
Title: ***Testosterone***.

[Link to Patient Education Sheet: English Version]

Source: Clinical Pharmacology.

Generic Name: Testosterone

Brand Name: Andro®; AndroGel®; depoAndro®; Depo®-***Testosterone***; Androderm®; Testoderm®; Testoderm TTS®; Testopel®

Subset: Drug Monograph

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Testosterone

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NOTE: ***Testosterone*** is a schedule C-III controlled substance.

Description

Testosterone is the primary androgen found in the body. Endogenous ***testosterone*** is synthesized by cells in the testis, ovary, and adrenal cortex. Therapeutically, ***testosterone*** is used in the management of hypogonadism, either congenital or acquired. ***Testosterone*** is also the most effective exogenous androgen for the palliative treatment of carcinoma of the breast in postmenopausal women. Anabolic steroids, derivatives of ***testosterone***, have been used illicitly and are now controlled substances. ***Testosterone*** was in use in 1938 and approved by the FDA in 1939. ***Testosterone*** is administered parenterally in regular and delayed-release (depot) dosage forms. Two transdermal forms are available for the treatment of male hypogonadism. Testopel® Implants contain ***testosterone*** in sterile pellets that are implanted subcutaneously for extended-release over 3–6 months. Two ***testosterone*** topical skin gel products are available: Androgel®, approved in February 2000, and Testim™, approved October 31, 2002. A ***testosterone*** buccal system (Striant™) was FDA approved in July 2003; the system is a mucoadhesive product that adheres to the buccal mucosa and provides a controlled and sustained release of ***testosterone***. Other topical dosage forms are under investigation, including a transdermal patch for hormone replacement in women; daily dosages used for ***testosterone*** replacement in women are much

lower than those found in products for use in males. ***Testosterone*** was reclassified as a controlled substance in 1991.

Mechanism of Action

Endogenous ***testosterone*** is responsible for sexual maturation at all stages of development throughout life. Synthetically, it is prepared from cholesterol. The function of androgens in male development begins in the fetus, is crucial during puberty, and continues to play an important role in the adult male. Women also secrete small amounts of ***testosterone*** from the ovaries. The secretion of androgens from the adrenal cortex is insufficient to maintain male sexuality.

Increased androgen plasma concentrations suppress gonadotropin-releasing hormone (reducing endogenous ***testosterone***), luteinizing hormone, and follicle-stimulating hormone by a negative-feedback mechanism. ***Testosterone*** also affects the formation of erythropoietin, the balance of calcium, and blood glucose. Androgens have a high lipid solubility, enabling them to rapidly enter cells of target tissues. Within the cells, ***testosterone*** undergoes enzymatic conversion to 5-alpha-dihydrotestosterone and forms a loosely bound complex with cystolic receptors. Androgen action arises from the initiation of transcription and cellular changes in the nucleus brought about by this steroid-receptor complex.

Normally, endogenous androgens stimulate RNA polymerase, resulting in an increased protein production.These proteins are responsible for normal male sexual development, including the growth and maturation of the prostate, seminal vesicle, penis, and scrotum. During puberty, androgens cause a sudden increase in growth and development of muscle, with redistribution of body fat. Changes also take place in the larynx and vocal cords, deepening the voice. Puberty is completed with beard development and growth of body hair. Fusion of the epiphyses and termination of growth is also governed by the androgens, as is the maintenance of spermatogenesis. When endogenous androgens are unavailable, use of exogenous androgens are necessary for normal male growth and development.

Pharmacokinetics

Testosterone is administered IM, as a topical gel or ointment, by implantation of long-acting pellets, or via buccal or transdermal systems. ***Testosterone*** is absorbed from the GI tract, but because of extensive first-pass metabolism, oral bioavailability is poor.

Buccal absorption: Following application to the buccal mucosa, the buccal mucoadhesive system (Striant™) slowly releases ***testosterone*** where it is absorbed through gum and cheek surfaces that are in contact with the buccal system. Venous drainage from the mouth is to the superior vena cava, therefore transbuccal delivery of ***testosterone*** circumvents first-pass metabolism. Maximum ***testosterone*** concentrations are achieved within 10–12 hours of application of the system.

Intramuscular absorption: Parenteral formulations have been developed that reduce the rate of ***testosterone*** secretion, with esters being less polar and slowly absorbed from intramuscular sites. Esters have a duration of action of 2–4 weeks following IM administration. The esters are hydrolyzed to free ***testosterone***, which is inactivated in the liver.

Subcutaneous implantable pellets: The duration of action of ***testosterone*** pellets (Testopel®) is usually 3–4

months, but may last as long as 6 months.

Topical skin gel/ointment absorption: Roughly 10% of an applied topical dosage of ***testosterone*** skin gel or ointment is systemically absorbed with once daily dosing; absorption of the gel from the skin occurs continually over the 24 hour dosing interval which indicates that the skin acts as a reservoir for sustained-release.

Transdermal patch absorption: There are three brands of ***testosterone*** patches available. Testoderm® patches are applied to the scrotum and serum concentrations of ***testosterone*** rise to a maximum after 2–4 hours, returning to baseline two hours after patch removal. Serum concentrations of ***testosterone*** approach those of normal males, and reach a plateau after 3–4 weeks. The scrotal skin is about five times more permeable than normal skin and Testoderm® will not achieve desired serum concentrations if applied to other skin sites. Testoderm® TTS patches achieve adequate serum concentrations when applied to the arm, back, or upper buttocks; serum ***testosterone*** concentrations peak at 2–4 hours and return towards baseline within roughly 2 hours of patch removal. Androderm® patches can be applied to any healthy skin site other than on the scrotum or bony areas. Daily application of two Androderm® skin patches at 10 PM results in serum ***testosterone*** concentrations that approach those of healthy young men and follow normal circadian variation. The first day of dosing results in morning serum ***testosterone*** concentrations within the normal range. There is no ***testosterone*** accumulation with continued use. Following removal of Androderm®, hypogonadal status returns within 24 hours. Baseline serum ***testosterone*** concentrations may be reduced because endogenous secretion of ***testosterone*** may be suppressed by Androderm®.

Distribution, metabolism and excretion: In serum, ***testosterone*** is bound to protein. ***Testosterone*** has a high affinity for sex hormone binding globulin (SHBG) and a low affinity for albumin. The albumin-bound portion freely dissociates. The affinity for SHBG changes throughout life. It is high during prepuberty, declines during adolescence and adult life, then rises again in old age. The active metabolite DHT has a greater affinity for SHBG than ***testosterone***. Elimination half-life is 10–100 minutes and is dependent on the amount of free ***testosterone*** in the plasma.

Testosterone is metabolized in the liver to various 17-keto steroids. Estradiol and dihydrotestosterone (DHT) are the major active metabolites, and DHT undergoes further metabolism. ***Testosterone*** activity appears to depend on formation of DHT, which binds to cytosol receptor proteins. Further metabolism of DHT takes place in reproductive tissues.

About 90% of a ***testosterone*** dose is excreted in the urine as conjugates of glucuronic and sulfuric acids. About 6% is excreted in the feces, largely unconjugated.

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