

AUSTRALIAN PRODUCT INFORMATION – ANDROFORTE® 2 (TESTOSTERONE) 2% W/V CREAM

ANDROFORTE 2 is indicated for use in both men and women. It is important to understand that the dosing and site of application is gender specific as stated in section 4 of this PI. To make it easier to understand, this document is written in 3 different colours. Black sections refer to both men and women, green to only women and blue to only men.

1 NAME OF THE MEDICINE

Testosterone

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

ANDROFORTE 2 contains 2% w/v testosterone (20 mg in 1 mL).

Contains tree nut products (almond oil) and hydroxybenzoates.

For the full list of excipients, see section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Cream.

ANDROFORTE 2 is a white, opaque, oil-in-water cream.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

In men, ANDROFORTE 2 is indicated for use as testosterone replacement therapy for male hypogonadism when testosterone deficiency has been confirmed by clinical features and biochemical tests.

In women, ANDROFORTE 2 is indicated for the treatment of hypoactive sexual desire dysfunction (HSDD) in postmenopausal women.

Therapeutic intervention with ANDROFORTE 2 should only be initiated in women following failure of appropriate education and correction of modifiable biopsychosocial factors (which may include neuroendocrine imbalance, physical ill health or disease, interpersonal difficulties, psychological distress or specific cultural or religious beliefs), according to the International Society for the Study of Women's Sexual Health (ISSWSH) process of care (see Figure 1).

4.2 DOSE AND METHOD OF ADMINISTRATION

Adult men (18 years old and above): Application to the scrotum

The recommended starting dose of ANDROFORTE 2 when applied to the entire scrotum is 1.25 mL of cream (i.e. 25 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 and/or laboratory response in individual patients, not exceeding 2.5 mL of cream per day. The adjustment of dosage should be achieved by 0.6 mL increments.

The application should be administered by the patient himself, onto clean, dry, healthy skin on the scrotum. The scrotum is not required to be shaved prior to application.

Adult women (18 years old and above): *Application to the upper outer thigh or buttock*

The recommended starting dose is 5 mg testosterone (0.25 mL) applied once daily, at approximately the same time each day, to either the upper outer thigh or buttock.

If no improvement in symptoms is seen within 3 months and if the testosterone concentration is within the premenopausal reference range a dose increase up to 10 mg testosterone (0.5 mL) daily can be used with follow up clinical and biochemical monitoring. This dose should only rarely be exceeded. (See Monitoring)

Clinical trials have shown that there is a four to eight-week time lag between starting testosterone treatment and an improvement in sexual motivation. If there is no improvement in symptoms after 6 months of continuous therapy, treatment should be discontinued and alternative options be considered.

Method of administration

The patient should be directed to measure the appropriate dose using the supplied graduated applicator and immediately apply to clean dry skin at the appropriate site of application. The cream should be 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.

Absorption may be more variable if applied to other areas of the body. The dose can be varied according to severity of symptoms and clinical response.

Do not apply to the female genitalia or perineum.

Prior to prescribing

Female sexual dysfunction, including HSDD, has many etiologies including biopsychosocial factors such as neuroendocrine imbalance, physical ill health or disease, interpersonal difficulties, psychological distress and specific cultural or religious beliefs.

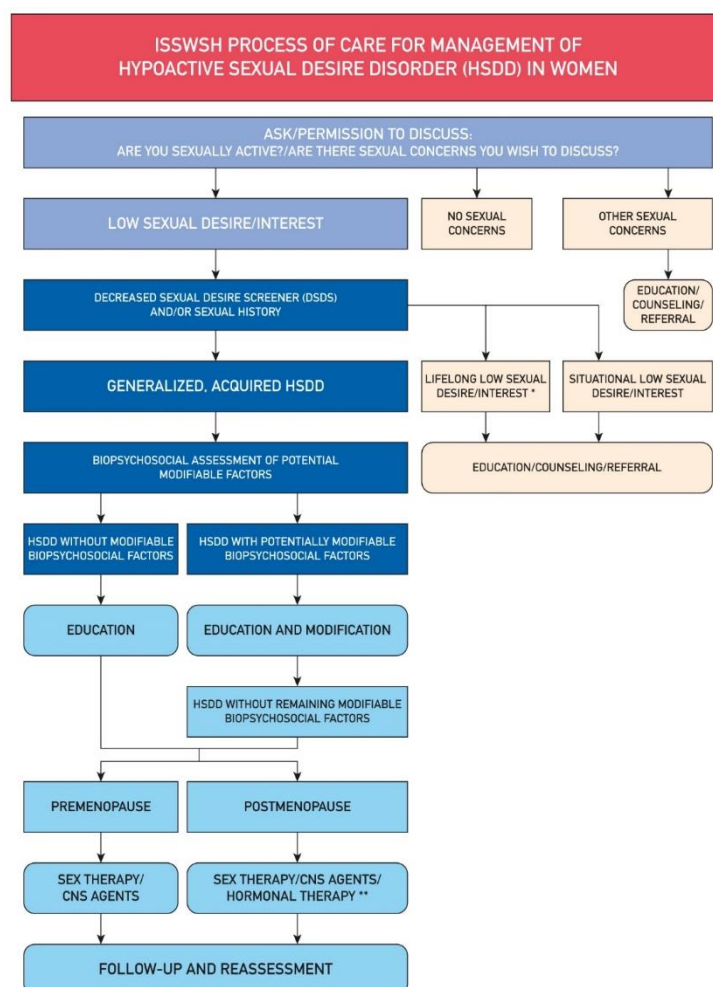
The diagnosis of HSDD in clinical practice should be based on thorough clinical assessment guided by diagnostic criteria such as ISSWSH or the International Classification of Diseases 11th Edition (ICD-11).

Therapeutic intervention with ANDROFORTE 2 should only be initiated in women following failure of alternative treatment options and correction of modifiable risk factors.

Figure 1 provides a management algorithm to assist in making a diagnosis prior to initiating therapy. If the patient meets the treatment criteria, counselling as to the benefits and potential risks of testosterone therapy should be provided, including discussions on the lack of data on the safety of long-term use.

The baseline total testosterone concentration should be measured before commencement, with a repeat level 3-6 weeks after treatment initiation (see Monitoring).

Figure 1. The ISSWSH process of care for management of hypoactive sexual desire disorder (HSDD) in women¹



*Women with lifelong low sexual desire/interest without distress/bother may characterise themselves as asexual and should not be considered for treatment. **Women in the late reproductive years.

1. Adapted and reproduced with permission from Elsevier publishers. Reference: Clayton AH, Goldstein I, Kim NN et al. The International Society for the Study of Women's Sexual Health Process of Care for the management of hyposexual desire disorder in women. Mayo Clinic Proc, 2018; 93(4): 467-487.

Monitoring

Adult men (18 years old and above)

Hypogonadal symptom control is the primary aim of testosterone therapy via achieving a serum testosterone concentration sufficient to restore physiological androgen status to that comparable with eugonadal men. Biochemistry is an adjunct indicator of treatment response together with the identification and monitoring of the man's leading symptom. Trough testosterone levels should be within the lower limit of the reference interval for eugonadal men.

Eugonadal serum testosterone concentrations are generally reached within 24 hours of a single dose of ANDROFORTE 2 applied scrotally. Absorption is variable between individuals and will have a different pharmacokinetic profile for men changing from non-scrotal testosterone products. In order to adjust the testosterone dose for scrotal application it is recommended that two (2) serum testosterone concentrations be measured at 3 hours (peak) and 24 hours (trough) from prior application after the 15th day of starting treatment. Results of clinical and/or biochemical monitoring may prompt dose titration.

Adult women

It is recommended that serum testosterone monitoring be used as an aid to treatment rather than as the primary measure of efficacy. The primary determinant of efficacy should be based on the improvement in sexual function considered relevant to each individual woman.

Baseline testosterone and sex hormone binding globulin (SHBG) levels should be obtained prior to initiation of testosterone therapy.

It is recommended that women should ideally attend the same laboratory for baseline testosterone biochemistry prior to and during treatment.

The patient should have a follow-up blood test taken three to six weeks after initiating treatment.

Optimally, the serum concentration of total testosterone should be maintained within the approximate physiological range for premenopausal women. The dose should be titrated as deemed clinically appropriate up to a maximum of 10mg (0.5mL). It is recommended that if the serum testosterone concentration exceeds the upper limit of the premenopausal range of the assay being used that clinical evaluation is needed to screen for evidence of hyperandrogenism and a dose reduction considered. Women with total testosterone concentrations greater than 50% above the upper limit of the premenopausal reference range for the assay being used should be advised to reduce the dose of the applied cream. Follow-up should occur at 12 weeks including a full assessment of treatment efficacy and safety then review of serum testosterone levels 6 monthly thereafter.

A dose of up to 10 mg daily is usually sufficient to provide adequate improvement in symptoms and should rarely be exceeded. If no benefit is experienced by 6 months, treatment should be ceased.

Women should be made aware prior to initiating testosterone treatment of the lack of long-term clinical trial safety data beyond 24 months associated with use of testosterone in physiological doses in women. Treatment with ANDROFORTE 2 should include regular monitoring and it should be an informed decision between physician and patient if treatment is to be continued beyond 24 months.

Caution should be exercised when patients are taking products that may increase or decrease SHBG or free-testosterone levels (see section 4.5 Interactions with other medicines and other forms of interactions).

Paediatric use

ANDROFORTE 2 is not indicated for use in children and has not been evaluated clinically in males or females under 18 years of age.

4.3 CONTRAINDICATIONS

ANDROFORTE 2 is contraindicated in patients with known sensitivity to testosterone, tree nuts (almond oil) or any of the excipients listed in section 6.1 List of excipients.

It is contraindicated in male and females with known or suspected carcinoma of the breast or [prostate](#), known or suspected androgen-dependent neoplasia, nephrotic syndrome, history of thromboembolism or hypercalcaemia.

It is contraindicated in pregnancy and lactation.

It 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.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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

ANDROFORTE 2 should not be used by women (other than for the treatment of hypoactive sexual desire dysfunction in postmenopausal women) or children due to possible virilising effects.

Prior to testosterone initiation, all patients must undergo a detailed examination in order to assess for 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 supplementation in women must be monitored closely, especially at onset of treatment (see section 4.2: Dose and method of administration, Monitoring).

Female testosterone requirements are between ten and twenty times less than that of males.

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.

Normal ranges for testosterone may vary between laboratories and between different assay methods, therefore all measures of testosterone should be carried out in the same laboratory.

Androgenic side-effects may occur if doses are too high, therefore individual assessment and monitoring needs to be implemented on a patient-by-patient basis. If unwanted androgenic side-effects are experienced treatment should be halted and recommenced after reduced serum testosterone levels have been established. Levels typically return to baseline 2-5 days after ceasing treatment.

Testosterone concentrations should be monitored when switching the patient from another testosterone product to ANDROFORTE 2 or when switching from upper body application to scrotal application and vice versa.

Modest elevations of serum dihydrotestosterone (DHT) concentrations are commonly observed after scrotal and non-scrotal administration of testosterone, however there is no evidence to suggest that high circulating DHT concentrations have a deleterious effect on the prostate and cardiovascular safety profile.

In addition to monitoring the testosterone concentrations in male 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.

Clotting disorders

Testosterone should be used with caution in male patients with thrombophilia or risk factors for venous thromboembolism (VTE), as there have been post-marketing studies and reports of thrombotic events (e.g. deep-vein thrombosis, pulmonary embolism, ocular thrombosis) in these patients during testosterone therapy. In thrombophilic patients, VTE cases have been reported even under anticoagulation treatment, therefore continuing testosterone treatment after first thrombotic event should be carefully evaluated. In case of treatment continuation, further measures should be taken to minimise the individual VTE risk.

With specific reference to ANDROFORTE 2, 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 2 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 2 is not taken orally hepatotoxicity is not a risk factor.

Gynecomastia occasionally develops and occasionally persists in male 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 2 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

Transdermal testosterone cream 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.

Patients should be made aware of the consequences of making sustained long-term close physical contact with young children. Long-term continual exposure may result in passive absorption and 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 physician should inform the patient carefully about the risk of testosterone transfer and about safety instructions (see below). ANDROFORTE 2 should not be prescribed to patients with a major risk of non-compliance with safety instructions (e.g. severe alcoholism, drug abuse and severe psychiatric disorders).

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.

For the patient:

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

For people not being treated with ANDROFORTE 2:

- 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 female partner safety men using scrotal application should shower or wash the genital area with a damp warm flannel 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 2 application sites. In case of pregnancy of the partner, the patient must particularly be careful to avoid potential transfer.

Use in hepatic impairment

No formal studies were conducted with ANDROFORTE 2 involving patients with hepatic impairment. Lower doses may be required in hepatic impairment.

Use in renal impairment

No formal studies were conducted with ANDROFORTE 2 involving patients with renal impairment. Lower doses may be required in renal impairment.

Cardiovascular risk factors

There are currently few data available assessing the long-term effect of testosterone supplementation in women on cardiovascular disease beyond 24 months or in a more “at risk” patient population. Testosterone should be used with caution in women at risk for or with current cardiovascular disease.

Lipid concentrations

In clinical trials in women, transdermal testosterone does not significantly alter the serum concentrations of total cholesterol, LDL cholesterol, and triglyceride, however a small, but a statistically significant decreased the HDL concentration may be observed, particularly with higher doses.

Blood pressure

In clinical trials a small mean increase in both systolic and diastolic blood pressure (≤ 3 mmHg) in postmenopausal women was observed after 4 years of treatment with transdermal testosterone. This change is not considered to be clinically significant.

Body weight

In clinical trials a small mean increase in weight (1.52 kg, fat and muscle weight were not assessed separately) was observed in postmenopausal women who used a transdermal testosterone patch for 3 years.

Carbohydrate metabolism

In clinical trials no significant difference in serum glucose or insulin was observed between transdermal testosterone and placebo in women treated for 24 months.

Effect on Breast Tissue

Evidence for long-term effects of testosterone supplementation on breast cancer is limited. Testosterone should be used with caution in women at risk for breast cancer.

Clinical studies have found no statistically significant difference in the mean increase in the amount of dense breast tissue or area of dense breast was associated with testosterone supplementation in postmenopausal women. Testosterone has been shown to inhibit total breast cell proliferation in postmenopausal women using estrogen/progesterone hormone therapy. Epidemiology studies conducted for up to 5 years have found no statistically significant increase in breast cancer risk.

In women over 50 years of age the BreastScreen Australian recommendation for mammographic screen is every 2 years, unless there is an individual need e.g. family history. This applies to women using AndroForte 2 therapy.

Effect on endometrium

Short-term treatment with testosterone does not appear to stimulate endometrial proliferation, however the longer-term effects of testosterone on endometrial proliferation and the risk of endometrial cancer are unknown. Testosterone should be used with caution in women at risk for or with current endometrial hyperplasia or cancer.

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.

Paediatric use

The safety and efficacy of ANDROFORTE 2 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 2 has been applied in case of contact with children.

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.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

All oral estrogens (oral contraceptives and oral HRT) will result in an increase in SHBG which will bind testosterone and reduce bioavailability. Patients using oral estrogen should be changed to transdermal estrogen before being considered for testosterone therapy.

The concurrent use of tibolone or glucocorticoids with testosterone may result in elevated testosterone levels due to a decrease in SHBG.

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 ciclosporin may result in increased ciclosporin toxicity and elevated ciclosporin 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 2. Examples of herbal products include: ancreamica dahurica, chapparal, comfrey, eucalyptus, germander tea, Jin Bu Huan, kava, penny royal oil, skullcap, and valerian.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

ANDROFORTE 2 has not been evaluated for possible effects on human fertility but fertility studies in animals have shown that treatment with testosterone can **impair fertility by suppressing spermatogenesis in a dose dependent manner and has the potential to disrupt ovulation and impair fertility in females.**

Use in pregnancy

Category D

Testosterone is contraindicated in women who are or who anticipate becoming pregnant (see section 4.3 Contraindications). Pregnant women must avoid any contact with ANDROFORTE 2 application sites.

Studies with testosterone in pregnant animals indicate the potential for adverse effects on embryofetal development, including on the reproductive tract and cardiovascular system.

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 should not be used by breast-feeding women. **Testosterone suppresses prolactin in lactating females and may cause adverse effects in the infant. ANDROFORTE 2 must not be used in breast-feeding women (see section 4.3 Contraindications).** In the event of accidental contact, women are advised to immediately wash with soap and water.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

According to the literature, additional undesirable events that are possibly or probably related to testosterone use are shown in Table 1.

Table 1

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 ,
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 benign prostatic hyperplasia (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 high-density lipoprotein (HDL)

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

The following adverse events have been reported in clinical trials in postmenopausal women, using transdermal testosterone preparations providing similar systemic exposure to testosterone as ANDROFORTE 2 when used as directed in section 4.2: Dosage and administration. That is, when physiological testosterone concentrations for premenopausal women are approximated.

Table 2. Common adverse events reported in clinical trials

Adverse Events	Testosterone N (%)	Placebo N (%)
Acne	122 (7.5)	83 (0.5)
Increased hair growth	212 (8.6)	106 (6.1)
Alopecia	55 (4.5)	55 (4.4)
Voice change	48 (3.7)	44 (3.4)

Headache, abdominal bloating, and constipation have been reported in association with ANDROFORTE 2.

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.

Potential side effects from excessive testosterone doses may include:

- Nausea, vomiting, jaundice or swelling of the ankles
- Increased body hair
- Increased acne
- Signs of virilisation
- Weight gain
- Persistent headaches
- Deepening of the voice
- Electrolyte disturbances
- Polycythemia.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

No cases of overdose with ANDROFORTE 2 have been reported in clinical trials.

Treatment of overdose would consist of discontinuation of ANDROFORTE 2 together with appropriate symptomatic and supportive care. Wash the skin with soap and water.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

ANDROFORTE 2 is an androgen replacement therapy containing the hormone testosterone. Testosterone and its 5 α -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 and testes in men.

In males, testosterone and its major metabolite dihydrotestosterone (DHT), are responsible for the normal growth and 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.

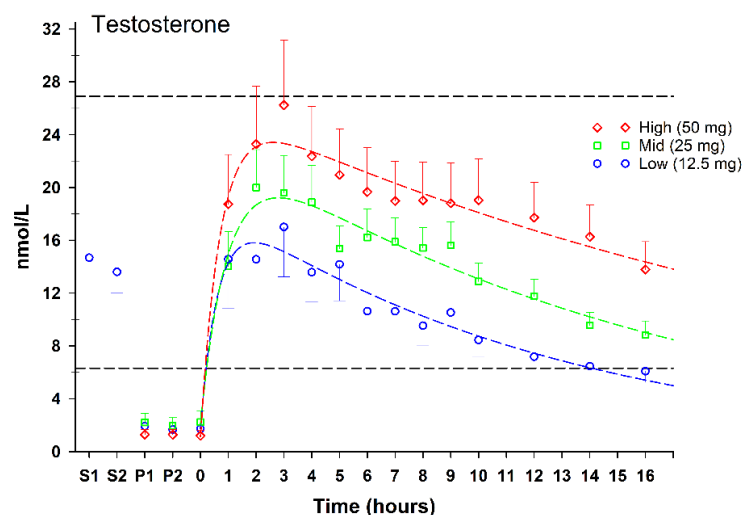
In women androgens act directly via the androgen receptors in tissues, such as bone, skin fibroblasts, hair follicles and sebaceous glands. Testosterone is a precursor hormone for estrogen biosynthesis in the ovaries and at extragonadal sites - bone, brain, cardiovascular and adipose tissues. Testosterone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

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**.

Clinical trials

A three-phase single-dose cross-over pharmacokinetic study of testosterone cream in endogenous testosterone suppressed healthy volunteers (n=11) described by Iyer 2017¹ demonstrated a nonlinear dose-dependent increase in serum testosterone C_{max} following scrotal administration of testosterone doses of 12.5 mg, 25 mg and 50 mg. Testosterone was rapidly absorbed from the scrotal skin with a mean T_{max} of 3.3-5.3 h. The mean C_{max} (\pm SEM) for the 12.5 mg, 25 mg and 50 mg testosterone doses was 19.8 ± 3.8 , 21.9 ± 2.8 and 28.8 ± 3.8 nmol/L, respectively. Serum testosterone concentrations were maintained within the physiological reference range of 1.8-7.8 ng/mL (6.2-26.9 nmol/L) for at least 12 h at the lowest 12.5 mg dose and for over 16 h for the 25 mg and 50 mg dose levels. Serum DHT concentrations after scrotal testosterone administration were higher than the physiological reference range of 0.07-0.64 ng/mL (0.24-2.21 nmol/L) and independent of dose with a mean C_{max} of 4.5-4.9 nmol/L. Serum estradiol concentrations were independent of testosterone dose and remained within the physiological range of 15-68 pg/mL (55-250 pmol/L) for 16 h post-dose. Testosterone cream was well tolerated when applied to the scrotum with no complaints of skin irritation or discomfort after application.

Figure 1: Serum testosterone concentrations following application of three doses (12.5, 25, 50 mg) of testosterone to the scrotal skin. Data are plotted as mean and standard error of the mean. Biexponential curves are fitted to all data for each dose. Y-axis units modified from Iyer 2017¹.



¹ Iyer R, Mok SF, Savkovic S, et al. Pharmacokinetics of testosterone cream applied to scrotal skin. *Andrology*. 2017 Jul;5(4):725-731.

The clinical efficacy of ANDROFORTE 2 cream on female is supported by literature evidence consisting of four meta-analyses and/or systematic reviews and four individual clinical trials. Of these publications, the meta-analysis by Achilli 2017 and clinical trial by El-Hage 2007 are considered pivotal and are summarised below.

The meta-analysis Achilli 2017 was designed to systematically review and summarise the existing evidence related to the efficacy and safety of transdermal testosterone in postmenopausal women when used to treat hypoactive sexual desire disorder (HSDD).

The criteria used to select individual studies for analysis were, that they should be randomised clinical trials, and that they were performed in postmenopausal women who were either on estrogen \pm progesterone hormone therapy (HT) or not on HT (both surgically and naturally postmenopausal women) with HSDD, and who were treated with transdermal testosterone. The study outcomes were compared with either placebo or no treatment. Transdermal testosterone therapy could be administered as a patch or gel formulation.

Seven studies were included enrolling 3,035 participants. The sample size per study varied across the trials and ranged from 76 to 814 participants. In total, 1,350 women were randomised to treatment with transdermal testosterone and 1,379 women were randomised to placebo.

The assessment of methodological quality for risk of bias was based on Cochrane risk of bias assessment tool which considers allocation (random sequence generation and allocation concealment), blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selective reporting, and other bias. The overall risk of each source of bias affecting studies was generally rated as low, with the exception of attrition bias (incomplete outcome data).

Hypoactive Sexual Desire Disorder symptoms were assessed using the same instruments [Sexual Activity Log (SAL), Profile of Female Sexual Function (PFSF), and Personal Distress Score (PDS)] in all seven studies.

Compared to placebo, transdermal testosterone produced:

- significantly more Satisfying Sexual Episodes (MD, 0.92; 95% CI, 0.65, 1.19; $P < .00001$);
- significantly more desire (MD, 6.09; 95% CI, 4.51, 7.68; $P < .00001$);
- significant reduction in personal distress scores (MD, -8.15; 95% CI, -10.60, -5.70; $P < .00001$);
- no difference in plasma lipid profiles, carbohydrate metabolism, and renal and liver function as assessed by clinical chemistry and haematology indices.

El-Hage 2007 study is a placebo-controlled, double blind cross over trial comparing the safety and efficacy of 10 mg of testosterone cream to placebo in postmenopausal women with HSDD.

The primary hypothesis was that the BISF-W scores of menopausal women who have taken estrogen and testosterone cream for a period of 3 months will be significantly higher (20%) at 80% power ($p < 0.05$) than the scores of women using estrogen alone the BISF-W is a 22-item multiple-choice questionnaire that has been used in previous studies of menopausal women. It provides scores for sexual thoughts, arousal, frequency of sex, sexual receptivity, pleasure, satisfaction with their relationship and sexual problems. The total BISF-W score ranges from -16 (poor function) to +75 (maximal function).

The study consisted of two double-blind, 12-week treatment periods separated by a single blind, 4-week, washout period. Subjects were then randomised to either 10 mg testosterone or placebo cream, 1mL daily applied to the non-blood collecting forearm for 12 weeks. At the end of the first period, all subjects stopped the test cream for 4 weeks (wash-out period), then proceeded to the second period where they received the alternate cream for another 12 weeks.

Participants were required to have undergone a hysterectomy, have decreased sexual motivation (a BISF-W score less than 33.6), be in a stable relationship for at least 6 months (assessed by the sex therapist), have a thyroid stimulating hormone (TSH) serum concentration of between 0.220 and 3.20 mIU/L (i.e. normal thyroid function) and record a postmenopausal follicle stimulating hormone (FSH) concentration of more than 30 U/L.

Participants were evaluated by a psychologist, who undertook a comprehensive psychosexual history, to exclude depression or underlying socio-sexual problems that may be contributing to their HSDD.

Thirty-six women were randomised and 33 completed the study. Their mean age was 54 years and average body mass index was 25.4 kg/m²

The mean (\pm standard deviation) BISF-W composite scores were similar for the two groups at the commencement of the study. After 12 weeks of treatment, no effect on the BISF-W scores was seen in the placebo group (21.05 ± 10.41 at baseline versus 21.52 ± 12.57 at week 12). In contrast, the testosterone active treatment saw a mean increase by 8.8 points (from 19.85 ± 10.67 to 28.45 ± 11.28 ; 44% increase, $p=0.000$). Table 2 summarises the findings in the seven domains contributing to the BISF-W score.

Table 2: Results for the seven individual BISF-W domain scores-testosterone versus placebo treatment (mean \pm SD)³

	<i>First visit</i>	<i>Last visit</i>	<i>Last – first visit</i>	<i>t Score</i>	<i>p Value</i>
<i>BISF (total score)</i>					
Treatment	19.85 \pm 10.67	28.45 \pm 11.28	8.76 \pm 7.46	3.935	0.000
Placebo	21.05 \pm 10.41	21.52 \pm 12.57	0.54 \pm 9.16		<i>t test</i>
<i>D1 (Thoughts/desire)</i>					
Treatment	1.15 \pm 1.29	2.55 \pm 1.96	1.41 \pm 2.08	2.312	0.024
Placebo	1.51 \pm 1.41	1.73 \pm 1.95	0.18 \pm 2.17		<i>t test</i>
<i>D2 (Arousal)</i>					
Treatment	4.13 \pm 2.80	5.51 \pm 2.19	1.41 \pm 2.41	1.424	0.159
Placebo	4.17 \pm 2.41	2.61 \pm 2.80	0.48 \pm 2.84		<i>t test</i>
<i>D3 (Frequency of sex)</i>					
Treatment	1.34 \pm 1.09	2.09 \pm 1.33	0.78 \pm 1.38	2.108	0.039
Placebo	1.55 \pm 1.22	1.64 \pm 1.46	0.12 \pm 1.13		<i>t test</i>
<i>D4 (Receptivity/initiation)</i>					
Treatment	5.39 \pm 3.18	8.34 \pm 3.30	2.94 \pm 3.61	3.809	0.000
Placebo	6.24 \pm 3.59	5.97 \pm 3.31	–0.28 \pm 3.13		<i>t test</i>
<i>D5 (Pleasure/orgasm)</i>					
Treatment	2.61 \pm 2.19	3.95 \pm 2.07	1.30 \pm 2.17	1.835	0.071
Placebo	2.63 \pm 2.06	3.49 \pm 2.28	0.84 \pm 2.01		<i>t test</i>
<i>D6 (Relationship satisfaction)</i>					
Treatment	9.03 \pm 2.88	8.94 \pm 2.64	–0.13 \pm 2.61	0.881	0.382
Placebo	8.64 \pm 2.98	7.94 \pm 3.20	–0.63 \pm 2.78		<i>t test</i>
<i>D7 (Sexual problems)</i>					
Treatment	3.81 \pm 1.94	3.21 \pm 2.01	–0.66 \pm 2.21	–0.165	0.870
Placebo	3.72 \pm 2.18	3.11 \pm 1.68	–0.58 \pm 1.88		<i>t test</i>

The mean serum total testosterone concentrations were similar between the testosterone (2.1 ± 1.2 nmol/L) and placebo groups (1.6 ± 0.5 nmol/L) at the commencement of the study. The normal reference range was taken to be <2.6 nmol/L.

The mean serum testosterone concentration in women on active treatment was 4.1 ± 1.8 nmol/L at week 6 and 3.8 ± 2.5 nmol/L at week 12. At the end of 12 weeks, the active treatment

increased serum testosterone by an average of 1.8 nmol/L. No such rise was seen for the placebo group. Serum estradiol and SHBG levels were similar in both groups and in all phases.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

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 2, 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 a single dose 1.25 mL of ANDROFORTE 2 (25mg testosterone) to the scrotum of healthy eugonadal volunteers with endogenous testosterone suppressed by administration of nandrolone decanoate produced a C_{max} serum testosterone concentration of 19.1 nmol/L with a T_{max} around 2.8 hours after application.

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

After the single-dose application of 5 mg of ANDROFORTE 2 cream to the upper thigh / lower buttock at steady state (day 22), the mean peak level (C_{max}) of total testosterone (TT) was found to be 2.437 ± 1.668 nmol/L (range 0.728 – 6.275 nmol/L) and that of free testosterone (fT) was found to be 28.99 ± 22.99 pmol/L (range 10.47 – 88.40 pmol/L).

Across the 24-hour blood sampling period, the mean C_{avg} for TT and fT were 1.505 ± 0.856 nmol/L (range 0.433 – 3.571 nmol/L) and 17.34 ± 11.72 pmol/L (range 7.94 – 50.27 pmol/L), respectively.

Distribution

The majority of testosterone binds to SHBG and albumin and is biologically inactive. Testosterone also circulates unbound as a free hormone and is considered biologically active.

Metabolism

Testosterone is metabolised primarily in the liver and also in peripheral tissue. The major active metabolites of testosterone are DHT and oestradiol.

DHT is produced by reduction through the action of the enzyme 5-alpha reductase, which is present in genital tissue and skin. DHT is further metabolised to 3-alpha and 3-beta androstenediol. DHT binds with greater affinity to SHBG than does testosterone. E2 is produced by aromatisation of testosterone.

Excretion

Testosterone is excreted, mostly in urine as glucuronide and sulphate conjugates of testosterone and its metabolites, and in faeces as conjugated testosterone metabolites.

5.3 PRECLINICAL SAFETY DATA

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.

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.](#)

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

dl-alpha-tocopheryl acetate
almond oil
cetomacrogol 1000
cetostearyl alcohol
carbomer 940
trolamine
butylated hydroxytoluene
Phenonip (PI 10352) contains hydroxybenzoates
citric acid
purified water.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

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 2 should be used within 125 days of opening.

6.5 NATURE AND CONTENTS OF CONTAINER

ANDROFORTE 2 is supplied in a 50 mL sealed tube with a graduated syringe-style measuring device in a carton.

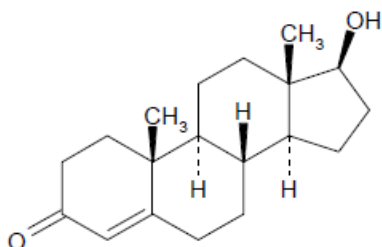
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

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



Chemical Formula: C₁₉H₂₈O₂

Molecular Weight: 288.4 g/mol

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.

CAS number

58-22-0

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 PRESCRIPTION ONLY MEDICINE

8 SPONSOR

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9 DATE OF REVISION

August 2021

Summary table of changes

Section changed	Summary of new information
All	All info for use in female
All	Reformatted in line with the revised Australian form for providing product information
4.2	Dose and site of application
5.1	Clinical trials
6.4	In use shelf life increased to 125 days