Testosterone

Drug Description

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

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 (Intrinsa™) for hormone replacement in women; the daily dosages used for testosterone replacement in women are much lower than those found in products for use in males. However, the FDA ruled in late 2004 that it would delay the approval of Intrinsa™ women's testosterone patch and is requiring more data regarding safety, especially in relation to cardiovascular and breast health. Testosterone was reclassified as a controlled substance in 1991.

Revision Date: 12/17/2009 11:43:00 PM

Classifications

Genitourinary Agents
- Impotence Agents

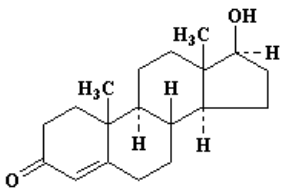
Hormones and Hormone Modifiers
- Androgens

Brand Names

- Andro-L.A.
- Androderm
- AndroGel
- Delatestryl
- Depandrate
- Depo-Testosterone
- First-Testosterone
- First-Testosterone MC
- Striant
- Testa Span
- Testerone
- Testim
- Testoderm
- Testone CYP 200
- Testopel
- Testosterone Cypionate
- Testosterone Enanthate
- Testosterone Propionate
- Tostrelle
- Tostrex
- Virilon Injection

Chemical Structures

Testosterone
$C_{19}H_{28}O_2$



Mechanism of Action

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.

Revision Date: 12/17/2009 11:43:00 PM

Pharmacokinetics

Pharmacokinetics:
Testosterone is administered IM, as a topical gel or ointment, by implantation of long-acting pellets, or via buccal or transdermal systems.

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.

•Route-Specific Pharmacokinetics
Oral Route
Testosterone is absorbed from the GI tract, but because of extensive first-pass metabolism, oral bioavailability is poor.

Intramuscular Route
Parenteral testosterone 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 Route
The duration of action of testosterone subcutaneous implantable pellets (Testopel) is usually 3—4 months, but may last as long as 6 months.

Topical Route
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.

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.

Other Route(s)
Buccal Route
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.

Revision Date: 12/17/2009 11:43:00 PM

Indications

- AIDS-associated wasting syndrome †
- andropause †
- anemia †
- cryptorchidism †
- delayed puberty
- erectile dysfunction (ED)
- hypogonadism
- lichen sclerosus †
- microphallus †
- palliative treatment of breast cancer
- trans-sexualism †

† non-FDA-approved indication

For androgen replacement therapy in males:
•for the treatment of erectile dysfunction (ED) (impotence):
Intramuscular dosage (testosterone suspension or testosterone propionate):
Adult males: 10—25 mg IM two or three times a week.
Intramuscular dosage (testosterone cypionate or testosterone enanthate):
Adult males: 50—400 mg IM once every 2—4 weeks.
•for the treatment of hypogonadism (primary and hypogonadotropic types) or symptoms associated with andropause†:
Intramuscular dosage (testosterone suspension or testosterone propionate):
Adult males: 10—25 mg IM two or three times per week.
Intramuscular dosage (testosterone cypionate or testosterone enanthate):
Adult males: 50—400 mg IM once every 2—4 weeks.
Children: For the initiation of pubertal growth: 40—50 mg/m^2 IM monthly until the growth rate falls to prepubertal levels. For the terminal growth phase: 100 mg/m^2 IM monthly until growth ceases. Maintenance of virilization may be achieved with a dose of 100 mg/m^2 twice monthly.
Subcutaneous dosage (Testopel Pellets):
Adult males and Children: Generally, 150—450 mg (2—6 pellets) is inserted subcutaneously by a health care professional every 3—6 months. The dosage is based on the minimal daily requirements of testosterone propionate determined by a gradual reduction of the amount administered parenterally. For every 75 mg/week of testosterone propionate, 150 mg (2 pellets) should be implanted every 3—6 months. Therapeutic effects of the pellets typically lasts for 3—4 months, but sometimes as long as 6 months. If testosterone therapy needs to be discontinued (e.g., for severe adverse reactions), the pellets may need to be removed by a health care professional.
Topical gel dosage (only for AndroGel):
Adult males >= 18 years: Initially 5 g of 1% gel (containing 50 mg of testosterone and delivering 5 mg of testosterone systemically) applied once daily (preferably in the morning) to clean, dry, intact skin of the upper arms and/or abdomen. Measure serum testosterone level 14 days later to ensure proper dosage. If the serum testosterone level is below the normal range or if the desired clinical response is not achieved, may increase to 7.5 g of gel once daily (containing 75 mg of testosterone

and delivering 7.5 mg/day of testosterone systemically), and then to 10 g of gel once daily (containing 100 mg of testosterone and delivering 10 mg/day of testosterone systemically) as clinically indicated. The maximum dosage is 10 g/day of gel based on clinical trials.

Topical gel dosage (only for Testim):

Adult males >= 18 years: Initially 5 g gel (one tube containing 50 mg of testosterone and delivering 5 mg of testosterone systemically) applied once daily (preferably in the morning) to clean, dry, intact skin of the shoulders and/or upper arms; do not apply to the genitals or abdomen. Measure morning serum testosterone levels roughly 14 days later to ensure proper dosage. If the serum testosterone level is below the normal range or if the desired clinical response is not achieved, may increase to 10 g (two tubes, delivering a total of 10 mg/day testosterone systemically) applied once daily. The maximum recommended dosage is 10 g/day of gel based on clinical trials.

Transdermal dosage (only for Testoderm):

Adult males >= 18 years: Initially, apply a 60 cm^2 patch (delivering 6 mg/day of testosterone systemically) to the scrotal area. The patch should be worn for 22 hours out of 24. For optimal contact the skin should be dry, clean, and dry-shaved if necessary. If the scrotal area is inadequate a 40 cm^2 patch (delivers 4 mg/day of testosterone systemically) may be applied. Determine serum testosterone levels after 3—4 weeks of use. If results are inadequate after 6—8 weeks, another form of replacement therapy should be used.

Children and Adolescents < 18 years: Safety and efficacy have not been established.

Transdermal dosage (only for Testoderm TTS):

Adult males >= 18 years: Apply a patch (one system) to an area of dry, clean skin on the arm, back, or upper buttocks every 24 hours. This patch will deliver 5 mg/day of testosterone systemically. Serum testosterone concentrations should be taken to determine whether normal serum testosterone levels have been achieved. Dose may be increased as appropriate.

Children and Adolescents < 18 years: Safety and efficacy have not been established.

Transdermal dosage (only for Androderm):

Adult males: Apply one patch (one system) nightly to an area of dry, clean skin on the upper arms, thighs, back or abdomen. The patch should be worn for 24 hours. The usual dose is 5 mg, changed daily, provided by two patches worn simultaneously at different sites. Serum testosterone concentrations should be taken to determine whether normal serum testosterone levels have been achieved. Depending on these results, the maintenance dose may be increased to 3 patches or reduced to 1 patch daily. Therapy for non-virilized patients should be started at 1 patch nightly.

Children and Adolescents < 18 years: Safety and efficacy have not been established.

Buccal Administration (only for Striant):

Adult males: Apply one 30 mg buccal system to the gum region just above the incisor tooth twice daily, approximately every 12 hours; when applying a new system, the old system should be removed and discarded. Place the rounded side surface of the buccal system against the gum and hold firmly in place with a finger over the lip and against the product for 30 seconds to ensure adhesion. The site of application should be rotated to alternate sides of the mouth with each application.

For the treatment of delayed puberty in males:

Intramuscular dosage (testosterone suspension or testosterone propionate):

Adolescent males: Up to 100 mg IM per month for a limited period, usually between 4—6 months. Different dosage schedules have been employed dependent on patients chronological and skeletal age, and response.

Intramuscular dosage (testosterone cypionate or testosterone enanthate):

Adolescents males: 50—200 mg IM once every 2—4 weeks for a limited period. Or, 40—50 mg/m^2/dose IM monthly for 6 months.

Subcutaneous dosage (Testopel Pellets):

Adolescent males: Generally, 150—450 mg (2—6 pellets) is inserted subcutaneously by a health care professional every 3—6 months, although the lower end of the dosing range is typically sufficient. Treatment is usually only required for 4—6 months. The dosage is based on the minimal daily requirements of testosterone propionate determined by a gradual reduction of the amount administered parenterally. For every 75 mg/week of testosterone propionate, 150 mg (2 pellets) should be implanted every 3—6 months. Therapeutic effects of the pellets typically lasts for 3—4 months, but sometimes as long as 6 months. If testosterone therapy needs to be discontinued (e.g., for severe adverse reactions), the pellets should be removed by a health care professional.

For palliative treatment of breast cancer that is inoperable in women:

Intramuscular dosage (testosterone suspension or testosterone propionate):

Adults: 50—100 mg IM three times a week.

Intramuscular dosage (testosterone cypionate or testosterone enanthate):

Adults: 200—400 mg IM once every 2—4 weeks.

For the treatment of postpubertal cryptorchidism†:

Intramuscular dosage (testosterone suspension or testosterone propionate):

Adult males: 10—25 mg IM two or three times per week.

For the treatment of microphallus†:
Intramuscular dosage (testosterone enanthate):
Children: 25—50 mg IM once a month for 3—6 months.
Topical dosage (testosterone propionate):
Children: Apply a 5% ointment topically to the penis twice daily for three months.

For the treatment of anemia† in patients with chronic renal failure:
Intramuscular dosage (testosterone enanthate):
Adults: Initially, 400 mg IM daily for one week, then 400 mg IM once or twice a week. Maintenance dose is 200—400 mg IM once every 4 weeks.

For female-to-male gender change (trans-sexualism†):
Intramuscular dosage (testosterone cypionate or testosterone enanthate):
Adults: 200 mg IM once every 2 weeks. Higher doses may be required for cessation of menses.

For the treatment of lichen sclerosus†:
Topical dosage (testosterone ointment):
Adults: Apply a 1% or 2% ointment topically to the vulva twice daily for six weeks or until itching is relieved. Decrease dosage to minimum effective dose.

For the treatment of AIDS-associated wasting syndrome†:
Intramuscular dosage:
Adults: In a randomized double-blind, placebo-controlled study, 51 HIV-positive men with AIDS-associated wasting syndrome were randomly assigned to receive testosterone enanthate 300 mg IM or placebo every 3 weeks for 6 months. Compared to patients treated with placebo, testosterone-treated patients had significant increases in lean body mass and an overall improvement in quality of life.[25533] In another study, the effects of testosterone enanthate (200 mg/week IM) or placebo, each with or without progressive resistance training three times weekly, were compared.[27069] Testosterone administration significantly increased lean body mass, muscle area, and muscle strength. Resistance exercise, independent of testosterone administration, also increased lean body mass and muscle area but had no effect on muscle strength; the increase in lean body mass with exercise alone was equivalent to the effects seen with anabolic steroids and lower doses of testosterone.[27069]

Maximum Dosage Limits
•Adults
Dependent on indication for therapy.
•Elderly
Dependent on indication for therapy.
•Adolescents
Dependent on indication for therapy.
•Children
Dependent on indication for therapy.

Patients with Hepatic Impairment Dosing
Generally, androgen use is contraindicated in patients with severe hepatic dysfunction. Specific guidelines for dosage adjustment in hepatic impairment are not available; use caution in patients with mild to moderate hepatic disease.

Patients with Renal Impairment Dosing
Specific guidelines for dosage adjustments in renal impairment are not available; it appears that no dosage adjustments are needed.

†non-FDA-approved indication

Revision Date: 7/23/2010 10:49:00 AM

Administration Information

General Administration Information
For storage information, see the specific product information within the How Supplied section.

Route-Specific Administration

Injectable Administration

- Administer intramuscularly. Do not inject intravenously.
- Visually inspect parenteral products for particulate matter and discoloration prior to administration whenever solution and container permit.

Intramuscular Administration:

- Use of a wet needle will cause a cloudy solution but will not alter potency.
- Inject IM deeply into the upper outer quadrant of the gluteal muscles; care should be taken to inject slowly; respiratory adverse reactions have been reported in patients receiving testosterone enanthate (Delatestryl), immediately after injection (see Adverse reactions).
- Aspirate prior to injection to avoid injection into a blood vessel.

Topical Administration

- Apply topically for subcutaneous absorption as transdermal patches, skin gels, or ointments.
- Wash hands before and after application of any of these dosage forms. Take care not to touch the eyes or other mucous membranes.

Cream/Ointment/Lotion Formulations:

- *AndroGel packet:* Open dosage form(s) needed for proper dosing. If using the packets, squeeze the entire contents of the dose into the palm of the hand and then immediately apply to the skin site; alternatively, squeeze a portion of the gel from the packet into the palm of the hand and apply to the application sites, repeating until the entire contents of the packet have been applied. Apply once daily (preferably in the morning) to clean, dry skin on the shoulders, upper arm or the abdomen. Do not apply to the genitals.
- *AndroGel Pump:* If using the pump applicator, each actuation of the metered dose pump dispenses 1.25 g of gel when fully depressed once (i.e., 4 pumps = 5 g; 6 pumps = 7.5 g; 8 pumps = 10 g) The pump must be primed before the first use by fully depressing the pump mechanism 3 times, and discarding any gel that is released during the priming. The entire dosage needed may be pumped into the palm of the hand and then immediately apply to the skin site or each individual actuation may be delivered into the palm of the hand and applied to the application sites, repeating until the entire contents of the packet have been applied. Alternatively, the gel can be directly applied to the application site which can prevent loss of product that may occur during transfer from the palm of the hand onto the application site. Apply once daily (preferably in the morning) to clean, dry skin on the shoulders, upper arm or the abdomen. Do not apply to the genitals.
- *Testim packet:* Open dosage form(s) needed for proper dosing. Squeeze the entire contents of the dose into the palm of the hand and then immediately apply to the skin site; alternatively, squeeze a portion of the gel from the packet into the palm of the hand and apply to the application sites, repeating until the entire contents of the packet have been applied. Patients should be advised that topical gels are typically flammable, therefore fire, flame, and smoking should be avoided during use. Apply once daily (preferably in the morning) to clean, dry skin on the shoulders and/or upper arm. Do not apply to the genitals or abdomen.
- For all products, allow the site to dry a few minutes before putting on clothing.
- In order to maintain serum testosterone levels in the normal range, the application site should not be washed for at least 2 hours after applying gel. For optimal response, showering and swimming should be avoided for 5—6 hours after applying AndroGel and for 2 hours after applying Testim.
- Direct contact of the gel-medicated skin with the skin of another person can result in the transfer of residual testosterone and absorption by the other person. It is recommended that the treated area be clothed at all times prior to washing off residual drug. If direct skin-to-skin contact with another person is anticipated, the application sites must be washed thoroughly with soap and water. In clinical studies, vigorous contact with a female partner for 15 minutes resulted in serum female testosterone levels > 2 times normal values. In the case of direct contact, the other person should wash the area of contact with soap and water as soon as possible.
- Patients should be advised that topical gels are typically flammable; therefore, fire, flame, and smoking should be avoided during use.

Transdermal Patch Formulations:

NOTE: Mild skin irritation may be ameliorated by treatment of the affected skin with over-the-counter topical hydrocortisone cream applied after system removal. Additionally, applying a small amount of 0.1% triamcinolone acetonide cream to the skin under the central drug reservoir of the transdermal system has been shown to reduce the incidence and severity of skin irritation. The administration of 0.1% triamcinolone acetonide cream does not significantly alter transdermal absorption of testosterone from the system. Ointment formulations should not be used for

pretreatment as they may significantly reduce testosterone absorption.

- Androderm: Apply patch to a dry, clean area of skin on the upper arms, thighs, back or abdomen. Rotate sites daily and do not reuse a site for 7 days. Do not apply to the scrotum or bony areas of the body. Removal of the Androderm patch before undergoing magnetic resonance imaging (MRI) is recommended because the patch contains aluminum (see Contraindications).
- Testoderm: Apply patch to a dry, clean, dry-shaved area on the scrotum. Do not use chemical depilatories to remove hair.

Extemporaneous Compounding-Topical:
Extemporaneous compounding of a Testosterone Ointment:
NOTE: The extemporaneous compounded testosterone ointment is not approved by the FDA for topical administration.

- Extemporaneously prepare 15 grams of a 2% ointment by using 3 ml of 100 mg/ml testosterone propionate injection and 12 grams of white petrolatum. To make 15 grams of a 5% ointment, use 7.5 ml of 100 mg/ml testosterone propionate injection and 7.5 grams of white petrolatum.

Other Administration Route(s)
Buccal Administration

- Wash hands before and after application.
- Take care not to swallow the system.
- *Application of Striant:* Apply to the upper gum just above the incisor tooth on either side of the mouth, rotating the site of application to alternate sides of the mouth with each application. The rounded side surface of the buccal system should be placed against the gum and held firmly in place with a finger over the lip and against the product for 30 seconds to ensure adhesion. To remove, gently slide the buccal system downwards from the gum towards the tooth to avoid scratching the gum.

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Contraindications / Precautions

Absolute contraindications are italicized

- *breast cancer*
- *females*
- *pregnancy*
- *prostate cancer*
- *soya lecithin hypersensitivity*
- *tartrazine dye hypersensitivity*
- B accidental exposure
- breast-feeding
- cardiac disease
- B children
- coronary artery disease
- diabetes mellitus
- elderly
- heart failure
- hepatic disease
- hypercalcemia
- intramuscular administration
- intravenous administration
- magnetic resonance imaging (MRI)
- myocardial infarction
- obesity
- polycythemia
- prostatic hypertrophy
- pulmonary disease
- renal disease
- tobacco smoking

The manufacturers of AndroGel and Striant state that their products are contraindicated in patients with *soybean, soy, or soya lecithin hypersensitivity* because they are derived partially from soy plants. Some preparations of testosterone contain tartrazine dye and should be used with caution in patients with a known *tartrazine dye hypersensitivity*. Patients allergic to aspirin are often at risk. Topical gels are typically flammable, therefore exposure to fire, flame, and tobacco smoking should be avoided while using any topical gel formulation of testosterone.

Because some testosterone transdermal systems (e.g., Androderm) contain aluminum or other metal components, patients should be instructed to remove the patch before undergoing magnetic resonance imaging (MRI). Metal components contained in the backing of some transdermal systems can overheat during an MRI scan and cause skin burns in the area where the patch is adhered.

Testosterone injections are administered intramuscularly. Do not inject via intravenous administration.

Respiratory adverse events have been reported immediately after intramuscular administration of testosterone enanthate (see Adverse reactions). Care should be taken to ensure slow and deep gluteal muscle injection of testosterone.

Testosterone replacement is not indicated in elderly patients who have age-related hypogonadism only or andropause because there is insufficient safety and efficacy information to support such use. Testosterone can stimulate the growth of cancerous tissue and is contraindicated in male patients with *prostate cancer* or *breast cancer*. Patients with prostatic hypertrophy should be treated with caution because of the possible development of malignancy. Elderly patients and other patients with clinical or demographic characteristics that are recognized to be associated with an increased risk of prostate cancer should be evaluated for the presence of prostate cancer prior to initiation of testosterone replacement therapy. In patients receiving testosterone therapy, surveillance for prostate cancer should be consistent with current practices for eugonadal men.

During treatment with androgens, edema occurs because of water retention in association with sodium retention. Testosterone should be used cautiously in patients with severe cardiac disease, severe hepatic disease, or severe renal disease because of possible exacerbation of these conditions. In addition, patients with heart failure, nephritis, nephrosis, coronary artery disease, myocardial infarction, or existing edema should be treated with caution. Patients with severe hepatic disease or hepatic dysfunction also can be at risk of drug accumulation because of reduced clearance.

The treatment of hypogonadal men with testosterone esters may potentiate sleep apnea, especially in patients that have risk factors for apnea such as obesity or chronic pulmonary disease.

Patients receiving high doses of testosterone are at risk for polycythemia. Periodically, patients receiving testosterone should have their hemoglobin and hematocrit concentrations measured to detect polycythemia.

Testosterone is absolutely contraindicated during *pregnancy* because of probable adverse effects on the fetus (FDA pregnancy risk category X). Women of childbearing potential who are receiving testosterone treatments should utilize adequate contraception.

AndroGel specifically is contraindicated in *females*; the drug is for males only; the dosage form supplies testosterone in excess of what should be prescribed to females under certain endocrine situations. Women should be aware that accidental exposure to some testosterone dosage forms (i.e., ointments and gels) may occur if they come into direct contact with a treated patient. In clinical studies, within 2—12 hours of gel application by male subjects, 15-minute sessions of vigorous skin-to-skin contact with a female partner resulted in serum female testosterone levels > 2 times the female baseline values. When clothing covered the treated site on the male, the transfer of testosterone to the female was avoided. Accidental exposure to topical testosterone gel has also occurred in pediatric patients after contact between the child and the application site in treated individuals. The adverse events reported include genitalia enlargement, development of pubic hair, advanced bone age, increased libido, and aggressive behavior. Symptoms resolved in most patients when exposure to the product stopped. However, in a few patients, the genitalia enlargement and advanced bone age did not fully return to expected measurements. The FDA recommends taking precautions to minimize the potential for accidental exposure by washing hands with soap and warm water after each application, covering application site with clothing, and removing medication with soap and water when contact with another person is anticipated. In the case of direct skin-to-skin contact with the site of testosterone application, the non-treated person should wash the area with soap and water as soon as possible.

Testosterone distribution into breast milk has not been determined, but it may have adverse effects on the infant. Alternative methods to breast-feeding are recommended in lactating women receiving testosterone therapy.

Androgen therapy, such as testosterone, can result in loss of diabetic control and should be used with caution in patients with diabetes mellitus. Close monitoring of blood glucose is recommended.

Testosterone has induced osteolysis and should be used with caution in patients with hypercalcemia, which can be exacerbated in patients with metastatic breast cancer.

Use of testosterone in children should be undertaken only with extreme caution. Testosterone may accelerate bone maturation without stimulating compensatory linear growth, sometimes resulting in compromised adult stature. If testosterone is administered to prepubertal males, radiographic examinations of the hand and wrist should be performed every 6 months to assess the rate of bone maturation and the effect of the drug on epiphyseal centers. Once the epiphyses have closed, growth is terminated. Even after discontinuation of treatment, epiphyseal closure can be enhanced for several

months. Accidental exposure to topical testosterone gel has also occurred in pediatric patients after skin to skin contact between the child and the application site in treated individuals. The adverse events reported include genitalia enlargement, development of pubic hair, advanced bone age, increased libido, and aggressive behavior. Symptoms resolved in most patients when exposure to the product stopped. However, in a few patients, the genitalia enlargement and advanced bone age did not fully return to expected measurements. The FDA recommends taking precautions to minimize the potential for accidental exposure by washing hands with soap and warm water after each application, covering application site with clothing, and removing medication with soap and water when contact with another person is anticipated. In the case of direct skin-to-skin contact with the site of testosterone application, the non-treated person should wash the area with soap and water as soon as possible.

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Pregnancy / Breast-feeding

Testosterone is absolutely contraindicated during *pregnancy* because of probable adverse effects on the fetus (FDA pregnancy risk category X). Women of childbearing potential who are receiving testosterone treatments should utilize adequate contraception.

Testosterone distribution into breast milk has not been determined, but it may have adverse effects on the infant. Alternative methods to breast-feeding are recommended in lactating women receiving testosterone therapy.

Revision Date: 4/13/2010 8:12:00 AM

Interactions

Level 1 - Severe

Level 2 - Major

- 5-Alpha reductase inhibitors
- Goserelin
- Leuprolide
- Saw Palmetto, Serenoa repens

Level 3 - Moderate

- Ambrisentan
- Antidiabetic Agents
- Corticosteroids
- Cyclosporine
- Epoetin Alfa
- Propranolol
- Ranolazine
- Somatropin, rh-GH
- Soy Isoflavones
- Warfarin

Level 4 - Minor

- Conivaptan
- Fluconazole
- Voriconazole

NOTE: Testosterone is a substrate for hepatic cytochrome P450 (CYP) 3A4 isoenzyme.[11580] Testosterone is also both transported by and an inhibitor of P-glycoprotein transport.[11581]

Testosterone can increase the anticoagulant action of warfarin.[367] Serious bleeding has been reported with this drug-drug interaction. Although the mechanism is unclear, testosterone may reduce procoagulant factors. Reduction of warfarin dosage may be necessary if testosterone therapy is coadministered. It is unclear if testosterone can augment the anticoagulant response to heparin therapy in a similar manner.

Based on case reports with methyltestosterone and danazol, androgens may increase plasma concentrations of cyclosporine, leading to a greater risk of nephrotoxicity.[6632] [6790] [6806] [7560]

Coadministration of corticosteroids and testoterone may increase the risk of edema, especially in patients with underlying cardiac or hepatic disease. Corticosteroids with greater mineralocorticoid activity, such as fludrocortisone, may be more likely to cause edema. Administer these drugs in combination with caution.[10551]

Goserelin [5322] and leuprolide [6940] inhibit steroidogenesis. Concomitant use of androgens with goserelin or leuprolide is relatively contraindicated and would defeat the purpose of goserelin or

leuprolide therapy.

Androgens can increase the risk of hepatotoxicity and therefore should be used with caution when administered concomitantly with other hepatotoxic medications. Patients should be monitored closely for signs of liver damage, especially those with a history of liver disease.

Androgens may be necessary to assist in the growth response to human growth hormone, but excessive doses of androgens in prepubescent males can accelerate epiphyseal maturation.[6807]

Androgens are known to stimulate erythropoiesis.[6808] Despite the fact that endogenous generation of erythropoietin is depressed in patients with chronic renal failure, other tissues besides the kidney can synthesize erythropoietin, albeit in small amounts. Concurrent administration of androgens can increase the patient's response to epoetin alfa, reducing the amount required to treat anemia. Because adverse reactions have been associated with an abrupt increase in blood viscosity, this drug combination should be avoided, if possible. Further evaluation of this combination needs to be made.

The antiandrogenic effects of the 5-alpha reductase inhibitors (i.e., dutasteride, finasteride) are antagonistic to the actions of androgens; it would be illogical for patients taking androgens to use these antiandrogenic drugs.[5321] [5608]

Drug interactions with Saw palmetto, Serenoa repens have not been specifically studied or reported. Saw palmetto extracts appear to have antiandrogenic effects.[1797] [6195] The antiandrogenic effects of Saw palmetto, *Serenoa repens* would be expected to antagonize the actions of androgens; it would seem illogical for patients taking androgens to use this herbal supplement.

Limited data suggest that testosterone concentrations increase during fluconazole administration. It appears that fluconazole doses of 200 mg/day or greater are more likely to produce this effect than doses of 25—50 mg/day.[6809] The clinical significance of this interaction is unclear at this time. Although data are not available, a similar reaction may occur with voriconazole. Both fluconazole and voriconazole are inhibitors of CYP3A4, the hepatic microsomal isoenzyme responsible for metabolism of testosterone.[4718]

Exogenously administered androgens (testosterone derivatives or anabolic steroids) have variable effects on blood glucose control in patients with diabetes mellitus. In general, low testosterone concentrations are associated with insulin resistance. Further, when hypogonadal men (with or without diabetes) are administered exogenous androgens, glycemic control typically improves as indicated by significant reductions in fasting plasma glucose concentrations and HbA1c. In one study in men with diabetes, testosterone undecenoate 120 mg PO/day for 3 months decreased HbA1c concentrations from a baseline of 10.4% to 8.6% ($p < 0.05$); fasting plasma glucose concentrations decreased from 8 mmol/l at baseline to 6 mmol/l ($p < 0.05$). Significant reductions in HbA1c and fasting plasma glucose concentrations did not occur in patients taking placebo.[10772] Similar results have been demonstrated with intramuscular testosterone 200 mg administered every 2 weeks for 3 months in hypogonadal men with diabetes.[10773] In healthy men, testosterone enanthate 300 mg IM/week for 6 weeks or nandrolone 300 mg/week IM for 6 weeks did not adversely affect glycemic control; however, nandrolone improved non-insulin mediated glucose disposal.[10774] It should be noted that some studies have shown that testosterone supplementation in hypogonadal men has no effect on glycemic control.[10775] [10776] Conversely, the administration of large doses of anabolic steroids in power lifters decreased glucose tolerance, possibly through inducing insulin resistance.[10777] While data are conflicting, it would be prudent to monitor all patients with type 2 diabetes on antidiabetic agents receiving androgens for changes in glycemic control, regardless of endogenous testosterone concentrations. Hypoglycemia or hyperglycemia can occur; dosage adjustments of the antidiabetic agent may be necessary.

In vitro, both genistein and daidzein inhibit 5 alpha-reductase isoenzyme II, resulting in decreased conversion of testosterone to the potent androgen 5-alpha-dihydrotestosterone (DHT) and a subsequent reduction in testosterone-dependent tissue proliferation.[3036] The action is similar to that of finasteride, but is thought to be less potent. Theoretically, because the soy isoflavones appear to inhibit type II 5-alpha-reductase, the soy isoflavones may counteract the activity of the androgens.

Conivaptan is a potent inhibitor of CYP3A4 and may increase plasma concentrations of drugs that are primarily metabolized by CYP3A4. Testosterone is a substrate for CYP3A4 isoenzymes.[4718] The clinical significance of this theoretical interaction is not known.

Testosterone is an inhibitor of P-glycoprotein transport.[4718] Ranolazine is a substrate of P-glycoprotein, and inhibitors of P-glycoprotein may increase the absorption of ranolazine.[8747] In addition, ranolazine inhibits CYP3A [8747] and may increase plasma concentrations of drugs that are primarily metabolized by CYP3A4 such as testosterone [4718].

Ambrisentan is a substrate for P-glycoprotein transport, an energy-dependent drug efflux pump.[10171] The inhibition of P-glycoprotein, by drugs such as testosterone [4718], may lead to a decrease in the intestinal metabolism and an increase in the oral absorption of ambrisentan. If ambrisentan is coadministered with a P-glycoprotein inhibitor, patients should be monitored closely for adverse effects.

Coadministration of oxyphenbutazone and testosterone may lead to elevated concentrations of oxyphenbutazone. Monitor patients for adverse effects when coadministering these drugs together.[10551]

Testosterone cypionate has been shown to increase the clearance of propranolol in one study. Monitor patients taking testosterone and propranolol together for decreased therapeutic efficacy of propranolol.[10551]

Revision Date: 12/23/2008 3:07:00 PM

Adverse Reactions

- acne vulgaris
- alopecia
- amenorrhea
- anxiety
- apnea
- cough
- dental pain
- depression
- dysgeusia
- elevated hepatic enzymes
- epididymitis
- epiphyseal closure
- erythema
- erythrocytosis
- feminization
- gingivitis
- gynecomastia
- headache
- hepatitis
- hypercalcemia
- hypercholesterolemia
- injection site reaction
- insomnia
- jaundice
- libido decrease
- libido increase
- mastalgia
- nausea
- oligomenorrhea
- peliosis hepatis
- peripheral edema
- priapism
- prostatic hypertrophy
- pruritus
- secondary malignancy
- skin discoloration
- skin irritation
- virilization
- vomiting
- weight gain

Disruption of the regular menstrual cycle secondary to testosterone-induced suppression of gonadotropin secretion can lead to amenorrhea or oligomenorrhea.

When androgens are given to women, virilization, manifested by acne, growth of facial hair, enlarged clitoris, reduced breast size, and deepening of the voice, can occur. If testosterone treatment is discontinued when these symptoms first appear, they usually subside. Prolonged treatment can lead to irreversible masculinity, so the benefit of treatment should be measured against the risk.

Male patients can experience feminization during prolonged therapy with testosterone, which is believed to result from inhibition of gonadotropin secretion and conversion of androgens to estrogens. These effects are more pronounced in patients with concurrent hepatic disease and include breast soreness and gynecomastia. Feminizing effects are generally reversible.

Priapism and excessive sexual stimulation, more common in geriatric males, are generally the effect of excessive testosterone dosage. Oligospermia and decreased ejaculatory volume may occur in patients receiving long-term therapy or excessive doses. Alopecia resembling male pattern baldness has also occurred.

Prostate cancer as a secondary malignancy or prostatic hypertrophy can develop during prolonged therapy with testosterone and are more likely to occur in elderly male patients. Signs of acute epididymitis (e.g., fever, chills, pain in the inguinal region) and/or urinary urgency should prompt withdrawal of the drug and reevaluation of dosage. In 162 hypogonadal men receiving testosterone gel (AndroGel) during a 3-year open-label extension trial, increases in serum PSA concentrations (defined as >= 2x baseline concentrations or any single absolute value >= 6 ng/ml) were seen in approximately 18% of patients (n=29). The majority of these increases were seen in the first year of therapy (23/29 or 79%). Four patients had a single value >= 6 ng/ml: two of these patients had prostate cancer detected upon biopsy. In patients receiving testosterone therapy, surveillance for

prostate cancer should be consistent with current practices for eugonadal men.

Testosterone patches can cause scrotal skin irritation, erythema, and/or pruritus at site of application. Blister reactions may occur under the system. These reactions will usually decrease or disappear over time. The patches can also cause skin discoloration. Chronic skin irritation resulted in 5% of patients to discontinue treatment. Mild skin irritation may be ameliorated by treatment of affected skin with over-the-counter topical hydrocortisone cream applied after transdermal system removal. Additionally, applying a small amount of 0.1% triamcinolone acetonide cream to the skin under the central drug reservoir of the transdermal system has been shown to reduce the incidence and severity of skin irritation. The administration of 0.1% triamcinolone acetonide cream does not significantly alter transdermal absorption of testosterone from the system. Ointment formulations should not be used for pretreatment as they may significantly reduce testosterone absorption. Similar to other testosterone products, the patches can cause nausea/vomiting, priapism, edema, urinary difficulties, and mastalgia. Headache has been reported in about 5% of patients during use of testosterone patches.

The testosterone buccal mucoadhesive system can cause dental pain, such as gum or mouth irritation (9.2%), a bitter taste in the mouth (dysgeusia, 4.1%), gum pain (3.1%), gum tenderness (3.1%), headache (3.1%), gum edema (2%), or taste perversion (dysgeusia, 2%). The majority of gum-related adverse events were transient; gum irritation generally resolved in 1—8 days and gum tenderness resolved in 1—14 days. The following adverse events occurred in 1 patient during clinical trials: buccal mucosal roughening, gingivitis, gum blister, nose edema, stinging of lips, and toothache. In clinical trials, 4.1% of patients discontinued treatment due to gum or mouth-related adverse events. Gum examinations were conducted in one study to assess for gingivitis, gum edema, oral lesions, ulcerations or leukoplakia with no new or worsening cases of any of these anomalies reported.

When androgens are used in the treatment of immature males, early virilism can be a disadvantage because it is accompanied by premature epiphyseal closure. Monitoring of skeletal maturation should be undertaken at about 6-month intervals. Once the epiphyses have closed, growth is terminated. Even after discontinuation of testosterone treatment, epiphyseal closure can be enhanced for several months.

Peripheral edema can occur as the result of increased water retention (in association with sodium chloride) and is manifested by weight gain. If normal therapeutic testosterone doses are used in the treatment of hypogonadism, only a moderate amount of fluid retention occurs. In the treatment of patients with impaired renal function or congestive heart failure, the water retention is of greater significance.

Testosterone therapy is related to growth and secretion of the sebaceous glands, which can cause an acne indistinguishable from acne vulgaris.

Hepatic dysfunction can occur from use of testosterone. Elevated hepatic enzymes are more common than overt jaundice. Hepatic effects have been shown to be more likely with administration 17-alpha-alkylandrogens such as methyltestosterone. The drug should be discontinued if cholestatic jaundice or hepatitis occurs. Peliosis hepatis and hepatic neoplasms occur rarely, but when they do, they are potentially life-threatening.

Testosterone therapy has induced osteolysis and can exacerbate hypercalcemia. Androgen-induced hypercalcemia occurs especially in immobile patients and those with metastatic carcinoma of the breast.

Testosterone has a stimulatory effect on the formation of erythropoietin. Increased erythropoiesis, especially in women, can lead to erythrocytosis (secondary polycythemia) and its complications including: dizziness, headache, tiredness, unusual bleeding, flushing, or redness of the skin. Periodic hemoglobin and hematocrit determinations should be considered in patients receiving long-term therapy.

Observational studies in post-menopausal women, bodybuilders, and weightlifters using anabolic steroids have revealed 'pro-atherogenic' changes in lipid profiles, including decreases in HDL concentrations and increases in LDL concentrations. Synthetic androgens may produce a greater lowering of the HDL-C:LDL-C ratio than does testosterone. Oral dosage forms may produce greater changes than parenteral dosage forms. Although the implications of androgen-induced hypercholesterolemia are unclear, caution should be exercised, particularly in patients predisposed to dyslipidemia or atherosclerosis.

Testosterone therapy can produce libido decrease or libido increase. Geriatric males have been found to be more likely to experience excessive sexual stimulation.

Miscellaneous adverse reactions to testosterone therapy have included nausea/vomiting, chills, bladder irritability, insomnia, anxiety, and mental depression.

Intramuscular administration of anabolic steroids can cause inflammation, urticaria, post injection induration and furunculosis. Patients should be observed for any signs of an injection site reaction. Inflammation and pain at the site of insertion of testosterone pellets is possible. Testosterone pellets may slough out from the insertion site, which is usually secondary to superficial implantation or aseptic technique.

Transient respiratory reactions including the urge to cough, coughing fits, and respiratory distress immediately after intramuscular injection of testosterone enanthate have been reported during post-marketing surveillance. Care should be taken to ensure slow and deep gluteal muscle injection of testosterone preparations.

The treatment of hypogonadal men with testosterone esters may increase the risk of sleep apnea, especially in patients with risk factors for sleep apnea, such as obesity or chronic lung disease.

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Legend = Compatible = Incompatible

Click result icon for detailed study information.

= Results uncertain, variable or dependent on conditions ND = No Data Available

From Trissel's 2™ Clinical Pharmaceutics Database

IV Compatibility of Testosterone with:

	Admixture	Syringe	Y-Site Administration	For Dilution
Normal saline- Sodium chloride 0.9%	ND	ND	ND	

How Supplied

Testosterone Bulk powder

Testosterone Micronized Powder for Compounding (00574-0460) (Paddock Laboratories Inc)

Testosterone Cypionate Oil for injection

Depo-Testosterone 100mg/ml in Oil for Injection (00009-0347) (Pfizer US Pharmaceuticals)
Depo-Testosterone 200mg/ml in Oil for Injection (00009-0417) (Pfizer US Pharmaceuticals)
Testosterone Cypionate 100mg/ml in Oil for Injection (00781-3073) (Sandoz Inc)
Testosterone Cypionate 200mg/ml in Oil for Injection (00574-0820) (Paddock Laboratories Inc)
Testosterone Cypionate 200mg/ml in Oil for Injection (00781-3074) (Sandoz Inc)
Testosterone Cypionate 200mg/ml in Oil for Injection (00703-6125) (Teva Pharmaceuticals)
Testosterone Cypionate 200mg/ml in Oil for Injection (00703-6121) (Teva Pharmaceuticals)
Testosterone Cypionate 200mg/ml in Oil for Injection (00591-3223) (Watson Pharmaceuticals Inc)
Virilon 200mg/ml in Oil for Injection (00076-3010) (Star Pharmaceuticals Inc) (off market)

Testosterone Enanthate Oil for injection

Andro LA-200 200mg/ml in Oil for Injection (00456-0604) (Forest Pharmaceuticals Inc) (off market)
Delatestryl 200mg/ml in Oil for Injection (54396-0328) (BTG Pharmaceuticals

Corp Sub Biotechnology General Corp)

Delatestryl 200mg/ml in Oil for Injection (67979-0501) (Endo Pharmaceuticals Solutions Inc. formerly Indevus)

Testosterone Enanthate 200mg/ml in Oil for Injection (00574-0821) (Paddock Laboratories Inc) 

Testosterone Enanthate 200mg/ml in Oil for Injection (00591-3221) (Watson Pharmaceuticals Inc) 

Testosterone Implant

Testopel Pellet 75mg for Implantation (10116-1001) (Slate Pharmaceuticals, Inc.)

Testopel Pellet 75mg for Implantation (43773-1001) (Slate Pharmaceuticals, Inc.)

Testosterone Muco-adhesive buccal tablet

Striant 30mg Buccal System (55056-3060) (Columbia Laboratories Inc) 

Testosterone Propionate Bulk powder

Testosterone Propionate Powder for Compounding (00574-0461) (Paddock Laboratories Inc)

Testosterone Propionate Oil for injection

Testosterone Propionate 100mg/ml Oil for Injection (00314-0772) (Hyrex Pharmaceuticals) (off market)

Testosterone Propionate Solution for injection

Testosterone Propionate 100mg/ml in Oil for Injection (11695-0383) (WA Butler Co) (off market)

Testosterone Propionate Topical cream

First-Testosterone MC 2% Compounding Kit (65628-0021) (CutisPharma, Inc) 

Testosterone Propionate Topical ointment

First-Testosterone 2% Compounding Kit (65628-0020) (CutisPharma, Inc) 

Testosterone Solution for injection

Testosterone 100mg/ml Solution for Injection (00182-0714) (Ivax Corporation a Division of Teva USA) (off market)

Testosterone Suspension for injection

Testosterone 100mg/ml Suspension for Injection (00314-0771) (Hyrex Pharmaceuticals) (off market)

Testosterone 50mg/ml Suspension for Injection (00314-0083) (Hyrex Pharmaceuticals) (off market)

Testosterone Topical gel

Androgel 1% Metered Dose Pump Transdermal Gel (00051-8488) (Unimed Pharmaceuticals Inc) 

Androgel 1% Metered Dose Pump Transdermal Gel (00051-8444) (Unimed Pharmaceuticals Inc)

Androgel 1% Transdermal Gel (00051-8450) (Unimed Pharmaceuticals Inc) 

Androgel 1% Transdermal Gel (00051-8425) (Unimed Pharmaceuticals Inc) 

Testim 1% Topical Gel (66887-0001) (Auxilium Pharmaceuticals Inc) 

Testosterone Transdermal Patch - 24 Hour

Androderm 2.5mg/24hr Transdermal System (52544-0469) (WatsonPharma Inc) 

Androderm 5mg/24hr Transdermal System (52544-0470) (WatsonPharma Inc)	
Testoderm 4mg/24hr Transdermal Patch (17314-4608) (Alza Corp) (off market)	
Testoderm 5mg/24hr Transdermal Patch (17314-4717) (Alza Corp) (off market)	
Testoderm 6mg/24hr Transdermal Patch (17314-4609) (Alza Corp) (off market)	
Testoderm 6mg/24hr Transdermal Patch (17314-2836) (Alza Corp) (off market)	

Monitoring Parameters

- LFTs

References

367. Wells PS, Holbrook AM, Crowther NR et al. Interaction of warfarin with drugs and food. Ann Intern Med 1994;121:676—83.

1797. Robbers JE, Tyler VE. *Tyler's Herbs of Choice: the Therapeutic Use of Phytomedicinals*. Binghamton NY: Haworth Herbal Press, Inc.; 1999.

3036. Aldercreutz H, Mazur W. Phyto-estrogens and western diseases. Annals of Medicine 1997;29:95—120.

4718. Hansten PD, Horn JR. Cytochrome P450 Enzymes and Drug Interactions, Table of Cytochrome P450 Substrates, Inhibitors, Inducers and P-glycoprotein, with Footnotes. In: *The Top 100 Drug Interactions - A guide to Patient Management*. 2008 Edition. Freeland, WA: H&H Publications; 2008:142—157.

5321. Propecia® (finasteride) package insert. Whitehouse Station, NJ: Merck & Co., INC.; 2003 Oct.

5322. Zoladex® (goserelin acetate) package insert. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2003 Dec.

5608. Avodart™ (dutasteride) package insert. Research Triangle Park, NC: GlaxoSmithKline; 2005 May.

6195. German Commission E. Saw Palmetto berry, *Sabal fructus*, monograph Published March 2, 1989 and revised January 17, 1991. In: Blumenthal, M et al ., eds. The complete German Commission E Monographs -Therapeutic Guide to Alternative Medicines. Boston MA: Integrative Medicine Communications for the American Botanical Council; 1998:132.

6632. Goffin E, Pirson Y, Geubel A, et al. Cyclosporine-methyltestosterone interaction. Nephron 1991;59:174—5.

6790. Borras-Blasco J, Rosique-Robles JD, Peris-Marti J, et al. Possible cyclosporin-danazol interaction in a patient with aplastic anaemia. *Am J Hematol* 1999;62:63—4.

6806. Moller BB, Ekelund B. Toxicity of cyclosporine during treatment with androgens. N Engl J Med 1985;313:1416.

6807. Humatrope™ (somatropin);package insert. Indianapolis, IN: Eli Lilly and Company; 2003 Jul.

6808. Androderm® (testosterone transdermal system) package insert. Corona, CA: Watson Pharma, Inc.; 1999 Jan.

6809. Lazar JD, Wilner KD. Drug interactions with fluconazole. Rev Infect Dis 1990;12:S327—33.

6940. Viadur® (leuprolide implant) package insert. Westhaven, CT: Bayer Pharmaceuticals; 2002 May.

7560. Ross WB, Roberts D, Griffin PJ, et al. Cyclosporin interaction with danazol and norethisterone. *Lancet* 1986;1:330.

8747. Ranexa™ (ranolazine extended-release tablets) package insert. Palo Alto, CA: CV Therapeutics, Inc.; 2008 Nov.

10171. Letairis™ (ambrisentan) package insert. Foster City, CA: Gilead Sciences, Inc; 2008 Oct.

10551. Androgel® (testosterone gel) package insert. Montrogue, France: Laboratories Besins International; 2005 Aug.

10772. Boyanov MA, Boneva Z, Christov VG. Testosterone supplementation in men with type 2

diabetes, visceral obesity, and partial androgen deficiency. *Aging Male* 2003;6:1—7.

10773. Kapoor D, Goodwin E, Channer KS, et al. Testosterone replacement therapy improves insulin resistance, glycaemic control, visceral adiposity, and hypercholesterolaemia in hypogonadal men with type 2 diabetes. *Eur J Clin Endocrinol* 2006; 154:899—906.

10774. Hobbs CJ, Jones RE, Plymate SR. Nandrolone, a 19-nortestosterone, enhances insulin-independent glucose uptake in normal men. *J Clin Endocrinol Metab* 1996; 81:1582—5.

10775. Corrales JJ, Burgo RM, Garcia-Berrocal B, et al. Partial androgen deficiency in aging type 2 diabetic men and its relationship to glycemic control. *Metabolism* 2004;53:666—72.

10776. Lee CH, Kuo SW, Hung YJ, et al. The effect of testosterone supplement on insulin sensitivity, glucose effectiveness, and acute insulin response after glucose load in male type 2 diabetics. *Endocrine Res* 2005;31:139—148.

10777. Cohen JC, Hickman R. Insulin resistance and diminished glucose tolerance in powerlifters ingesting anabolic steroids. *J Clin Endocrinol Metab* 1987;64:960—3.

11580. Krauser JA, Guengerich FP. Cytochrome P450 3A4-catalyzed testosterone 6beta-hydroxylation stereochemistry, kinetic deuterium isotope effects, and rate-limiting steps. *J Biol Chem* 2005;280:19496—506.

11581. Barnes KM, Dickstein B, Cutler GB Jr, et al. Steroid transport, accumulation, and antagonism of P-glycoprotein in multidrug-resistant cells. *Biochemistry* 1996;35:4820—7.

25533. Grinspoon S, Corcoran C, Askari H, et al. Effects of androgen administration in men with the AIDS wasting syndrome: a randomized, double-blind, placebo-controlled trial. Ann Intern Med 1998;129:18-26.

27069. Grinspoon S, Corcoran C, Parlman K, et al. Effects of testosterone and progressive resistance training in eugonadal men with AIDS wasting. Ann Intern Med 2000;133:348-355.
