular feminization to Reifenstein's Syndrome to mild defects. Serum testosterone levels are not reduced and LH and estradiol levels may be increased.
2. 5 α -reductase deficiency: May present with selective signs of partial androgen deficiency. Serum testosterone levels are not reduced.

TUE should only be approved for androgen deficiency that has an organic etiology. TUE should not be approved for androgen deficiency due to functional disorder. TUE for androgen deficiency should not be approved for females.

* The list is representative of observed conditions and not necessarily complete

** May be approved for limited time until puberty is attained

B. Medical Evaluation

The TUE application must include the following information submitted to the appropriate Antidoping organization (ADO). This information must be submitted in a letter from the treating physician (preferably a specialist in endocrinology). This submission must include information listed below, dates of evaluation, copies of laboratory and testing results. If androgen deficiency is iatrogenic in origin (orchiectomy, pituitary surgery or irradiation, radiotherapy or chemotherapy), details of the diagnosis and treatment including surgery reports should be submitted. The evaluation for androgen deficiency, unless otherwise stated, must include:

1. History:

- a. Pubertal progression - incomplete or delayed sexual development
- b. Reduced libido and sexual activity
- c. Decreased spontaneous erections and/or ejaculations
- d. Hot flushes, sweats
- e. Non specific symptoms – decreased energy, depressed mood, dysthymia, poor concentration, sleep disturbance, hypersomnolence, mild anemia, reduced muscle bulk & strength, increased body fat and BMI, diminished work performance
- f. Low or zero sperm count (may not be associated with low testosterone)
- g. Low bone density (loss of height or low trauma fractures)
- h. History of cryptorchidism, torsion or significant testicular injuries
- i. History of significant head injuries
- j. History of orchitis
- k. Family history of delayed puberty

2. Physical Exam:

- a. Gynecomastia
- b. Changes in hair pattern (axillary & pubic), reduced shaving, absence of temporal recession
- c. Decreased testicular volume (small testes) <15cc by orchidometry or ultrasound

3. Testing/Laboratory evaluation (blood drawn in the morning) to demonstrate consistent androgen deficiency should be provided with the TUE application including:

- a. Total testosterone – assay using an accurate and reliable method

- b. Free testosterone – using an accurate and reliable method (e.g. calculated free testosterone from total testosterone and SHBG measurements or free testosterone by equilibrium dialysis), if available
- c. LH and FSH
- d. SHBG
- e. Semen analysis including sperm count if fertility an issue
- f. DEXA scan if bone density an issue
- g. Urine drug screens may be requested and organized by the Anti-Doping Organization

a, b (if available) & c must be drawn on at least two occasions at least a week apart in a 4-week period.

- 4. If hypogonadotropic hypogonadism or hypopituitarism is diagnosis:
 - a. MRI of brain with pituitary (sella) cuts with and without contrast
 - b. Pituitary function tests if appropriate
 - c. Other appropriate diagnostics to identify an organic etiology for secondary hypogonadism (e.g. prolactin, iron studies and genetic testing for hereditary hemochromatosis).
 - d. Documentation of appropriate evaluation of the etiology of hypogonadism should be provided with the TUE application.

3. Medical Treatment

A. Name of prohibited substances

Testosterone or human Chorionic Gonadotropin (hCG)

B. Route/Dosage/Frequency

Treatment with approved testosterone formulations or hCG (if athlete has secondary hypogonadism documented and desires fertility)

1. Testosterone may be administered by regular intramuscular injection. The treatment must be recorded by a health professional and kept available for control at any time. The administration of intramuscular testosterone will be by IM injection every one to two weeks to replace endogenous secretion. If every week, then the dose should be lower than every two week dosing. If testosterone undecanoate ester is the medication prescribed, the dosing intervals are every 12 weeks on average.

2. Testosterone may also be administered by transdermal patch or gel. The testosterone patch or gels have a daily dosing regimen. A buccal testosterone tablet applied twice daily is also available.

3. Testosterone may be administered by oral preparation testosterone undecanoate, usually twice or thrice daily with meals. 17 α -methyl testosterone is not suggested due to hepatotoxic side effects and potential liver toxicity.

4. Human Chorionic Gonadotropin (hCG) may be used in doses of 1000-2000 IU IM 2-3 times per week for those individuals requesting fertility. Higher doses may be needed in some men in order to maintain physiological testosterone levels. FSH, if required, is not a prohibited substance.

C. Monitoring dosage

The dosage and frequency are to be determined by the prescribing endocrinologist utilizing standard dosage regimens. The dosage should be monitored with trough serum testosterone levels for injectable testosterone. The testosterone product, dosage and timing of the previous treatment with injectable testosterone products must be recorded and submitted for annual review or for dosage changes. Gel testosterone can be monitored by serum testosterone levels at any time. HCG should be monitored with trough serum testosterone levels. The dosage and timing of treatments with hCG must be recorded and submitted for annual review or for dosage changes. Any change in product, dosage or treatment schedule of testosterone or hCG should be approved by ADO.

D. Duration of treatment

The duration of treatment may be lifelong but annual renewal including evidence of well-controlled therapy including dosage and timing of treatments, serum testosterone levels must be submitted for review.

4. Other non-prohibited alternative treatments?

If the diagnosis is confirmed, there is not a non-prohibited substance alternative treatment.

5. Consequences to health if treatment is withheld

Under developed genitals (if before puberty), muscle weakness, osteoporosis, diminished libido, erectile dysfunction/impotence, infertility, depression.

6. Treatment monitoring

Regular physician visits with documentation that testosterone treatment improved clinical manifestations of androgen deficiency in medical record are required.

The athlete is responsible for maintaining a complete record of testosterone prescriptions of oral, gel or buccal testosterone products and date, dosage and name of medical personnel administering injections of testosterone or hCG. Frequent testing of serum testosterone including unannounced urine and blood testing as ordered by ADO (at least 1-2 times per year) should be required and related to injection timing or gel application. Treatment should return the testosterone to mid-normal levels.

7. TUE validity and recommended review process

The duration of approval will be limited to 4 years in all cases at a maximum. In all cases the annual review process demonstrating testosterone level and symptom control of well adapted dose should occur every year. Copies of medical records of visits with prescribing physician, laboratory reports for serum testosterone levels (with dates and times) must be provided and accompanied by prescriptions for oral, transdermal or buccal preparations and the product, dosage, dates and names of administering medical personnel of all injectable testosterone or hCG administrations. Another independent specialist may be consulted as necessary. Documentation in medical records of the reason for changes in the dosage of testosterone and testosterone levels before and after a dosage change should be provided with a report prior to dosage change. The ADO should approve any changes in the dosage of testosterone or hCG.

8. Any appropriate cautionary matters

In the particular case of a young athlete with delayed puberty, the opinions of a pediatrician and an endocrinologist must confirm the diagnosis and a need for testosterone supplementation. This should be accompanied by the report of a relevant clinical examination. The approval must always be for a period of no more than one year.

Given the potential controversy associated with the approval of a TUE for testosterone, the opinion of an independent endocrinologist with expertise in Andrology is strongly suggested.

9. References

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