NEW ZEALAND DATA SHEET

1 ANDROFEME® 1 (10 MG/ML TOPICAL CREAM)

AndroFeme® 1 (testosterone) 10 mg/mL topical cream

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

AndroFeme® 1 contains 1% w/v testosterone (10 mg testosterone per 1 mL).

Excipients with known effect

Contains tree nut products (almond oil), phenoxyethanol, butylhydroxytoluene, cetostearyl alcohol and hydroxybenzoates.

Please see Section 4.4 Special warnings and precautions for use.

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

3 PHARMACEUTICAL FORM

Topical 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 total serum testosterone concentration is within the premenopausal reference range, the dose may be increased incrementally to 10 mg testosterone (1.0 mL) daily.

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 in patients over 70 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 increase with age beyond the age of 70 years, thus adding to the uncertainty of use in women beyond the age of 70 years.

Paediatric population

AndroFeme® 1 is not indicated in 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.

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.

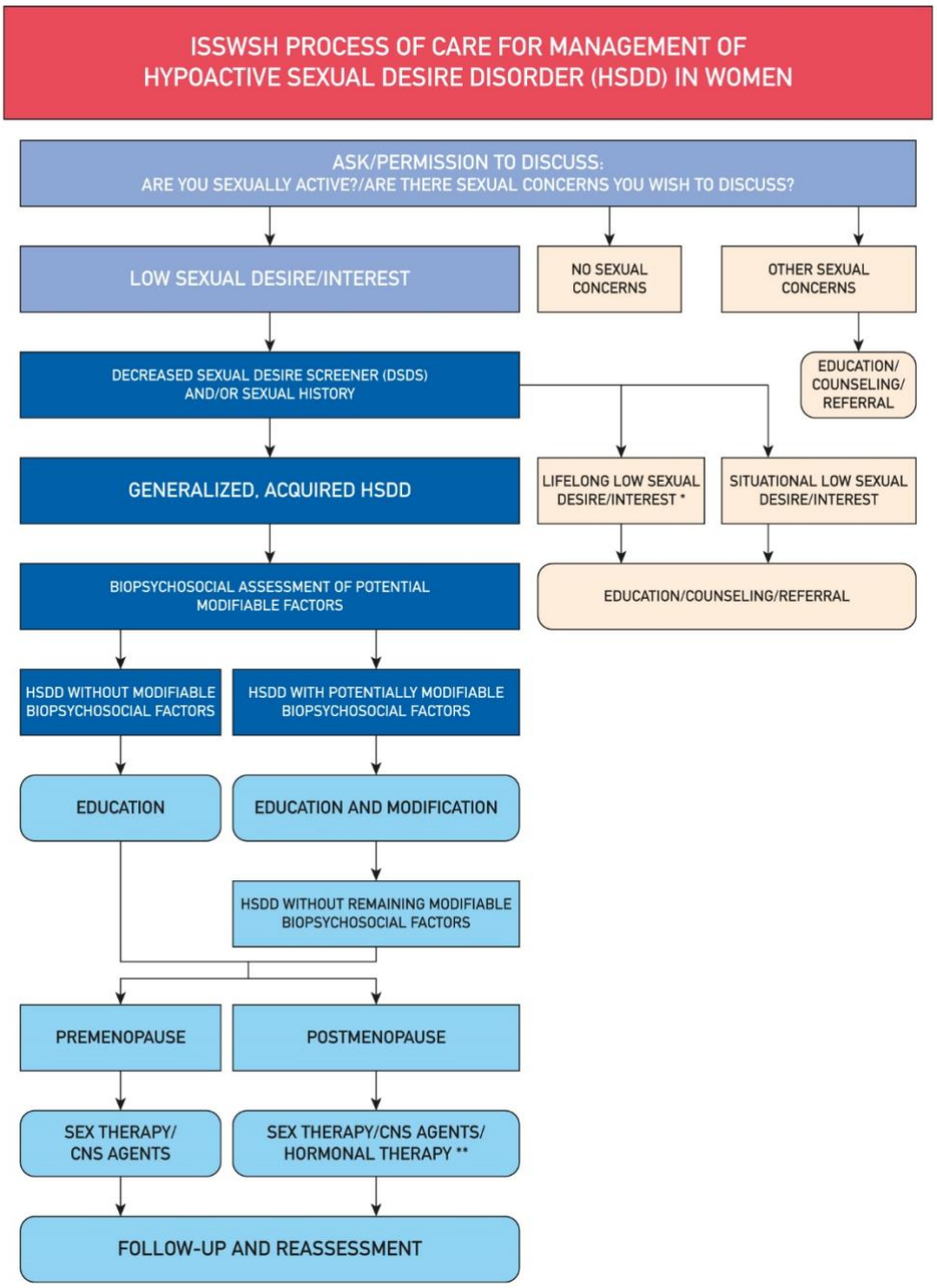
The diagnosis of HSDD in clinical practice should be based on thorough clinical assessment guided by diagnostic criteria such as ISSWSH or the International Classification of Diseases 11th Edition (ICD-11).

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 Interaction with other medicines and other forms of interaction).

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.

Known, suspected or past history of cancer of the breast or known or suspected oestrogen-dependent neoplasia, or any other condition consistent with the contraindications for the use of oestrogen.

AndroFeme® 1 is contraindicated in pregnancy and lactation (see Section 4.6 Fertility, 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 (see Section 4.6 Fertility, pregnancy and lactation).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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.

Androgenic reactions

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.

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.

Patients with cardiac, hepatic or renal disease.

All patients with pre-existing cardiac, hepatic or renal 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.

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.

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 associated with testosterone supplementation in postmenopausal women. Epidemiology studies conducted for up to 20 years have found no statistically significant increase in breast cancer risk.

In women 45 years of age and over the BreastScreen Aotearoa recommendation for mammographic screen is every 2 years, unless there is an individual need e.g. family history. This applies to women using AndroFeme® 1 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.

Effect on ovary

The longer-term effects of testosterone on the risk of ovarian cancer are unknown. Testosterone should be used with caution in women at risk for or with current ovarian cancer.

Use in women on concomitant conjugated equine oestrogens (CEE)

AndroFeme® 1 is not recommended in women taking CEE. In clinical studies with a transdermal testosterone patch, the subgroup of patients receiving CEE did not demonstrate a significant improvement in sexual function (see Section 4.5 Interaction with other medicines and other forms of interaction).

Effect on thyroid hormone levels

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.

Parahydroxybenzoates may cause allergic reactions (possibly delayed).

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

4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

No interaction studies have been performed 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 (see Section 4.4 Special warnings and precautions for use).

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.

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

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.

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 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: Dose and method of administration. That is, when physiological testosterone concentrations for premenopausal women were approximated.

Table 1. Common (≥ 1/100 to < 1/10) 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)

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.

Reporting suspected adverse effects

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare

professionals are asked to report any suspected adverse reactions at https://pophealth.my.site.com/carmreportnz/s/.

4.9 OVERDOSE

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

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

Pharmacotherapeutic group: Androgens. ATC code: G03B A03

Mechanism of action

Testosterone, the primary circulating androgen in women, is a naturally occurring steroid, secreted by the ovaries and adrenal glands. In premenopausal women, the rate of production of testosterone is 100 to 400 micrograms/24 hours, of which half is contributed by the ovary as either testosterone or a precursor. Serum levels of androgens fall as women age. In women, who have undergone bilateral oophorectomy, serum levels of testosterone decline by approximately 50% within days after surgery.

In post-menopausal women with HSDD, in doses that approximate physiological testosterone concentrations for premenopausal women, AndroFeme® 1 cream improves loss of sexual desire with associated personal distress.

Clinical trials

The clinical efficacy of AndroFeme® 1 cream is based on 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 indication and dose regimen are supported by meta-analyses and individual clinical studies with other testosterone products in post-menopausal women with HSDD, including seven large randomised controlled trials with a previously licenced transdermal testosterone patch.

The primary endpoint in the AndroFeme® 1 study was based on the brief index of sexual functioning for women (BISF-W). This is a 22-item multiple-choice questionnaire which 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, 1 mL 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 evaluated by a psychologist, who undertook a comprehensive psychosexual history, to exclude depression or underlying socio-sexual problems that may have been 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

Following application of the cream, maximum serum concentrations of testosterone are reached within several hours, however there is wide inter-individual variability.

Distribution

In serum, testosterone is predominantly bound to SHBG and to a lesser extent serum albumin, cortisol-binding globulin and orosomucoid. A small percentage circulates as free testosterone.

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. Oestradiol 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

Toxicological studies of testosterone in animals have only revealed effects which can be explained by its hormonal activity.

Testosterone has been found to be nongenotoxic in a number of studies. A relationship between high dose testosterone exposure and cancer in the liver and reproductive tract has been found in animal studies. No correlation between these findings and the actual risk in human beings has been established.

Fertility

The administration of exogenous testosterone has been reported to suppress spermatogenesis in the rat, dog and non-human primates, which was reversible on cessation of the treatment.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

almond oil

butylhydroxytoluene

carbomer 940

macrogol cetostearyl ether

cetostearyl alcohol

citric acid

DL-alpha tocopheryl acetate

phenoxyethanol

ethyl parahydroxybenzoate

iso-butyl parahydroxybenzoate

methyl parahydroxybenzoate

propyl parahydroxybenzoate

butyl parahydroxybenzoate

purified water

trolamine

6.2 INCOMPATIBILITIES

In the absence of compatibility studies, this medicine must not be mixed with other medicines.

6.3 SHELF LIFE

3 years.

After first opening, use within 125 days.

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.

6.5 NATURE AND CONTENTS OF CONTAINER

AndroFeme® 1 is supplied in a 50 mL aluminium laminated tube closed with a foil tamper evident seal and a polypropylene cap. The tube is packed in a carton with a dose applicator marked with 0.25 mL graduations and patient information leaflet.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

Alchemy Health Limited
120 Ngapuhi Road
Remuera
Auckland 1050
NEW ZEALAND

Medical enquires: 0508 ALCHEMY (0508 252436)

9 DATE OF FIRST APPROVAL

24 April 2025

10 DATE OF REVISION OF THE TEXT

24 April 2025