East Surrey CCG, Guildford & Waverley CCG, North West Surrey CCG, Surrey Downs CCG, Surrey Heath CCG, Crawley CCG, Horsham & Mid-Sussex CCG

Evidence review for Prescribing Clinical Network

Medicine and proposed indication	Unlicensed indication of testosterone gel for low libido in post-menopausal women
Requested by	Surrey Heath CCG

SUMMARY

Clinical Effectiveness

Current NICE guidance for the diagnosis and management of menopause[1], published in November 2015, recommends the use of off-label testosterone as supplementation for menopausal women with low sexual desire if HRT alone is not effective. This recommendation is based on limited evidence which is described further in the evidence review section. Given that the use of testosterone for this indication is off-label, prescribing information on CKS[2] (Clinical Knowledge Summaries) makes the following recommendation:

- The Guideline Development Group (GDG) advised that the prescriber should follow relevant professional guidance, taking full responsibility for the decision to prescribe testosterone and that consent should be obtained and documented. CKS advises that specialist advice should be sought before prescribing testosterone for this indication in primary care.

From the guidance available from various agencies, including the Royal College of Obstetrics and Gynaecologists and the Faculty of Sexual and Reproductive Healthcare of the Royal College of Obstetricians and Gynaecologists, no concrete dosing/monitoring recommendations were located. Thereby, given the specialist nature of this product, its use being off-label and the current recommendations according to CKS, it would be appropriate to refer any patients that the GP feels are suitable for testosterone therapy to a specialist or to consult a specialist for prescribing advice at the very least.

Safety

The combined therapy use of testosterone and HRT is associated with a higher incidence of hair growth, acne and a reduction in HDL cholesterol. 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[3]. Also there are no long term safety data evaluating the risk of breast cancer, stroke, and coronary heart disease and the ideal duration of treatment is still unclear.

Masculinizing effects[4] **-** The potential masculinizing effects of androgen therapy include acne, hirsutism, deepening of the voice, androgenic alopecia and clitoral hypertrophy. These effects are dose related and are uncommon in the relatively short-term trials to date if supraphysiological hormone levels are avoided.

Breast cancer - a prospective case control study found there was an association between testosterone therapy and breast cancer risk, although oestradiol levels were not taken into account in the analysis. Other recent studies have not shown a significant association between breast cancer risk and testosterone. No RCTs have been adequately powered to detect an increase in breast cancer risk[5.6]. The relationship between testosterone and breast cancer remains unclear[5].

Endometrial cancer - A paper has confirmed that when adjusted for oestradiol and oestrone levels there is not an association between free testosterone and endometrial cancer. Transdermal testosterone is associated with endometrial atrophy[5.6].

Cardiovascular risk - There are conflicting reports for the association of testosterone therapy and cardiovascular risks. There seems to be an optimal range of serum testosterone in postmenopausal women for cardiovascular safety; a study in 639 postmenopausal women measured serum testosterone at baseline and followed cardiovascular events for an average duration of 12.3 years. In age-adjusted analyses, the lowest quintile of serum testosterone was associated with a 1.62-fold increased risk of cardiovascular events (95% CI 1.10 to 2.39) compared with higher levels. Bioavailable testosterone showed a U-shaped association with events, as the age-adjusted relative risks for the lowest and highest quintiles of bioavailable testosterone were 1.79 (95% CI 1.03 to 3.16) and 1.96 (95% CI 1.13 to 3.41), respectively. The FDA has recently updated its cautions relating to the use of testosterone products for low testosterone due to aging; and requires a

labelling change to inform of possible increased risk of heart attack and stroke with use. It needs to be noted that this advice relates to use in men. However, two large studies, the results of which have yet to be fully published, state that the difference in the cardiovascular event rate was not statistically significant between those treated with topical testosterone and those who were not. Again these studies are only in men and are not fully published and have not caused a review of the recent FDA alert[5.6].

Patient factors

There have been increasing requests from patients for this treatment. Patients must be counselled and informed consent obtained as it is an unlicensed indication and there is lack of long term safety data. It may be difficult for the patient to accurately measure the small doses required, with a potential risk of administering higher doses than that needed which could lead to adverse effects.

Need to ascertain if specialists would be happy to receive referrals for this. From a GP perspective we would need to understand if they would consider prescribing on the recommendation of a specialist and what information would be required. From a commissioner's perspective, would introducing a pathway recommending referrals to a specialist be considered as a priority?

Cost implications

The cost of testosterone gel is relatively inexpensive as a tube is expected to last 10 days. Approximate annual costs would be £39.

Additional costs include referrals to specialists and monitoring requirements

Relevant guidance / reviews

NICE - Menopause: diagnosis and management (2015) (NG23)[1] states the following:

For altered sexual function -

Consider testosterone supplementation for menopausal women with low sexual desire if HRT alone is not effective. (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. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information).

The menopause CKS[2] states the following:

Sexual disorders

- Limited evidence showed that testosterone may increase the frequency of sexual episodes for women in surgical menopause when compared with placebo. Given the limited evidence and the fact the testosterone does not currently have a marketing authorization for this indication in women, the GDG emphasized that it should only be offered as an option for improving low sexual desire when hormone replacement therapy (HRT) is not effective.
- CKS has extrapolated this recommendation to include women who are unable or unwilling to take HRT.
- The GDG advised that the prescriber should follow relevant professional guidance, taking full responsibility for the decision to prescribe testosterone and that consent should be obtained and documented. CKS advises that specialist advice should be sought before prescribing testosterone for this indication in primary care.

The following guidance is for the use of testosterone patch (Intrinsa®), which has now been withdrawn, for the treatment of female hypoactive sexual desire disorder:

MTRAC (October 2007)[7]**:** The testosterone patch is not considered suitable for prescribing. Current clinical evidence for efficacy is weak, based on short-term (24-week) trials using subjective outcomes. The size of benefit found was small, with questionable clinical relevance and a large placebo effect. There is concern about

potential harmful effects of long-term use on breast tissue and the cardiovascular system (and endometrium if used outside the product license).

Scottish Medicines Consortium (August 2007)[8]**:** Not recommended for use within NHS Scotland for the treatment of hypoactive sexual desire disorder (HSDD) in bilaterally oophorectomised and hysterectomised (surgically induced menopause) women receiving concomitant oestrogen therapy. The manufacturer did not present a sufficiently robust economic analysis to gain acceptance by SMC.

The Endocrine Society Clinical Practice Guideline recommends that there is evidence which supports the short-term efficacy and safety of high physiological doses of testosterone treatment for postmenopausal women with sexual dysfunction due to hypoactive sexual desire disorder. It recommends for those women with HSDD, a 3 to 6 months trial of testosterone, for those who are properly diagnosed and in whom therapy is not contraindicated[4].

Likely place in therapy relative to current treatments

For use in postmenopausal women who are distressed by low libido and who have no other identifiable cause (e.g. physical and psychosocial factors and medications), may be candidates for testosterone therapy if HRT alone is not effective. However, women with a SHBG (Sex Hormone Binding Globulin) level above 160nmol/l are unlikely to benefit from testosterone therapy.

Recommendation to PCN

If evidence of efficacy and safety is deemed sufficient, it is recommended that testosterone gel should be considered as blue on the traffic light system for the treatment of low libido in post-menopausal women when hormone replacement therapy (HRT) is not effective, or women who are unable or unwilling to take HRT.

To be initiated by a specialist or GP with a special interest in this area.

The prescriber should follow relevant professional guidance in relation to unlicensed indications, taking full responsibility for the decision to prescribe testosterone and ensuring that consent is obtained and documented.

Medicine details	
Name and brand name	Testim 50mg/5g gel and Testogel 50mg/5g gel
Licensed indication, formulation and usual dosage	Licensed indications is hypogonadism due to testosterone deficiency in men Intrinsa patch 300mcg/24 hours (now withdrawn for commercial reasons) was designed to release 300mcg of testosterone per day. Recommended doses are 1 pack over 7 – 10 days[9,10] Testogel – percutaneous absorption ranges from approx. 9-14% of the applied dose for use in men (based on 1/10th of pack daily 450mcg – 700mcg in 24 hours).
Summary of mechanism of action, and relevant pharmacokinetics	The role of androgens in maintaining well-being in women is not fully understood. Between a women's mid 30's and early 60's, adrenal androgen production reduces by about 2/3rds. After a natural menopause, ovarian production continues to a varying degree. After bilateral oophorectomy, ovarian production of androgens and precursor sex hormones is lost[11]. In the peripheral blood, 66% of testosterone has high affinity binding to SHBG, 30% is loosely bound to albumin, and only 2% to 3% is free testosterone. The combined albumin-bound and free portion of testosterone is called bioavailable testosterone and is thought to be the fraction that is able to enter target cells and exert its

	biological activity through binding to intracellular androgen receptors. The SHBG bound fraction is not easily available to the tissues. There is good correlation between free testosterone and bioavailable testosterone, except in acute illness, pregnancy, and chronic illness, such as cirrhosis of the liver. No level of serum testosterone is considered diagnostic for HSDD[12].
Important drug interactions	Antidiabetics - testosterone possibly enhances hypoglycaemic effect of antidiabetics Coumarins - testosterone enhances anticoagulant effect of coumarins Phenindione - testosterone enhances anticoagulant effect of phenindione
Monitoring requirements	An MI query[13] looked at the guidance available from various agencies, including the Royal College of Obstetrics and Gynaecologists and the Faculty of Sexual and Reproductive Healthcare of the Royal College of Obstetricians and Gynaecologists and no concrete dosing/monitoring recommendations was located. It is recommended that any woman receiving testosterone therapy be monitored for signs and symptoms of androgen excess. The Endocrine Society Clinical Practice Guideline recommends, for those women with HSDD, a 3 to 6 months trial of testosterone, for those who are properly diagnosed and in whom therapy is not contraindicated. Baseline testosterone levels should be measured after 3 to 6 weeks. If there is no response after 6 months of therapy, treatment should be discontinued. If therapy is continued testosterone levels should be measured every 6 months to monitor excessive use and signs of androgen excess. There is no safety and efficacy data for testosterone therapy after 24 months. It is important to note that these recommendations are derived from evidence from transdermal testosterone patches[4]. The aim is to have a serum testosterone level no higher than in young women (2.8 nml/L) in order to avoid androgenic side effects[14]. A total testosterone level in not very informative as testosterone is significantly protein bound. Measure the sex hormone binding globulin (SHBG) and calculate a Free Androgen Index: Testosterone/SHBG x 100. No level of serum testosterone is considered diagnostic for HSDD[12]. Women with a SHBG level above 160nmol are unlikely to benefit from testosterone therapy. Although there is no consistent correlation between sexual functioning and levels of androgen across a wide age group, in some women testosterone therapy can improve sexual desire. In any one women, changes in androgens may or may not be relevant to sexual functioning. Monitoring should include subjective assessments of sexual response, desire and satisfaction as well as evaluation for potential adverse effects. It is good practice to measure fasting lipid and glucose levels after 6 months of therapy, if clinically indicated (e.g. by diabetes or hyperlipidaemia). If these are abnormal, a decision should be made regarding to how to improve them. If lifestyle changes or lipid lowering drugs are inadequate, it may be prudent to consider stopping testosterone therapy[11]. As long-term safety data is lacking, the International Consultation on Sexual Medicine did not support long-term therapy. They recommended annual health monitoring, with breast and pelvic examinations and mammograms[12].
Prescribing considerations	Blue – specialist or GP specialist initiated
Other	Appropriate identification of patients is required as risk factors for female sexual

considerations	dysfunction may be non-hormonal or hormonal (oestrogen and androgen deficiency). Non-hormonal factors could include conflict between partners, insomnia, inadequate stimulation, life stress and depression. Concomitant medical disease e.g. hypothyroidism or diabetes, medications and sexual problems in the women's partner could contribute. Need to ascertain if local specialists would support the use of testosterone for this indication. If they do see a use, information on the range of doses that they would consider appropriate, how they would measure successful outcomes and what monitoring would be required.

Potential patient group (if appropriate to include)	
Brief description of disease	Between a women's mid 30's and early 60's, adrenal androgen production reduces by about 2/3rds. After a natural menopause, ovarian production continues to a varying degree. After bilateral oophorectomy, ovarian production of androgens and precursor sex hormones is lost. Natural and surgical menopause and endocrine disorders that alter oestrogen and androgen precursors may affect female sexual function. However, hormones are only one component of the many factors that contribute to normal sexual function in women. The common sexual disorders in women are categorised as: - Sexual desire disorders – hypoactive sexual desire disorder (HSDD) and sexual aversion disorder (SAD) - Sexual arousal disorders - Orgasmic disorder - Sexual pain disorders Risk factors for female sexual dysfunction may be non-hormonal or hormonal. No level of a single androgen is predictive of low sexual function in women and there appears to be no important role for androgens in various aspects of sexual functioning. However, postmenopausal oestrogen deficiency does cause atrophic changes and the vaginal mucosa becomes thinner, the vulva and the vaginal walls become pale and thin and lose their elasticity. Vaginal secretions also decrease, leading to reduced lubrication[11].
Potential patient numbers per 100,000	Generally the prevalence of 'low sexual desire' is around 30%. The age-stratified prevalence of any distressing sexual problem is highest in women aged 45-64 years (15%); lowest in women 65 years or older (9%), and intermediate in women aged 18-44 (11%). The prevalence of true HSDD in women is around 10%; the prevalence of arousal and orgasmic disorders is approx. 5% each. Less than 30% of female patients with sexual problems discuss treatments with their GP and only a third of these are likely to accept medications. Fewer than 10% of patients are asked about their sexual health during a routine visit to their doctor[11].
Outcomes required	Subjective assessments of sexual response, desire and satisfaction as well as evaluation for potential adverse effects[11].

Summary of current treatment pathway

There are no local treatment guidelines of using this currently.

NICE guidelines 23: Menopause: diagnosis and management (2015)[1], states the following:

For Altered sexual function: Consider testosterone supplementation for menopausal women with low sexual desire if HRT alone is not effective.

Evidence review

Guidance, dosing and monitoring

Current NICE guidance for the diagnosis and management of menopause, published in November 2015[1], recommends the use of off-label testosterone as supplementation for menopausal women with low sexual desire if HRT alone is not effective. This recommendation is based on limited evidence which is described in further detail below:

Evidence base for testosterone gel (taken from previous evidence review which was completed 2013, literature search updated – no further evidence identified (15)

There is a fairly large body of evidence for the use of testosterone for postmenopausal women to treat low libido with most research focussing on transdermal testosterone patches (designed to deliver a smaller dose of testosterone and licensed for the treatment of hypoactive sexual desire disorder in women with surgically induced menopause receiving concomitant oestrogen therapy – however the marketing authorisation for this product (Intrinsa) was cancelled, subsequently this is now unlicensed).

As requested, the evidence base presented here is focused on the use of testosterone gel for this indication. Testosterone gel is not licensed for the requested indication but a small cross-over study suggests an improvement in sexual function in women receiving HRT. Furthermore, a Cochrane review reported that adding testosterone (all formulations) to HRT has a beneficial effect on sexual function in post-menopausal women but the study was limited by methodological issues.

RCT of Testogel for low libido in postmenopausal women receiving HRT (16)

Only one study was identified which specifically evaluated the effect of testosterone on sexual life in postmenopausal women receiving HRT and presenting with low libido. This was a cross-over study which randomised 53 women to 10mg of a 1% testosterone gel (Testogel) once daily (n=27) or a matching placebo (n=26) for three months, after which they swapped therapy to the alternative gel for three months. A modified Swedish version of the McCoy questionnaire was used to assess sexual life. Quality of life was evaluated with the 'Psychological general well-being - questionnaire' (PGWB).

Women were healthy with no concomitant treatment (except HRT), had a preserved uterus and ovaries and were using combined HRT - either cyclic or continuous HRT. The mean age was 55 years, mean weight was 65.4 kg and the mean BMI was 23.6.The following results were reported after six months:

- The scores in the sex questionnaire concerning "frequency of sexual activity, orgasm, and intercourse", "sexual arousal, fantasy, 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 ($P<0.001$ for all scores).
- The total PGWB score as well as the subscales depicting 'anxiety' and 'positive well-being' demonstrated statistically significant improvements both before and after crossover for the testosterone arm compared with placebo. For the subscales concerning 'depressed mood' and 'general health' no differences between the two treatments were found.
- There were no significant differences between the two treatments in the number of experienced adverse events such as headache, weight gain, increased appetite, acne, or facial hair.
- There were no significant differences between the groups for liver enzymes, total cholesterol, triglycerides and HDL and LDL.
- Endometrial thickness did not change significantly during treatment and haemoglobin and erythropoietin remained unchanged.

The authors concluded that testosterone gel had positive effects on several aspects of sexual life such as frequency of sexual activity, orgasm, arousal, fantasies and sexual interest in postmenopausal women on HRT. They noted that the 10mg dose resulted in too high serum levels, therefore a decreased dose should be considered in future studies.

Cochrane review of testosterone (all formulations) for postmenopausal women taking HRT (3)

This Cochrane review included randomised comparisons of testosterone (all formulations) plus HRT (unopposed oestrogen therapy or oestrogen therapy with combined cyclic or continuous progestin therapy) versus HRT alone in perimenopausal women or women who had either a natural or surgically-induced menopause(n= 35 trials with 4,768 participants). The main outcomes of interest were sense of wellbeing, unexplained fatigue and sexual

function and the findings are described below:

- 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.
- Testosterone was most commonly administered orally (only one study used percutaneous gel - described above)
- The major methodological limitations were attrition bias and lack of a washout period in the crossover studies.
- Meta-analysis of sexual function (nine studies eligible) suggested that the addition of testosterone to HT regimens improved sexual function scores and number of satisfying sexual episodes for postmenopausal women. The improvement, reported in terms of the standardized mean difference (SMD), was 0.29 (95% CI 0.20 to 0.38) for the number of satisfying sexual events, 0.25 (95% CI 0.17 to 0.34) for the total number of sexual events, 0.30 (95% CI 0.21 to 0.39) for the total number of orgasms, 0.35 (95% CI 0.26 to 0.43) for desire, 0.28 (95% CI 0.19 to 0.37) for orgasm, 0.36 (95% CI 0.27 to 0.45) for arousal, 0.33 (95% CI 0.22 to 0.43) for pleasure, 0.32 (95% CI 0.22 to 0.41) for sexual concerns, 0.32 (95% CI 0.23 to 0.40) for responsiveness, 0.26 (95% CI 0.16 to 0.35) for sexual self-image, and 0.41 (95% CI 0.15 to 0.67) for the composite sexual function score.
- The decrease in mean personal distress scores in the T-HT group was significantly greater than the decrease in the HT group. The difference was -8.13 (95% CI -10.59 to -5.67). One study provided data that showed that use of testosterone was associated with an improved outcome: SMD of 0.98 (95% CI 0.24 to 1.72) for satisfaction, 1.37 (95% CI 0.59 to 2.15) for fantasy, and 0.29 (95% CI 0.20 to 0.38) for frequency of desire.
- Significant adverse effects were decreased 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 0.83 to 1.19).

The authors concluded that "there is good evidence that adding testosterone to HT has a beneficial effect on sexual function in post-menopausal women. However, the combined therapy is associated with a higher incidence of hair growth and acne and a reduction in HDL cholesterol. 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."

Overall, the data for testosterone gel in post-menopausal women with low libido on HRT is limited to a short-term, single, small cross-over study which suggested some benefit in this patient population but further data are required to confirm these findings. Because of the complex nature of female sexual dysfunction, the unspecific diagnosis of hypoactive sexual desire disorder and lack of evidence based treatments available, there are no treatment guidelines to guide treatment choice, nor are there any recommendations on dosing or monitoring. Also there are no long term safety data evaluating the risk of breast cancer, stroke, and coronary heart disease and the ideal duration of treatment is still unclear. Finally, it is worth noting that physiological, age-associated decline in androgen production is not an indication for androgen replacement. In established cases of severe androgen deficiency, the use of testosterone replacement may have possible benefits on health related quality of life and sexuality (17).

Search Strategy:

In house- enquiry database – MiDatabank

Electronic Medicines Compendium

British National Formulary

National Institute for Health and Care Excellence (NICE)

Martindale

AHFS

Micromedex

UpToDate

NHS Evidence

Clinical Knowledge Summaries

Faculty of Sexual and Reproductive Healthcare of the Royal College of Obstetricians and Gynaecologists

Royal College of Obstetricians and Gynaecologists

Embase/Medline

1 EMBASE exp TESTOSTERONE/ 103748

2 EMBASE exp "LIBIDO DISORDER"/ 5572

3 EMBASE exp POSTMENOPAUSE/ 59708

4 EMBASE (1 AND 2 AND 3) 102

5 Medline exp TESTOSTERONE/ 65513

6 Medline exp LIBIDO/ 4372

7 Medline exp POSTMENOPAUSE/ 21273

8 Medline (5 AND 6 AND 7) 40

9 EMBASE (1 AND 2 AND 3) 18

10 Medline (5 AND 6 AND 7) 6

Equity / Stakeholder views (if relevant)	
Decisions of local Trusts DTCs and neighbouring APCs	Nil
Recommendations from national / regional decision making groups	There are no national recommendations. Other regional group decisions include: The menopause clinic at Northwick Park recommends 7mg of Testogel daily (= 1/7th of 50mg sachet) to HSDD patients with menopause[10]. Recommendation from Lancashire medicines management group[9]: BLACK Testosterone gel (Testim®) is not recommended for female sexual dysfunction post oophorectomy or primary ovarian failure.
Stakeholder views	Use the enclosed proforma to obtain views from clinicians Summarise who has been consulted e.g. secondary care consultants, what their views are and any declared conflict of interest Have views of patient groups been sought?
CCG priorities	Increasing request in primary care from variety of sources

Health economic considerations	
Cost per year per patient	The cost of testosterone gel is relatively inexpensive as a tube is expected to last 10 days. Approximate annual costs would be £39. Testim 30 x 5g = £32 = £39 annually Testogel 30 x 5g £31.11 = £38 annually
Alternative treatments cost per patient per year	N/A
Other financial considerations (if relevant)	Referrals and monitoring
Health economic data (if available)	N/A

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