BSW guidance for the off-label use of topical testosterone in women on HRT AMBER 3 MONTHS

Bath and North East Somerset, Swindon and Wiltshire Together

BSW Formulary positioning

Off-label use of testosterone in women on HRT for low sexual desire has an AMBER-initiated traffic light status across NHS BSW and the specialist will initiate and supply the first 3 months of supplies **before** prescribing moves to the patient's own GP. The patient will then be discharged from specialist care if they are stable with access to patient-initiated follow-up (PIFU) for 1 year if under secondary care. GPs will be able to seek further advice from secondary care specialists via advice & guidance on Cinapsis.

- A "specialist in menopause", for the purposes of this local guidance, is a British Menopause Society (BMS) accredited specialist or equivalent prescriber who can demonstrate that they have received training in and have clinical experience of treating women with testosterone preparations. **This could be a consultant gynaecologist, GPwSI, GP, pharmacist or a specialist nurse working in primary care.**
- A "GP", for the purposes of this local guidance, is defined as the primary care giver who is taking over prescribing and monitoring after initiation of treatment by the specialist.

1. Summary of condition and treatment aims

Background

Women who are distressed by decreased sexual interest can be considered for Testosterone replacement therapy (NICE NG23 recommendation), where oestrogen replacement therapy (ERT) alone has not been effective.

Other identifiable causes should be excluded prior to initiating testosterone treatment. These include vulvo-vaginal atrophy, relationship or psychosexual factors and review of all their other medications, particularly SSRIs.

There is currently no evidence base for the relief of symptoms other than decreased sexual desire (HSDD) but studies are on-going.

Oestrogen replacement therapy should be used first and dose titrated to resolve oestrogen deficiency symptoms.

Tibolone™ can be considered, see BSW HRT guidance (p2) for further information.

Oral oestrogens can reduce the effectiveness of testosterone by increasing SHBG levels. Switching women with HSDD from oral to transdermal oestrogens can be beneficial as this can increase the proportion of circulating free testosterone without requiring exogenous testosterone (i.e. avoid the need to prescribe any testosterone).

It is preferable that women should be changed to the transdermal route of administration of ERT prior to consideration for testosterone therapy.

Testosterone will only very rarely be given in isolation without oestrogen and these patients would stay under secondary / specialist care for the duration of treatment. Androgenic side effects are more common in this group.

There is currently no licensed testosterone preparation available in the UK for women. There are preparations of different strengths that are licensed for use in men.

NICE have published Menopause Guidance and Management NG23 (updated in 2024) regarding altered sexual function[1] which states the following:

1.4.8 *Consider testosterone supplementation for menopausal women with low sexual desire if HRT alone is not effective.*

However, it notes: "At the time of publication (November 2015), testosterone did not have a UK marketing authorisation for this indication in women. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented.

The British Menopause Society (BMS) guidance[2] (https://thebms.org.uk/publications/tools-for-clinicians/testosterone-replacement-in-menopause) also acknowledges that there are no commercially available products for testosterone replacement in women in the UK.

2. Efficacy and safety

Evidence review:

- NICE NG23 Menopause: diagnosis and management full guidance p97: 8.2.5.2.4 Comparison of testosterone verses no treatment/placebo. Results: Significant increase in frequency of satisfying sexual intercourse.
- BMS Testosterone replacement in menopause
- BMS statement on testosterone

Indications

There is no available data to support or not support the use of testosterone in pre-menopausal women, or to treat depression, bone loss or prevent cognitive decline.

Testosterone should not usually be used alone or in combination with oestrogens in breast cancer patients.

Potential Side effects

Increased hair growth, acne, greasy skin

Rare potential side effects – Alopecia, Voice deepening, Clitoromegaly

Risk and Benefits

Risks change as patients age (e.g. gain weight or developing conditions such as diabetes) so it is important to re-evaluate the risks vs benefits of using testosterone annually.

Oral vs transdermal ERT

All oral oestrogens (oral contraceptives and oral ERT) will result in an increase in SHBG which will bind testosterone and reduce bioavailability. Patients using oral oestrogen should be ideally changed to transdermal oestrogen before being considered for testosterone therapy.

Exclusions to Guidance

- Use of testosterone without ERT
- Use in breast cancer patients.
- Transgender patients assigned female at birth wishing to transition

3. Details of medication - Product choice (see individual SPCs for further information)

Several topical testosterone products are included on BSW formulary. A**ll are used outside their license (off-label) when prescribed for use in women.**

Topical testosterone should be **prescribed by brand** as strength and presentation vary.

Lower dose preparations of 1 -1.62% are preferred for off label use in women.

1. Testogel® 1.62% (1.62mg/g) 40.5mg Testosterone in 2.5g gel in each sachet of gel

Starting dose usually 1/8th of a sachet applied **daily**, equates to 5mg/day. One sachet to last 8 days.

Prescribe 8 sachets for 2 month, 12 sachets for 3 months, 15 sachets for 4 months

Usual dose range 3-10mg

2. Testogel® 16.2% (16.2mg/g) 20.25mg of Testosterone in each measure of 1.25g gel in a multi-dose pump action container

Starting dose is one measure **every 4 days** = 5mg per day

This is equivalent to 2 measures per week, applied on the same day as the HRT patch is changed. Usual dose range is 3-10mg per day. Using every 3rd day will give a dose of 7mg per day. Prescribe one or two dispensers. One dispenser contains 60 doses and will last 7 weeks if used twice a week.

3. Tostran® 2% (20mg/g) gel in a multi-dose pump action container

Starting dose is one measure = 10mg every other day to give a dose of 5mg per day.

Prescribe one dispenser, which contains 120 doses and will last 8 months at 5mg/day

4. Testavan® 2% (20mg/g) 23mg of Testosterone in each measure of 1.15g gel in a multi-dose pump action container

Starting dose is one measure every 5 days for a dose of 6mg per day

Prescribe one dispenser, which contains 56 doses and will last 9 months at 6mg/day

NOTE: *Tostran and Testavan are not usually recommended locally and further information on these products is not included in this document.*

4. Usual dose and frequency

Testosterone Dosing Guide

Start treatment if total testosterone (<1nmol/l) and FAI (<2%) are in the lower third of the female range. Testosterone treatment will usually be initiated at a dose of 5mg per day. The dose can then be increased or decreased depending on the patient's clinical response and guided by blood test results.

Please note that as there are no licensed testosterone products available for use in women, the doses/frequencies in the tables below have been suggested by BMS specialists. Doses outside the normal recommended prescribing range should be advised by the Specialist and not initiated by the GP but can be prescribed by the GP with appropriate monitoring.

Table 1 Testogel 40.5mg in 2.5mg sachets, 1.62% testosterone

	High		**Standard**		**Low**	
Sachet to last	4 days	6 days	8 days	10 days	14 days	20 days
Dose	10mg	7mg	5mg	4mg	3mg	2mg
Number of sachets (available in box of 30)						
2 months	15	10	8	6	4	3
4 months	30	20	15	11	8	6
6 months	46	31	23	17	11	9

Table 2 Testogel® 16.2mg/g (20.25mg) of testosterone in each measure of 1.25g gel in a pump container.

	High		**Standard**	**Low**
Dose	10mg	7mg	5mg	2.5mg
Directions	1 measure every other day	1 measure every 3rd day	1 measure every 4th day	1 measure once a week
Device will last	120 days 4 months		240 days 8 months	

Application technique for the recommended products: The gel should be applied in the morning and spread, without rubbing, over dry, intact skin on the lower abdomen or upper thighs. Allow 3 - 5 minutes to dry before dressing. Wash hands with soap and water after applications. The application site should be rotated to minimise application site reactions.

Duration of use and review: The BMS[2] advise 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 be trialled for a minimum of 3 months and maximally for 6 months before being discontinued due to lack of efficacy.

Women should be made aware, prior to initiating testosterone treatment, of the lack of long-term clinical trial safety data beyond 24 months associated with use of testosterone in physiological doses in women. Treatment should include regular monitoring, and it should be an informed decision between physician and patient if treatment is to be continued beyond 24 months.[4]

There is no particular time limit for the use of testosterone. Testosterone can be used as long as a woman is on ERT and should be stopped when ERT is stopped. It is not usually used alone without oestrogen and this would be on specialist recommendation only.

5. Investigations & monitoring

- The “HRT Monitoring” blood test set (FSH E2 TT SHBG) is recommended at each stage to assess the balance between the hormones.
- Baseline blood tests to be taken before starting testosterone replacement therapy should include Total testosterone, SHBG and FAI.
- Assessment of blood pressure and BMI (primary care data can be used)
- Assess clinical response and repeat blood test at 3-4 months of treatment
- Assess clinical response and repeat blood test annually to check absorption, compliance and continued appropriateness of treatment.

The BMS recommend that the gold standard would be to measure free testosterone. Free testosterone assays vary between each laboratory and are unreliable in the low female range. The calculation can be performed to work out the Free androgen index (TT x SHBG/100 = FAI %) which can be useful in

practice. Blood test monitoring can be useful for determining appropriateness of testosterone initiation, response to treatment and maintaining levels in normal range and thus reducing risk of hormonal side effects. It is useful and is recommended in the global consensus statement[3], although clinical response is of paramount importance.

Women with a SHBG level above 160nmol/l are unlikely to benefit from testosterone therapy.[4] A low FAI < 2.0% in women with symptoms of low sexual desire, supports the use of testosterone supplementation. Repeat estimation at the 3 month follow up visit should be performed to demonstrate if there has been an increase in levels. It is also useful to demonstrate that values are being maintained within the female physiological range, typically < 3-6% (4-9% for RUH lab), thus making androgenic side effects less likely.[2,5,6]

6. Guide to blood test results

The amount of each hormone needed is very dependent on age and circumstance. Younger women and specific groups of women may need higher doses of HRT. Physiological testosterone serum levels decrease with increasing age in both men and women. This is a rough guide for women in their 50s. The most important factor in dose titration is clinical response, as long as the Free Testosterone / FAI levels remain within these normal physiological levels.

Table 3 Guide to blood test results

Before treatment	**Monitoring at 3-4 months**	**Annual monitoring**
Baseline blood test	Assess clinical response	Assess clinical response
Check BP and BMI	HRT monitoring blood test	HRT monitoring blood test
		As part of GP HRT review

	Low	**Medium**	**High***
Total testosterone nmol/l	<1	1-2	>2 (>2.7nmol/l for RUH lab)
SHBG nmol/l	0-40	40-120	>120[ŧ]
Free androgen index %	<2.9	3-5.9	>6 (9% for RUH lab)
Interpretation of results	Start or increase treatment	No treatment or maintain current treatment	No treatment or reduce current treatment

Take blood samples at the right timing according to the product used to avoid contamination of sample. If daily application every morning, then take blood in the middle of the day. If less frequent dosing, try and take blood midway between doses.

If TT is > 2.0 (2.7 for RUH lab) OR FAI is >6%,

1. Discuss with patient how they are using gel. Could there be contamination of blood sample?
2. Discuss with patient how they are feeling, symptoms / side effects?
3. Consider decrease dose of testosterone gel to next dosing point
4. Re-test blood after 3 months

If TT is < 1.0 or FAI is <2%

1. Discuss with patient how they are using the gel
2. Discuss with patient how they are feeling – symptoms / side effects?
3. Consider increase dose of testosterone to next dosing point
4. Re-test blood after 3 months

If concern about results or very abnormal

1. Consider dose adjustment as per section 3, tables 1-3 above
2. Consider contacting Specialist via cianapsis to discuss the results

7. Cautions and contra-indications (see individual SPCs for further information):

Cautions

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. In such case, treatment must be stopped immediately.
Caution in renal impairment, nephrotic syndrome,
Caution hepatic impairment.
Testosterone may potentiate sleep apnoea in some patients, especially those with risk factors such as obesity or chronic lung disease.
Caution with skeletal metastases due to the risk of hypercalcaemia / hypercalcuria developing from androgen therapy.
Epilepsy and migraine (conditions may be aggravated)
Thrombophilia; some reports of thrombotic events
Testosterone may cause a rise in blood pressure
History of liver tumour - only use cautiously with specialist involvement
Limited experience of the use of testosterone in patients over 65 years of age. Currently, there is no consensus about age specific testosterone reference values.
Competitive athletes
Women with upper normal or high baseline total and FAI

Contraindications[4]

Pregnancy and breastfeeding
In cases of known or suspected hormone sensitive cancers e.g. breast carcinoma, androgen-dependent neoplasia, except with specialist advice. Off label exceptions to this may be agreed in fully informed women with intractable symptoms not responding to alternatives.
Known hypersensitivity to the active substance or any of the excipients.

8. Pregnancy & breastfeeding[4]

It is the responsibility of all clinicians to provide advice on the need for contraception to patients upon initiation and at each review.
Topical testosterone is contra-indicated for pregnant or breastfeeding women. No studies on women have been carried out. Pregnant women should avoid all contact with skin treated with testosterone.
Testosterone can give rise to adverse, virilising effects on the fetus. In the event of contact with treated skin, the area should be washed with soap and water as soon as possible.

9. Drug interactions

For a comprehensive list, consult the BNF or Summary of Product Characteristics (SPC)

Oral anticoagulants	Increased monitoring of international normalised ratio (INR) recommended particularly when started or stopped.
Corticosteroids	Increased risk of developing oedema. Co-administer with caution.
Insulin	Improved insulin sensitivity may occur in patients treated with androgens who achieve normal testosterone plasma concentrations following replacement

10. Adverse effects

Adverse Effect	Action to be taken if detected
Most common (10%) are skin reactions. See SPC for the full list of side effects[7]. Symptoms of androgen excess, such as hirsutism and acne, weight gain, are common with testosterone therapy, usually mild, dose dependent and reversible.	If severe, contact specialist for further advice.

11. Advice to patients and carers

Ensure that the patient understands that there are no licensed products available in the UK for this indication and that prescribing is off-label. Clearly document this discussion.

Close skin contact with the area of application within an hour of application, by a partner or children should be avoided. This may result in the partner or child absorbing some testosterone through the skin contact. Cover the application area with clothing once applied.

Testosterone for women. Women's Health Concern. Feb 2022 https://www.womens-health-concern.org/help-and-advice/factsheets/testosterone-for-women/

Report any of the following side-effects:

- Irritability/nervousness/weight gain
- Nausea/vomiting, changes in skin colour or ankle swelling
- Breathing disturbances, including those associated with sleep
- Severe skin application site reaction

12. Specialist contact information

Consultant contact details		
RUH consultants	E-mail	ruh-tr.Gynaecology@nhs.net or Cinapsis
SFT consultants		Cinapsis e-opinion
GWH consultants	E-mail	gwh.obstetricsandgynaecologyadvice@nhs.net or cinapsis if available

13. References & useful information

1.) NICE Menopause Guidance and Management NG23 (2015) Altered sexual function. https://www.nice.org.uk/guidance/ng23/resources/menopause-diagnosis-and-management-pdf-1837330217413
2.) The British Menopause Society Tool for Clinicians; Testosterone replacement in menopause Feb 2019 https://thebms.org.uk/wp-content/uploads/2019/03/08-BMS-ToolforClinician-Testosterone-replacement-in-menopause-02D.pdf
3.) Global consensus position statement on the use of testosterone therapy for women. Davis S R et al. J Clin Endocrinol Metab 104: 4660–4666, 2019
4.) Androfeme Summary of product characteristics ANDROFEME 1 Product Information (myhealthbox.eu) (Accessed 10/05/2022. Last Revised 23/211/2020)
5.) Testosterone therapy for menopausal women. Drug Ther Bull. 2017 May;55(5):57–60. Available at http://www.dtb.bmj.com
6.) British Society for Sexual Medicine. Guidelines on the management of sexual problems in women: the role of androgens (2010). Available from: https://www.bashhguidelines.org/media/1096/3117.pdf
7.) Summary of Product Characteristics for Tostran 2%, Testogel 40.5mg/g gels via https://www.medicines.org.uk/emc

To be read in conjunction with the following documents:

BSWPartnership: Guidance for prescribers when patients access both NHS and private services. Adopted for BSW April 2022. Accessed via: https://bswpartnership.nhs.uk/medicines/wp-content/uploads/sites/3/2022/02/Private-Treatments-BSW-guidance-.pdf

Written by (Author Name, Organisation & Role):	Dr Rachel Hobson, Lead Clinical Effectiveness Pharmacist, NHS BSW CCG Ms A P Hawkins, O+G Consultant and BMS Menopause Specialist SFT Miss J Fiquet, O+G Consultant, RUH BATH
Contributors:	RUH/GWH/SFT obs/gynae teams
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Specialist assessment and recommends treatment. Informed consent required for off-label use.

Do not consider testosterone replacement for androgen deficiency, cognitive dysfunction, bone health, well-being or cardiovascular/metabolic benefits.

Contra-indications to Testosterone replacement:

- In cases of known or suspected breast carcinoma, known or suspected androgen-dependent neoplasia, nephrotic syndrome, history of thromboembolism or hypercalcaemia
- In cases of known hypersensitivity to the active substance or any of the excipients.
- Pregnancy & breastfeeding
- High total testosterone >2nmol/l OR High FAI >6%* (>9% for RUH lab)

Measure baseline

BP

BMI

Blood test: TT SHBG FAI

Testosterone therapy for postmenopausal women, in doses that approximate physiological testosterone concentrations for pre-menopausal women, is not associated with serious adverse events (Level I, Grade A).

Caution

Cardiac/hepatic/renal insufficiency; Migraine; Epilepsy; Diabetes Mellitus; IHD; Polycythaemia; Elderly; HTN; Competitive athletes; may potentiate sleep apnoea in some patients, especially those with risk factors such as obesity or chronic lung disease.

Review at 3 - 4 months

TT SHBG FAI (reduce dose if FAI>6%*)(9% for RUH lab)
Stop if no clinical response
If good response and FAI 2-6%* (9% for RUH lab) continue
Agree monitoring schedule, target FAI, and how to obtain advice/support
Monitor for signs & symptoms of androgen excess (hirsutism, acne, alopecia, voice deepening)

Review annually thereafter (GP)

Topical testosterone should be stopped when ERT is stopped or if the specialist advises for it to stop.