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TUE Application for Testosterone – Physician Worksheet

Attention Physicians - USADA will not process Therapeutic Use Exemptions (TUE) for the use of testosterone unless all of the requirements for documentation are submitted. Please review the bulleted list below for adequate background before proceeding.

Required Documentation for a TUE Application (INCOMPLETE OR DISORGANIZED APPLICATIONS WILL BE RETURNED)

1. A complete TUE application form-pages 1 & 2 filled out by the athlete, pages 3 & 4 filled out by the physician.
2. The Hormone Measurements Summary Data Table must be filled out with details that are validated by the lab and/or clinical notes included in the application.
 - ***If currently on T - therapy, see page 11, WADA TUE Physician Guidelines-ANDROGEN DEFICIENCY/ MALE HYPOGONADISM for washout period guidelines prior to having any samples collected. Anabolic urine screens during washout should be included in the lab data section.***
 - *Results of at least two baseline measurements of Serum total testosterone, Serum LH, Serum FSH, & Serum SHBG. (When indicated, semen analysis including sperm count & motility if fertility is a consideration. A DEXA scan may be included if appropriate.)*
 - *Samples collected in the morning, while fasting between 0700-1000 (within a 4-week period, at least one week apart)*
 - *Results analyzed by an accurate and reliable method. Free-T measured by equilibrium dialysis may be submitted as well as calculated free-T from Total-T. **Direct free-T by immunoassay will not be accepted.***
3. ***Diagnosis by a physician (preferably a specialist in endocrinology or andrology) consisting of but not limited to:***
 - *Dates of evaluation (including history & physical exam), copies of laboratory values (with reference ranges) and results. If testosterone deficiency is iatrogenic in origin (orchiectomy, pituitary surgery or irradiation, radiotherapy or chemotherapy), details of the diagnosis and treatment including surgical reports should be submitted. **See Section 2-Diagnosis-Paragraph B. Medical Evaluation-subsections 1-4 of the WADA TUE Physician Guidelines for a detailed list of medical evaluation requirements.***
4. ***Copies of ALL PERTINENT LAB TESTS IN CHRONOLOGICAL ORDER (most recent first going backwards).***
 - *A cover sheet for this appendix is provided in this packet. Place cover sheet on top of the lab tests before you scan, mail, or fax the packet to USADA so we can clearly identify them.*
5. ***Copies of ALL RELEVANT CLINICAL NOTES IN CHRONOLOGICAL ORDER (most recent first going backwards).***
 - *A cover sheet for this appendix is provided in this packet. Place cover sheet on top of the clinical notes before you scan, mail, or fax the packet to USADA so we can clearly identify them.*



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Physician Considerations for Testosterone TUE Applications

- Low levels (within or outside normal reference ranges) of any endogenous hormone absent a defined organic etiology will not justify the granting of a TUE, even if within standard of care & prescribed by a physician.
- USADA evaluates all complete TUE applications submitted by both males and females under the applicable ISTUE criteria. An unequivocal organic etiology must be demonstrated in all cases.
- The use of Testosterone (T) as an anti-aging medication is not justification for a TUE. Similarly, generalized fatigue, slow recovery from exercise and decreased libido are not, in isolation, justification for granting a TUE.
- It is extremely unlikely that a TUE will be approved for "functional" hypogonadism (a diagnosis of hypogonadism based on low T levels without a defined, organic etiology).
- All TUE applications for T based on secondary hypogonadism should include a detailed history of corticosteroid & opiate use & exclusion of hematochromatosis. Additionally, a pituitary MRI with and without contrast plus pituitary function tests (e.g. morning cortisol, ACTH stimulation, TSH, free T4, Prolactin) may be appropriate.
- The Therapeutic Use Exemption Committee (TUEC) will review the entire evaluation and need enough medical information, to make the same diagnosis & arrive at the same treatment plan without ever seeing the patient.

<i>Diagnosis-Please select one option below and indicate the ICD10 code. If "other," please annotate below:</i>	
Primary Hypogonadism	Secondary Hypogonadism
<input type="checkbox"/> Klinefelter Syndrome <input type="checkbox"/> Bilateral Anorchia <input type="checkbox"/> Cryptorchidism <input type="checkbox"/> Bilateral Orchiectomy <input type="checkbox"/> Other Organic Etiology	<input type="checkbox"/> Panhypopituitarism <input type="checkbox"/> Congenital Hypogonadotropic Hypogonadism <input type="checkbox"/> Constitutional Delay of Puberty <input type="checkbox"/> Hypothalamic or Pituitary Tumor, Destruction or Infiltrative Disease



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*Attachment 2: Clinical and Exam Notes
Organized in Chronological Order*

(Most recent first)

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

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 (testosterone 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, steroidogenesis (testosterone production) and spermatogenesis can fail independently. Testosterone deficiency is the focus of this document.

2. Diagnosis

A. Etiology

Hypogonadism may be **primary**, due to a problem with the testes, or **secondary**, due to a problem with the hypothalamus or pituitary gland or **combined primary and secondary**. The etiology of testosterone deficiency may be **organic**, in which there is a pathological structural or congenital defect within the hypothalamic-pituitary-testicular axis. Hypogonadism may be **functional** in which there is no observable pathological change in the structures within the hypothalamic-pituitary-testicular axis. Organic hypogonadism is usually long-lasting or permanent while functional hypogonadism is potentially reversible.

TUE should only be approved for hypogonadism 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.

Organic causes of hypogonadism (See Appendix A for a more detailed list)

❖ **Organic primary hypogonadism may be due to:**

1. Genetic abnormalities
2. Developmental abnormalities
3. Testicular trauma, bilateral orchiectomy, testicular torsion
4. Orchitis
5. Radiation treatment or chemotherapy.

❖ **Organic secondary hypogonadism may be due to:**

1. Genetic abnormalities of pituitary and hypothalamus
2. Pituitary or hypothalamic tumors
3. Other anatomical (structural), destructive and infiltrative disorders of the pituitary or hypothalamus.

❖ **Organic defects in androgen action or production (Disorders of Sex Development (46,XY DSD)):**

1. 46,XY DSD due to androgen receptor defects that range from males with complete androgen insensitivity (CAIS, formerly known as testicular feminization) who have a near-normal female phenotype to males with partial androgen insensitivity (PAIS or MAIS) who have near-normal male phenotype.
2. 46,XY DSD due to 5 α -reductase deficiency (5ARD2) in genetic males who have ambiguous genitalia at birth.

❖ **Constitutional delayed puberty** is viewed as a special category since TUE may be approved for treatment with testosterone. (see **Section 8** and **Appendix A**)

Functional causes of hypogonadism (The list is representative of observed conditions and not necessarily complete).

❖ **Functional hypogonadism may be due to:**

1. Severe psychological/emotional stress
2. Obesity (WHO grade III or IV – BMI>30)
3. Untreated obstructive sleep apnea
4. Overtraining, malnutrition/nutritional deficiency, eating disorders
5. Medication such as opioids, androgens, anabolic steroids, GnRH analogues, selective androgen receptor modulators, (SARMs), glucocorticoids, progestins, estrogens, medication-induced hyperprolactinemia
6. Chronic systemic illness (kidney, liver, lung, heart failure, diabetes mellitus, malignancy, inflammatory joint disease, HIV infection, Crohn's disease, inherited metabolic storage diseases)
7. Aging/Late onset hypogonadism (LOH)
8. Alcohol excess
9. Cannabinoid abuse.

❖ **Varicocele is not a cause of organic hypogonadism and not an acceptable diagnosis for TUE for testosterone treatment.**

❖ **Andropause** is not an acceptable diagnosis for TUE for hypogonadism.

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

B. Medical Evaluation

A complete medical evaluation is necessary for a TUE application; nevertheless a TUE will only be granted if a full picture of hypogonadism TUE of organic etiology is demonstrated.

The TUE application must include the following information submitted to the appropriate Anti-Doping Organization (ADO). This information must be submitted in a letter from the treating physician (preferably a specialist in endocrinology or andrology). This submission must include information listed below, dates of evaluation (including history and physical examination), copies of laboratory values (with reference ranges) and testing results. If testosterone 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 testosterone deficiency, unless otherwise stated, **must** include:

1. Required history:

- a. Pubertal progression - incomplete or delayed sexual development
- b. Libido and frequency of sexual activity – duration and severity of any problems
- c. Erections and/or ejaculations
- d. Hot flushes, sweats
- e. Testicular disorders – cryptorchidism, testicular torsion, testicular injuries,
- f. Significant head injuries
- g. Orchitis
- h. Family history of delayed puberty
- i. Non-specific symptoms – decreased energy, depressed mood, dysthymia, poor concentration, sleep disturbance or sleepiness, mild anemia, reduced muscle bulk & strength, increased body fat and BMI, diminished work performance.

2. Physical Exam features **must be addressed:**

- a. Gynecomastia
- b. Changes in hair pattern (axillary & pubic), reduced shaving, absence of temporal recession
- c. Testicular volume by orchidometer or ultrasound (abnormal is <15 ml)
- d. Height and weight – BMI
- e. Muscular development and tone.

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

Required Testing:

To be drawn before 10 AM with Serum total testosterone and Serum LH drawn on two occasions within a 4-week period at least a week apart

1. Serum total testosterone – assay using an accurate and reliable method before 10 AM
2. Serum LH
3. Serum FSH
4. Serum SHBG

Testing when indicated:

1. Semen analysis including sperm count if fertility an issue (should submit at least two semen analyses)
2. DEXA scan if appropriate
3. Inhibin B when considering Congenital Isolated Hypogonadotropic Hypogonadism or Constitutional Delayed Puberty

Free testosterone

Free testosterone – free testosterone measured by equilibrium dialysis may be submitted. Direct analog-based free T assays are not permitted. TUE will not be granted as a result of low free testosterone only.

Drug screening during evaluation for hypogonadism

1. Urine drug screens may be requested and organized by the ADO.

Athletes who are already taking testosterone supplementation will need to stop the medication for a sufficient time-period to properly evaluate the need for testosterone. It is expected that endogenous testosterone levels will be transiently low in the period immediately following cessation of exogenous supplementation. The washout schedule, which is in Appendix B, is to be followed prior to re-testing.

For diagnosis of Organic Hypogonadotropic-Hypogonadism

1. MRI of pituitary with and without contrast
2. Pituitary function tests as indicated – e.g. morning cortisol, ACTH stimulation test, TSH, free T4, prolactin
3. Other appropriate diagnostics to identify an organic etiology for secondary hypogonadism (e.g. prolactin, iron studies and genetic testing for hereditary hemochromatosis)
4. Documentation ruling out any potential functional causes of hypogonadotropic hypogonadism.

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). Only products and dosage regimens approved by drug regulatory agencies are allowed.

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 enanthate or cypionate or mixed testosterone esters is typically a 100 mg injection every week or 150-250 mg every two weeks to replace endogenous secretion. If testosterone undecanoate ester is the medication prescribed, the standard dosage is 750-1000 mg dependent upon drug regulatory agency, with the dosing intervals of every 10-12 weeks on average
2. Testosterone may also be administered by transdermal patch, cream, gel or lotion. The testosterone patches, creams, gels or lotions have a daily dosing regimen. A buccal testosterone tablet and nasal spray administered twice daily are also available
3. Testosterone may be administered by oral preparation testosterone undecanoate in 40 mg capsules, usually twice or thrice daily with meals. 17 α -methyl testosterone is hepatotoxic and should not be used due to 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 and induction of spermatogenesis and fertility. 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 replacement dosage regimens. The dosage should be monitored with mid-interval (midway between two successive injections) or trough (at the time of next scheduled injection) 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. Transdermal testosterone patches, gels, creams or solutions 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 review of evidence of well-controlled therapy must be submitted. The evidence submitted must include medication logs, injection logs and pharmacy records, dosage and timing of treatments as well as regular testing of serum testosterone levels.

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

Underdeveloped genitals (if before puberty), muscle weakness, osteoporosis, diminished libido, sexual dysfunction (impotence or erectile dysfunction), infertility.

6. Treatment monitoring

Regular physician visits with documentation that testosterone treatment improved clinical manifestations of testosterone deficiency in medical record are required. **The athlete is responsible for maintaining a complete record of testosterone prescriptions of oral, transdermal (patches, gels, creams, solutions) or buccal testosterone products and date, dosage (pharmacy records) 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 use standard testosterone doses which should return the mid-interval 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 temporary testosterone treatment of a pre-determined fixed duration and subject to repeat after review of progress and ongoing need for testosterone treatment. This should be accompanied by the report of a relevant clinical examination including Tanner stage. 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 or male reproductive endocrinology is strongly suggested.

9. References

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APPENDIX A

Organic Causes of Hypogonadism*

The list is representative of observed conditions and not necessarily complete

Organic primary hypogonadism may be due to:

1. Genetic abnormalities
 - a. Klinefelter's Syndrome and variants (i.e. 47,XYY/46,XY)
 - b. Dysgenetic testes
 - c. Myotonic dystrophy.
2. Developmental abnormalities
 - a. Cryptorchidism
 - b. Congenital anorchia.
3. Direct testicular trauma, bilateral orchiectomy, testicular torsion.
4. Orchitis – severe bilateral with subsequent testicular atrophy due to mumps or other infections.
5. Radiation treatment or chemotherapy.
6. 46,XY DSD due to defects in testosterone biosynthesis (formerly male pseudohermaphroditism).
7. LH/hCG receptor defects.

Organic secondary hypogonadism may be due to:

1. Genetic abnormalities of pituitary and hypothalamus
 - a. Congenital isolated hypogonadotropic hypogonadism (IHH), including Kallmann Syndrome
 - b. Congenital isolated LH deficiency
 - c. Congenital pituitary defects causing multiple pituitary hormone deficiency (MPHD) complex congenital syndromes.
2. Pituitary or hypothalamic tumors
 - a. Adenomas
 - b. Prolactin secreting pituitary tumor resulting in hyperprolactinemia
 - c. Craniopharyngioma.
3. Infections
4. Iron Overload Syndromes
 - a. Hemochromatosis
 - b. Hemoglobinopathies

- i. β -Thalassemia
 - ii. Sickle cell disease.
5. Structural, destructive and infiltrative disorders of the pituitary or hypothalamus
 - a. CNS developmental abnormalities, infection
 - b. Granulomatous diseases
 - c. Lymphocytic hypophysitis.
 6. Anatomical problems of the pituitary or hypothalamus
 - a. Pituitary stalk section
 - b. Hypophysectomy
 - c. Pituitary-hypothalamic disease
 - d. Severe or repeated traumatic brain injury causing pituitary dysfunction.
 7. Hypogonadotropic Hypogonadism combined with adrenal insufficiency (X-linked adrenal hypoplasia (AHC)).

Organic defects in androgen action or production (Disorders of Sex Development (46,XY DSD))

1. 46,XY DSD due to androgen receptor defects that range from males with complete androgen insensitivity (CAIS, formerly known as testicular feminization) who have a near-normal female phenotype to males with partial androgen insensitivity (PAIS or MAIS) who have near-normal male phenotype. Serum testosterone levels may be normal and LH levels may be elevated.
2. 46,XY DSD due to 5 α -reductase deficiency (5ARD2) in males who have ambiguous genitalia at birth and may be raised as female, but who at puberty, develop near-normal male somatic phenotype with normal male range testosterone levels.

Constitutional delayed puberty is a special category. Constitutional delayed puberty is not a permanent condition, although it may have a genetic component. TUEs should be allowed for this condition as prescribed by the treating endocrinologist or pediatrician but treatment should never extend past the initiation of puberty.

Comment on IHH

Idiopathic Hypogonadotropic Hypogonadism (IHH) has sometimes been confused with **Isolated Hypogonadotropic Hypogonadism**. Isolated HH is an old term that distinguished a series of genetic disorders that led to gonadotropin deficiency and pubertal failure from panhypopituitarism. Isolated HH is due to **organic** disorders and therefore can justify the granting of a TUE. Idiopathic HH is a term that has been used frequently in recent years. It includes isolated HH but extends as an umbrella term to include various acquired (non-genetic) **functional** disorders (e.g. obesity, cardiovascular disease, depression, opiate or exogenous androgen use, overtraining, etc.) which are associated with a low circulating testosterone. Idiopathic Hypogonadotropic Hypogonadism is not an acceptable diagnosis for TUE application.

Appendix B

Washout Table

Product with route of administration	Washout period^{1 2}	Urine test (anti-doping)	Blood tests LH, FSH, Testosterone
<i>Transdermal testosterone (testosterone patch, gel or cream)</i>	<i>2 weeks</i>	<i>At beginning of wash-out (week 0)</i>	<i>End of wash-out (week 2) and again between weeks 3-4</i>
<i>Oral (testosterone undecanoate) or buccal testosterone</i>	<i>2 weeks</i>	<i>At beginning of washout period (week 0)</i>	<i>End of wash-out (week 2) and again between weeks 3-4</i>
<i>Intermediate acting testosterone by IM injection (testosterone enanthate, testosterone cypionate or mixed esters)</i>	<i>8 weeks</i>	<i>At week 0 plus 1 random between weeks 3-7</i>	<i>1 test at week 8 and then another within the next 4 weeks, at least one week apart.</i>
<i>Long acting testosterone by IM injection (testosterone undecanoate)</i>	<i>26 weeks</i>	<i>At week 0 plus 2 random tests between weeks 3-25</i>	<i>1 test at week 26 and then another within the next 4 weeks, at least one week apart.</i>
<i>Subcutaneous testosterone pellets</i>	<i>40 weeks</i>	<i>Week 0 plus 2 or 3 random tests during weeks 8-38</i>	<i>1 test at week 40 and then another within the next 4 weeks, at least one week apart.</i>

¹ Washout period represents the time that the exogenous testosterone would have left the system and one would likely see recovery from medication effects for men using standard testosterone doses for limited amount of time. For those using higher than standard doses for prolonged periods, the washout period for the medication and the full reproductive axis recovery can be more prolonged.

² During washout period, drug testing to prevent the continued use of testosterone products or analogs is critical to insure adherence to medication abstinence.