BSW APC: BaNES, Swindon & Wiltshire (BSW) CCG, Avon & Wiltshire Mental Health Partnership NHS Trust (AWP), Royal United Hospitals Bath NHS Foundation Trust, Great Western Hospitals NHS Foundation Trust, Salisbury NHS Foundation Trust, Virgin Care, Swindon Community Health Services, Wiltshire Health & Care

SHARED CARE AGREEMENT

OFF-LABEL Topical Testosterone for low libido in menopause in adult women on HRT

Amber TLS – 3 Months

Principles of Shared Care

Shared care agreements provide a framework for the seamless transfer of care from a hospital or specialist service setting to general practice, where this is appropriate and, in the patient's, best interest. When a specialist considers a patient's condition to be stable or predictable, they may seek the agreement of the GP (or other primary care prescriber) concerned and the patient to share their care.

Patients and/or carers must be centrally involved in any decision-making process. They should be supported by good quality information that helps them to both come to an informed decision about engagement in a shared care arrangement and sets out the practical arrangements for ongoing supplies of medicines.

The existence of a shared care agreement does not necessarily mean that the GP has to agree to and accept clinical and legal responsibility for prescribing; they should only do so if they feel clinically confident in managing that condition. Clinical responsibility for prescribing is held by the person signing the prescription, who must also ensure adequate monitoring.

Responsibilities of Secondary Care Specialist

- Confirm diagnosis and indication for topical testosterone in-line with this shared care agreement.
- Initiate treatment and prescribe for the length of time agreed (3 months) – this should be a sufficient amount of time to allow optimisation of treatment and demonstrate that the patient's response is consistent. The GP will take over prescribing at this stage as long as the dose and free androgen index (FAI) are stable.
- Discuss the benefits and side effects of treatment with the patient, including time to response, potential side-effects, the need for blood tests and that it is an off-label use of testosterone. Informed consent should be obtained and documented.
- Review concurrent medications for potential interactions prior to initiation.
- Undertake the clinical assessment and relevant monitoring at baseline and during the initiation period.
- Communicate details of treatment to GP (in writing or via secure email) within the first month of treatment and ask the GP whether he or she is willing to participate in shared care once the patient is stable.
- Discuss shared care arrangements with the patient/carer, obtain their consent and explain their responsibilities.
- Review the patient's condition and monitor response to treatment regularly where indicated.
- Inform the GP after each clinic attendance if there is any change to treatment or monitoring.
- Inform GP if patient does not attend scheduled clinic appointments.
- Ensure that clear arrangements exist for GPs to obtain advice and support.
- Report adverse events to the MHRA via the yellow card scheme.
- Stop treatment where appropriate or provide GP with advice on when to stop.
- Review patient within 12 weeks after initiation of treatment and then annually in clinic to review disease activity and adverse effects of treatment and to adjust the dose if necessary.

Responsibilities of GP/Primary Care Prescriber

- Reply to the request as soon as practicable if they are **unable** to support shared care (in writing or via secure email).
- Prescribe medicine at the dose recommended after the initiation as long as the dose and free androgen index (FAI) are stable.
- Undertake ongoing clinical assessment and relevant monitoring following initiation period.
- Review any new concurrent medications for potential interactions.
- Notification of specialist of any changes in the patient's condition, any adverse drug reactions, or if the patient fails to attend for blood monitoring.
- Report to and seek advice from the specialist on any aspect of patient care that is of concern and may affect treatment.
- Report adverse events to the specialist and MHRA via the yellow card scheme.
- Stop treatment on the advice of the specialist.

Responsibilities of Patient/Carer

- Report to the specialist or GP if he or she does not have a clear understanding of the treatment.
- Share any concerns in relation to treatment with medicine.
- Report any adverse effects to the specialist or GP whilst taking the medicine.
- Attend appointments for blood tests, clinical review and monitoring.

1. Summary of condition and treatment aims Include links to relevant clinical guidelines e.g. NICE	**Background** In postmenopausal women who are distressed by low libido and where there is no other identifiable cause (e.g. physical and psychosocial factors and medications), and where estrogen replacement therapy (ERT) alone has not been effective, testosterone therapy can be considered. **There is currently no licensed treatment available in the UK for women** who experience lack of libido associated with the menopause following the withdrawal of testosterone implants and patches from the market. Standard ERT including tibolone should always be considered and when this fails to resolve symptoms, testosterone replacement has historically been used as an alternative option. NICE have published Menopause Guidance and Management NG23 (2015) 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. **Use of testosterone treatment in women:** • Testosterone replacement in menopausal women is used where ERT alone has not been effective. **Testosterone should not be given in isolation; women should be oestrogenised first (i.e. on ERT) with testosterone added in if if symptoms of declining testosterone (low libido, lack of energy, low desire, poor sexual satisfaction and anorgasmia) are still experienced.**
2. Details of medicine and indication Please state whether licensed or unlicensed (off-label) use. Note that shared care is generally unsuitable for off-label prescribing unless it is a widely recognised use (e.g. included in BNF)	**Efficacy & safety: evidence review** NICE NG23 Menopause: diagnosis and management (Nov 2015) full guidance p97: 8.2.5.2.4 Comparison of testosterone verses no treatment/placebo Frequency of sexual intercourse: One RCT (n=562) found a significant increase in frequency of sexual activities at 24-week follow-up in menopausal women who received testosterone compared with those who did not receive testosterone. The quality of the evidence for this outcome was low. Moderate quality evidence from 1 RCT (n=519) found a significant increase in the frequency of satisfying sexual activity at 4-week follow-up in menopausal women who received testosterone compared with those who did not receive testosterone. Both studies reporting results for the outcome of frequency of sexual intercourse included the majority of women with surgical menopause. p107 conclusion: In relation to the other short-term outcomes, 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.

	A recent systematic review and meta-analysis of safety and efficacy of testosterone use in women[3] found that 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. The effects of testosterone on individual wellbeing and musculoskeletal and cognitive health, as well as long-term safety, warrant further investigation. Overall, testosterone treatment was associated with a small but significant increase in weight, such that patients should be advised of this effect if testosterone treatment is being considered (mean difference 0.48, 95% CI 0.16 to 0.79). Testosterone treatment administered at doses intended to approximate physiological replacement to levels seen in premenopausal women is associated with a greater likelihood of acne and hair growth, but not alopecia, voice deepening, or cliteromegaly, compared with a comparator or placebo. Therefore, women who initiate testosterone treatment must be warned that these side-effects can occur and counselled against applying more than the prescribed dose. **Risks vs benefit** A patients risk level will change as they get older, they might e.g. gain weight or develop conditions such as diabetes, so it is important to keep re-evaluating the risks vs benefits of using testosterone when the specialist reviews the patient annually. There needs to be a review of CV risk as patients get older and a more extensive review of BMI/BP and lipids. **Oral vs transdermal ERT** All oral estrogens (oral contraceptives and oral ERT) will result in an increase in sex hormone binding globulin (SHBG) which will bind testosterone and reduce bioavailability. Patients using oral estrogen should be changed to transdermal estrogen before being considered for testosterone therapy[4]. **Exclusions from this SCA:** • Use of testosterone without ERT • Use in breast cancer patients	
3. Pharmaceutical aspects	Route of administration:	Topical
	Formulation:	See below
	Administration details:	See below
	Other important information:	See below
4. Usual dose and frequency (including details of dose adjustments, e.g. in renal impairment) and duration of therapy Transfer of monitoring and prescribing to Primary care is normally after the patient is on regular dose and with satisfactory investigation results. All dose or formulation adjustments will be the responsibility of the initiating specialist unless directions have been discussed and agreed with the primary care clinician. The duration of treatment will be determined by the specialist, based on clinical response and tolerability. Termination of treatment will be the responsibility of the specialist.	**Dose range**: 3-10mg/day (rarely over 7mg/day), as advised by specialist on case by case basis and individual circumstances. Dose titrated according to FAI levels taking into account that physiological testosterone serum levels lower with increasing age. **Product choice[2,8]:** Several topical testosterone products are included on BSW formulary; **all are used outside their license (off-label) when prescribed for use in women**. Topical testosterone should be **prescribed by brand;** strength and presentation varies. **Testim® 50mg/5g gel.** One box contains 30 x tubes. Each tube holds 5g gel containing 50mg testosterone. **Testogel® 40.5mg/2.5g gel.** One box contains 30 x sachets. Each sachet holds 2.5g gel containing 40.5mg testosterone. **[NOTE NEW PRESENTATION.** Testogel® previously available in 50mg/5g gel sachets. The manufacturers expect stocks of this strength to be exhausted end May 2022 and have replaced with new 40.5mg/2.5g sachet preparation]. **Starting dose when gel is applied from Testim® tube/Testogel® sachet:** Usually 1/10th of a 5g tube or 1/5th of a 2.5g sachet each day. i.e. **each tube/sachet should last 5-10 days**. **…Continued overleaf**	

<table>
<tr><td></td><td>Tostran® 20mg/g gel in a multi-dose pump action container. Each pump delivers 0.5g gel containing 10 mg testosterone.

Starting dose when gel is applied from Tostran® pump dispenser: Usually 3 pumps over 7-14 days i.e. one pump dispenser should last 240 days.

Application technique: The gel should be applied daily 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 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].
Local specialists advise that testosterone can be used as long as a woman is on ERT and should be stopped when ERT is stopped.</td></tr>
<tr><td>5. Baseline investigations and initial monitoring to be undertaken by specialist</td><td>Baseline investigations

• Baseline blood tests to be taken before starting testosterone replacement therapy: FAI, FBC.
• Blood pressure and BMI are also measured.
The BMS advise that testosterone assays can be performed to support a diagnosis of Female Androgen Deficiency Syndrome (FADS) also referred to as Hyposexual Sexual Desire Disorder/ Female Sexual Interest and Arousal Disorder, however there can be practical problems with obtaining these. They recommend that the gold standard would be to measure free testosterone, however a calculation can be performed to work out the Free Androgen Index (FAI) which is used in practice. FAI 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. Women with a SHBG level above 160nmol/l are unlikely to benefit from testosterone therapy.[4] Although it is not mandatory to perform testosterone level estimation prior to or for monitoring treatment, it can be useful and is recommended in the global consensus statement[5]. A low FAI < 1.0% 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 should be performed to demonstrate if there has been an increase in levels, though clinical response is of paramount importance. It is also useful to demonstrate that values are being maintained within the female physiological range, typically < 5%, thus making androgenic side effects less likely.[2,6,7]

<table>
<tr><th>Monitoring</th><th>Frequency</th></tr>
<tr><td>• Free Androgen Index, FBC
• LFTs/U&Es and lipids: only if indicated by the specialist
• BP and BMI to be assessed at baseline and when required thereafter</td><td>• FAI: If above 5%, specialist to review
• Repeat FAI after 3 months and then every 12 months - should not be >5%.
• FBC to be measured annually</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><td rowspan="2">6. Ongoing monitoring requirements to be undertaken by primary care</td><td>Monitoring</td><td>Frequency</td></tr>
<tr><td>• FAI
• Full blood count (FBC)</td><td>• Annually
• If Hb greater than 18 g/dL discuss venesection with haematologist.
• FAI- annually should be <5%; If above 5% contact specialist for further advice</td></tr>
<tr><td>7. Action(s) to be taken by primary care if abnormal result(s)</td><td colspan="2">• Discuss abnormal test results with the specialist</td></tr>
<tr><td>8. Cautions and contraindications
Please note this does not replace the Summary of Product Characteristics (SPC) and should be read in conjunction with it.</td><td colspan="2">Cautions
• 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. In such case, treatment must be stopped immediately.
• Caution in renal and 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 post-marketing studies and reports of thrombotic events
• History of hormone sensitive breast cancer – off label exceptions to this may be agreed in fully informed women with intractable symptoms not responding to alternatives
• Competitive athletes – care must be taken to maintain levels well within the female physiological range
• Women with upper level or high baseline testosterone levels / FAI.
• Risk of testosterone transfer
• Testosterone may cause a rise in blood pressure
• History of liver tumours- only use cautiously with specialist involvement
• There is 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.
Contraindications[4]
• 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</td></tr>
<tr><td>9. Significant medicine and food interactions and management
For a comprehensive list, consult the BNF or Summary of Product Characteristics (SPC)</td><td colspan="2"><table><tr><td>Oral anticoagulants</td><td>Increased monitoring of international normalised ratio (INR) recommended particularly when started or stopped.</td></tr><tr><td>Corticosteroids</td><td>Increased risk of developing oedema. Co-administer with caution.</td></tr><tr><td>Insulin</td><td>Improved insulin sensitivity may occur in patients treated with androgens who achieve normal testosterone plasma concentrations following replacement therapy.</td></tr></table></td></tr>
<tr><td></td><td>Adverse Effect</td><td>Action to be taken if detected</td></tr>
</table>

10. Adverse effects and management Include details of incidence, identification, importance and management.	• Most common (10%) were skin reactions. See SPC for the full list of side effects[8]. • Symptoms of androgen excess, such as hirsutism and acne, weight gain, are common with testosterone therapy, although these effects are often mild.	• If severe, contact specialist for further advice.

11. Advice to patients and carers
The specialist will counsel the patient with regard to the benefits and risks of treatment and will provide the patient with any relevant information and advice, including patient information leaflets on individual medicines.
	• Ensure that the patient understands that there are no licensed products available in the UK for this indication and so prescribing is off-label.
	• Testosterone for women. Womens 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. Pregnancy and breast feeding It is the responsibility of the specialist to provide advice on the need for contraception to male and female patients on initiation and at each review but the ongoing responsibility for providing this advice rests with both the GP and the specialist.	• 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 foetus. In the event of contact with treated skin, the area should be washed with soap and water as soon as possible.	
13. Specialist contact information		
GWH (Mon-Fri)	gwh.obstetricsandgynaecologyadvice@nhs.net	
RUH	ruh-tr.Gynaecology@nhs.net	Preferably use consultant on call phone number
SFT	sft.gynaecology@nhs.net	Mark for attention of Annie Hawkins
14. Additional information For example, process for when Specialist or GP changes roles; specific issues related to patient age/ capacity/ specific monitoring.	• Available data do not support use of testosterone in **pre**menopausal women, and testosterone should not be used to treat depression or bone loss or to prevent cognitive decline.	
15. References	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.) RM Islam, RJ Bell, S Green, M Page, S Davis. Safety and efficacy of testosterone for women: a systemic review and meta-analysis of randomised controlled trial data. Lancet Diabetes Endocrinol Jul 25 2019. https://www.thelancet.com/journals/landia/article/PIIS2213-8587(19)30189-5/fulltext 4.) Androfemme Summary of product characteristics ANDROFEME 1 Product Information (myhealthbox.eu) (Accessed 10/05/2022. Last Revised 23/211/2020) 5.) 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 6.) Testosterone therapy for menopausal women. Drug Ther Bull. 2017 May;55(5):57–60. Available at http://www.dtb.bmj.com	

	7.) 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 8.) Summary of Product Characteristics for (Tostran 2% ; Testim 50mg/5g; Testogel 40.5mg/g gels) via https://www.medicines.org.uk/emc
9.) To be read in conjunction with the following documents	• NHS England: Responsibility for Prescribing Between Primary & Secondary/ Tertiary Care. Ref 07573, Version 1.0, Published January 2018. Accessed via: https://www.england.nhs.uk/publication/responsibility-for-prescribing-between-primary-and-secondary-tertiary-care/ • 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

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BSW APC: BaNES, Swindon & Wiltshire (BSW) CCG, Avon & Wiltshire Mental Health Partnership NHS Trust (AWP), Royal United Hospitals Bath NHS Foundation Trust, Great Western Hospitals NHS Foundation Trust, Salisbury NHS Foundation Trust, Virgin Care, Swindon Community Health Services, Wiltshire Health & Care

BSW Pathway for the use of testosterone in women for Hypoactive sexual desire /dysfunction

Specialist diagnoses Hypoactive sexual desire/dysfunction clinically in post-menopausal women ONLY (testosterone levels do not correlate with symptoms). *Definition: Deficient or absent sexual fantasies and desire for sexual activity causing marked distress or interpersonal difficulty or reduced sexual arousal from external sexual or erotic cues.*

1

Take informed consent – off label use

2

Measure baseline:

- FAI (Testosterone and SHBG, FAI <1% supports testosterone use; do not prescribe if >5%)
- FBC (U&E, LFT and full lipid profile depending on individual patients risks)
- BP
- BMI

3

Review at approximately 3 months:

- FAI (stop or reduce dose if FAI>5%)
- Stop if no clinical response
- If good response and FAI 1-5% **Ask GP to take over shared prescribing**
- Send GP shared care agreement with monitoring schedule, target FAI, and how to obtain advice/support

4

Review annually thereafter:

- Stop if no clinical response
- FAI (stop or reduce dose if FAI>5%)
- FBC (stop if HCT >53% and re-challenge at lower dose when HCT normalised)
- Other tests as per individual patient circumstances/risks.

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 FAI >5%

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.

GP

GP on-going review: (*GP to order blood tests 2 weeks before specialist annual review appointment)*

- Monitor for signs and symptoms of androgen excess (hirsutism, acne, alopecia, voice deepening)
- FAI (stop or reduce dose if FAI>5%)
- FBC (stop if HCT >53% and re-challenge at lower dose when HCT normalised)
- *U&E LFT Full lipid profile- only if required as per specialist advice*
- *BP & BMI- only if required as per specialist advice*

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

Exclusions from shared care: Use of Testosterone without HRT; Use in breast cancer patients