SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

AndroFeme 10 mg/mL cream

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One millilitre of cream contains 10 mg testosterone.

Excipients with known effect:

The cream contains cetostearyl alcohol, butylhydroxytoluene (E321), methyl parahydroxybenzoate (E218), ethyl parahydroxybenzoate (E214), propyl parahydroxybenzoate (E216), isobutyl parahydroxybenzoate, and butyl parahydroxybenzoate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Cream for transdermal use.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

AndroFeme cream is indicated for the treatment of hypoactive sexual desire dysfunction (HSDD) in postmenopausal women on optimised hormone replacement therapy (HRT) (see sections 4.2, 4.4 and 4.5 for concomitant administration with oral oestrogens).

Therapeutic intervention with AndroFeme cream should only be considered after a review of psychological and social factors and after other treatable causes of HSDD have been identified and, where possible, managed.

Consideration should be given to official clinical guidelines.

4.2 Posology 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 up to a maximum of 10 mg testosterone (1.0 ml) daily with review of the serum testosterone concentration approximately 3 weeks after dose adjustment and a clinical review three months after that to evaluate efficacy.

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.

Treatment on optimised dosing with AndroFeme requires regular monitoring at 6 monthly intervals to ensure no evidence of overuse of drug by clinical assessment (acne or hirsutism), with measurement of serum testosterone and sex hormone binding globulin (SHBG), and dose adjustment if indicated.

If there is no improvement in symptoms after 6 months of continuous optimised therapy, treatment should be discontinued and alternative options considered.

Women should be made aware before initiating testosterone treatment of the lack of long-term clinical trial safety data beyond 24 months, for doses that approximate physiological concentrations in premenopausal women. Treatment with AndroFeme should be an informed decision between physician and patient if treatment is to be continued beyond 24 months.

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

Paediatric population

AndroFeme is not indicated in children.

Concomitant oral conjugated equine oestrogen (CEE) administration

Patients using CEE should be changed to non-conjugated oral or transdermal oestrogen before being considered for testosterone therapy (see sections 4.4 and 4.5).

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 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. Contact between condoms and the product should be avoided.

4.3 Contraindications

Known sensitivity to testosterone, tree nuts (almond oil) or any of the excipients listed in section 6.1.

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

4.4 Special warnings and precautions for use

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.

Patients with cardiac, hepatic or renal diseases

All patients with pre-existing cardiac, hepatic or renal diseases need to be monitored closely when undergoing androgen treatment.

Use in athletes

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

Potential for 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 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:

- 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.

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.

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.

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 increase in the amount of dense breast tissue associated with testosterone supplementation in postmenopausal women. Epidemiology studies conducted for up to 5 years have found no statistically significant increase in breast cancer risk.

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 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).

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

AndroFeme contains cetostearyl alcohol and butylhydroxytoluene, which may cause local skin reactions (e.g. contact dermatitis). Butylhydroxytoluene may also cause irritation to the eyes and mucous membranes.

AndroFeme contains various parahydroxybenzoate (paraben) esters as preservatives, which may cause allergic reactions (possibly delayed).

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed with AndroFeme.

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).

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 glucocorticosteroids 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.

4.6 Fertility, pregnancy and lactation

Effects on fertility

AndroFeme 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. Spermatogenesis may be reversibly suppressed with this medicine.

Use in pregnancy

AndroFeme must not be used in women who are or who anticipate becoming pregnant. Pregnant women must avoid any contact with application sites. Studies with testosterone in pregnant animals indicate the potential for adverse effects on embryofoetal development, including on the reproductive tract and cardiovascular systems. Exposure of a foetus 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 must not be used in breast-feeding women. Care should be taken by breast-feeding women to avoid any contact with AndroFeme. 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

Tabulated list of adverse reactions

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 when used as directed in section 4.2, when physiological testosterone concentrations for premenopausal women were approximated.

Table 1. Common (≥ 1/100 to < 1/10) adverse events reported in clinical trials

System organ class	Adverse Events

Skin and subcutaneous tissue disorders	Acne Increased hair growth Alopecia
Respiratory, thoracic and mediastinal disorders	Voice change

Post marketing adverse reaction reports include thinning of hair and dizziness. The frequency of these side effects cannot be estimated from the available data.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via the national reporting system - Yellow Card Scheme; Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Features

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

Management

Treatment of overdose would consist of discontinuation of AndroFeme and 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 improves loss of sexual desire with associated personal distress.

Clinical trials

The clinical efficacy of AndroFeme cream is based on a placebo-controlled, double blind cross over trial comparing the safety and efficacy of 10 mg of AndroFeme cream to placebo in postmenopausal women with HSDD (n = 36).

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 AndroFeme or placebo cream, 1 mL daily.

Subjects' mean age was 54 years and average body mass index was 25.4 kg/m^2. 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.

The mean (±standard deviation) BISF-W (Brief Index of Sexual Functioning for Women) 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).

Testosterone cream significantly improved sexual desire (p = 0.024), frequency of sex (p = 0.039), receptivity and initiation (p = 0.000) as measured by the BISF-W score. It did not change mood, energy, lipids, blood pressure or weight over the study period.

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.

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 also in peripheral tissue. DHT and oestradiol are products of testosterone metabolism. DHT is also 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

Macrogol cetostearyl ether

Cetostearyl alcohol

Butylhydroxytoluene (E321)

Almond oil

Phenoxyethanol

Methyl parahydroxybenzoate (E218)

Ethyl parahydroxybenzoate (E214)

Propyl parahydroxybenzoate (E216)

Isobutyl parahydroxybenzoate

Butyl parahydroxybenzoate

Citric acid

Trolamine

Carbomer

All-rac-alpha-tocopheryl acetate

Purified water

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

2 years.

After first opening, use within 4 months.

6.4 Special precautions for storage

Store below 30 ºC. Do not freeze.

6.5 Nature and contents of container

The product is presented in a laminated aluminium tube containing 50 ml of cream, with a high density polyethylene tube head, a peelable, laminated, metallised polyethylene terephthalate foil seal, and polypropylene screw-cap. The tube is packed in a carton with a dosing syringe.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

PLGB 57336/0002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25/07/2025

10 DATE OF REVISION OF THE TEXT

25/07/2025