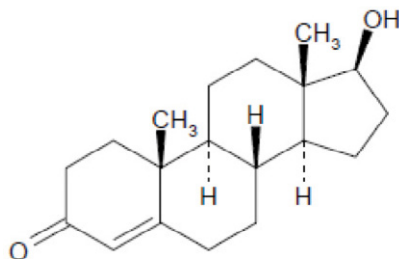


PRODUCT INFORMATION

ANDROFORTE® 5

NAME OF THE MEDICINE

Testosterone is an androgen. Chemically testosterone is 17β-hydroxyandrost-4-en-3-one and has the following structural formula:



Chemical Formula: C₁₉ H₂₈ O₂

Molecular Weight: 288.4

CAS No: 58-22-0

DESCRIPTION

Testosterone is a white, crystalline powder, odourless or almost odourless produced semi synthetically from plant origin. It is practically insoluble in water, freely soluble in ethanol (96%); slightly soluble in ethyl oleate. ANDROFORTE® 5 is a white, opaque, oil-in-water cream containing 5% testosterone (50 mg in 1 mL or 100mg in 2mL) and the excipients: dl-α-tocopheryl acetate (vitamin E), almond oil, cetomacrogol 1000, cetostearyl alcohol, carbopol 940, triethanolamine, butylated hydroxytoluene, Phenonip®, anhydrous citric acid and purified water.

PHARMACOLOGY

Pharmacodynamic properties

ANDROFORTE® 5 is an androgen replacement therapy containing the male hormone testosterone.

Endogenous androgens, principally testosterone, secreted by the testes and its major metabolite dihydrotestosterone (DHT), are responsible for the development of the external and internal genital organs and for maintaining the secondary sexual characteristics (stimulating hair growth, deepening of the voice, development of the libido); for a general effect on protein anabolism; for development of skeletal muscle and body fat distribution; for a reduction in urinary nitrogen, sodium, potassium, chloride, phosphate and water excretion.

Testosterone does not produce testicular development: it reduces the pituitary secretion of gonadotropins.

The effects of testosterone in some target organs arise after peripheral conversion of testosterone to oestradiol, which binds to oestrogen receptors in the target cell nucleus e.g. the pituitary, fat, brain, bone and testicular Leydig cells.

Pharmacokinetics

Following percutaneous absorption, testosterone diffuses into the systemic circulation at relatively constant concentrations during the 24 hour cycle.

Serum testosterone concentrations increase from the first hour after an application of ANDROFORTE® 5, reaching eugonadal levels within 24 hours. Daily changes in testosterone concentrations are then of similar amplitude to those observed during the circadian rhythm of endogenous testosterone. The percutaneous route avoids blood peaks or the first pass effect of oral androgen therapy.

Administration of 2 mL of ANDROFORTE® 5 (100mg testosterone) to the torso produces an average testosterone concentration increase in hypogonadic men of approximately 7.7 nmol/L in plasma with a T_{max} around 14.8 hours after application.

The major active metabolites of testosterone are DHT and oestradiol.

Testosterone is excreted, mostly in urine, and in faeces as conjugated testosterone metabolites.

The half-life of testosterone is controlled by skin permeation and not clearance/metabolism.

CLINICAL TRIALS

The pivotal study was a Phase II, randomised, crossover bioequivalence study of ANDROFORTE® 5 and a commercially available non-scrotal 1% transdermal testosterone gel (Testogel®). Hypogonadal men (N = 15) were assigned to receive 2mL ANDROFORTE® 5 (100mg testosterone) per day, or 50mg testosterone gel (5mL of a 1% gel) per day for 30 days. The primary efficacy analysis was designed to demonstrate the bioequivalence of ANDROFORTE® 5 with the 1% testosterone gel on the basis of AUC and C_{avg} serum testosterone levels being within the eugonadal range. Other efficacy variables that were examined included: testosterone concentrations at day 30, dihydrotestosterone, oestradiol, luteinising hormone, follicle stimulating hormone and steroid hormone binding globulin concentrations, sexual questionnaire, mood/energy questionnaire, general health survey and erectile function questionnaire. ANDROFORTE® 5 was bioequivalent to Testogel® for the key pharmacokinetic parameters of C_{max}, C_{avg} and AUC using adjusted and unadjusted for baseline values.

The Table below demonstrates the C_{max} and C_{avg} serum testosterone levels (nmol/L) achieved from baseline up to 30 days of treatment in hypogonadal men from the pivotal Phase-II comparator trial in the same hypogonadal subjects.

	ANDROFORTE 5 100mg/day	TESTOSTERONE GEL 50mg/day
C _{max} Day 30	16.3 ± 6.5	19.4 ± 12.8
C _{avg} Day 30	11.4 ± 5.2	11.3 ± 3.7

INDICATIONS

ANDROFORTE® 5 is indicated for use as testosterone replacement therapy for male hypogonadism when testosterone deficiency has been confirmed by clinical features and biochemical tests.

CONTRAINDICATIONS

Testosterone is contraindicated in men with known or suspected carcinoma of the breast or prostate.

Hypersensitivity to the active substance (testosterone) or to any of the excipients.

PRECAUTIONS

Androgens may accelerate the progression of sub-clinical prostate cancer and benign prostatic hyperplasia.

ANDROFORTE® 5 should not be used by women or children due to possible virilising effects.

Prior to testosterone initiation, all patients must undergo a detailed examination in order to exclude the risk of pre-existing prostate cancer. Careful and regular monitoring of

the prostate gland (digital rectal examination and estimation of serum PSA (Prostate Specific Antigen) and breast must be performed in accordance with recommended practice in patients receiving testosterone therapy at least once yearly and twice yearly in elderly and at risk patients (those with clinical or familial risk-factors).

Testosterone should be used only if hypogonadism (hyper- and hypogonadotrophic) has been demonstrated and if other aetiology, responsible for the symptoms, has been excluded before treatment is started. Testosterone insufficiency should be clearly demonstrated by clinical features (regression of secondary sexual characteristics, change in body composition, asthenia, reduced libido, erectile dysfunction etc.) and confirmed by two separate blood testosterone measurements. Due to variability in laboratory values, all measures of testosterone should be carried out in the same laboratory.

Testosterone concentrations should be monitored when switching the patient from another testosterone product to ANDROFORTE® 5.

In addition to monitoring the testosterone concentrations in patients on long-term androgen therapy the following laboratory parameters should be checked periodically: haemoglobin, haematocrit (to avoid the risk of polycythaemia), liver function tests, and lipid profile.

Increases in haematocrit may require reductions in dose or discontinuation of testosterone therapy. Increased haematocrit may increase the risk for a thromboembolic event. Changes in serum lipid profile may require dose adjustment or discontinuation of testosterone therapy.

With specific reference to ANDROFORTE® 5, erythrocytosis and skin reactions are at the lowest end of the risk scale when transdermal testosterone is the mode of delivery. If the patient develops a severe application site reaction, treatment should be assessed and discontinued if necessary.

Testosterone is not a treatment for male sterility or impotence in men with normal serum testosterone levels.

With large doses of exogenous androgens, spermatogenesis may be suppressed through feedback inhibition of pituitary follicle-stimulating hormone (FSH) which could possibly lead to adverse effects on semen parameters including sperm count.

Certain clinical signs: irritability, nervousness, weight gain, prolonged or frequent erections may indicate excessive androgen exposure requiring dosage adjustment.

In patients suffering from severe cardiac, hepatic or renal insufficiency or ischemic heart disease, treatment with testosterone may cause severe complications characterised by oedema with or without congestive cardiac failure. In such case, treatment must be stopped immediately. There are no studies undertaken to demonstrate the efficacy and safety of ANDROFORTE® 5 in patients with renal or hepatic impairment. Patients with pre-existing cardiac, hepatic or renal diseases need to be monitored closely when undergoing androgen treatment. Because ANDROFORTE® 5 is not taken orally hepatotoxicity is not a risk factor. Gynecomastia occasionally develops and occasionally persists in patients being treated with androgens for hypogonadism.

There are published reports of increased risk of sleep apnoea in hypogonadal men treated with testosterone, especially those with risk factors such as obesity or chronic lung disease.

Testosterone should be used with caution in patients with epilepsy and migraine as these conditions may be aggravated.

Testosterone should be used with caution in cancer patients at risk of hypercalcaemia (and associated hypercalciuria), due to bone metastases. Regular monitoring of serum calcium

concentrations is recommended in these patients.

Testosterone may cause an increase in blood pressure and should be used with caution in patients with hypertension.

Changes in insulin sensitivity may occur in patients treated with androgens who achieve normal testosterone plasma concentrations following replacement therapy.

Athletes should be informed that ANDROFORTE® 5 contains an active substance (testosterone), which may give positive results in an anti-doping test. Androgens are not indicated for enhancing muscular development in healthy individuals.

Potential for transfer

Testosterone solution can be transferred to other persons by close skin to skin contact, resulting in increased testosterone serum levels and, with repeated contact, possibly adverse effects. In women, this may cause growth of facial and/or body hair, deepening of the voice, irregularities of the menstrual cycle; in children this may cause premature puberty and genital enlargement, in case of repeat contact (inadvertent androgenisation). If virilisation occurs, testosterone therapy should be promptly discontinued until the cause has been identified.

The risk of transfer is substantially reduced by wearing clothes covering the application area. The majority of residual testosterone is removed from the skin surface by washing with soap and water prior to contact.

The physician should inform the patient carefully about the risk of testosterone transfer and about safety instructions (see below). ANDROFORTE® 5 should not be prescribed to patients with a major risk of non-compliance with safety instructions (e.g. severe alcoholism, drug abuse, severe psychiatric disorders and children).

As a result, the following precautions are recommended:

For the patient:

- Wash hands thoroughly with soap and water after applying the solution.
- Cover the application area with clothing once the solution has dried.
- Wash before any situation in which skin-to-skin contact is foreseen.

For people not being treated with ANDROFORTE® 5:

- In the event of contact with an application area which has not been washed or is not covered with clothing, wash the area of skin onto which testosterone may have been transferred as soon as possible, using soap and water.
- Report the development of signs of excessive androgen exposure such as acne or hair modification.

To improve partner safety the patient should be advised to wear a T-shirt covering the application site during the contact period or to shower before sexual intercourse.

Furthermore, it is recommended to wear clothing covering the application site during contact periods with children in order to avoid transference to children.

Pregnant women must avoid any contact with ANDROFORTE® 5 application sites. In case of pregnancy of the partner, the patient must reinforce his attention to the precautions for use.

Effects on Fertility

Fertility studies in rodents and primates have shown that treatment with testosterone can impair fertility by suppressing spermatogenesis in a dose dependent manner.

Use in Pregnancy

Pregnancy category D.

Testosterone is contraindicated in women who are or who anticipate becoming pregnant (see Contraindications). Pregnant women must avoid any contact with ANDROFORTE® 5 application sites. Exposure of a fetus to androgens may result in varying degrees of virilisation. In the event of contact, women are advised to wash with soap and water as soon as possible.

Use in Lactation

Testosterone is contraindicated during breast-feeding. In the event of accidental contact, women are advised to immediately wash with soap and water.

Use in the Elderly

There is limited experience of the use of testosterone in elderly patients over 65 years of age. Currently, there is no consensus about age specific testosterone reference values. However, it should be taken into account that physiological testosterone serum levels are lower with increasing age.

Carcinogenicity

A relationship between androgen treatment and certain cancers has been found in laboratory animals. Experimental data in rats have shown increased incidences of prostate cancer after treatment with testosterone. Sex hormones are known to promote the growth of certain hormone-dependent tissues and tumours. Subcutaneous implantation of testosterone produced cervical-uterine tumours in female mice, which metastasised in some cases. Metastasising prostatic adenocarcinomas occurred in male rats after chemical induction and subcutaneous implantation of testosterone. Testosterone is also known to increase the number of tumours and decrease the degree of differentiation of chemically induced carcinomas of the liver in rats. Hepatocellular carcinoma has been reported in patients receiving long-term therapy with androgens.

Hypogonadal men receiving androgen replacement therapy require surveillance for prostatic disease similar to that recommended for eugonadal men of comparable age.

Genotoxicity

The genotoxic potential of testosterone has not been fully investigated in a comprehensive battery of genotoxicity studies. However, testosterone was found not to be clastogenic when tested *in vitro* in assays with hamster lung fibroblasts or in mouse or hamster embryo fibroblasts, or in *in vivo* chromosome aberration assays in mouse bone marrow cells and spermatocytes. Testosterone was also negative in assays for unscheduled DNA synthesis in rat and human hepatocytes.

INTERACTION WITH OTHER MEDICINES

Changes in insulin sensitivity, glucose tolerance, glycaemic control, blood glucose and glycosylated haemoglobin have been reported with androgens. In diabetic patients, medication requirements may change.

When androgens are used simultaneously with anti-coagulants, the anti-coagulant effects may be increased. More frequent monitoring of INR and prothrombin time is recommended in patients taking anticoagulants, especially at the initiation and termination of androgen therapy.

The concurrent use of testosterone with ACTH or corticosteroids may result in increased fluid retention and should be monitored, particularly in patients with cardiac, renal or hepatic disease.

Concurrent administration of oxyphenbutazone and

androgens may result in elevated serum levels of oxyphenbutazone.

In diabetic patients, the metabolic effects of androgens may decrease blood glucose levels, and therefore, insulin requirements.

Concurrent administration of testosterone and bupropion may result in a lowered seizure threshold.

Concurrent administration with cyclosporin may result in increased cyclosporin toxicity and elevated cyclosporin blood levels.

Theoretically, in general, any substance which affects liver function should not be taken with testosterone, although this may not be as problematic with transdermal preparations such as AndroForte 5. Examples of herbal products include: ancreamica dahurica, chapparal, comfrey, eucalyptus, germander tea, Jin Bu Huan, kava, penny royal oil, skullcap, and valerian.

Effects on Ability to Drive and Operate Machinery

No studies on the effects on the ability to drive and use machines have been performed.

Effects on Laboratory Tests

Androgens may decrease levels of thyroxine-binding globulin resulting in decreased total T4 serum levels and increased resin uptake of T3 and T4. Free thyroid hormone levels remain unchanged, however, and there is no clinical evidence of thyroid dysfunction.

ADVERSE EFFECTS

According to the literature, additional undesirable events that are possibly or probably related to testosterone use are shown in the following table:

System Organ Class	Adverse Events
Blood and Lymphatic System disorders	Changes in laboratory tests (polycythaemia, lipids), Blood creatinine increased
Endocrine disorders	Increase in male pattern hair distribution, Hirsutism
Metabolism and Nutrition disorders	Electrolyte changes (retention of sodium, potassium, chloride, calcium, inorganic phosphate, water) during high dose or prolonged treatment, Appetite increased, Oedema,
Psychiatric disorders	Mood disorders, Nervousness, Hostility
Nervous system disorders	Amnesia, Hyperesthesia, Smell disorder, Taste disorder
Vascular disorders	Blood pressure diastolic decreased, Flushing, Vasodilation
Respiratory, thoracic and mediastinal disorders	Worsening of Sleep apnoea, Dyspnoea
Hepatobiliary disorders	Abnormal liver enzyme/ liver function tests (including bilirubin) ¹

System Organ Class	Adverse Events
Skin and subcutaneous tissue disorders	Alopecia, Urticaria, Discoloured hair, Skin reactions including seborrhoea
Musculoskeletal and connective tissue disorders	Muscle cramps, Muscle pain
Renal and Urinary disorders	Prostatic disorders, Worsening symptoms of BPH, Impaired urination, Urinary tract infections, Urinary tract obstruction
Reproductive System and Breast disorders	Virilisation of foetuses, infants, children and women, Foetal harm, Suppression of lactation, Gynaecomastia/mastodynia, Sensitive nipples, Libido changes, Increased frequency of erections, Suppression of spermatogenesis, Reduction in the size of the testicles/testicular atrophy, Priapism
General Disorders and Administration Site Conditions	Hypersensitivity reactions, Asthenia, Malaise
Investigations	Decreased HDL

(1) Other rare known undesirable effects associated with testosterone include hepatic neoplasms.

Hepatic or renal impairment

No formal studies were conducted with ANDROFORTE® 5 involving patients with renal or hepatic impairment. Lower doses may be required in renal or hepatic impairment.

Paediatric population

The safety and efficacy of ANDROFORTE® 5 in children and adolescents aged under 18 years of age has not been established.

The patient should be advised to wash their hands well with soap and water after ANDROFORTE® 5 has been applied in case of contact with children.

DOSAGE AND ADMINISTRATION

Adult men (18 years old and above)

The recommended dose is 2 mL of cream (i.e. 100 mg of testosterone) applied once daily at about the same time, preferably in the morning. The daily dose should be adjusted by the doctor depending on the clinical or laboratory response in individual patients, not exceeding 4 mL of cream per day. The adjustment of dosage should be achieved by 1 mL of cream steps.

The application should be administered by the patient himself, onto clean, dry, healthy skin to the torso. The torso includes the abdomen and the sides of the body from the waist to just below the armpits. It is preferable to apply to areas with minimal hair and body fat. After opening the tube, the total contents must be extracted using the supplied dose measuring syringe and applied immediately onto the skin. The cream has to be simply spread on the skin gently and massaged in until vanished. Typically this takes 30 seconds or so. Wash hands with soap and water after applications. To clean the applicator after use rinse in hot water.

Eugonadal plasma testosterone concentrations are generally reached within 24 hours of a single dose of ANDROFORTE® 5. Absorption is variable between individuals and dose titration may be required. In order to adjust the testosterone dose, serum testosterone concentrations must be measured in the morning before application from the 15th day on after starting treatment. The dose may be reduced if the plasma testosterone concentrations are raised above the desired level. If the concentrations are low, the dosage may be increased, not exceeding 4 mL of cream per day.

Paediatric use

ANDROFORTE® 5 is not indicated for use in children and has not been evaluated clinically in males under 18 years of age.

OVERDOSAGE

No cases of overdose with AndroForte® 5 have been reported in clinical trials. Treatment of overdose would consist of discontinuation of AndroForte® 5 together with appropriate symptomatic and supportive care.

If you think that you or anyone else may have used too much AndroForte® 5, immediately contact your doctor or call the Poisons Information Centre on 13 11 26 for advice. Do this even if there are no signs of discomfort or poisoning. Wash the skin with soap and water.

PRESENTATION AND STORAGE CONDITIONS

ANDROFORTE® 5 is presented as single boxed tube with a graduated syringe-style measuring device. ANDROFORTE® 5 is supplied in a 50mL sealed tube and contains 50mg testosterone per 1 mL of cream.

The tube should not be opened until immediately prior to application of the cream.

Store below 25°C. Do not freeze.

In-use storage: ANDROFORTE® 5 should be used within 12 weeks of opening.

Shelf Life: ANDROFORTE® 5 has a 36 month shelf-life from the date of manufacture.

For the expiry date and batch number please see the crimp of the tube.

NAME AND ADDRESS OF THE SUPPLIER

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POISON SCHEDULE OF THE MEDICINE: S 4

PRESCRIPTION ONLY MEDICINE

AUST R 123764

Date of first Inclusion in the Australian Register of Therapeutic Goods (ARTG):

11/07/2014

Date of most recent amendment: 19/02/2015