

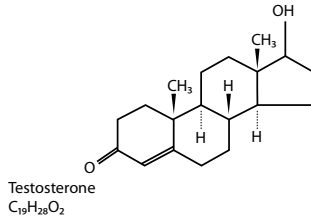
PRODUCT INFORMATION

Composition Active: Testosterone B.P.

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

Molecular Weight: 288.4

CAS: 58-22-0.



Description

ANDROFEME® 1% w/v testosterone cream is a transdermal drug delivery system consisting of a white vanishing cream intended for use in women.

ANDROFEME® 1% w/v testosterone cream contains dl-α-tocopherol acetate (vitamin E) and almond oil formulated to optimise 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 in the adrenal glands and the ovaries in females.

In males, testosterone is responsible for the normal growth and development of the male sex organs and for maintenance of secondary characteristics.

In women androgens act directly via the androgen receptors in tissues, such as bone, skin fibroblasts, hair follicles and sebaceous glands. Testosterone is a precursor hormone for estrogen biosynthesis in the ovaries and at extragonadal sites - bone, brain, cardiovascular and adipose tissues. Testosterone exerts a strong influence on female sexuality and has a physiological role in bone development and maintenance of mineralisation.

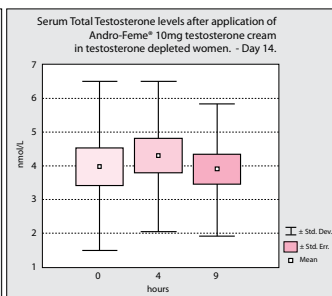
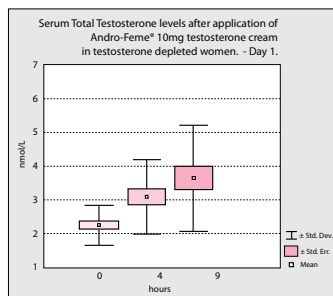
Pharmacokinetics

The majority of testosterone binds to sex hormone-binding globulin (SHBG) and is biologically inactive. Testosterone also circulates unbound as a free hormone 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 and skin. DHT is further metabolized to 3-α and 3-β androstane-2,3-diol. DHT binds with greater affinity to SHBG than does testosterone. E2 is produced by aromatisation of testosterone. 90% of testosterone is excreted in the urine as glucuronide and sulphate conjugates of testosterone and its metabolites.

Following ANDROFEME® application to the skin, serum testosterone begins to rise within an hour of application. A steady-state level is achieved within 2 weeks of initiating therapy. A single daily application of 1ml via measured applicator (10mg testosterone) of ANDROFEME® to the inner aspects of the forearm results in a serum concentration profile in the upper range to that observed in healthy young females.



Indications

ANDROFEME® is indicated for testosterone replacement therapy for confirmed testosterone insufficiency in females.

Contraindications

Testosterone is contraindicated in females with known or suspected carcinoma of the breast, known or suspected androgen-dependent neoplasia, nephrotic syndrome, history of thromboembolism or hypercalcaemia.

Known sensitivity to testosterone, ANDROFEME® or any of its components. ANDROFEME® contains almond oil.

ANDROFEME® is contraindicated in pregnancy and while lactating.

High level athletes need to be aware of the rules governing androgen use if prescribed ANDROFEME® cream.

Close skin contact with the area of application within an hour of application by a partner or child should be avoided. This may result in the partner or child absorbing some testosterone through the skin contact.

Precautions

Androgen supplementation in women must be monitored closely, especially at onset of treatment. Female requirements for testosterone are between ten and twenty times less than that of males.

Normal ranges for testosterone may vary between laboratories and between different assay methods. Supraphysiological levels may be achieved if doses are too high, therefore individual assessment and monitoring needs to be implemented on a patient-by-patient basis. If high levels are achieved treatment should be halted and recommenced after reduced levels have been established. Levels typically return to baseline 2-5 days after ceasing treatment.

All patients with pre-existing cardiac, hepatic or renal diseases need to be monitored closely when undergoing androgen treatment.

ANDROFEME® testosterone therapy is contraindicated in women with normal reproductive function because of the potential for virilisation of a female fetus unless adequate contraceptive measures are being utilised.

Use in Pregnancy

Category D. ANDROFEME® is not to be used in pregnant women under any circumstance. Testosterone is known to have the potential to cause serious birth defects when administered during pregnancy. (See Contraindications)

Use in Lactation

Testosterone suppresses prolactin in the lactating female and may cause adverse effects in the infant. ANDROFEME® must not be used in breast-feeding women. (see Contraindications)

Care should be taken by breast-feeding women to avoid any contact with ANDROFEME®. In the event of contact, wash with soap and water as soon as possible.

Paediatric Use

This product is not suitable for children.

Care should be taken to ensure that children do not come into contact with ANDROFEME® application sites. In the event of contact, wash with soap and water as soon as possible.

Adverse Reactions

ANDROFEME® is characterised by its significant lack of side effects in clinical use. No skin irritation has been reported at the sites of application.

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
- Deepening of the voice
- Electrolyte disturbances
- Polycythemia

Whilst none of these effects have been reported with ANDROFEME®, either in trials or clinical use, they are a potential side effect from excessive prolonged testosterone usage.

In women, the inhibitory action of androgens on the activity of the anterior pituitary may result in the suppression of ovarian activity and menstruation. Continued administration of large doses may produce symptoms of virilism, such as male-pattern hirsutism or baldness, deepening of the voice, atrophy of the breasts and endometrial tissue, oily skin, acne, hypertrophy of the clitoris and suppression of lactation.

Patients should contact their doctor if any of the above should occur.

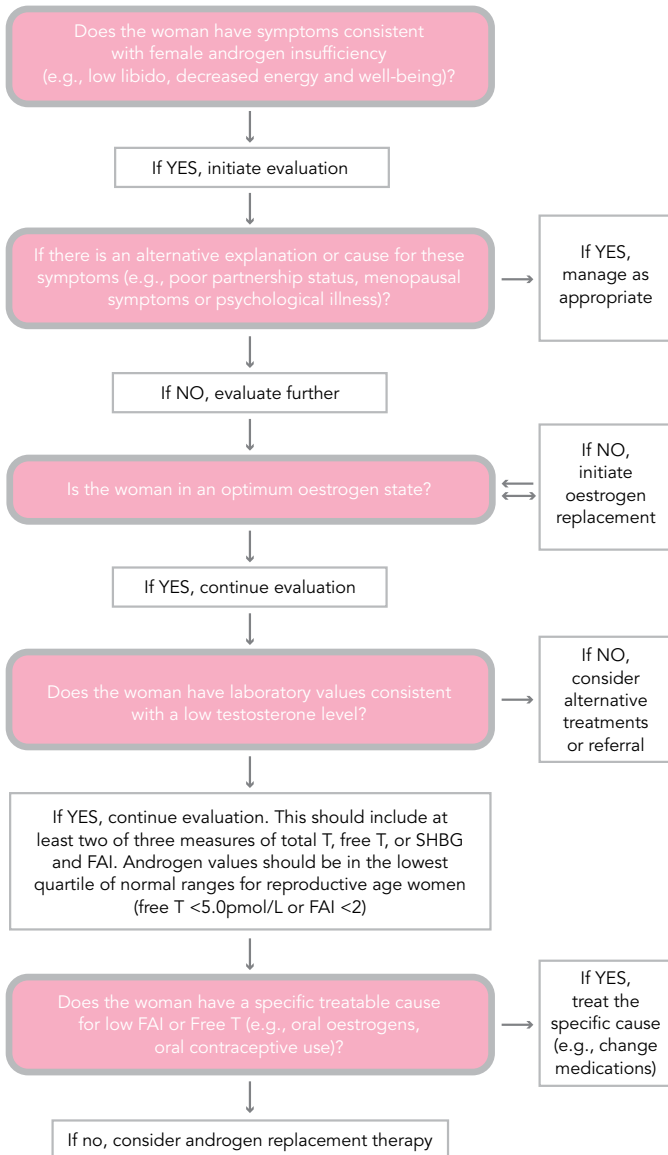
Patients should be made aware of the consequences of making sustained long-term close physical contact with young children. There is the potential for passive transfer of testosterone from the area of application to the skin of individuals with whom close contact is made. Long term continual exposure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

PRODUCT INFORMATION (cont'd)

Dosage and Administration

Prior to prescribing:

Topical application provides a convenient and acceptable delivery method for administering testosterone to women. Clinical manifestations of testosterone deficiency in testosterone deficient women differ vastly in individuals and may be present in tandem with other clinical disorders. The following flowchart* provides a management algorithm to assist in making a diagnosis prior to initiating therapy.



* Adapted from Bachmann. Female androgen insufficiency. Fertil Steril 2002.

If the patient meets the above criteria, counselling as to the benefits and potential risks of androgen therapy should be provided, including discussions on the lack of data on the safety of long-term use.

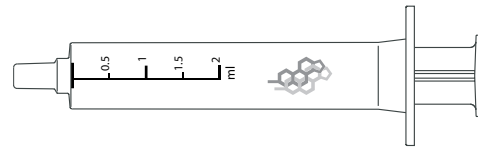
If the patient consents to initiating testosterone therapy careful monitoring should be provided for the initial three months of treatment and an evaluation of treatment be undertaken at the conclusion of the third month. Testing at this time should include monitoring of the liver function, haemoglobin and lipids. It is at the physician's discretion if treatment is to continue.

Directions for Use

ANDROFEME® 1% cream contains 10mg testosterone BP per 1ml via measured applicator. A baseline total serum testosterone level, sex hormone-binding globulin (SHBG) and free-testosterone or free-androgen index (FAI) should be measured before initiating treatment.

The usual starting dose of ANDROFEME® is 10mg testosterone (1ml of cream via applicator) applied once daily to the inner aspects of the forearm. Dose is variable according to severity of symptoms and clinical response. The patient should have follow-up levels taken fourteen days after initiating treatment. Levels should be maintained at the upper range of normal therapeutic range for females. Dose should be titrated as deemed appropriate. Follow-up should occur at 4 weeks and an evaluation of the treatment be undertaken at the conclusion of the third month.

The mode of administration is via the transdermal route (topically). ANDROFEME® is supplied with a dose applicator calibrated in 0.5ml graduations. Each 0.5ml delivers a 5mg dose of testosterone. The patient should be directed to measure the appropriate dose using the graduated applicator and then apply to the skin.



ANDROFEME® should be applied to clean dry skin. The recommended area for application is the inner aspects of the forearms between the wrist and the elbow or upper outer thigh. Absorption may be more variable if applied to other areas of the body. Do not apply to the genitalia or perineum. ANDROFEME® should be applied immediately after being dispensed from the tube. ANDROFEME® once applied to the skin should be massaged evenly until absorption is complete. This process typically takes 30-60 seconds. ANDROFEME® is only recommended for use in testosterone deficient women and is not recommended for use in any other female population.

Women should be made aware prior to initiating testosterone treatment of the lack of long term safety data associated with testosterone use in women. Treatment with ANDROFEME® should be on a short term basis – 3 months with regular monitoring (see Directions for use) – and it is at the physician's discretion if treatment is to be continued. Caution should be exercised when patients are taking products that may decrease sex hormone-binding globulin (SHBG) or increase free-testosterone levels.

Overdose

This is not likely due to the mode of administration.

Presentation

ANDROFEME® 1% cream containing 10mg/mL testosterone BP in a 50ml boxed tube.

ANDROFEME® is supplied with a dose applicator marked with 0.5ml graduations. Each 0.5ml delivers a 5mg dose of testosterone. The patient should be directed to measure the appropriate unit dose using the graduated applicator and then apply to the skin.

Storage

Store below 25°C. DO NOT FREEZE.

Shelf-life under these conditions is two years.

Once opened, the contents of the tube should be used within 12 weeks.

Name and Address of Sponsor

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