Medicines & Healthcare products
Regulatory Agency

Public Assessment Report

National Procedure

AndroFeme 10 mg/mL cream

testosterone

PLGB 57336/0002

Andro Pharmaceuticals Ltd

LAY SUMMARY

AndroFeme 10 mg/mL cream
testosterone

This is a summary of the Public Assessment Report (PAR) for AndroFeme 10 mg/mL cream. It explains how this product was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use this product.

This product will be referred to as AndroFeme in this lay summary for ease of reading.

This application was approved under International Recognition Procedure (IRP). The Reference Regulator (RR) was the Therapeutic Goods Administration (TGA) with the procedure number PM-2019-04304-1-1. The procedure followed route B.

This application was approved under Regulation 50 of the Human Medicines Regulation 2012, as amended (previously Article 8.3 of Directive 2001/83/EC, as amended).

For practical information about using AndroFeme, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What is AndroFeme and what is it used for?
This application is a full-dossier application. This means that the results of pharmaceutical, non-clinical and clinical tests have been submitted to show that this medicine is suitable for treating the specified indications.

AndroFeme is used to treat hypoactive sexual desire dysfunction (HSDD) in postmenopausal women on optimised hormone replacement therapy (HRT). Women with this condition often feel distress because they have a very low sexual desire / interest to have sex. Testosterone can help reduce sexual concerns and distress in postmenopausal women, by improving:

- Sexual desire
- Pleasure
- Orgasm

AndroFeme is a cream that can applied to the skin. The skin absorbs testosterone, which then travels to the bloodstream and throughout the body.

How does AndroFeme work?
AndroFeme contains the active ingredient testosterone. Testosterone belongs to a group of medicines called androgens and this form of testosterone is identical to the testosterone produced by the ovaries of women.

How is AndroFeme used?
The pharmaceutical form of this medicine is a cream and the route of administration is transdermal use (application through the skin).

The usual starting dose is 0.5 ml (5 mg) of cream by measured applicator per day.

The patient should not use more than 1.0 ml (10 mg testosterone) of cream per day.

If the patient takes the wrong dose, AndroFeme may not work as well, and the patient's problem may not improve. The patient will need to return to their doctor after starting treatment so that the dose can be checked via a blood test and adjusted if required. It may take up to 2 months for the patient to notice an improvement. If symptoms do not improve after 6 months, the patient should discuss an alternative treatment with their doctor. The patient should continue taking their medicine for as long as their doctor tells them.

There is currently limited safety information on the use of AndroFeme beyond 2 years. The patient's doctor will discuss the benefits and risks of longer use with the patient.

When to use AndroFeme:
The patient should apply once per day at approximately the same time each day.

- Applying the cream at the same time each day will have the best effect. It will also help the patient remember when to apply it.
- The patient should avoid swimming or showering for at least 4 hours after application.
- The patient should avoid using cosmetics or sunscreen on the area of application. Contact between condoms and the product should also be avoided.

How to use AndroFeme:

- To open the tube, remove the cap and peel off the foil seal.
- A measuring applicator (syringe style) in a sealed sleeve is enclosed in the AndroFeme box. The applicator is marked with 0.5 ml graduations for dosing accuracy.
  The usual starting dose is 0.5 ml and the patient should not use more than 1.0 ml of cream per day.
- To measure the correct dose of cream:
  - Gently squeeze the base of the AndroFeme tube until cream reaches the open nozzle of the tube.
  - Insert the tip of the applicator into the open nozzle of AndroFeme cream so that the nozzle and the shoulder of the applicator are in contact.
  - Invert the tube and the applicator so the cream will flow with gravity when squeezed.
  - Carefully squeeze the base of the AndroFeme tube and at the same time slowly withdraw the red plunger of the applicator. The cream will flow into the barrel of the applicator. Do not try to squeeze the cream into the syringe.
  - Fill the applicator to the required dose. For example: a 0.5 ml dose of AndroFeme (5 mg testosterone) needs the flat part of the plunger level with the 0.5 ml mark.
  - If there are any air bubbles in the measured dose, fill slightly past the required dose mark then depress the plunger so that the excess cream flows back into the tube. Stop at the required dose mark.
  - Remove the applicator from the nozzle of the tube and replace the cap firmly on the tube.
- To apply the cream:
  - Always apply AndroFeme directly onto clean, dry, healthy skin of either the upper outer thigh or buttock.
  - Massage the cream into the area until absorbed. Typically, this takes about 30 seconds.
  - Cover the application area with clothing once applied.

  - Never apply the cream to broken or damaged skin. The patient should not use AndroFeme on the genitals or other areas.
- Following application:
  - The patient should wash their hands thoroughly with soap and water after applying the cream.
  - Be careful to avoid potential transfer to others.
  - Rinse the applicator in hot water after use and replace in the box with the AndroFeme cream.
- For contacts:
  - If someone comes into regular contact with the skin where the patient has applied the cream, the patient should advise them to wash the affected area on their body with warm, soapy water as soon as possible.

For further information on how AndroFeme is used, refer to the PIL and Summary of Product Characteristics (SmPC) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

The patient should always take the medicine exactly as their doctor/pharmacist has told them. The patient should check with their doctor or pharmacist if they are not sure.

What benefits of AndroFeme have been shown in studies?
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.

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.

What are the possible side effects of AndroFeme?
For the full list of all side effects reported with this medicine, see Section 4 of the PIL or the SmPC available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on their behalf by someone else who cares for them, directly via the Yellow Card scheme at https://yellowcard.mhra.gov.uk or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

Why was AndroFeme approved?
It was concluded that AndroFeme has been shown to be effective in the treatment of hypoactive sexual desire dysfunction (HSDD) in postmenopausal women on optimised hormone replacement therapy (HRT). Furthermore, the side effects observed with use of this product are considered to be typical for this type of treatment. Therefore, the MHRA decided that the benefits are greater than the risks and recommended that this medicine can be approved for use.

What measures are being taken to ensure the safe and effective use of AndroFeme?
As for all newly-authorised medicines, a Risk Management Plan (RMP) has been developed for AndroFeme. The RMP details the important risks of AndroFeme, how these risks can be minimised, any uncertainties about AndroFeme (missing information), and how more information will be obtained about the important risks and uncertainties.

The following safety concerns have been recognised for AndroFeme:

Important identified risks	Androgenic effects
Important potential risks	Cardiovascular risk factors Effect on breast tissue Off-label use and abuse Passive transfer of testosterone Endometrial hyperplasia/cancer Ovarian cancer
Missing information	Skin reactions Long term use beyond 24 months and very rare adverse events in the target population Excluded populations in clinical trial development programme – (Actual post authorisation use in women with cardiovascular impairment, elderly women >65 years of age, women from different socioeconomic backgrounds)

The information included in the SmPC and the PIL is compiled based on the available quality, non-clinical and clinical data, and includes appropriate precautions to be followed by healthcare professionals and patients. Side effects of AndroFeme are continuously monitored and reviewed including all reports of suspected side-effects from patients, their carers, and healthcare professionals.

An RMP and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

Other information about AndroFeme
A marketing authorisation was granted in the United Kingdom on 25 July 2025.

The full PAR for AndroFeme follows this summary.

This summary was last updated in September 2025.

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I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the application for AndroFeme 10 mg/mL cream (PLGB 57336/0002) could be approved.

The product is approved 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 of the SmPC 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.

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.

This application was approved under International Recognition Procedure (IRP). The Reference Regulator (RR) was the Therapeutic Goods Administration (TGA), with the procedure number PM-2019-04304-1-1.

This application was approved under Regulation 50 of the Human Medicines Regulation 2012, as amended (previously Article 8.3 of Directive 2001/83/EC, as amended).

In line with the legal requirements for children's medicines, the application included a licensing authority decision on the granting of a class waiver MHRA-03-22-CW09.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product at all sites responsible for the manufacture, assembly and batch release of this product.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

Advice was sought from the Commission of Human Medicines (CHM) on 21 November 2024 on grounds relating to quality and efficacy. Following provision of additional data the CHM were reassured on the quality of the product.

A marketing authorisation was granted on 25 July 2025.

II. PRODUCT INFORMATION

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

The SmPC is in line with current guidelines and is satisfactory.

PATIENT INFORMATION LEAFLET (PIL)

The PIL is in line with current guidelines and is satisfactory.

LABEL

The labelling is in line with current guidelines and is satisfactory.

III. QUALITY ASPECTS

MHRA considered that the quality data submitted for this application is satisfactory.

The grant of a marketing authorisation was recommended.

IV. NON-CLINICAL ASPECTS

MHRA considered that the non-clinical data submitted for this application is satisfactory.

The grant of a marketing authorisation was recommended.

V. CLINICAL ASPECTS

Clinical pharmacology

The PK and PD properties of testosterone following systemic delivery are well-established.

Pharmacokinetic data is based on an extensive discussion of literature studies utilising a number of dermally applied products. Difficulties in collectively considering literature studies include problems with and differences between the study designs (including timing of serum testing), the use of alternative testosterone products to AndroFeme, different application sites, and the variety of assay methods used.

Three studies utilised this product and showed good absorption across the skin, the most relevant was Davis 2017. The estimated Cav of testosterone at steady state following application of a 5mg dose of AndroFeme cream o.d., were 1.18, 1.49 and 1.88 nmol/L. Similarly, in the 5 studies which applied the 10mg dose of testosterone, the Cav ranged from 2.08 nmol/L (single dose) to 3.16 nmol/L (steady state), while the Cmax was 2.71 nmol/L (single dose) and 4.00 nmol/L at steady state. In the two studies which also estimated free testosterone, the mean average concentrations following the application of 5mg of testosterone were 13.7 and 17.4 pmol/L (3.95 and 5.00 pg/mL, single dose) and 14.4 pmol/L (4.14 pg/mL) at steady state. The target range for testosterone is suggested to be ≤2.6 nmol/L (El-Hage, 2007). The studies by Davis, 2017 and Fooladi, 2015, show that the application site does affect the PK profile, with overall lower serum levels achieved with application to the thigh/gluteal region compared to the arm and some variability over the 24 hour sampling period, indicating that the time a sample is taken relative to the administered dose may be important when comparing the effects of dose adjustment.

Overall, there is a limited understanding of the pharmacokinetics for the product in terms of time dependency, dose proportionality and exposure in special populations which normally would not be acceptable, however given that the product is well characterised generally, and is individualised in each patient, this could be accepted for this application. In particular it was argued that there is a wide variation in serum androgen in the normal population and that there is no definitive serum concentration that can be used for any measured circulating

androgen to differentiate women with sexual dysfunction, as circulating blood levels do not equate to tissue levels or tissue sensitivity. It is therefore recommended that treatment of postmenopausal women with testosterone needs to be individualised, with assessment of efficacy to be determined by responsiveness of symptoms to treatment. Measurement of serum testosterone is used to monitor for elevated concentrations of testosterone, which may contribute to an increase in undesirable side-effects, but should not be used as the primary guide for patient management.

No relevant pharmacodynamic information pertaining to the target population or indication was submitted.

Clinical efficacy

NICE Guideline NG23 (NICE 2015 (updated 2019)) considered the diagnosis and management of menopause. This was last updated in 2019 and is currently under review. It recommends that testosterone supplementation be considered for women with low sexual desire, if HRT alone is not effective. Neither this recommendation nor guidance from the British Menopause Society differentiates between naturally or surgically menopausal women. Both suggest a trial with HRT before testosterone supplementation is considered. However, this is not aligned with the more recent recommendations of the Global Position Statement (Davis, Baber et al. 2019). This is supported by the APHRODITE Study which demonstrated the efficacy and safety of transdermal testosterone in postmenopausal women not using concurrent oestrogen therapy (Davis, Moreau et al. 2008).

Single and multiple dose studies with AndroFeme cream show good but variable absorption across the skin at different sites, including at the proposed site of administration - lateral side of thighs/buttocks. No consistent correlation between efficacy and serum concentration of testosterone is established across the recommended dose range, therefore serum testosterone in isolation cannot be used to diagnose HSDD or monitor the effectiveness of treatment. Indirect comparison between AndroFeme cream 10 mg/day and 300 µg/day Intrinsa patch is made, although significant overlap between the 5 and 10 mg doses is noted.

Therefore, biochemical measurement of serum testosterone should be used as part of the initial clinical evaluation of women with HSDD to exclude women with high baseline levels, and to monitor against supraphysiological concentrations in women being treated with testosterone. Treatment of postmenopausal women with testosterone must be individualised, and assessment of efficacy determined by symptom relief, not a biochemical target concentration. The primary indicators of supraphysiological testosterone levels are the clinical effects (primarily acne or increased facial/body hair growth) determined by the patient and clinician.

The “pivotal” study is that of El-Hage (El-Hage, Eden et al. 2007), a double-blind, randomised, placebo-controlled, cross-over study. Thirty-six patients were randomised to receive either a 10 mg daily dose of AndroFeme cream or placebo for 12 weeks. After a 4-week washout period, participants then received the alternative cream for another 12 weeks. The primary hypothesis was that BISF-W scores would be higher following use of AndroFeme cream compared with placebo for a 12-week period. The study met pre-specified success criteria ($p<0.05$) for the primary hypothesis. BISF-W improved in the active treatment group by 44% (Baseline 19.85 ± 10.67, result at 12 weeks 28.45 ± 11.28). Secondary analyses suggested significant changes from baseline in the BISF-W domains of sexual desire, self-reported frequency of sexual intercourse, and sexual initiation by the female partner. No effect on the BISF-W scores was seen in the placebo group. No

significant differences between groups were seen for DASS and POMS scores at commencement or after testosterone or placebo treatment. Whilst this study provides support for the use of AndroFeme cream for the treatment of HSDD, the low number of subjects, use of a different dose and the inconsistent results seen across different parameters studied, particularly the lack of effect on the distress symptom (claimed to be the main component of HSDD), make this single study on its own not robust enough to demonstrate efficacy and safety. However, this study demonstrates that this formulation is able to deliver therapeutic levels of testosterone to women.

A comparison is made between the El-Hage study and a study with the 300 µg Intrinsa patch (Shifren, Braunstein et al. 2000). These studies are comparable in design, population, and endpoints. Based on the essentially similar findings, the sponsor proposes that the published Intrinsa TTP data be considered as supporting evidence for the safety and efficacy of AndroFeme cream. Seven of the 9 Intrinsa studies were large double-blind, placebo-controlled studies, of at least 24 weeks duration, using the same laboratory for testosterone measurement, and the same efficacy variables (PFSF, SAL and PDS) as primary/secondary outcome measures. These data include both surgically menopausal women and women with a natural menopause, as well as women taking oestrogen concurrently and those not taking oestrogens.

Four meta-analyses examining the effect of testosterone treatment on sexual function and personal distress are provided in support of the application. Broadly, statistically significant improvements were demonstrated for elements of sexual function and distress following the use of testosterone in post-menopausal women. However, heterogeneity in the study populations, testosterone products, and outcome measures in the meta-analyses, limit the ability of these results to inform our understanding of efficacy for the proposed product. In addition, the possibility of attrition bias and selection bias impacting results cannot be excluded. However these literature studies demonstrate that irrespective of the topical product, it is the systemic testosterone concentration which is important to mediate benefits and given that there is clinical data with AndroFeme from the “pivotal study” even if it is small, to show that this formulation can mediate the same benefits, which is considered adequate in this clinical context where the treatment is titrated to clinical response in individual patients. This product was accepted by the TGA (reference regulator) based on a similar rationale.

The overall results from studies with AndroFeme and other testosterone products (including Intrinsa patches), using different dosage regimens and different sites of application, show a positive trend of the use of testosterone on the increase in sexual activity in women with HSDD. According to the Global position statement, treatment with testosterone leads to an increase of one sexual encounter over a 4 week period. According to the literature, anti-depressants can also help in this condition. Due to the multifactorial nature of HSDD, it is difficult to firmly establish the efficacy of low dose testosterone alone for the treatment of HSDD. Therefore, a multidisciplinary approach is required.

Clinical safety

Safety has been reviewed in clinical studies, in a meta-analysis and in epidemiological studies. In addition, there are now post-marketing safety data with AndroFeme cream. From 1999 to 30 September 2022, a total of 282,791 units of AndroFeme cream have been sold worldwide corresponding to an estimated 77,477 patient years. No global figures are available to calculate the lengths of exposure for these data.

The most common treatment-related AEs from AndroFeme cream are acne and increased hair growth. There were no reports of voice changes or other signs of virilisation, and these events were not seen in the meta-analysis. Androgenic changes were generally minor, generally related to dose and resultant serum testosterone levels, and in studies rarely led to discontinuation of treatment. In the clinical studies with AndroFeme cream, there are no reports of local or systemic hypersensitivity reactions, other issues with local tolerability, other skin reactions or photosensitivity.

The SmPC and Patient Information Leaflet detail measures to reduce the risk of passive transfer of the cream to others. The abuse potential of AndroFeme cream is considered low given that other anabolic steroids, and other testosterone preparations giving much higher systemic levels are available and more likely to be used for this purpose.

In short-term studies, testosterone in doses that approximate physiological testosterone concentrations for premenopausal women has shown no significant adverse effects on cardiometabolic risk factors. Further long-term randomised controlled safety data are needed in postmenopausal women to quantify any benefits of testosterone replacement. 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, which is labelled in the SmPC.

The long-term effects on the endometrium, breast, and ovary have also been considered. Short-term (52-week) treatment with testosterone does not stimulate endometrial proliferation, there are no data beyond 1 year however the risk due to testosterone treatment alone is considered to be very small. For breast cancer, epidemiology studies conducted for up to 5 years have found no statistically significant increase in breast cancer risk, and short-term data show no effect on mammographic density. Ovarian cancer has been less studied and there are some conflicting data – however, to date, no signal of ovarian cancer has been reported in RCTs of testosterone supplementation in postmenopausal women, nor in post-marketing safety data for AndroFeme cream.

MHRA considered that the clinical data submitted for this application is satisfactory.

The grant of a marketing authorisation was recommended.

VI. RISK MANAGEMENT PLAN (RMP)

The applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, as amended. In addition to routine pharmacovigilance and risk minimisation measures, pharmacovigilance activities have been proposed (see table below for the risk minimisation measures and pharmacovigilance activities for all safety concerns):

Important identified risk 1: Androgenic effects	
Evidence for linking the risk to the medicine	The reports of acne, hair growth, facial hair, alopecia, voice deepening and clitoral enlargement in clinical trials of women treated with low dose transdermal testosterone were summarised from three meta-analyses, two placebo controlled randomised trials and one long term open label uncontrolled extension study based on two randomised controlled trials. The strength of evidence is therefore considered high. The events are related to the physiological role of testosterone. These adverse events are consistent with the changes observed during male puberty. The lower incidence of these adverse events observed in women are most likely due to the low dose administered (5 to 10mg) and subsequent testosterone serum concentration target (<2.5nmol/L), compared to the physiological concentration of testosterone in an eugonadal male (12 to 20nmol/L).
Risk factors and risk groups	None observed in clinical trial data set.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4 and 4.8 SmPC section 4.4. with recommendation for monitoring of potential androgenic reactions (by physicians and patients). PL section 4 Use of the graduated applicator to measure the appropriate dose Pack size Prescription only medicine
	Additional risk minimisation measures: None.

Important potential risk 1: Cardiovascular risk factors	
Evidence for linking the risk to the medicine	Parameters measuring lipid profile, body weight, glucose metabolism and blood pressure following the administration of low dose testosterone to women were assessed in 3 meta-analyses, 2 placebo controlled randomised trials and one long term uncontrolled, follow up study, in publications included in the registration application (Module 2.7.4). It is also noted that the initial PSUR (November 2018) included the following information. In Australia the TGA sought advice from ACSOM and issued a statement in September 2016 that there was evidence of a weak signal of increased cardiovascular risk with the use of testosterone medication in general but not for specific events. The TGA noted this advice and concluded it is not necessary to update the PI for testosterone products. This conclusion concurs with the Endocrine Society of Australia's position statement November 2014 which states the current evidence regarding testosterone treatment and cardiovascular outcomes is contradictory and inconclusive. The PSUR concluded that ongoing monitoring of heart attack risk and stroke risk is required following FDA comments and changes to other testosterone PI in males. TGA have confirmed this is a weak signal not requiring a change to the PI. This PSUR also identified an epidemiological study evaluating the association between serum testosterone concentrations and the prevalence of atherosclerosis and incidence of CVD in 2578 women aged >55 years postmenopausal women. It was concluded that persistent high androgen levels in women after menopause were associated with an increase in surrogate markers of CVD but did not show a robust association with CVD. While the amount of testosterone delivered by AndroFeme 10 mg/mL cream is much less than formulations indicated for testosterone replacement therapy in males, this information supports the inclusion of cardiovascular risk as an important potential risk to be considered in the RMP.
Risk factors and risk groups	Women with pre-existing cardiovascular disease, diabetes or other factors known to effect cardiovascular risk may be at increased risk when prescribed transdermal testosterone.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4

	Use of the graduated applicator to measure the appropriate dose Pack size Prescription only medicine Additional risk minimisation measures: None.

Important potential risk 2: Effect on breast tissue	
Evidence for linking the risk to the medicine	Evidence relevant to the potential effect of low dose testosterone on breast tissue in women was provided in two meta-analyses (Somboonporn 2005 and Islam 2019), one systematic review (Gera 2018) and one randomised, double blind, placebo controlled parallel group trial designed to assess the effect of 150 or 300µg daily of transdermal testosterone on breast density in surgically or naturally menopausal women. Several additional epidemiological studies were presented and discussed in the clinical Overview. The evidence base is strong, based on the design methodologies applied to studies and analyses.
Risk factors and risk groups	While no data were provided, women with a history of breast cancer or strong family history may be at higher risk of developing breast tissue changes.
Risk minimisation measures	Routine risk minimisation measures *SmPC section 4.4* *Use of the graduated applicator to measure the appropriate dose* *Pack size* *Prescription only medicine* Additional risk minimisation measures *None.*

Important potential risk 3: Off-label use and abuse	
Evidence for linking the risk to the medicine	The current indication for AndroFeme 10 mg/mL cream is for the treatment of hypoactive sexual desire dysfunction (HSDD) in postmenopausal women on optimised hormone replacement therapy (HRT). An observational post-marketing cohort study (prescription-event monitoring) conducted by Osborne 2014 on INTRINSA testosterone patch examined off-label use in the UK between

	March 2007 and August 2010. The findings can be extrapolated for the proposed indication of AndroFeme 10 mg/mL cream. Of 3,073 eligible women 523(17.3%) were using testosterone for indications other than HSDD; 184 women were premenopausal (mean age 44 years) and 148 (80.4%) with HSDD. Over the past few decades, there has been an unprecedented rise in off-label use and misuse of testosterone. Testosterone therapy is often promoted to men for the treatment of low energy, lower libido, erectile dysfunction, and other symptoms.
Risk factors and risk groups	Primarily younger male body builders and athletes.
Risk minimisation measures	Routine risk minimisation measures *None.* Additional risk minimisation measures *None.*

Important potential risk 4: Passive transfer of testosterone	
Evidence for linking the risk to the medicine	There were no reports of adverse events possibly linked to the passive transfer of testosterone in the clinical studies included in the AndroFeme 10 mg/mL cream registration application. There were two published reports describing pre-pubesent virilization in two boys and two girls whose fathers were using topical testosterone preparations for male related hypogonadal issues. In one case, the preparation contained 15% testosterone in a liposomal formulation.
Risk factors and risk groups	Close family contacts, including children, and partners.
Risk minimisation measures	Routine risk minimisation measures *SmPC section 4.4* *PL section 2 and 3* *Specific precautions for patients and non-treated women and children are included in SmPC Section 4.4.* *Precautions for patients and contacts are included in PIL Section 2 and 3.* Additional risk minimisation measures *None.*

Important potential risk 5: Endometrial hyperplasia/cancer	
Evidence for linking the risk to the medicine	Based on the data from one meta-analysis (Islam, Bell et al. 2019) and two individual studies (Zang, Sahlin et al. 2007), (Chaikittisilpa, Soimongkol et al. 2019) which evaluated the effect of low dose testosterone on endometrial thickness in postmenopausal women, low dose testosterone (the recommended starting dose of AndroFeme® is low (5 mg), with the expected systemic exposure to testosterone well below normal (male) physiological range, and consistent with the approximate physiological testosterone concentrations for premenopausal women) has no significant effect on the endometrium after up to 12 weeks of treatment. However, consequences of long-term use on endometrial proliferation and cancer are still unknown.
Risk factors and risk groups	Patients with any condition leading to increased estrogen exposure, e.g., patients under hormone replacement therapy, obese patients, patients with polycystic ovary syndrome.
Risk minimisation measures	Routine risk minimisation measures *Specific precautions for patients are included in SmPC Section 4.4.* *Precautions for patients are included in PIL Section 2.* Additional risk minimisation measures *None.*

Important potential risk 6: Ovarian cancer	
Evidence for linking the risk to the medicine	Based on the data from one study (Russo, Angela et al. 2023), it was suggested that increased testosterone may favor tumor cell survival and proliferation. The experiments suggest that increased testosterone levels may contribute to an enhancement of the migratory properties of the fallopian tube epithelium.
Risk factors and risk groups	Patients with any condition leading to increased estrogen exposure, e.g., patients under hormone replacement therapy, obese patients, patients with polycystic ovary syndrome.
Risk minimisation measures	Routine risk minimisation measures *Specific precautions for patients are included in SmPC Section 4.4.* *Precautions for patients are included in PIL Section 2.* Additional risk minimisation measures *None.*

Missing information 1: Skin reactions	
Risk minimisation measures	Routine risk minimisation measures *SmPC section 4.4 and 4.8* *PL section 2 and 4* Additional risk minimisation measures *None.*

Missing information 2: Long term use beyond 24 months and very rare adverse events in the target population	
Risk minimisation measures	Routine risk minimisation measures *None.* Additional risk minimisation measures *None.*

Missing information 3: Excluded populations in clinical trial development programme – (Actual post authorisation use in women with cardiovascular impairment, elderly women >65 years of age, women from different socioeconomic backgrounds)	
Risk minimisation measures	Routine risk minimisation measures *SmPC section 4.2* Additional risk minimisation measures *None.*

This is acceptable.

VII. USER CONSULTATION

A full colour mock-up of the Patient Information Leaflet (PIL) was provided with the application in accordance with legal requirements, including user consultation.

VIII. OVERALL CONCLUSION, BENEFIT/RISK AND RECOMMENDATION

The quality of the product is acceptable. The non-clinical and clinical data submitted have shown the positive benefit/risk of this product in the treatment of hypoactive sexual desire dysfunction (HSDD) in postmenopausal women on optimised hormone replacement therapy (HRT).

The Summaries of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory.

In accordance with legal requirements, the current approved UK versions of the SmPC and PIL for this product are available on the MHRA website.

IX. TABLE OF CONTENT OF THE PAR UPDATE

Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations, where significant changes are made, are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPCs and/or PIL available on the MHRA website.

Application type	**Scope**	**Product information affected**	**Date of grant**	**Outcome**	**Assessment report attached Y/N**