New Medicine Recommendation

Testosterone (transdermal)

As supplementation for postmenopausal women with low sexual desire if HRT alone is not effective

Recommendation: Amber 1 (with shared care) for the following indication:

As supplementation for postmenopausal women with low sexual desire if HRT alone is not effective.

- The diagnosis of HSDD must involve a full clinical assessment and other factors contributing to female sexual arousal disorder (FSD) must be identified and addressed before testosterone therapy is initiated.
- Women must be counselled on the absence of long term safety data for the use of testosterone in women.
- Women must be counselled on the unlicensed nature of the testosterone products available and the implications of this.
- Tostran should be considered before other preparations as the dose is measurable. We recommend a dose not exceeding one full depression of the canister piston (10 mg testosterone) on alternate days.
- Patients should be monitored for their clinical response to treatment and assessed for signs of androgen excess with a serum total testosterone level every 6 months, to screen for overuse. If no benefit is experienced by 6 months, treatment should be ceased.
- In the absence of long-term safety data, women with a history of breast cancer or with a known high risk of breast cancer should not be prescribed testosterone.
- In the absence of long-term safety data, women with cardiovascular disease and/or uncontrolled hypertension should not be prescribed testosterone.
- In patients receiving long-term androgen therapy, the following laboratory parameters should also be monitored regularly: haemoglobin, and haematocrit (to detect polycythaemia), liver function tests, and lipid profile.
- Improved insulin sensitivity may be observed in patients treated with androgens and may require a decrease in the dose of antidiabetic medications.

Summary of supporting evidence:

- Several systematic reviews of the data conclude that testosterone improves sexual function in post-menopausal women.
- A range of formulations, routes of administration and dosages were used across the studies. None of the systematic reviews specify an optimal dose. Several studies use a patch formulation, which is no longer available.
- The patient populations vary between and within studies – notably some patients are on concurrent HRT, some are not, some women have experienced a natural menopause and some a surgically induced menopause.
- Safety data on the summary of product characteristics is based on studies in a male population.
- Consensus needed on serum testosterone monitoring.

- Further research needed on a suitable duration of testosterone treatment in women.
- Long term safety data lacking, including long term breast cancer risk.
- Women at high cardiometabolic risk were excluded from study populations.
- The company which manufactured the licensed testosterone patch, Intrinsa, withdrew its application to extend the marketing authorisation to include post menopausal women with HSDD in 2010. The Committee for Medicinal Products for Human Use noted that there was insufficient long-term data on the safety of the medicine in this larger group of patients and was therefore of the opinion that the medicine's benefits in these women did not outweigh its risks.

Details of Review

Name of medicine (generic & brand name)**:**

Testosterone gel

Strength(s) and form(s):

Testogel 50mg/5g gel in sachet

Testim 50mg/5g gel in tube

Tostran 2% gel in cannister – not available in doses described in BNF for use under review

Dose and administration:

By transdermal application.

BNF listing

Listed for 'Low sexual desire in postmenopausal women (administered on expert advice)'

50mg/5g gel/sachet: Apply 50 mg every week, the contents of a 5-g sachet or 5-g tube (containing 50 mg/5 g of testosterone) to be divided for daily dosing and applied to non-hair areas, such as the abdomen or upper thighs, over the period of 1 week.[1]

Testogel

The recommended dose is 5 g of gel (i.e. 50 mg of testosterone) applied once daily at about the same time, preferably in the morning. The daily dose should be adjusted by the doctor depending on the clinical or laboratory response in individual patients, not exceeding 10 g of gel per day. The adjustment of posology should be achieved by 2.5 g of gel steps.[2]

Testim

The recommended starting dose of TESTIM is testosterone 50mg (1 tube)/per day.[3]

Tostran

2% gel in cannister: Each full depression of the canister piston delivers one half gram of gel (10 mg testosterone). The dose can be applied to the abdomen, or to both inner thighs. Daily rotation between the abdomen and inner thighs is recommended to minimise application site reactions.[4]

NB. The BNF does not give directions for use of the 2% gel. Note difference in daily dose between the 2 preparations.

BNF therapeutic class / mode of action:

Androgen

Licensed indication(s):

Testosterone replacement therapy for male hypogonadism when testosterone deficiency has been confirmed by clinical features and biochemical tests[2,3,4]

Proposed use (if different from, or in addition to, licensed indication above):

As supplementation for menopausal women with low sexual desire if HRT alone is not effective

Course and cost:

Testogel 50mg/5g gel in sachet = £31.11 for 30 sachets

Annual cost of treatment = £53.92

Tostran 2% gel in cannister = £28.63 for 60g

Annual cost of treatment = £85.89 (maximum. 3 cannisters/year depending upon dose, each cannister containing 120 doses)

Testim 50mg/5g gel in tube = £30.50 for 30 tubes

Annual cost of treatment = £52.87

Prices taken from drug tariff September 2021

Current standard of care/comparator therapies:

Treatments that have been used for menopause-related symptoms include lifestyle advice, HRT, herbal remedies, other complementary (alternative) therapies and antidepressants.[5]

Relevant NICE guidance:

NICE Guideline 23: Menopause: Diagnosis and Management (2015)[5]

- Consider testosterone supplementation for menopausal women with low sexual desire if HRT alone is not effective (off-label use).
- Loss of libido may also be a result of declining levels of oestrogen and testosterone as the ovaries fail; the lack of testosterone can be more marked in women who have their ovaries removed by surgery.
- Limited data was found for the outcome of frequency of satisfying sexual intercourse, but testosterone (10 mg/day; gel) was found to significantly increase frequency compared with placebo although the majority of women included in these trials were surgically menopausal. The other evidence identified comparing tibolone versus oestrogen plus progestogen did not show a significant difference in the frequency of satisfying sexual activities. Given the limited availability of evidence, the group incorporated their clinical experience to decide that testosterone, although unlicensed for this indication in women, should only be offered as an option of improving low sexual desire for women in menopause when HRT is not effective.

Background and context

There are more than 11 million women over the age of 45 in the UK according to the Office of National Statistics 2011 census. This number has been steadily increasing and is forecast to continue to rise. The associated increase in the number of women going through the menopause is expected to result in more GP consultations and more new referrals to secondary care of women needing short-term symptom control and those who have associated long-term health issues. A cross-sectional study in 2012 found that more than 60% of women managed their menopausal symptoms without any contact with healthcare professionals, often through social support and obtaining advice from friends, family and the Internet.[5]

The assessment and then treatment of a change in libido, or a change in the desire to partake in sexual activity, during the menopausal transition and beyond has been a challenging and elusive area of clinical research. This is partly due to the multidimensional nature of female sexuality, the difficulties of measuring testosterone in women in a reliable and accurate manner, and the complexity of the neurobiology and neurobehavior of female sexual desire. In addition, there is a lack of evidence for diagnostic specificity of low free testosterone levels for the symptom of low libido in women for whom there are no confounding interpersonal or psychological factors; although, in the symptomatic population of surgically or naturally menopausal women, a low level of free testosterone often accompanies a complaint of reduced desire/libido.[6]

Currently, only testosterone formulations for men are available which are adjusted for women and prescribed off label.

Summary of evidence

Summary of efficacy data in proposed use:

Global Consensus position statement 2019[7]

The only evidence-based indication for the use of testosterone in women is for the treatment of postmenopausal women who have been diagnosed as having HSDD after formal biopsychosocial assessment. More adequately powered, double-blind RCTs, without selection bias and with consistent reporting of standardised outcomes, are needed to comprehensively establish the benefits and risks of testosterone therapy for women. It was considered of utmost importance that the diagnosis of HSDD involves a full clinical assessment and that other factors contributing to female sexual arousal disorder (FSD) must be identified and addressed before testosterone therapy is initiated. A blood total testosterone level should not be used to diagnose HSDD. Treatment should only be with formulations that achieve blood concentrations of testosterone that approximate premenopausal physiological concentrations. Because no approved female product is presently approved by a national regulatory body, male formulations can be judiciously used in female doses and blood testosterone concentrations must be monitored regularly

Should a trial of testosterone therapy begiven for Hypoactive sexual desire disorder/dysfunction (HSDD), a baseline total testosterone concentration should be measured before commencement, with a repeat level 3–6 weeks after treatment initiation. Patients should be monitored for their clinical response to treatment and assessed for signs of androgen excess with a serum total testosterone level every 6 months, to screen for overuse. If no benefit is experienced by 6 months, treatment should be ceased.

The British Menopause Society & Women's Health Concern 2016[8]

Women with distressing low sexual desire and tiredness should be counselled that androgen supplementation is an option particularly, if HRT in the form of oestrogen with or without progesterone has not been effective. Assessment of serum androgen levels is unlikely to be beneficial as there is poor correlation between circulating androgen levels and clinical symptoms.

Testosterone implants and patches have been withdrawn by pharmaceutical companies for commercial, not safety reasons. Tibolone has a weak androgenic effect which can have a beneficial effect on mood and libido. Testosterone gels licensed for male use are available in 50 mg, 5 mL sachets or tubes. Unlicensed prescribing by specialists is an option for female androgen replacement, at a reduced dosage of 0.5 to 1.0 mL/day or ¼ sachet/tube on alternate days.

Randomised controlled trials

Panay et al 2010 (n=272)[9]

A total of 272 naturally menopausal women, predominantly not using hormone therapy, were randomized in this 6-month, placebo-controlled, double-blind, multicentre study to receive twice weekly either testosterone patch or an identical placebo. The testosterone patch group demonstrated significant improvements in satisfying sexual episodes (p = 0.0089) as well as in sexual desire (p = 0.0007) and reduced personal distress (p = 0.0024) versus placebo at 6 months (intent-to-treat analysis, n = 247). The results were significant for all three endpoints in the subgroup (n = 199) not using hormone therapy.

Davis et al study 2008 (n=814)[10]

Double-blind, placebo-controlled, 52-week trial in which 814 women with hypoactive sexual desire disorder (HSDD) were randomly assigned to receive a patch delivering 150 or 300 µg of testosterone per day or placebo. At 24 weeks, the increase in the 4 week frequency of satisfying sexual episodes was significantly greater in the group receiving 300 µg of testosterone per day than in the placebo group (an increase of 2.1 episodes vs. 0.7, P<0.001) but not in the group receiving 150 µg per day (1.2 episodes, P=0.11). Both groups receiving testosterone had significant increases in scores for sexual desire and decreases in scores for personal distress from baseline to week 24, as compared with the placebo group. Treatment effects did not differ significantly between women who had undergone natural menopause and those who had undergone surgically induced menopause.

Nathorst-Boos et al 2006 (n=53)[11]

Fifty-three postmenopausal women participated. As a complement to their already on-going HRT, 10 mg of a testosterone gel (Testogel) or placebo was administered. Treatment continued for three plus three months in a double blind, randomized, crossover design. The primary objective of this study was to elucidate if percutaneous treatment with 10 mg testosterone gel per day could enhance sexuality and psychological well-being in postmenopausal women on HRT presenting problems with low libido. The scores concerning “frequency of sexual activity, orgasm and intercourse”, “sexual arousal, fantasies and enjoyment”, “satisfaction with orgasms”, and “interest in sex” were all significantly improved for testosterone addition as compared to placebo both before and after crossover.

Simon et al 2005 (n=562)[12]

Primary objective was to evaluate the efficacy and safety of a testosterone patch in surgically menopausal women with HSDD. The design was a randomized, double-blind, parallel-group, placebo-controlled, 24 week study. The participants were aged 26–70 years, with HSDD after bilateral salpingo-oophorectomy who were receiving concomitant oestrogen therapy. Placebo (n279) or testosterone 300 µg /d (n283) was administered twice weekly. At 24 weeks, there was an increase from baseline in the frequency of total satisfying sexual activity of 2.10 episodes/4 week in the testosterone group, which was significantly greater than the change of 0.98 episodes/4 week in the placebo group (P0.0003). The testosterone group also experienced statistically significant improvements in sexual desire and a decrease in distress.

Systematic reviews

Islam et al 2019[13]

The search found 46 reports of 36 randomised controlled trials comprising 8480 participants.

The meta-analysis showed that, compared with placebo or a comparator (eg, oestrogen, with or without progestogen), testosterone significantly increased sexual function, including satisfactory sexual event frequency (mean difference 0·85, 95% CI 0·52 to 1·18), sexual desire (standardised mean difference 0·36, 95% CI 0·22 to 0·50), pleasure (mean difference 6·86, 95% CI 5·19 to 8·52), arousal (standardised mean difference 0·28, 95% CI 0·21 to 0·35), orgasm (standardised mean difference 0·25, 95% CI 0·18 to 0·32), responsiveness (standardised mean difference 0·28, 95% CI 0·21 to 0·35), and self-image (mean difference 5·64, 95% CI 4·03 to 7·26), and reduced sexual concerns (mean difference 8·99, 95% CI 6·90 to 11·08) and distress (standardised mean difference –0·27, 95% CI –0·36 to –0·17) in postmenopausal women.

Alexander et al 2006[6]

Review of randomized, controlled studies, both recent and older, illustrates a positive benefit to add-back testosterone in some surgically or naturally postmenopausal women. It also illustrates that a behavioural intervention in the form of a randomized, controlled trial will lead to improvement in sexual function, although not as dramatically as testosterone replacement. With these randomized, controlled trials, it is not possible to ascertain the cohort of women who have a significant improvement from testosterone replacement versus the women who have modest or no improvement. The pharmacokinetics of the different delivery systems are important in establishing dosing guidelines and achieving physiological levels of free and total testosterone. All of these trials demonstrated an increase in sexual function with testosterone treatment. Oestrogen replacement was largely oral in these studies, with some having less than a quarter of their patients receiving transdermal oestrogen replacement.

Cochrane 2005[14]

The primary objective was to determine the benefits and risks of testosterone therapy for postmenopausal women taking hormone therapy. Thirty-five trials with a total of 4768 participants were included in the review. The median study duration was six months (range 1.5 to 24 months). Most of the trials were of adequate quality with regard to randomisation and concealment of allocation sequence. The major methodological limitations were attrition bias and lack of a washout period in the crossover studies. The pooled estimate suggested that the addition of testosterone to HT regimens improved sexual function scores and number of satisfying sexual episodes for postmenopausal women.

Summary of safety data:

Global Consensus position statement**Error! Bookmark not defined.**

Meta-analyses of the available data show no severe adverse events during physiological testosterone use, with the caveat that women at high cardiometabolic risk were excluded from study populations. Data from RCTs are insufficient to assess long-term breast cancer risk. Safety data for testosterone in physiologic doses are not available beyond 24 months of treatment. The safety of long-term testosterone therapy has not been established.

Systemic testosterone therapy for post-menopausal women, in doses that approximate physiological testosterone concentrations for premenopausal women, is associated with mild increases in acne and body/facial hair growth in some women, but not with alopecia, clitoromegaly, or voice change.

Islam et al 2019[13]

A significant rise in the amount of LDL-cholesterol, and reductions in the amounts of total cholesterol, HDL-cholesterol, and triglycerides, were seen with testosterone administered orally, but not when administered non-orally (eg, by transdermal patch or cream). An overall increase in weight was recorded with testosterone treatment. No effects of testosterone were reported for body composition, musculoskeletal variables, or cognitive measures, although the number of women who contributed data for these outcomes was small. Testosterone was associated with a significantly greater likelihood of reporting acne and hair growth, but no serious adverse events were recorded.

The effects of testosterone on individual wellbeing and musculoskeletal and cognitive health, as well as long-term safety, warrant further investigation.

The British Menopause Society & Women's Health Concern 2016[8]

Androgenic side effects and risks are minimal and reversible if testosterone levels are maintained within the female physiological range. Some studies have shown benefits on the skeleton, cognition, well being and the vagina, although these findings require further assessment.

Cochrane 2005[14]

Significant adverse effects were decreased high-density lipoprotein (HDL) cholesterol levels and an increased incidence of hair growth and acne. The discontinuation rate was not significantly greater with the addition of testosterone therapy (OR 0.99, 95% CI 0.83to 1.19). These adverse events may differ by the different doses and route of testosterone administration. There is insufficient evidence to determine the effect of testosterone in long term use.

Nathorst-Boos et al 2006 (n=53)[11]

As a complement to their already on-going HRT, 10 mg of a testosterone gel (Testogel) or placebo was administered. Liver enzymes, total cholesterol, triglycerides, HDL and LDL revealed no significant differences between any of the periods or groups. Endometrial thickness did not change significantly during treatment. Haemoglobin and erythropoietin remained unchanged. No significant differences in the number of experienced side effects were found. Testosterone levels increased more than 10-fold during treatment while DHT-levels were more than doubled. The given dose resulted in too high serum levels. Even if no negative effects were observed, monitoring of serum levels and a decreased dose should be considered in future studies.

Summary of product characteristics[2]

Contraindicated in cases of known or suspected prostatic cancer or breast carcinoma and in cases of known hypersensitivity to the active substance or any of the excipients.

Caution in cancer patients at risk of hypercalcaemia (and associated hypercalciuria), due to bone metastases.

In patients suffering from severe cardiac, hepatic or renal insufficiency or ischaemic heart disease, treatment with testosterone may cause severe complications characterised by oedema with or without congestive cardiac failure.

Testosterone may cause a rise in blood pressure and this medicine should be used with caution in hypertension.

Testosterone should be used with caution in patients with thrombophilia or risk factors for venous thromboembolism (VTE), as there have been post-marketing studies and reports of thrombotic events.

In patients receiving long-term androgen therapy, the following laboratory parameters should also

be monitored regularly: haemoglobin, and haematocrit (to detect polycythaemia), liver function tests, and lipid profile.

This medicine should be used with caution in patients with epilepsy and migraine as these conditions may be aggravated.

Improved insulin sensitivity may be observed in patients treated with androgens and may require a decrease in the dose of antidiabetic medications.

Testosterone gel can be transferred to other persons by close skin to skin contact, resulting in increased testosterone serum levels and possibly adverse effects.

Note on the market withdrawal of the Intrinsa testosterone patch:

On 28 July 2006 the European Commission issued a marketing authorisation valid throughout the European Union for the medicinal product Intrinsa (testosterone). Intrinsa was approved for the treatment of hypoactive sexual desire disorder (HSDD) in bilaterally oophorectomised and hysterectomised (surgically induced menopause) women receiving concomitant estrogen therapy. The Marketing Authorisation Holder (MAH) responsible for Intrinsa was Warner Chilcott UK Ltd. The European Commission was notified by letter dated 13 March 2012 of the MAH's decision to voluntarily withdraw the marketing authorisation for Intrinsa for commercial reasons.[15]

In 2010 an application was made to extend the marketing authorisation for Intrinsa to treat HSDD in postmenopausal women with or without hormone treatment. This was to include all women who have been through the menopause and not only those who are 'surgically postmenopausal' as result of having had their womb or ovaries removed. The company presented results of four studies in a total of 2,245 women with HSDD. The application was withdrawn after 'day 90'. This means that the CHMP had evaluated the documentation provided by the company and formulated two lists of questions. After the CHMP had assessed the company's responses to the questions, there were still some unresolved issues. Based on the review of the data and the company's response to the CHMP's lists of questions, at the time of the withdrawal, the CHMP had some concerns and was of the provisional opinion that Intrinsa could not have been approved for use in all postmenopausal women who have HSDD. The CHMP noted that there was insufficient long-term data on the safety of the medicine in this larger group of patients and was therefore of the opinion that the medicine's benefits in these women did not outweigh its risks.

The company stated the withdrawal was based on commercial considerations.

The withdrawal assessment report for Intrinsa summarised:[16]

- Treatment with Intrinsa induced weight gain to a higher incidence than in the placebo group.
- Acne was more often seen in patients treated with Intrinsa (5.5%) compared to placebo treated patients (4.9%).
- Treatment with Intrinsa increases the risk of developing increased facial hair growth, which was observed in 9% in Intrinsa treated patients versus 6.6% in the placebo group.
- An increased incidence of enlarged clitoris was observed in patients treated with Intrinsa (0.5%; 13 out of 2794 patients) compared with placebo (<0.1%; 1 out of 1848 patients) and was more often seen in long term studies (12 and 24 month studies) compared to studies with shorter duration.
- A majority of the patients on Intrinsa with invasive and in-situ breast cancer had been on oral contraceptive or were using hormone replacement therapy, and the assessor concluded that the patients had been exposed to oestrogen. The potential increase in risk with Intrinsa alone is difficult to evaluate from the performed clinical trials. Mammographic breast density is related to increased risk for breast cancer. With Intrinsa alone there was no statistically significant change from baseline to week 52 in the percentage of breast

density compared to placebo in women without hormone replacement therapy. In the presented data there was no effect on proliferation from Intrinsa, but a significant increase in proliferation in patients on oestrogen and progestin therapy. The result on proliferation in Intrinsa group was reassuring, but limited for prediction of breast cancer risk during long term treatment. However, published observational studies and in vitro data indicate that there is no consensus on an increased risk of breast cancer in postmenopausal women using testosterone.

- No endometrial cancers were reported in the clinical trial program. However, these results are too limited to be predictive of endometrial cancer risk following long-term treatment.
- The short-term CV safety data obtained in the studies submitted in this variation application have not revealed any unexpected findings. However, there are serious concerns related to the long term safety aspects of testosterone in women.
- Currently, long term safety data (i.e. more than 2 years exposure) for treatment with Intrinsa in women with naturally menopausal is very limited, particularly for women not on hormone therapy (n=45 for more than 2 years exposure). Although available data do not suggest any cardiovascular risk, invasive breast cancer risk, ovarian cancer or endometrial cancer/hyperplasia risk with Intrinsa in the different subpopulations investigated, the data do not remove the safety concern.
- It must be concluded that the long-term safety risks with testosterone treatment in women with intact ovaries - the proposed target population of this variation - cannot be meaningfully evaluated based on the documentation submitted by the company and, therefore, the safety issue cannot be considered resolved.
- Conclusion: The benefit/risk balance is considered negative for the proposed indication.

Strengths and limitations of the evidence:

Strengths

- Several systematic reviews of the data conclude that testosterone improves sexual function in post-menopausal women

Limitations

- A range of formulations, routes of administration and dosages were used across the studies. None of the systematic reviews specify an optimal dose. Several studies use a patch formulation, which is no longer available.
- The patient populations vary between and within studies – notably some patients are on concurrent HRT, some are not, and some women have experienced a natural menopause and some a surgically induced menopause.
- Safety data on the summary of product characteristics is based on studies in a male population
- Consensus needed on serum testosterone monitoring
- Further research needed on a suitable duration of testosterone treatment in women
- Long term safety data lacking, including long term breast cancer risk
- Women at high cardiometabolic risk were excluded from study populations
- The company which manufactured the licensed testosterone patch, Intrinsa, withdrew its application to extend the marketing authorisation to include post menopausal women with HSDD in 2010. The Committee for Medicinal Products for Human Use noted that there was insufficient long-term data on the safety of the medicine in this larger group of patients and was therefore of the opinion that the medicine's benefits in these women did not outweigh its risks.

Summary of evidence on cost effectiveness:

None available

Prescribing and risk management issues:

There are no transdermal, testosterone products licensed for use in women.

There is no licensed recommended daily dose for use in women.

Australia have a licensed testosterone product for use in women called ANDROFEME® 1. This is a 1% w/v cream. The recommended starting dose is 5 mg testosterone (0.5 mL) applied once daily. Serum testosterone monitoring is required during treatment[17].

The available gel products are inconsistent in the daily testosterone dose they provide and in the case of the sachet and tube are difficult to accurately measure a daily dose.

Storage and potential contamination issues if using an opened sachet or tube over the course of a week.

Do not apply to the genital areas as the high alcohol content may cause local irritation.

Testosterone is a schedule 4 CD (anab).

Commissioning considerations:

Innovation, need and equity implications of the intervention:

There are no transdermal, testosterone products licensed for use in women.

There is no licensed recommended daily dose for use in women.

NICE recommend consideration of testosterone supplementation for menopausal women with low sexual desire if HRT alone is not effective.[5]

Financial implications of the intervention:

EPACT prescribing data from June 2020 to July 2021 showed that approximately 34818 patients were prescribed HRT in primary care across Lancashire and South Cumbria. This equates to 1.9% of a 1,794,244 population.

It is unclear what the potential uptake of testosterone gel in this cohort of patients could be. Approximate annual costs of testosterone therapy:

- 1% uptake = £18,398 - £29,889
- 10% uptake = £184,093 - £299,068
- 50% uptake = £920,413 - £1,495,259

Costs of potential blood monitoring not included.

Service Impact Issues Identified:

If it is considered that testosterone blood level monitoring is required, the requirements and parameters are not yet clear.

Equality and Inclusion Issues Identified:

No licensed testosterone products available for women suffering from HSDD.

Cross Border Issues Identified:

The **Pan Mersey APC** does not currently recommend the use of testosterone for testosterone deficiency in Women (RAG rated grey).

The **Greater Manchester Medicines Management Group** (GMMMG) recommends the off-label use of testosterone (Testogel or Tostran) in women with low sexual desire, only when HRT alone is ineffective. GMMMG have given this a RAG rating of 'Green following specialist initiation' (Drugs that are suitable for initiation by primary care following written or verbal advice from a specialist service. Little or no monitoring is required).

GMMMG notes that Tostran comes in a multi-dose canister providing measured doses, thus may more easily allow administration of lower doses. Not for use in non-menopausal women.

Legal Issues Identified:

Schedule 4 (CD Anab)[1]

The attention of athletes is drawn to the fact that this proprietary medicinal product contains an active substance (testosterone) which may produce a positive reaction in anti-doping tests.[4]

Media/ Public Interest:

There have been queries from members of the public about testosterone treatment in menopause.

Grading of evidence (based on SORT criteria):

Levels	Criteria	Notes
Level 1	Patient-oriented evidence from: • high quality randomised controlled trials (RCTs) with low risk of bias • systematic reviews or meta-analyses of RCTs with consistent findings	High quality individual RCT= allocation concealed, blinding if possible, intention-to-treat analysis, adequate statistical power, adequate follow-up (greater than 80%)
Level 2	Patient-oriented evidence from: • clinical trials at moderate or high risk of bias • systematic reviews or meta-analyses of such clinical trials or with inconsistent findings • cohort studies • case-control studies	
Level 3	Disease-oriented evidence, or evidence from: • consensus guidelines • expert opinion • case series	Any trial with disease-oriented evidence is Level 3, irrespective of quality

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