

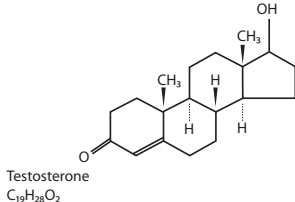
PRODUCT INFORMATION

Composition Active: Testosterone.

Chemical Name: 17-β-Hydroxyandrost-4-en-3-one

Molecular Weight: 288.4.

CAS: 58-22-0



Description

ANDROFORTE® 5 testosterone cream is a transdermal drug delivery system consisting of a white oil-in-water cream intended for scrotal administration. ANDROFORTE® 5 testosterone cream contains dl-α-tocopherol acetate (vitamin E) and almond oil formulated to optimize systemic absorption of the active ingredient. Also contains cetomacrogol 1000, cetostearyl alcohol, butylated hydroxytoluene, anhydrous citric acid, triethanolamine, carbomer 940, B & J Phenonip® and purified water.

Pharmacology

Testosterone is the primary androgenic hormone. Testosterone and its 5α-reduced metabolite dihydrotestosterone (DHT) activate the intracellular androgen receptor and modulate gene transcription. Testosterone is produced by the interstitial (Leydig) cells of the testes and the adrenal glands in males and by the ovary and adrenal glands in females. Testosterone is responsible for the normal growth and development of the male sex organs and for maintenance of secondary sex characteristics. Secondary sex characteristics include growth and maturation of the prostate, seminal vesicles, penis and scrotum, male hair distribution, deepening of the voice, changes in fat distribution and muscle mass.

Pharmacokinetics

The majority of testosterone produced (98-99%) is biologically inactive due to binding to sex hormone-binding globulin (SHBG) and albumin (55% and 45% respectively to the bound portion). Testosterone also circulates unbound as a free hormone (1-2%) and is considered biologically active. Testosterone is metabolized primarily in the liver and also in peripheral tissue. Dihydrotestosterone (DHT) and estradiol (E2) are products of testosterone metabolism. DHT is produced by reduction through the action of the enzyme 5-α reductase, which is present in genital tissue, skin and the prostate. DHT is further metabolized to 3-α and 3-β androstenediol. DHT binds with greater affinity to SHBG than does testosterone. E2 is produced by aromatization of testosterone. DHT:testosterone and E2:testosterone ratios in normal adult males are 1:10 and 1: 200 respectively. 90% of testosterone is excreted in the urine as glucuronide and sulphate conjugates of testosterone and its metabolites.

Scrotal skin is significantly more receptive to the absorption of steroids than other sites of application including the back, axilla and forearms¹. Daily application of ANDROFORTE® 5 to the scrotum results in a serum testosterone concentration profile within the normal range observed in healthy young men. Maximum serum testosterone concentration occurs three to five hours after application as shown in Figure 1.

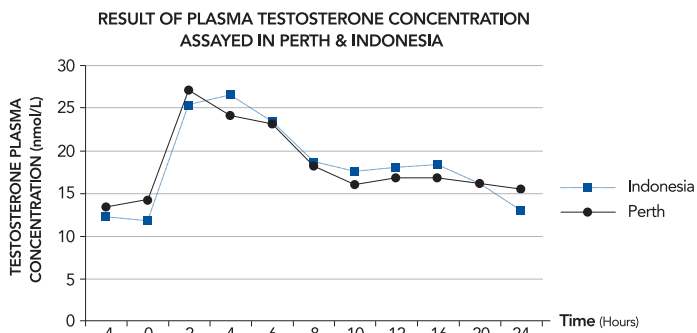


Fig. 1 Mean (SD) plasma testosterone concentrations using 50mg testosterone (1ml) scrotally once daily application of ANDROFORTE® 5 in 8 hypogonadal males.

Normal range serum testosterone concentrations are reached during the first day of dosing using a 50mg single dose applied to the scrotum. There is no accumulation of testosterone after steady-state level is reached. A steady-state level is achieved within 10 days of initiating therapy. A single daily application of 0.5-1.0ml of cream (25-50mg testosterone) of ANDROFORTE® 5 testosterone cream to the scrotum results in a serum concentration profile within the normal therapeutic range for healthy young males (10-35 nmol/L or 300-1100 ng/dL).

Indications

ANDROFORTE® 5 testosterone cream is indicated for testosterone replacement therapy for symptomatic testosterone deficient males, including confirmed primary hypogonadism, secondary hypogonadism and late-onset hypogonadism.

Contraindications

Testosterone is contraindicated in men with known or suspected carcinoma of the prostate, known or suspected carcinoma of the breast, known or suspected androgen-dependent neoplasia, nephrotic syndrome or hypercalcemia. Known sensitivity to testosterone, ANDROFORTE® 5 testosterone cream or any of its components. ANDROFORTE® 5 testosterone cream contains almond oil. ANDROFORTE® 5 testosterone cream has not been evaluated in women and is contraindicated in pregnancy and while lactating. The product is not suitable for children.

Precautions

EXTREMELY IMPORTANT: Before initiating ANDROFORTE® 5 testosterone cream treatment, surveillance for prostate cancer by means of digital rectal examination (DRE) and a blood test for Prostate-Specific Antigen (PSA) is recommended. Caution is warranted if the PSA is normal-high because in hypogonadal patients the PSA is generally inappropriately low. Furthermore, a post treatment increase in PSA more than the normal range should raise suspicion about prostate disease. International guidelines recommend reviewing PSA each three months for the first 12 months then each 12 months thereafter. If there is a 1.5 increase of PSA during a 12 month period, further evaluation is required even if under age-related normal cut-off. Hemoglobin and hematocrit should be checked periodically to detect polycythemia in patients receiving androgen therapy. Liver function, PSA, total and HDL cholesterol should also be monitored. Patients with pre-existing cardiac, hepatic or renal diseases need to be monitored closely when undergoing androgen treatment. High level athletes need to be aware of the rules governing androgen use if prescribed ANDROFORTE® 5 testosterone cream. Androgen supplementation in geriatric patients may increase the risk for the development of prostatic hyperplasia.

Pediatric Use

This product is not suitable for children. Care should be taken to ensure children do not come into contact with ANDROFORTE® 5 application sites. In the event of contact, wash with soap and water as soon as possible.

Adverse Reactions

Potential side-effects from excessive dosing may include:

- Nausea, vomiting, jaundice or swelling of the ankles
- Increased body hair
- Increased acne
- Signs of virilization
- Weight gain
- Persistent headaches
- Increased appetite
- Deepening of the voice
- Electrolyte disturbances
- Too frequent or persistent erections of the penis (priapism)
- Gynecomastia

PRODUCT INFORMATION (cont'd)

Whilst none of these effects has been reported with ANDROFORTE® 5 testosterone cream, either in trials or clinical use, they may potentially occur with excessive, prolonged testosterone usage.

Patients should be made aware of the consequences of making sustained long-term close physical contact with young children and partners. There is the potential for passive transfer of testosterone from the area of application to the skin of individuals with whom close contact is made. Long term continual exposure may result in passive absorption and may have adverse effects, including virilization, in young children.

Dosage and Administration

Administration via scrotal application provides a convenient, acceptable mode of administration. ANDROFORTE® 5 testosterone cream is absorbed from skin sites other than the scrotum including torso, back, chest, arms and legs. However, absorption may be variable and is not as complete as via scrotal application. If these other skin sites are to be used, the dose may need to be significantly increased to achieve comparable serum testosterone levels as for scrotal application. ANDROFORTE® 5 testosterone cream is supplied with a dose measuring applicator for measuring 0.5ml doses of ANDROFORTE® 5. Each 1ml delivers 50mg of testosterone.

The appropriate dose is achieved by directing the patient to apply a defined amount of cream to the scrotum and massaging until vanished. The scrotum is not required to be shaved prior to use. Absorption is likely to be less complete and variable if applied to other areas of the body and therefore administration should be solely to the scrotum.

Dosage

ANDROFORTE® 5 testosterone cream contains 50mg testosterone BP per 1ml via the applicator. A baseline total serum testosterone level, sex hormone-binding globulin (SHBG) or free testosterone should be measured before initiating treatment.

Recommended starting dose is 50mg testosterone (1 ml via dose measuring applicator) of cream applied once daily and massaged into the scrotum until the cream is absorbed (usually 30-60 seconds). Dose is variable according to severity of symptoms and clinical response.

Variations may occur between plasma levels achieved and their time course between different individuals.

Clinical response is usually observed three to four weeks after initiation of treatment whereupon the dose may be reduced to maintenance if desired. ANDROFORTE® 5 testosterone cream should be applied to clean, dry scrotal skin. There is no necessity to shave or remove hair from scrotum prior to use. ANDROFORTE® 5 testosterone cream should be applied immediately after being dispensed from the tube.

ANDROFORTE® 5 testosterone cream is only recommended for use in men.

Use in Pregnancy

Category D. Testosterone is suspected to cause birth defects when administered during pregnancy. ANDROFORTE® 5 testosterone cream has not been evaluated in women and is contraindicated during pregnancy. (See Contraindications)

Use in Lactation

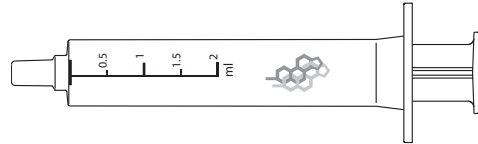
Testosterone will suppress prolactin in the lactating female and may cause adverse effects in the infant. ANDROFORTE® 5 testosterone cream has not been evaluated in women and should not be used in breastfeeding women. (See Contraindications)

Overdose

This is not likely due to the mode of administration. Blood testing of serum testosterone levels should be undertaken within one month of initiating therapy. To monitor therapy, regular blood testing is recommended. If serum testosterone levels are raised beyond the therapeutic normal range the dose can be adjusted downwards. Serum testosterone levels fall to baseline levels within 72 hours of ceasing treatment.

Presentation

ANDROFORTE® 5 testosterone cream containing 50mg/mL testosterone BP in a 50ml boxed tube. ANDROFORTE® 5 testosterone cream is supplied with a dose applicator calibrated in 0.5ml graduations. One millilitre (1 ml) of cream via the dose applicator provides 50mg testosterone. The patient should measure



the appropriate dose using the applicator and apply directly to the scrotal skin, massaging until absorbed.

Storage

Store below 25°C. DO NOT FREEZE

Shelf-life under these conditions is two years.

Name and Address of Sponsor

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ANDROFORTE® is a registered trademark.

Ref: 1. Feldmann RJ, Maibach HI. Regional variation in percutaneous penetration of 14C cortisol in man. J Invest Dermatol. 1967;48:181-3.