DERBYSHIRE JOINT AREA PRESCRIBING COMMITTEE (JAPC)

MENOPAUSE MANAGEMENT GUIDELINE

(based on NICE NG23/ British Menopause Society Guidance)

Whilst JAPC recommend a list of cost-effective treatments in this guidance, alternative available products may be prescribed during ongoing national supply shortage of Hormone Replacement Therapy (HRT). For current availability see Specialist Pharmacy Service (SPS) Prescribing available HRT products and British Menopause Society (BMS) update on HRT supply.

General Principles

- Diagnose menopause/ perimenopause without laboratory tests in otherwise healthy women aged over 45 years with menopausal symptoms. There should be a holistic and individualised approach in assessing menopausal women.
- All women should be able to access advice on how they can optimise their menopause transition and the years beyond. Give information in different formats on the cause of the menopause, common symptoms, long term health implications, health-improving lifestyle changes and interventions, benefits and risks of hormonal, non-hormonal and non-pharmaceutical treatments.
- The decision whether to use Hormone Replacement Therapy (HRT) should be made by each woman having been given sufficient accurate information to make a fully informed choice.
- HRT prescribed before the age of 60 has a favourable benefit / risk profile. This does not mean that HRT should be discontinued at age 60, but a discussion of the individual's medical history, taking into account benefits and risks.
- Offer HRT first-line for menopausal related vasomotor symptoms after discussing short term and long term benefits and risks. Review HRT treatment 3 months after commencing, and annually thereafter once settled on treatment. See appendix 1 for preferred formulary choices. Alternatives may be preferred on an individual basis.
- Arbitrary limits should not be placed on the duration of usage of HRT; if symptoms persist, the benefits of hormone therapy usually outweigh the risks. Offer women who are stopping HRT a choice of gradually reducing (may limit recurrence of symptoms short term) or immediately stopping treatment, which makes no difference to symptoms in longer term.
- Selective serotonin uptake inhibitors (SSRI), selective noradrenaline uptake inhibitors (SNRI) antidepressants or clonidine should **not** be routinely offered first line treatment for vasomotor symptoms. For menopause related low mood, consider HRT and or cognitive behavioural therapy (CBT) (SSRIs and SNRIs have not been shown to help unless depression is diagnosed)
- Offer and continue vaginal oestrogen to relieve symptoms of urogenital atrophy (usually long-term as symptoms recur on stopping vaginal oestrogen). Do not routinely measure endometrial thickness to monitor treatment. Women should be advised to report any unscheduled bleeding to their GP. (Higher dose may be indicated temporarily- contact a local menopause expert for advice)
- Off-label use of topical testosterone gel can be considered for the treatment for menopausal women with low sexual desire, if systemic HRT has not been effective (NICE NG23). Testosterone gel should not be started in primary care until women have had this 3-month trial with HRT- **see appendix 3**
- Women who are likely to start menopause because of medical or surgical treatment need support and information about it before treatment starts.

Premature Ovarian insufficiency (POI)

- Diagnose POI in women aged under 40 years based on: menopausal symptoms, including no or infrequent periods (taking into account whether the woman has a uterus) **and** elevated FSH levels on **two** blood samples taken 4–6 weeks apart. Investigate possible cause and consider referral to Obstetrics and Gynaecology / Endocrinology.

- Women with POI should be encouraged to use HRT at least until the average age of the menopause. HRT and the combined contraceptive pill (COCP) would both be suitable options to consider, however, HRT may result in a more favourable improvement in bone density and cardiovascular markers compared with the COCP.

Background

The average age for the natural menopause in the UK is 51: premature menopause affects 1 in 100 women under the age of 40. About 80% women experience some symptoms (est 1.5 million women nationally). Symptoms often last for 7-8 years but in about 10% of women can last for 12 years or more.

Menopause symptoms are often misunderstood, ridiculed and underestimated. However, they may severely affect a woman's health, quality of life, competence and confidence at work. Hot flushes and sweats can be so bad they constantly interrupt sleep and can leave sufferers drenched in sweat and exhausted. Menopause also can result in low mood, osteoporosis and urogenital changes that can cause vaginal dryness, urinary tract infections, and adversely affect a woman's sex life.

Definitions

Perimenopause	The time in which a woman has irregular cycles of ovulation and menstruation leading up to menopause and continuing until 12 months after her final period. The perimenopause is also known as the menopausal transition or climacteric.
Post menopause	The time after menopause has occurred, starting when a woman has not had a period for 12 consecutive months.
Premature ovarian insufficiency (POI)	Menopause occurring before the age of 40 years (also known as premature ovarian failure or premature menopause). It can occur naturally or as a result of medical or surgical treatment.
Early menopause	Menopause occurring between ages 40-44.
Urogenital atrophy	Thinning and shrinking of the tissues of the vulva, vagina, urethra and bladder caused by oestrogen deficiency. This results in multiple symptoms such as vaginal dryness, vaginal irritation, a frequent need to urinate and urinary tract infections.
Vasomotor symptoms	Menopausal symptoms such as hot flushes and night sweats caused by constriction and dilatation of blood vessels in the skin that can lead to a sudden increase in blood flow to allow heat loss. These symptoms can have a major impact on activities of daily living.

Benefits of HRT

Short term	Reduced vasomotor symptoms (e.g., hot flushes, night sweats) Improved psychological symptoms (e.g., low mood, anxiety) and quality of life Improved muscle and joint pains Can improve sexual problems including interest, arousal and pain.
Long term	Reduced genitourinary symptoms (vaginal dryness, pain on intercourse, urinary urgency).(BMS consensus statement Urogenital atrophy) Stops bone loss, reduces fracture risk, maintains muscle mass and strength.
	Reduced risk of bowel cancer with combined HRT (BMS HRT consensus statement 2016). HRT initiated before the age of 60 or within 10 years of the menopause is likely to be associated with a reduction in coronary heart disease and cardiovascular mortality**. Evidence from the Cochrane data-analysis as well as that from the long-term follow up data of the WHI showed no increase in cardiovascular events, cardiovascular mortality or all-cause mortality in women who initiated HRT more than 10 years after the menopause.

** If HRT is to be used in women over 60 years of age, lower doses should be started, preferably with a transdermal route of estradiol administration.

Risks associated with HRT in perspective (see also appendix 2)

HRT **does not** increase cardiovascular (CVS) risk– HRT is not contraindicated in women with optimally managed CVS risk factors (e.g., hypertension, diabetes).

Consider transdermal HRT in women with a higher background VTE and stroke risk including those with a BMI over 30 kg/m^2 as oral HRT is associated with a higher risk of venous thromboembolism.

MHRA Aug 2019- The risk of breast cancer is increased during use of HRT (except vaginal estrogens), and some risk persists for more than 10 years after stopping HRT. Risk of breast cancer is higher for combined estrogen-progestogen HRT (required in women with a uterus) than estrogen-only HRT. However, there is little or no increase in risk of breast cancer with current or previous use of HRT for less than 1 year. See Patient information leaflet.

The recent findings are in keeping with existing evidence; however, a woman has greater risk of developing breast cancer if she is obese compared to taking HRT. See BMS Fact sheet: HRT and breast cancer risk

Choice of HRT

The choice of HRT for an individual depends on an overall balance of indication, risk-benefit profile, side effects and convenience. Prescribe the lowest effective dose of HRT for the shortest time necessary but arbitrary limits should not be placed on the duration of usage of HRT.

Start at a low dose especially in older women (may be less tolerant of oestrogen) and increase if symptoms persist after a few months. Tailor the dose to the symptoms, as the ingested or applied dose may not be well absorbed.

Estradiol- equivalent doses*

	Low dose	Standard dose	High dose
estradiol	0.5/1mg	2mg	
conjugated oestrogens	300 microg	625 microg	1.25mg
estradiol patch	25/37.5 microg	50 microg	75/100 microg
estradiol pump	1 measure/	2 measures	3-4 measures
estradiol sachet	0.5mg	1-1.5mg	2-3mg
estradiol spray	2 sprays	3 sprays	-

* practical guide subject to significant individual variations in absorption and metabolism. Source: BMS HRT- Practical prescribing

Limited evidence suggests that micronised progesterone and dydrogesterone may be associated with lower risk of breast cancer and venous thrombosis compared to other progestogens

Side effects tend to be related to the progestogen component of combined HRT. Progestogenic side effects may include PMS type symptoms, breast tenderness, lower abdominal pain, backache, depressed mood, acne/greasy skin, headache.

If androgenic or PMS side effects occur on C19 progestogens (levonorgestrel/ norethisterone), advise change to C21 progestogen (dydrogesterone/ medroxyprogesterone), Mirena Intrauterine system, or micronised progesterone)

Transdermal administration of estradiol is unlikely to increase the risk of venous thrombosis or stroke above that in non-users and is associated with a lower risk compared with oral administration of estradiol. The transdermal route should therefore be considered as the first choice route of estradiol administration particularly in women with risk factors. Patches deliver a more steady level of hormone which can also be helpful in conditions triggered by fluctuating levels e.g., migraine.

Mirena

Mirena is a levonorgestrel-releasing intrauterine system (IUS) for use in combination with oestrogen as the progestogen element of sequential or continuous combined HRT. Although it is licensed for 4 years for this indication, (as opposed to 8 years when used solely for contraception or 5 years for heavy menstrual bleeding), its use for 5 years is endorsed by both the Faculty of Sexual and Reproductive Healthcare and the British Menopause Society (please note that the Sexual Health Service is now only commissioned to insert Mirena for contraception). This is particularly useful for women who experience heavy bleeding on sequential preparation, require contraception or suffer unacceptable side effects from the progestogen element of HRT.

Micronised Progesterone

This is available as 100mg oral capsules and is used as per the following criteria:

- Progesterone only component of combined HRT. Oral alternative to Mirena IUS.
- 2nd line option for women requiring combined HRT but unsuitable for or intolerant of standard combination preparations.
- Patient group includes women at high risk of VTE (e.g., migraines, BMI >30 kg/m2, PMH of VTE) in whom transdermal oestrogen is recommended, but in whom Evorel Conti is not tolerated or unsuitable because of the need for variable oestrogen dose.

The licensed dose is 200 mg at night for 12 days (Day 15 -26 of cycle) or 100 mg at bedtime from Day 1 -25 of cycle. Alternatively, women may be advised to take micronised progesterone 200mg at night for the first 12 days of each calendar month (cyclical) or 100mg at night on continuous basis. This dosing regimen differs slightly from licensed dosing, however, is endorsed by BMS and more practical for women.

Utrogestan 200mg vaginal capsules has been classified RED- Supplementation of luteal phase during assisted reproductive technology (ART) cycles

Tibolone

Tibolone is a synthetic steroidal compound with oestrogenic, progestogenic, and androgenic activity. It is licensed for the treatment of oestrogen deficiency symptoms in postmenopausal women (more than 1 year after menopause) and an option for postmenopausal women where progestin-containing therapy is not appropriate (e.g., progestogenic adverse effects). See MHRA information on risk vs benefit.

Useful Resources

British Menopause Society (BMS) https://thebms.org.uk/
Tool for clinicians including

- NICE NG23 Guideline Summary
- HRT Guide & HRT-Practical Prescribing
- Migraine and HRT

Royal College of Obstetricians & Gynaecologists (RCOG) information leaflet on treatments to manage menopausal symptoms.

Further information

NICE NG23 Menopause: diagnosis and management https://www.nice.org.uk/guidance/ng23.
'Information for Patients' which suggests points that women may find helpful to discuss with their doctor or nurse http://www.nice.org.uk/guidance/ng23/informationforpublic.
Other relevant NICE guidelines: NG101 Early and locally advanced breast cancer and CG164 Familial breast cancer.

These include advice to stop HRT if breast cancer is diagnosed. HRT may, in exceptional cases, be offered to women with a history of breast cancer with severe menopausal symptoms not responsive to non-hormonal alternatives and with whom the associated risks have been discussed. Advice to individual women with a family history of breast cancer on the use of HRT should vary according to the individual clinical circumstances (such as age, severity of menopausal symptoms, or osteoporosis).

Reference

NICE NG23 Menopause November 2015, updated December 2019 https://www.nice.org.uk/guidance/ng23.
The British Menopause Society http://www.thebms.org.uk/
Clinical Knowledge Summaries Accessed January 2018/ March 2023 https://cks.nice.org.uk/menopause
BMS summary consensus statement Hormone replacement therapy
https://thebms.org.uk/publications/consensus-statements/hormone-replacement-therapy/
FSRH contraception over age 40 Guideline https://www.fsrh.org/standards-and-guidance/documents/fsrh-guidance-contraception-for-women-aged-over-40-years-2017/

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Document update	Date updated
MHRA drug safety info on topical testosterone inserted	May 2023
Mirena duration of use extended from 5 years to 8 years for contraception, and 5 years in induction of idiopathic menorrhagia	January 2024
Testim 50mg/5g transdermal gel removed - discontinued	April 2024

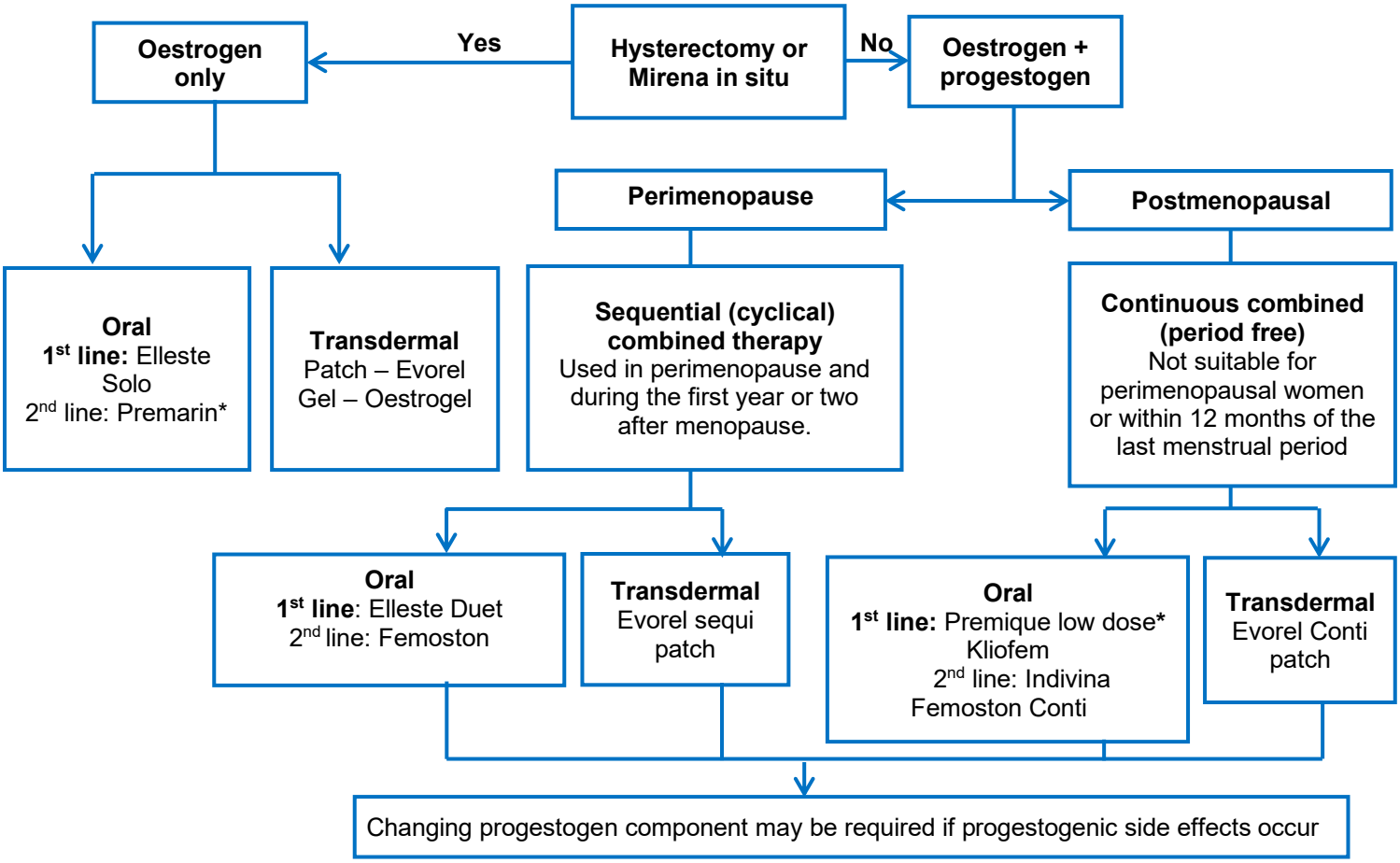
Utrogestan brand of micronised progesterone oral capsules removed – prescribe by generic name	February 2025

Appendix 1 Formulary choice of HRT

Below are preferred formulary choices. Alternatives may be preferred on an individual basis.
Whilst JAPC recommend a list of cost-effective treatments in this guidance, alternative available products may be prescribed during ongoing national supply shortage of Hormone Replacement Therapy (HRT). For current availability see Specialist Pharmacy Service (SPS) Prescribing available HRT products and British Menopause Society (BMS) update on HRT supply.

Systemic HRT treatment

(Flow chart adapted from BMS society HRT guide https://thebms.org.uk/wp-content/uploads/2022/12/04-BMS-TfC-HRT-Guide-NOV2022-A.pdf)



*the oestrogen in Premarin and Premique is horse oestrogen (from pregnant horse urine), these may not be acceptable to all women; all other preparations in which the oestrogens are identical to human oestrogens

Patches are more expensive than oral preparations but may be **suitable for patients with high risk of VTE** (e.g., those with a BMI over 30 kg/m^2). Consider referring those at high risk (strong family history of VTE or a hereditary thrombophilia) to a haematologist for assessment before considering HRT.

Transdermal routes avoid the first pass effect through the liver and are not associated with increased low-density lipoproteins, venous thrombosis or stroke. Patches deliver a more steady level of hormone which can be helpful in conditions triggered by fluctuating levels eg migraine.

Hormonal content of formulary HRT preparations (Prices as per MIMs March 2023)

Below are preferred formulary choices. Alternatives may be preferred on an individual basis.

OESTROGEN ONLY (Hysterectomy or Mirena in situ)					
Preparation	**Formulation**	**Oestrogen**	**Strength**	**Progestogen**	**3months cost**
Elleste Solo	1st line tablet	Estradiol	1mg 2mg	--	£5.07
Premarin*	2nd line tablet	Conjugated equine oestrogens	300microg 625microg 1.25mg	--	£6.06 £4.02 £3.57
Evorel	24h patch (replace every 3-4 days)	Estradiol	25,50microg/24hr 75,100microg/24hr	--	£10.26 £11.64 £12.36 £12.84
Oestrogel	Transdermal gel (pump)	Estradiol	0.06%	--	£12.60
Sandrena	Transdermal gel (sachet)	Estradiol	500mcg, 1mg	--	£15.24 - £17.55
Lenzetto	Transdermal spray	Estradiol	1.53mg per actuation	--	£10.35-£17.55
SEQUENTIAL COMBINED (Perimenopause)					
Preparation	**Formulation**	**Oestrogen**	**Strength**	**Progestogen**	**3months cost**
Elleste Duet	1st line tablet	Estradiol	1mg, 2mg	Norethisterone 1mg	£9.24
Femoston	2nd line tablet	Estradiol	1mg, 2mg	Dydrogesterone 10mg	£16.17
Evorel sequi	Patch (replace every 3-4 days)	Estradiol	50mcg/24hr	Norethisterone 170mcg	£33.27
CONTINUOUS COMBINED (Postmenopausal)					
Preparation	**Formulation**	**Oestrogen**	**Strength**	**Progestogen**	**3months cost**
Premique low dose*	1st line tablet	Conjugated oestrogens	300mcg	Medroxyprogesterone 1.5mg	£6.51
Kliofem	1st line tablet	Estradiol	2mg	Norethisterone 1mg	£11.43
Kliovance	Tablet- alternative continuous combined HRT	Estradiol	1mg	Norethisterone 500mcg	£13.20
Indivina	2nd line tablet	Estradiol	1mg, 1mg, or 2mg	Medroxyprogesterone 2.5mg, 5mg or 5mg	£20.58
Femoston conti	2nd line tablet	Estradiol	0.5mg, 1mg	Dydrogesterone 2.5mg, 5mg	£24.42
Bijuve	2nd line tablet	Estradiol	1mg	Progesterone 100mg	£24.42
Evorel Conti	Patches	Estradiol	50mcg/24hr	Norethisterone 170mcg	£39.00

***the oestrogen in Premarin and Premique is horse oestrogen (from pregnant horse urine), these may not be acceptable to all women; all other preparations in which the oestrogens are identical to human oestrogens

Appendix 2. Summary of HRT risks and benefits* during current use and current use plus post-treatment from age of menopause up to age 69 years, per 1000 women with 5 years or 10 years use of HRT (MHRA Aug 2019)

	Risks over 5 years use (with no use or 5 years current HRT use)		Total risks up to age 69 (after no use or after 5 years HRT use†)		Risks over 10 years (with no use or 10 years current HRT use)		Total risks up to age 69 (after no use or after 10 years HRT use†)	
	Cases per 1000 women with no HRT use	Extra cases per 1000 women using HRT	Cases per 1000 women with no HRT use	Extra cases per 1000 women using HRT	Cases per 1000 women with no HRT use	Extra cases per 1000 women using HRT	Cases per 1000 women with no HRT use	Extra cases per 1000 women using HRT
Risks associated with combined estrogen-progestogen HRT								
Breast cancer	13	**+8**	63	**+17**	27	**+20**	63	**+34**
Sequential HRT	13	**+7**	63	**+14**	27	**+17**	63	**+29**
Continuous combined HRT	13	**+10**	63	**+20**	27	**+25**	63	**+40**
Endometrial cancer	2	-	10	-	4	-	10	-
Ovarian cancer	2	**+ <1**	10	**+ <1**	4	**+1**	10	**+1**
Venous thromboembolism (VTE)§	5	**+7**	26	**+7**	8	**+13**	26	**+13**
Stroke	4	**+1**	26	**+1**	8	**+2**	26	**+2**
Coronary heart disease (CHD)	14	-	88	-	28	-	88	-
Fracture of femur	1.5	-	12	-	1	-	12	-
Risks associated with estrogen-only HRT								
Breast cancer	13	**+3**	63	**+5**	27	**+7**	63	**+11**
Endometrial cancer	2	**+4**	10	**+4**	4	**+32**	10	**+32**
Ovarian cancer	2	**+ <1**	10	**+ <1**	4	**+1**	10	**+1**
Venous thromboembolism (VTE)§	5	**+2**	26	**+2**	10	**+3**	26	**+3**
Stroke	4	**+1**	26	**+1**	8	**+2**	26	**+2**
Coronary heart disease (CHD)	14	-	88	-	28	-	88	-
Fracture of femur	0.5	-	12	-	1	-	12	-

*Menopausal symptom relief is not included in this table, but is a key benefit of HRT and will play a major part in the decision to prescribe HRT.
†Best estimates based on relative risks of HRT use from age 50 (see DSU table 2 for relative risks). For breast cancer this includes cases diagnosed during current HRT use and diagnosed after HRT use until age 69 years; for other risks, this assumes no residual effects after stopping HRT use. §Latest evidence suggests that transdermal HRT products have a lower risk of VTE than oral preparations.

Appendix 3. Topical testosterone for low sexual desire in menopausal women

See Shared care pathology menopause guideline prior to starting treatment and for ongoing monitoring

NICE NG23 recommends consider testosterone supplementation for menopausal women with low sexual desire if HRT alone is not effective. Topical testosterone gel is a recognised ***off-label*** treatment for menopausal women with low sexual desire, if systemic HRT has not been effective.

Testosterone gel should not be started in primary care until women have had this 3-month trial with HRT- see local menopause guideline

Prescribing information

The testosterone gel should be to be applied to clean dry skin (lower abdomen/upper thighs) and allowed to dry before dressing.

Preparation	Strength	Presentation	Dose	Quantity
Tostran	2% (20mg/g) 10mg/actuation	60g canister	Apply 1 metered pump of 0.5g (10mg) three times a week or on alternate days	each canister should last 240days
Testogel	16.2mg/g (40.5mg/2.5g)	2.5g sachets	Apply 1/8 of a sachet (approx. 5mg) each day	each sachet should last 8 days

Do not prescribe the following preparations

- Testogel ***pump*** or Testavan ***pump*** as unable to obtain required small dosage
- AndroFeme cream- preparation unlicenced in the U.K.

Notes

Skin contact with partners or children should be avoided until dry and hands should be washed immediately after application. The area of application should not be washed for 2-3 hours after application.

MHRA January 2023 Topical testosterone (Testogel): risk of harm to children following accidental exposure. Premature puberty and genital enlargement have been reported in children who were in close physical contact with an adult using topical testosterone and who were repeatedly accidentally exposed to this medicine. To reduce these risks, advise patients to wash their hands after application of topical testosterone, cover the application site with clothing once the product has dried, and wash the application site before physical contact with another adult or child.

Managing adverse effects

Adverse effects are uncommon if levels are maintained within the female physiological range (**see shared care pathology menopause guideline on monitoring**). The commonest are excess hair growth, acne and weight gain which are usually reversible with reduction in dosage or discontinuation. Alopecia, deepening of voice and clitoral enlargement are rare with physiological testosterone replacement (see 'managing adverse effects' section below). More data are required for the long-term effects on cardiovascular and breast outcomes but the short- term data from a recent meta-analysis are reassuring.

Issue	**advice**
Local skin reaction	Apply gel to a different site
Systemic changes (acne, hirsuitism, male pattern baldness)	• STOP testosterone treatment immediately • Recheck testosterone levels ASAP • Discuss with secondary care via A&G or more urgent method if deemed necessary
Severe systemic changes (broad shoulders, clitoromegaly, voice changes)	• STOP testosterone treatment immediately • Recheck testosterone levels ASAP • discuss with secondary care urgently as these changes are usually irreversible

testosterone levels outside physiological range	• STOP testosterone treatment immediately • discuss with secondary care via an A&G or more urgent method if deemed necessary

Further information

The British Menopause society tool for clinicians contains detailed background information on menopause, HRT and testosterone replacement in menopause.

Patient information leaflet on testosterone
https://www.womens-health-concern.org/wp-content/uploads/2022/12/22-WHC-FACTSHEET-Testosterone-for-women-NOV2022-B.pdf
Inform patients that the patient information leaflet from topical testosterone gels only relates to male use and to refer to above information leaflet.

Reference

1. The British Menopause Society (BMS). Tools for Clinicians. Testosterone Replacement in Menopause. Dec 2022. https://thebms.org.uk/publications/tools-for-clinicians/testosterone-replacement-in-menopause/
2. NICE. Menopause: diagnosis and management. NICE guideline [NG23]. Published November 2015, last updated December 2019. https://www.nice.org.uk/guidance/ng23
3. Global Consensus Position Statement on The use of Testosterone Therapy for Women. J Clin Endocrinol Metab, October 2019, 104(10):4660–4666.
4. Joint position statement by the British Menopause Society, Royal College of Obstetricians and Gynaecologists and Society for Endocrinology on best practice recommendations for the care of women experiencing the menopause. DOI: 10.1177/20533691221104879
5. PrescQIPP. Bulletin 299 Menopause. April 2022.