AUSTRALIAN PRODUCT INFORMATION – ANDROFEME® 1 (TESTOSTERONE) 1% W/V CREAM

1 NAME OF THE MEDICINE

Testosterone

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

ANDROFEME 1 contains 1% w/v testosterone (10 mg testosterone per 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.

ANDROFEME 1 is a white, opaque, oil-in-water cream.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

ANDROFEME 1 is indicated for the treatment of hypoactive sexual desire dysfunction (HSDD) in postmenopausal women.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dose

The recommended starting dose is 5 mg testosterone (0.5 mL) applied once daily to either the inner aspects of the lower torso, upper outer thigh or buttock.

A dose of up to 10 mg testosterone (1.0 mL) daily is usually sufficient to provide adequate improvement in symptoms and should rarely be exceeded.

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, then alternative treatments should be considered.

Method of administration

The patient should be directed to measure the appropriate dose using the graduated applicator and immediately apply to clean dry skin on the inner aspects of the lower torso, upper outer thigh or buttock. The cream should be massaged evenly until absorption is complete (typically around 30 seconds). 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 genitalia or perineum, unless required for a specified purpose.

Prior to prescribing

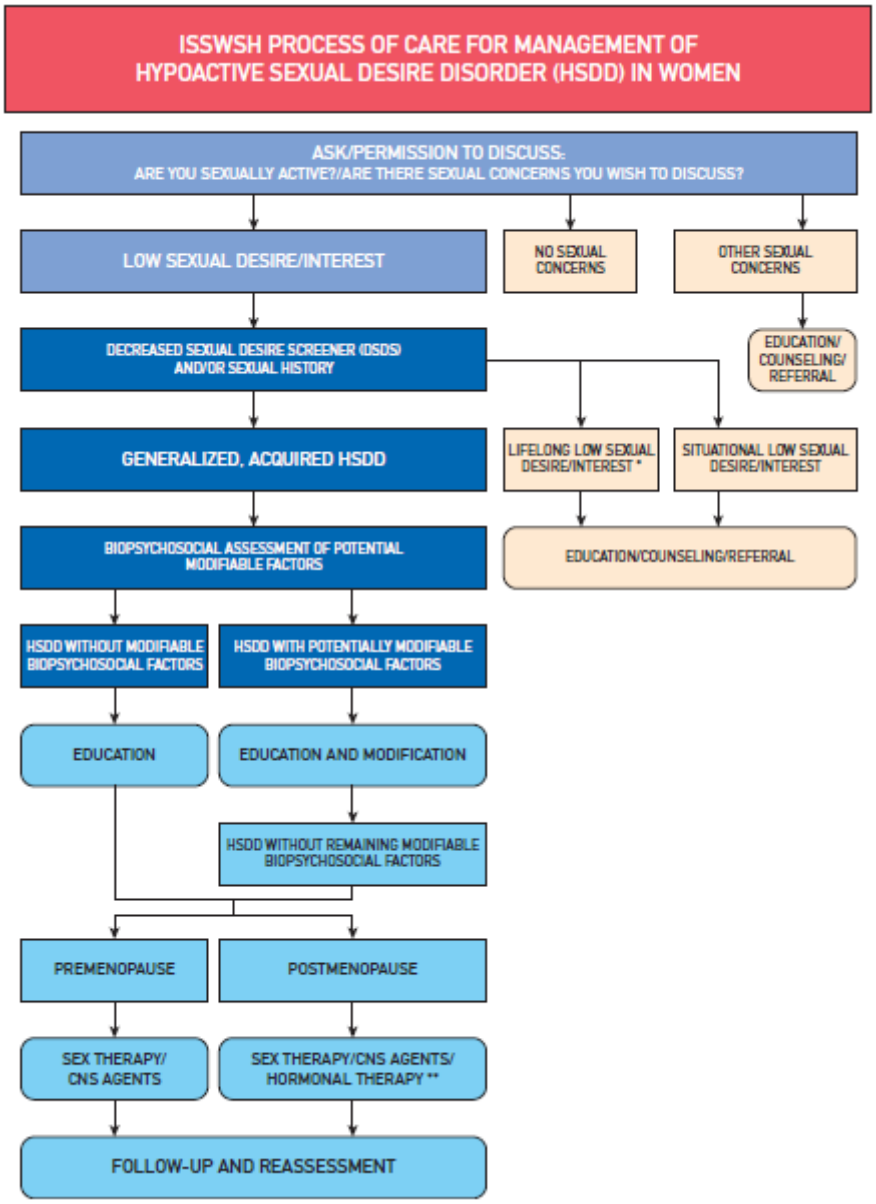
Female sexual dysfunction, including HSDD, has many etiologies including biopsychosocial factors such as neuroendocrine imbalance, physical ill health or disease, interpersonal difficulties, psychological distress and sexually repressive cultural or religious values. Treatment should follow this biopsychosocial model and include pharmacologic options (hormone therapies and other pharmacologic agents), psychotherapy or multimodal treatments that combine both.[1]

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 androgen therapy should be provided, including discussions on the lack of data on the safety of long-term use.

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

[1] Davis SR, Baber R, Panay N, et al. Global consensus position statement on the use of testosterone therapy for women. Climacteric. 2019 Sep 2:1-6.

Figure 1. The ISSWSH process of care for management of hyposexual desire disorder (HSDD) in women[2]



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.

[2] Adapted and reproduced with permission from Goldstein I, Kim NN, Clayton AH, DeRogatis LR, et al. Hypoactive sexual desire disorder: International Society for the Study of Women's Sexual Health (ISSWSH) expert consensus panel review. Mayo Clinic Proceedings 2017; 92: 114-128.

Monitoring

Baseline testosterone and sex hormone binding globulin (SHBG) levels should be obtained prior to initiation of testosterone therapy. The patient should have a follow-up blood test taken within **three to six weeks** of initiating treatment. 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. 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 testosterone use in women. Treatment with ANDROFEME 1 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).

4.3 CONTRAINDICATIONS

ANDROFEME 1 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.

ANDROFEME 1 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.

ANDROFEME 1 is contraindicated in pregnancy and lactation.

ANDROFEME 1 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

Androgen 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.

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.

High level athletes need to be aware of the rules governing androgen use if prescribed ANDROFEME 1 cream.

Potential for transfer

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.

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 virilisation, in young children.

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.

However, applying ANDROFEME 1 cream in accordance with recommended directions is unlikely to affect the existing cardiovascular risk of individual women. This conclusion is based on observed changes in physiological parameters in women treated with testosterone supplementation known to affect cardiovascular (CV) risk and CV morbidity and mortality, as well as some observational studies assessing CV morbidity and mortality.

Lipid concentrations

In clinical trials 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 ($\leq$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.

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 oestrogen/progesterone hormone therapy. Epidemiology studies conducted for up to 5 years have found no statistically significant increase in breast cancer risk.

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

This product is not suitable for children.

Care should be taken to ensure that children do not come into contact with ANDROFEME 1 application sites. In the event of contact, wash with soap and water as soon as possible.

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

The concurrent use 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 buproprion may result in a lowered seizure threshold.

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

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No data available.

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 ANDROFEME 1 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 suppresses prolactin in lactating females and may cause adverse effects in the infant. ANDROFEME 1 must not be used in breast-feeding women (see section 4.3 Contraindications).

Care should be taken by breast-feeding women to avoid any contact with ANDROFEME 1. In the event of contact, wash with soap and water as soon as possible.

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)

The following adverse events have been reported in clinical trials in postmenopausal women, using transdermal testosterone preparations providing similar systemic exposure to testosterone as ANDROFEME 1.

Table 1. 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 ANDROFEME 1.

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 ANDROFEME 1 have been reported in clinical trials.

Treatment of overdose would consist of discontinuation of ANDROFEME 1 together with appropriate symptomatic and supportive care. Wash the skin with soap and water.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

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.

In a meta-analysis of the benefits and risks of testosterone therapy for postmenopausal women with HSDD compared with placebo or a comparator (eg, oestrogen, with or without progestogen), testosterone significantly increased sexual function, including satisfactory sexual event frequency, sexual desire arousal, orgasm, responsiveness and self-image and reduced sexual concerns and distress.

Clinical trials

The clinical efficacy of ANDROFEME 1 cream 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 Islam 2019 and clinical trial by El-Hage 2007 are considered pivotal and are summarised below.

The meta-analysis Islam 2019[3] was designed to explore available evidence supporting the potential beneficial effect of testosterone therapy on sexual health among postmenopausal women. The criteria used to select individual studies for the analysis were that they should be randomised clinical trials, have a duration of systemic testosterone treatment of at least 12 weeks, be at least single blind and have a placebo or comparator arm (e.g. estrogen, with or without progestogen). Systemic testosterone therapy could be administered as a transdermal or oral preparation, intra-muscular injection or subcutaneous implant.

Data included in the meta-analysis are from 8,480 participants obtained from 46 studies reporting the outcome from 36 individual trials. Of the 46 studies, 43 were conducted in postmenopausal women, two in premenopausal women and one in both pre and postmenopausal women. The Cochrane risk-of-bias tool was used to assess random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other biases. The overall risk of each source of bias affecting studies included in the meta-analysis was generally rated as low, apart from attrition bias which was rated as high for around 40% of studies.

A measure of sexual function was the primary outcome variable used in 20 of the 36 individual studies. The most commonly used scale was the Profile of Female Sexual Function (PFSF) (8 studies) or either the McCoy Sexual Satisfaction (McCoy SS) or Sabbatsberg Sexual Satisfaction (SSS) scales (6 studies). The personal distress scale (PDS) was used in 6 studies, and the Brief Index of Sexual Functioning for Women (BISF-W) in 4 studies.

Eight studies (n=3,238) reported the mean change in satisfying sexual events over a 4 week treatment period. Compared with placebo or a comparator, testosterone was associated with a significant increase in the number of satisfying sexual events (mean difference 0.85, 95% CI 0.2 to 1.18; p=0.014; 95% prediction interval -0.10 to 1.80). There was no apparent difference between the outcome observed in naturally or surgically induced menopause. The overall I^2 statistic was 58.1% indicating that the degree of heterogeneity across the studies was moderately high.

In postmenopausal women, compared with placebo or a comparator, testosterone augmented arousal (N=11; standardised mean difference 0.28, 95% CI 0.21 to 0.35), orgasm (N=10; standardised mean difference 0.25, 95% CI 0.18 to 0.32), pleasure (N=7; mean difference 6.86, 95% CI 5.19 to 8.52), responsiveness (N=8; standardised mean difference 0.28, 95% CI 0.21 to 0.35); and self-image (N=7; mean difference 5.64, 95% CI 4.03 to 7.26); moreover, testosterone reduced concerns (mean difference 8.99, 95% CI 6.90 to 11.08). Compared with placebo or a comparator, testosterone was associated with reduced personal sexual distress in all studies of postmenopausal women (N=6; standardised mean difference -0.27, 95% CI -0.36 to –0.17).

[3] Islam RM, Bell RJ, Green S, et al. Safety and efficacy of testosterone for women: a systematic review and meta-analysis of randomised controlled trial data. Lancet Diabetes Endocrinol. 2019;7(10):754-766.

In the meta-analysis comparing the effect of testosterone to placebo or active comparator on sexual desire, the standardised mean difference in effect across 15 studies was 0.36 (95% CI 0.22 to 0.50). There was no apparent difference between natural or surgical menopausal women, although heterogeneity was moderately high. This meta-analysis included women who were treated with IM, oral and testosterone cream, as well as 300 microgram transdermal patches, without materially impacting on outcome.

El-Hage 2007[4] study is a placebo-controlled, double blind cross over trial comparing the safety and efficacy of 10 mg of ANDROFEME 1 cream to placebo in menopausal women with HSDD. Serum concentrations of testosterone, estradiol and SHBG were also measured during the study.

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. It was calculated that 33 subjects would be required to test the hypothesis. Thirty six women were randomised and 33 completed the study. Their mean age was 54 years and average body mass index of 25.4 kg/m^2.

The secondary hypotheses were that testosterone improves energy levels and mood, raises total testosterone to the therapeutic range and does not adversely affect the safety parameters (serum creatinine, liver function tests and serum lipids). 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 ANDROFEME 1 or placebo cream, 2 cm 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 (TS) 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.

[4] El-Hage G, Eden JA and Manga RZ. A double-blind, randomized, placebo-controlled trial of the effect of testosterone cream on the sexual motivation of menopausal hysterectomized women with hypoactive sexual desire disorder. Climacteric. 2007;10(4):335-43.

The mean (±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 versus 21.52 ± 12.57). 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. Sexual desire (D1) improved significantly on active treatment. Testosterone therapy also significantly improved the frequency of sexual intercourse (D3) and sexual initiation (D4) by the female partner.

Table 2: Results for the seven individual BISF-W domain scores-testosterone versus placebo treatment[3]

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

The mean serum total testosterone concentrations were not statistically different 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

After the single-dose application of 5 mg of ANDROFEME 1 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. DHT and oestradiol (E_2) are products of testosterone metabolism.

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 androstanediol. DHT binds with greater affinity to SHBG than does testosterone. E_2 is produced by aromatisation of testosterone.

Excretion

90% of testosterone is excreted in the urine as glucuronide and sulphate conjugates of testosterone and its 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.

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 ºC. Do not freeze.

In-use storage: ANDROFEME 1 should be used within 125 days of opening.

6.5 NATURE AND CONTENTS OF CONTAINER

ANDROFEME 1 is supplied in a 50 mL sealed tube with a dose applicator marked with 0.25 mL graduations in a carton.

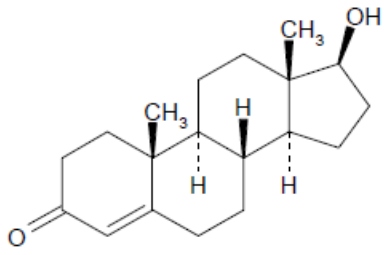
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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 17β-hydroxyandrost-4-en-3-one and has the following structural formula:



Chemical Formula: $C_{19}H_{28}O_2$

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

Lawley Pharmaceuticals Pty Ltd
Unit 2, 15A Harrogate Street,
West Leederville, 6007
Western Australia
Phone: 08 9388 0096
Website: www.lawleypharm.com.au
Email: info@lawleypharm.com.au

9 DATE OF FIRST APPROVAL

TBC