Hertfordshire and West Essex Integrated Care System

NHS Hertfordshire and West Essex Integrated Care Board

Testosterone gel for Hypoactive Sexual Desire Disorder/Female Androgen Deficiency Syndrome for women in the menopause

RECOMMENDED FOR RESTRICTED USE (AMBER INITIATION)

Name: generic (trade)	What it is	Indication	Date decision last revised	Decision status	NICE / SMC Guidance
Testosterone transdermal gel (Testim® Testogel® or Tostran®)	Transdermal testosterone for use as part of Hormone Replacement Therapy (HRT)	Hypoactive Sexual Desire Disorder/Female Androgen Deficiency Syndrome for women in the menopause*	May 2022‡	Final	• NICE (NG23)[1]: Consider testosterone supplementation for menopausal women with low sexual desire if HRT alone is not effective • SMC – No guidance

* off-label indication
‡ amended May 2022 following discontinuation of Testogel® 50mg/5g sachets

Recommendation:

Testosterone gel (Testim®/Testogel®/Tostran®) recommended for restricted use for women in the menopause with Hypoactive Sexual Desire Disorder (HSDD) / Female Androgen Deficiency Syndrome (FADS) if HRT alone is not effective. Recommend as AMBER INITIATION – i.e**. GPs may continue therapy after initiation and stabilisation (3-6 months)** by a clinician with expertise in the treatment of the menopause (defined as a Consultant Endocrinologist/Gynaecologist or a primary care clinician who has relevant experience and is clinically competent to prescribe).

Following discontinuation of Testogel® 50mg/5g sachets (in March 2022), **the first choice product within Hertfordshire is Testim® 50mg/5g gel tubes**. Testogel® 40.5mg/2.5g gel sachets or Tostran® 2% gel pump dispenser may be prescribed where there are specific circumstances (e.g. supply problems, or to permit transfer of prescribing for patients successfully initiated on these products at specialist clinics).

Given that use of testosterone gel for women in the menopause is unlicensed, the initiating menopause specialist must ensure that full information is provided and discussed with patients prior to prescribing. This is to permit patients to make an informed decision regarding use. A **Patient Information Leaflet** (PIL) has been developed to support and reinforce this verbal information (see below for link to PIL).

A **fact sheet for GPs** has also been developed (see link below) to provide additional information/prescribing support, including maximum quantities to be prescribed, blood testing requirements and other relevant information to ensure safe prescribing.

Background Information:

- Testosterone deficiency can lead to a number of distressing sexual symptoms such as low sexual desire, arousal and orgasm. Testosterone deficiency can also contribute to a reduction in general quality of life, tiredness, depression, headaches, cognitive problems, osteoporosis and sarcopenia.[2]
- The use of testosterone gel for the treatment of low sexual desire in menopausal women is an ‘off-label’; there are no testosterone products licensed for this indication in the UK.[1]
- While unlicensed for use in women, the British Menopause Society recommend the use of either Testim®, Testogel® or Tostran®:[2]
    - Testim gel [Endo Ventures Ltd] 1% testosterone gel in 5ml tubes: Starting dose 0.5ml (5mg) per day making each tube last for 10 days
    - Testogel [Besins Healthcare UK] (1% testosterone gel in 5.0g sachets containing 50mg testosterone): Starting dose 1/10 of a sachet/day = 5mg/day i.e. each sachet should last 10 days
    - Testogel [Besins Healthcare UK] (2.5g sachets containing 40.5mg testosterone): Starting dose 1/8 of a sachet/day = approx. 5mg/day i.e. each sachet should last 8 days. (new formulation)
    - Tostran [Kyowa Kirin Ltd] (2% testosterone gel in a canister containing 60g): Starting dose 1 metered pump of 0.5g = 10mg on alternate days – i.e. each canister should last 240 days

- NICE guidance (NG23) states that for altered sexual function, testosterone supplementation can be considered for menopausal women with low sexual desire if HRT alone is not effective.[1]
- Much of the clinical evidence relating to locally applied testosterone treatment relates to the use of transdermal patches (which are not commercially available in the UK). Evidence for testosterone gel is in the main, extrapolated. Studies suggest benefit ranging from modest to moderate.
- In both surgical and natural menopause, testosterone treatment has been shown to increase levels of sexual desire, although this effect can take up to 8-12 weeks. It is advised that treatment should be trialled for a minimum of 3 months and maximally for 6 months before being discontinued due to lack of efficacy.[2]
- Testosterone is well tolerated – symptoms of androgen excess, such as hirsutism and acne, are common with testosterone therapy, although these effects are often mild.[3]
- A systematic review and meta-analysis of the safety and efficacy of testosterone for women published in The Lancet Diabetes & Endocrinology in 2019 (see clinical effectiveness and safety section below for further information) concludes that testosterone is effective for postmenopausal women with low sexual desire causing distress.[4] The International Menopause Society have also endorsed a global consensus and position statement on the use of testosterone on women,[5] which concludes that the only evidence-based indication for testosterone therapy for women is for the treatment of HSDD, with available data supporting a moderate therapeutic effect.
- The recommendation for use covers approval for women in the menopause with HSDD/FADS. This is to ensure equity of access for women who may have symptoms of FADS, but are not in a relationship therefore unable to quantify their libido.

Blood test monitoring:

- It is **not** mandatory to perform testosterone level estimations, however, it is recommended as it can be useful. The assessment and interpretation of testosterone levels is problematic, particularly as the majority of testosterone is protein bound. Free testosterone assays are the gold standard but are rarely available, particularly in the public sector. Total testosterone can be measured, but for greater accuracy sex hormone binding globulin (SHBG) levels should be taken into account using the following calculation to work out the Free Androgen Index (FAI) = Total Testosterone x 100 / SHBG.[2]
- Although it is not mandatory to perform testosterone level estimation prior to treatment, a low FAI < 1% in women with symptoms of low sexual desire and arousal, supports the use of testosterone supplementation. Repeat estimation at the 2-3 month follow up visit can be performed to demonstrate if there has been an increase in levels, though clinical response is of paramount importance.[2]
- Ongoing blood test monitoring is needed to demonstrate that values are being maintained within the female physiological range, typically a FAI < 5%, thus making androgenic side effects less likely.[2] If results are above the female physiological range, the dosage of testosterone gel should be reduced, or treatment stopped. Advice should be sought from the initiating specialist if required.
- Recommended that total testosterone, sex hormone binding globulin (SHBG) tests and Free Androgen Index (FAI) estimates should be done **prior to starting treatment, then at 3 and 6 months post starting therapy, then annually**, with blood tests performed sooner if patients have symptoms. It was agreed that the initiating clinician does the first bloods and follow ups, then if stable to be handed over to GP, with clear instructions about when/what tests are required.
- Testosterone assays are available to GPs locally as follows:
    - WHHT – total testosterone and SHBG tests are available. If SHBG is requested, then FAI is also available.
    - ENHT – total testosterone & SHBG available – system does not currently calculate FAI, but this can be calculated as follows: FAI = Total Testosterone x 100 / SHBG.
- If patients experience androgenic adverse effects (see GP fact sheet for more information), blood monitoring should be performed. Where results are above the female physiological range, actions should be taken as above.

Fact sheet for GPs:

- A fact sheet has been developed to support GP prescribing of testosterone gel in women. This provides additional information/prescribing support, including maximum quantities to be prescribed, blood testing requirements and other relevant information to ensure safe prescribing. This is available here.

Patient Information Leaflet:

- A testoterone gel Patient Information Leaflet for women in the menopause is available here.

Other information of relevance:

- Testosterone products should be avoided or used with caution:
    - During pregnancy or breastfeeding
    - Active liver disease
    - History of hormone sensitive breast cancer – off label exceptions to this may be agreed in fully informed women with intractable symptoms not responding to alternative
- When treating low sexual desire/arousal it is also important that urogenital tissues are adequately oestrogenised in women with vulvovaginal atrophy/genitourinary syndrome of the menopause e.g. through use of vaginal oestrogen, to avoid dyspareunia.[2]

ASSESSMENT AGAINST THE ETHICAL FRAMEWORK

Evidence of Clinical Effectiveness and safety:

Clinical outcomes and trials

1) Drug and Therapeutics Bulletin (DTB): Testosterone therapy for menopausal women, 2017[6] – See Link

Summary: This was an update on the evidence of the effectiveness and safety of testosterone supplementation in menopausal women (initial review published in 2009).

Conclusions: 'There is a lack of evidence implicating deficient endogenous testosterone in the development of sexual dysfunction in menopausal women. Nevertheless, published randomised placebo-controlled trials suggest that testosterone therapy produces a small improvement in sexual function (equivalent to one additional satisfying sexual episode per month) compared with placebo. In the short term, testosterone therapy is commonly associated with acne and hirsutism. The long-term adverse effect profile in women is unknown. In our previous review of a testosterone transdermal patch (subsequently withdrawn from the market) licensed for the treatment of hypoactive sexual desire disorder in menopausal women, we did not recommend it on the basis that the published evidence only showed small improvements in measures of sexual function in a highly-selected population. In addition, the trials reported a large placebo response and common, sometimes irreversible, unwanted effects. There has been insufficient new evidence to change our opinion on the use of testosterone in menopausal women. We believe that the lack of a product licensed for women, limited evidence of efficacy and a lack of long-term data on safety means that we cannot recommend testosterone therapy in postmenopausal women with sexual dysfunction.'

2) The Lancet Diabetes & Endocrinology. Safety and efficacy of testosterone for women: a systematic review and meta-analysis of randomised controlled trial data, 2019[4] – See Link

Summary: Systematic review and meta-analysis of randomised controlled trials of testosterone in women within MEDLINE, Embase, the Cochrane Central Register of Controlled Trials, and Web of Science. The studies were restricted to those completed between 1990 and 2018. Inclusion criteria for studies were that they should be randomised clinical trials, have a duration of systemic testosterone treatment of at least 12 weeks, be at least single blind (i.e. participants and assessors had to be unaware of the intervention or interventions), and have a placebo or comparator arm (e.g. oestrogen, with or without progestogen). Participants could be aged 18–75 years and be premenopausal or postmenopausal. Reviewed 46 reports of 36 randomised controlled trials comprising of 8,480 participants.

Effectiveness outcome: The meta-analysis showed that, compared with placebo or a comparator (e.g. oestrogen, with or without progestogen), testosterone significantly increased sexual function, including satisfactory sexual event frequency, sexual desire, pleasure, arousal, orgasm, responsiveness, self-image, reduced sexual concerns and distress in postmenopausal women. 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.

Safety outcomes: An overall increase in weight was recorded with testosterone treatment. Testosterone was associated with a significantly greater likelihood of reporting acne and hair growth, but no serious adverse events were recorded for non-oral testosterone. Only non-oral testosterone should be prescribed due to the significant adverse lipoprotein effects with oral testosterone.

Conclusion: Testosterone is effective for postmenopausal women with low sexual desire causing distress, with administration via non-oral routes (e.g. transdermal application) preferred because of a neutral lipid profile.

3) Global Consensus Position Statement on the Use of Testosterone Therapy for Women, 2019[5] – See Link

Summary: The international panel concluded the only evidence-based indication for testosterone therapy for women is for the treatment of hypoactive sexual desire disorder/dysfunction (HSDD), with available data supporting a moderate therapeutic effect. 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. The safety of long-term testosterone therapy has not been established. It was considered of utmost importance that the diagnosis of HSDD involves a full clinical assessment and that other factors contributing to female sexual dysfunction (FSD) must be identified and addressed before testosterone therapy is initiated. A blood total testosterone level should **not** be used to diagnose HSDD.

National guidance

4) **NICE NG23[1] – See Link**
- Consider testosterone supplementation for menopausal women with low sexual desire if HRT alone is not effective.
- Testosterone (10 mg/day; gel) was found to significantly increase frequency of satisfying sexual intercourse compared with placebo although the majority of women included in these trials were surgically menopausal.
- Given the limited availability of evidence, the guideline development 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.

5) NICE CKS – See Link

If the woman has persistent altered sexual function and hormonal and/or non-hormonal, or non-drug treatments are ineffective:
- Seek specialist advice regarding the use of testosterone supplementation (off-label use).

Safety / possible adverse effects[2]:

Response to testosterone with regards to efficacy and adverse effects, is highly variable. This is most likely due to varying absorption, metabolism and sensitivity to testosterone. Clinical trials have demonstrated that as long as appropriate female physiological doses are prescribed adverse androgenic effects are not problematic and virilising problems do not occur.

Reported adverse effects are shown below; if thought to be linked, the dosage should be reduced, or treatment stopped.

- Increased body hair at site of application (occasional problem) – spread more thinly, vary site of application, reduce dosage.
- Generalised Hirsutism (uncommon)
- Alopecia, male pattern hair loss (uncommon)
- Acne and greasy skin (uncommon)
- Deepening of voice (rare)
- Enlarged clitoris (rare)

Randomised controlled trials and meta analyses have not shown an increased risk of cardiovascular disease or breast cancer although longer term trials would be desirable.

Cost of treatment and Cost Effectiveness:

Cost of testosterone gel when used for women in the menopause

	Dose	Unit cost *	Cost per 28 days	Annual Cost
Testogel® 50mg/5g gel unit dose sachets	5mg per day (i.e. 1 sachet every 10 days)	£31.11 / 30 sachets	£2.90	£37.85
Tostran® 2% gel (10mg per actuation)	10mg on alternate days	£28.63 / 60g (120 doses)	£3.34	£43.54
Testogel® 40.5mg/2.5g gel unit dose sachets	5mg per day (i.e. 1 sachet every 8 days)	£31.11 / 30 sachets	£3.63	£47.31
Testim® 50mg/5g gel tubes	5mg per day (i.e. 1 sachet every 10 days)	£30.50 / 30 tubes	£2.85	£37.11

* Prices from DM&D, May 2022

Estimated cost pressure

An extrapolation of estimated usage by South East London CCG (100 women/1.9 million people per year) suggests that the additional cost of testosterone gel per year for SWH (i.e. approx. 35 patients/660,000 population) would be between £1,300 and £1,500 depending on the preparation used. For ENH (i.e. approx. 32 patients/600,000 population) the additional cost per year would be between £1,200 and £1,400 depending on the preparation used. This does not include the cost of testosterone assays.
It is estimated that women will remain on treatment for approximately 5 years.

The needs of the population

The needs of the population appear to be high, as there are currently no other treatments available for women in the menopause with low sexual desire/FADS if HRT alone is not effective.

The needs of the community

Approval for use within Hertfordshire has potential to cause a minimal cost pressure given the low annual cost of treatment per patient and small numbers of patients estimated to require treatment.

Policy Drivers

National drivers

- NICE (NG23)[1]: Consider testosterone supplementation for menopausal women with low sexual desire if HRT alone is not effective.
- SMC: No decision on this.
- AWMSG: No decision on this.
- British Menopause Society[2]:
  In clinical trials of women with HSDD, approximately 2/3 of women responded positively to testosterone therapy (compared to 1/3 using placebo). Trials demonstrated that response may not be immediate, taking 8-12 weeks in some instances for the effect to become clinically significant. It is therefore advised that treatment should trialled for a minimum of 3 months and maximally for 6 months before being discontinued due to lack of efficacy. Duration of use should be individualised and evaluated at least on an annual basis, weighing up pros and cons according to benefits and risks, as per HRT advice from all menopause societies.

Local formulary status:

- **Bedfordshire, Luton and Milton Keynes CCG**: testosterone gel (Testogel®/Tostran®) for treating symptoms of low sexual desire in post-menopausal women considered by Area Prescribing Committee in September 2021. Agreed to add to both Joint Formularies in accordance with the recommendations included in NICE Guideline 23 i.e. if HRT alone is not effective. GPs may continue therapy after initiation and stabilisation by a clinician with expertise in the treatment of the menopause (defined as a Consultant Endocrinologist/Gynaecologist or a primary care clinician who has relevant experience and is clinically competent to prescribe). Fact sheet to be developed to assist GPs in taking over prescribing, including guidance regarding blood monitoring requirements and patient counselling. No prescribing until fact sheet developed and agreed.
- **North Central London Joint Formulary Committee** (Testogel®, Tostran®): GP-Red. Restricted to sexual function clinics only for women who have no improvement with oestrogen-based HRT alone (JFC April 2016). Secondary care prescribing only.
- **Buckinghamshire CCG** (Testogel®, Tostran®, Testim®): Amber Initiation by Consultant Specialist in Menopause care in the Menopause clinic with continuation by GPs. For hypoactive sexual desire disorder (HSDD) in peri and post-menopausal women when HRT has proven to be ineffective or unsuitable (unlicensed use).
- **South East London CCG** (Testogel®, Tostran®): Amber initiation. Approved off-label indication: For use in women with decreased libido in the menopause. Tostran® is first line option, Testogel® reserved for women who experience application site reactions to Tostran®.
- **Cambridge and Peterborough NHS Foundation Trust**: Testosterone supplementation for menopausal women with low sexual desire if HRT alone is not effective **has NOT** been considered by the CPJPG (July 2020) therefore is not recommended for prescribing in Primary Care.

Equity:

Testosterone gel for low sexual desire / Female Androgen Deficiency Syndrome in menopause is indicated only in women, who are members of a protected equality group under the Equality Act 2010. Recommending use has a positive impact for this equality group as it permits access to testosterone gel via NHS prescribing. Guidance applies to all relevant patients where indicated. There is no differential impact expected on one or more equality groups differently to others: Age; Disability; Gender reassignment; Marriage & Civil Partnership; Pregnancy & Maternity; Race; Religion & Belief; Sexual orientation.

Implementability:

Implementation requires:

- Development of a fact sheet for GPs & a Patient Information Leaflet

References

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3. Testosterone therapy for menopausal women. (2017). *Drug and Therapeutics Bulletin, 55*(5), 57. doi:http://dx.doi.org/10.1136/dtb.2017.5.0481
4. Islam RM, Bell RJ, Green S, Page MJ, Davis SR. Safety and efficacy of testosterone for women: a systematic review and meta-analysis of randomised controlled trial data. *The Lancet Diabetes & Endocrinology*. 2019 Oct 1;7(10):754-66
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6. Testosterone therapy for menopausal women. (2017). *Drug and Therapeutics Bulletin, 55*(5), 57. doi:http://dx.doi.org/10.1136/dtb.2017.5.0481

Version	1.1 Harmonisation of Hertfordshire Medicines Management Committee (HMMC) guidance and West Essex Medicines Optimisation Programme Board (WEMOPB) guidance updates include: • Rebadging with HWE ICB and removal of ENHCCG and HVCCG headers • Removal of reference to HMMC
Developed by	ENH and SWH PMOT
Approved by	HMMC and WEMOPB
Date approved/updated	HMMC May 2022 and WEMOPB May 2022
Review date:	The recommendation is based upon the evidence available at the time of publication. This recommendation will be reviewed upon request in the light of new evidence becoming available.
Superseded version	1.0