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 (see section 4.4 Special warnings and precautions for use, Excipients with known effects).

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.

Therapeutic intervention with ANDROFEME 1 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

Dose

The recommended starting dose is 5 mg testosterone (0.5 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 total serum testosterone concentration is within the premenopausal reference range, the dose may be increased incrementally to 10 mg testosterone (1.0 mL) daily with follow up clinical and biochemical monitoring. This dose should only rarely be exceeded. (See Monitoring)

Clinical trials of transdermal testosterone therapy 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.

Special populations

Renal impairment

No studies have been conducted in patients with renal insufficiency.

Hepatic impairment

No studies have been conducted in patients with hepatic impairment.

Elderly

There is limited experience of the use of testosterone in 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.

It should be taken into account that physiological testosterone serum levels increase with age beyond the age of 70 years, thus adding to the uncertainty of use in women beyond the age of 70 years.

ANDROFEME® 1 is not suitable for children.

Method of administration

Transdermal use

The patient should be directed to measure the appropriate dose using the graduated applicator and immediately apply to clean dry skin on the upper outer thigh or buttock. The cream should be massaged evenly until absorption is complete (typically around 30 seconds). The patient should be instructed to wash their hands with soap and water after each application. 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.

The patient should avoid bathing, showering or swimming until at least 4 hours after application, and avoid using cosmetics or sunscreen on the area of application.

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.

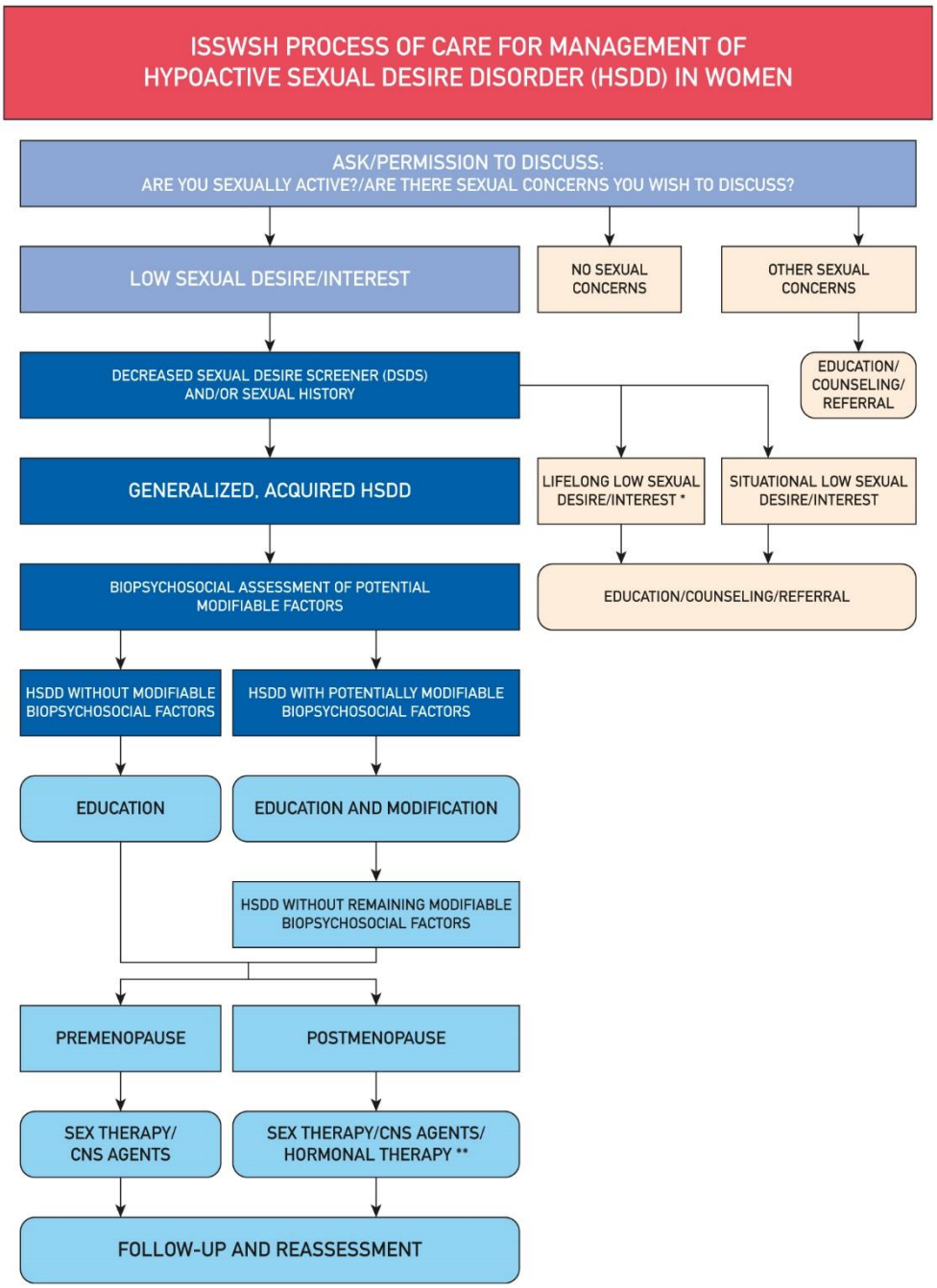
The diagnosis of HSDD in clinical practice should be based on thorough clinical assessment guided by diagnostic criteria such as ISSWSH or the International Classification of Diseases 11th Edition (ICD-11).

Therapeutic intervention with ANDROFEME 1 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 women[1]



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

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 (1mL). It is recommended that if the serum testosterone concentration exceeds the upper limit of the premenopausal range of the assay being used, 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 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

Androgenic Reactions

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.

Normal ranges for testosterone may vary between laboratories and between different assay methods. 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.

At regular intervals during treatment, physicians should monitor patients for potential androgenic undesirable reactions (e.g. acne, changes in hair growth or hair loss). Patients should be advised to self-assess for androgenic undesirable effects. Signs of virilisation, such as voice deepening, hirsutism or clitoromegaly, may be irreversible and discontinuation of treatment should be considered.

Use in Renal Impairment

All patients with pre-existing renal diseases need to be monitored when undergoing androgen treatment.

Use in Hepatic Impairment

All patients with pre-existing hepatic diseases need to be monitored when undergoing androgen treatment.

Patients with cardiac disease.

All patients with pre-existing cardiac diseases need to be monitored when undergoing androgen treatment.

Use in athletes

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

Potential for inadvertent testosterone transfer

It has been reported that high dose transdermal testosterone preparations used in men 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. While the recommended

dose of testosterone in ANDROFEME 1 is low by comparison to male doses, close skin contact with the area of application by a partner or child should be avoided.

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 have adverse effects, including virilisation, in young children.

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.

As a result, the following precautions are recommended:

For the patient:

- For external use only
- 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 women and children not being treated with ANDROFEME 1:

- In the event of sustained 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.

The patient must be particularly careful to avoid potential transfer to pregnant women.

Effects on the cardiovascular system

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.

Diabetic patients

In diabetic patients the metabolic effects of testosterone may decrease blood glucose and therefore insulin requirements. Patients with diabetes mellitus have not been studied.

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 (≤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 eg family history. This applies to women using ANDROFEME 1 therapy.

Use in women on concomitant conjugated equine oestrogens (CEE)

ANDROFEME® 1 is not recommended in women taking CEE (see Section 4.5 Interaction with other medicines and other forms of interaction).

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

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.

Excipients with known effect

Butylated hydroxytoluene may cause local skin reactions (e.g. contact dermatitis), or irritation to the eyes and mucous membranes.

Cetostearyl alcohol may cause local skin reactions (e.g. contact dermatitis).

Benzoates may cause local irritation.

Hydroxybenzoates may cause allergic reactions (possibly delayed).

AndroFeme® 1 contains almond oil. Caution should be taken in patients with tree nut (almond) allergies.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No interaction studies have been conducted with ANDROFEME 1.

Oral oestrogens, especially conjugated equine estrogen (CEE), can result in an increase in SHBG. Elevated SHBG has been associated with a reduced efficacy of transdermal testosterone. Patients using CEE should be changed to non-conjugated oral or transdermal oestrogen before being considered for testosterone therapy.

Tibolone and systemic glucocorticosteroids decrease SHBG. This will reduce total testosterone (TT) concentrations in the circulation due to increased clearance of testosterone. Tibolone and testosterone should not be co-prescribed and caution in the interpretation of testosterone blood levels in women receiving glucocorticosteroid therapy is warranted.

Changes in insulin sensitivity, glucose tolerance, glycaemic control, blood glucose and glycosylated haemoglobin have been reported with non-oral androgen therapy. While these changes have not been seen in studies of women treated with transdermal testosterone that approximates physiological concentrations for premenopausal women, diabetic patients should be monitored in case a change in their medication is required.

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 testosterone and buproprion may result in a lowered seizure threshold.

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

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

ANDROFEME 1 has not been evaluated for possible effects on human fertility. Studies in animals have shown that testosterone 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 ANDROFEME 1 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 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 when used as directed in section 4.2: Dosage and administration. That is, when physiological testosterone concentrations for premenopausal women are approximated.

Table 1. Common adverse events reported in clinical trials

Adverse Events	Testosterone N (%)	Placebo N (%)
Acne	122 (7.5)	83 (5.0)
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.
Post marketing adverse reaction reports include thinning of hair and dizziness.

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
- Clitoromegaly

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 an influence on female sexuality and has a physiological role in bone development and maintenance of mineralisation.

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 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 ± 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 ANDROFEME 1 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 ANDROFEME 1 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/m^2.

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 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 ± SD)

	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 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

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 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

Almond oil

butyl hydroxybenzoate

butylated hydroxytoluene

carbomer 940

cetomacrogol 1000

cetostearyl alcohol

citric acid

dl-alpha-tocopherol acetate

ethyl hydroxybenzoate

isobutyl hydroxybenzoate

methyl hydroxybenzoate

phenoxyethanol

propyl hydroxybenzoate

purified water

trolamine

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.

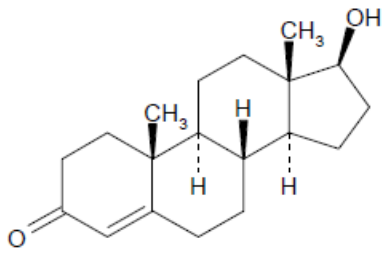
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

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9 DATE OF FIRST APPROVAL

23 November 2020

10 DATE OF REVISION

7 August 2025

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
2	Reference to "see section 4.4 Special warnings and precautions for use, Excipients with known effects" added
4.2	Wording changed for clarity, special populations added, addition of statement re bathing, showering, or swimming, avoiding use of cosmetics or sunscreen on the area of application
4.4	Androgenic reactions expanded, section reworded for clarity, minor editorial changes, section added on Diabetic patients and use in women on CEE, excipients of known effect added.
4.5	4.5 Reference to oxyphenbutazone deleted
4.8	Updated based on post marketing data