NHS
South West London

# Menopause and Hormone Replacement Therapy (HRT) Guidelines for South West London

## 1. Symptoms

Assessment of a woman with menopause should include asking about symptoms, including frequency, duration and understanding their impact on the patient's quality of life. Symptoms vary widely between individuals and may include any of the following:

**Table 1:** Symptoms of menopause

| Symptoms as listed in Menopause-specific Quality of Life Questionnaire (MENQOL) | Specific presentation may include one or more of the following |
|---|---|
| **Mood changes** | Being dissatisfied with their personal life, feeling anxious or nervous, feeling depressed, down or blue, being impatient with others, wanting to be alone, feeling tired or worn out or experiencing a lack of energy |
| **Cognitive disturbance** | Experiencing poor memory or concentration, accomplishing less than they used to |
| **Menstrual irregularities** | Change in normal pattern of periods. May be a change in flow, frequency or eventually may stop altogether |
| **Change in sexual desire** | Desire to avoid intimacy or loss of libido. Vaginal dryness during intercourse |
| **Joint and muscle pains** | Aches in back of neck or head, decrease in physical strength, decrease in stamina, low backache |
| **Skin changes** | Drying skin or changes to appearance, texture or tone of skin, increased facial hair |
| **Change in physical appearance** | Weight gain, reduction in muscle mass |
| **Hot flushes** | Hot flushes, night sweats, increased sweating compared to usual baseline |
| **Urinary problems** | Frequent urination, involuntary urination when laughing or coughing, frequent UTIs |
| **GI symptoms** | Flatulence, gas pains or feeling bloated |
| **Sleep disturbance** | Difficulty sleeping |

## 2. Diagnosis and investigations

- Diagnosis is made from a clinical history in a woman > 45years, but remember:
  - investigate any abnormal bleeding first and exclude other causes
  - consider differentials if symptoms are atypical
- Routine testing of follicle stimulating hormone (FSH) to diagnose menopause is **not recommended practice except** in the following groups of women (provided they are not taking combined hormonal contraception or high-dose progestogen as the diagnostic accuracy of the FSH blood test may be confounded by these treatments):
  - aged over 45 years with atypical symptoms
  - aged between 40–45 years with menopausal symptoms, including a change in their menstrual cycle
  - younger than 40 years in whom premature ovarian insufficiency is suspected – diagnosis in this group is based on elevated FSH on 2 blood samples taken 4-6 weeks apart and menopausal symptoms

## 3. Treatment choice and initiation

- HRT is available as transdermal or oral preparations. Transdermal preparations are the preferred route in most patients and should be the only route considered in the following instances:
  - individual preference
  - poor symptom control
  - gastrointestinal disorders affecting oral absorption
  - previous or family history of Venous Thromboembolism (VTE) or risk factors
  - Body Mass Index (BMI) > 30kg/$m^2$
  - variable blood pressure control, migraines (section 8.2), or gall bladder disease
  - current use of hepatic enzyme inducing medication
- Where a patient opts for oral therapy, ensure they are counselled on the increased risk of VTE with this route.
- Start at a low dose and increase if symptoms persist. Review the patient after 3 - 4 months if HRT has been started or changed, then at least annually thereafter, unless there are clinical indications to review earlier.

### 3.1 Specialist team responsibilities

For patients requiring initiation of HRT following surgery, specialist teams should communicate clearly with primary care:

- the type of hysterectomy performed
- preferred choice of HRT according to tables below or clinical practice if different
- ongoing needs for the patient in view of cervical screening

### 3.2 Table 2: HRT choice in women post-hysterectomy

| Type of hysterectomy | Recommended HRT |
|---|---|
| **Sub-total hysterectomy**<br>Uterus removed -<br>Remnant cervical stump may contain residual endometrial tissue. | It is common practice to consider sequential combined HRT* (see Table 3.3) as a progestogen challenge for up to 3 months, and if no withdrawal bleed is noted with this, to consider it unlikely that residual endometrium is present and oestrogen only HRT can be considered to be sufficient.<br>Ongoing continuous progestogen intake should be considered if there are concerns that the remnant cervical stump may contain residual endometrial tissue in women who experience cyclical bleeding with sequential combined HRT.<br>There is limited evidence to guide practice in relation to the role or need for progestogen replacement in women who have had subtotal hysterectomy. |
| **Total Hysterectomy**<br>Uterus and cervix removed. | Oestrogen only HRT |
| **Total hysterectomy with bilateral salpingo-oophorectomy (TH+BSO)**<br>Uterus, cervix, fallopian tubes and ovaries removed.<br>Often seen in patients with a significant history of endometriosis. | ***Following TH+BSO for severe endometriosis:*** Continuous combined HRT regimens should be considered to prevent reactivation of residual disease and to potentially prevent malignant transformation of residual deposits. However, there is limited evidence available on this to guide clinical practice.<br>***Following TH+BSO for other diagnosis:*** Oestrogen only HRT |

### 3.3 Table 3: HRT choice in women with uterus intact

| Stage of menopause | Recommended HRT | |
|---|---|---|
| **Women with premature ovarian insufficiency (POI)**<br>Patients with suspected POI should referred to menopause clinic for advice and guidance- see section 14.1 | Offer sequential combined HRT*<br><br>***OR***<br><br>Combined hormonal contraceptive<br><br>***OR***<br><br>Mirena® plus oestrogen only HRT | ***After one year of sequential combined HRT:**<br>After a minimum of one year of HRT, women who wish to avoid a monthly withdrawal bleed may attempt a switch to a continuous combined HRT regimen which aims to give bleed-free HRT – this will also minimise the risk of endometrial hyperplasia. The timing of switching from sequential to continuous combined HRT should be considered in relation to the woman's age and the frequency of her menstrual cycles (prior to commencing HRT). Women under the age of 50 who had shorter durations of amenorrhoea before starting HRT are likely to need to continue on sequential intake for a longer duration before switching to continuous combined HRT intake. |
| **Women in the peri-menopausal period:**<br><12 months since last bleed | ***Same as POI, however:***<br>Combined hormonal contraceptive age limit should not exceed UKMEC criteria | |
| **Women in the post-menopausal period:**<br>>12 months since last bleed | Offer continuous combined HRT | |
| **Women with an intact uterus with Mirena® IUS in place** | Offer oestrogen only HRT | |
| **Women who have undergone endometrial ablation** | Combined HRT regimens (sequential combined HRT or continuous combined HRT) should be used in women who have undergone endometrial ablation to ensure the entire residual endometrium is protected and reduce the risk of endometrial hyperplasia. | |

## 4. Counselling points

- Explain the risks and benefits of HRT (section 7) and the importance to commit to regular reviews and ensure patient understands the importance of progestogen uterine protection where applicable.
- Remind women in the peri-menopause or with premature ovarian insufficiency that HRT is not a contraceptive and contraceptive precautions are still necessary.
- Explain to patients about bleed patterns:
  - For patients who are still menstruating the use of continuous combined HRT will not stop menstruation
  - For women and people with a uterus, unscheduled vaginal bleeding is a common side effect of HRT within the first 3 months of treatment but should be reported at the 3-month review appointment, or promptly if it occurs after the first 3 months
- Be realistic in what HRT can achieve and emphasise the importance of treatment adherence.
- Advise patients that symptoms will usually start to improve by 4 weeks after HRT initiation.
- Weight gain is very common around the time of the menopause. HRT does not cause significant further weight gain.
- Counsel patients on continuing need to engage in national screening programmes including breast and cervical screening programmes.

## 5. Management of the menopause

- Before prescribing HRT conduct a full medical history, including personal, family and medication history and baseline checks for height/weight, BMI and blood pressure.
- For psychological symptoms, such as mood disturbance, anxiety, and depression, consider a referral for cognitive behavioural therapy (CBT) as per NICE recommendation. Further information can be found on the BMS website.
- NICE advise that SSRIs, SNRIs or clonidine should NOT be routinely offered first line due to limited efficacy and side effects.
- Vaginal oestrogens should be offered to patients with genitourinary syndrome of menopause (GSM) (including those on systemic HRT or for whom systemic HRT is contraindicated).
- The potential benefits of bioidentical hormone therapy can be achieved using conventionally licensed products, without having to resort to unregulated compounded varieties from specialist pharmacies. NHS South West London does not support the prescribing of unlicensed bioidentical HRT preparations.
- Body identical licensed HRT therapy is supported as per the HRT product list section of document.

### 5.1 Review & treatment duration

- Review the patient after 3-4 months if HRT has been started or changed, then at least annually thereafter, unless there are clinical indications to review earlier.
- At each review appointment:
  - ✓ Assess symptom control, tolerability and compliance
  - ✓ Reassess risk relating to current choice of HRT:
    - Long-term use of sequential combined HRT for >5 years may be associated with a small increase in risk of endometrial hyperplasia and endometrial cancer, with the risk being dose and duration dependent in relation to progestogen intake
    - Consider a reduction in dose of HRT as patients get older.
    - Recommend switch to transdermal preparation where appropriate to reduce risks of VTE
  - ✓ Check blood pressure
  - ✓ Emphasise the importance of:
    - Keeping up to date with national screening programmes including breast screening programme (mammogram) and cervical screening programmes
    - Regular breast self-examination - ensure patient is clear on how to perform this
    - Bone health optimisation
    - Contraception – see counselling points
    - Attending NHS health checks
- Regimen changes are not generally recommended in the first 12 weeks unless essential. This is to enable clinicians to get the best information on dosing and side effects before considering the need to change. At 3-4 month review after initiation or treatment change, if the patient continues to experience irregular bleeding offer adjustment of HRT (section 11).
- HRT should be continued for as long as the benefits of symptom control and improvement in quality of life outweigh risks.

## 6. Lifestyle and Self-care

Lifestyle modifications should be recommended as per Table 4 to help alleviate symptoms. These should be implemented at the same time as medical management – they should not delay treatment initiation.

Women who have been through the menopause are at an increased risk of developing osteoporosis - encourage patients to eat a healthy diet containing plenty of calcium, purchase vitamin D supplementation and encourage regular weight-bearing and resistance exercise.

Women should be advised to contact occupational health if support is needed in the workplace.

Isoflavones (soy), black cohosh and red clover may help relive vasomotor symptoms, however their safety is unknown and preparations may vary in terms of quality and purity. Advise patients with hormone dependent cancers to avoid using these products and speak to their specialist team for advice.

For patients with vaginal dryness, vaginal moisturisers and lubricants can be used alone or in addition to vaginal oestrogen. These can be purchased over the counter from pharmacies or retail outlets.

- **Vaginal moisturisers:** these are usually applied every few days via insertion directly into the vagina. The effects of a moisturiser generally last a bit longer than those of a lubricant. Many different brands are available to purchase.
- **Vaginal lubricants:** water-based and oil-based lubricants can be applied to the vulva and vagina just before sexual activity to reduce discomfort during sexual intercourse. Numerous brands are available to purchase. Avoid petroleum jelly or other petroleum-based products for lubrication if also using condoms, because petroleum can break down latex condoms on contact.

**Table 4:** Lifestyle recommendations to alleviate symptoms

| Symptom | Lifestyle Modification |
|---|---|
| **Hot flushes and night sweats** | Regular exercise, healthy BMI, wearing lighter clothing, sleeping in a cooler room with silk pillows, using a fan, reducing stress and avoiding possible triggers e.g. spicy foods, alcohol, caffeine, smoking. |
| **Sleep disturbances** | Avoiding exercise late in the day and maintaining a regular bedtime. Mindfulness and sleep apps may be helpful. NHS recommended wellbeing apps can be found here. |
| **Mood and anxiety disturbances** | Adequate sleep, regular physical activity and relaxation exercises, mindfulness. |
| **Cognitive symptoms** | Exercise and good sleep hygiene. |

## 7. Hormone Replacement Therapy

### 7.1 Indications

- Relief of short-term vasomotor symptoms e.g. hot flushes
- Alleviate low mood as a result of the menopause
- Urogenital atrophy
- Premature ovarian insufficiency
- Prevention of osteoporosis in postmenopausal women at high risk of future fractures

### 7.2 Benefits of HRT

- Reduction of vasomotor symptoms.
- Maintenance of bone mineral density and reduced risk of osteoporotic fractures.

### 7.3 Risks of HRT

Much controversy exists about the risks of HRT. The safety of HRT largely depends on age. Reassure healthy women younger than 60 years that they should not be concerned about the safety profile of HRT. For the majority of women, the potential benefits of HRT when given for a clear indication are many and the risks are few when initiated within a few years of menopause.

**Table 5:** Summary of the risks of HRT

| Risk | Information |
|---|---|
| **Venous Thromboembolism (VTE)** | • Oral HRT increases the risk of VTE compared to baseline population risk.<br>• When used at standard therapeutic doses, the risk associated with transdermal HRT is no greater than baseline risk. |
| **Breast Cancer** | • The baseline risk of breast cancer for women around menopausal age varies from one woman to another according to the presence of underlying risk factors.<br>• Lifestyle factors (obesity, excess alcohol) may have greater impact on breast cancer risk than HRT (see pie chart at bottom of link).<br>• HRT with oestrogen alone is associated with little or no change in the risk of breast cancer.<br>• Vaginal oestrogen treatment: no increase in risk of breast cancer compared to control.<br>• Combined HRT with oestrogen and progestogen: associated with an increased risk of breast cancer that is duration dependent.<br>• Micronised progesterone and dydrogesterone may be safest progestogens. |
| **Cardiovascular disease & Stroke** | • CVD is the commonest cause of death in postmenopausal women.<br>• HRT does not increase the risk of cardiovascular disease in women <65 years of age.<br>• HRT may be cardioprotective in younger postmenopausal women (<10years from last menstrual period) but the evidence is not currently strong enough to recommend for primary prevention of CVD.<br>• Stroke: Increased when oral (but not transdermal) HRT started in older women (> 60 years).<br>• **Tibolone** increases the risk of stroke approximately 2.2 times from the first year of treatment as per MHRA guidance. |
| **Ovarian Cancer** | • Slight increased risk has been suggested from epidemiological studies, although causation cannot be inferred. |
| **Endometrial Cancer** | • For women with an intact uterus, taking oestrogen-only HRT increases their risk of endometrial cancer.<br>• Continuous combined oestrogen and progestogen has been shown to have a neutral effect on the risk of endometrial cancer compared to placebo. Women's Health Initiative (WHI) showed significant reduction in endometrial cancer risk in the postintervention phase.<br>• Sequential combined HRT >5 years: may be associated with small increase in risk of endometrial cancer, with risk inversely proportional to number of days progestogen is given. |

## 8. HRT for Specific Clinical Indications

### 8.1 Bone health and HRT

- For the prevention and treatment of osteoporosis in women with premature ovarian insufficiency (POI) and menopausal women below 60 years of age, particularly those with menopausal symptoms, HRT should be considered the first-line therapeutic intervention.
- The bone-protective effect of oestrogen is related to dose and duration and the bone preserving effect of HRT declines after treatment discontinuation.
- Some low dose HRT preparations are not licensed to prevent post-menopausal osteoporosis. However, studies have shown a bone-preserving effect even with relatively low doses of oestrogen replacement. In addition, some studies have shown that the use of HRT for a few years around the menopause may provide a long-term protective effect many years after stopping HRT
- Please consult individual product literature via Electronic Medicines Compendium when prescribing and see comments in HRT products list. If prescribing a medication for an unlicensed indication, please discuss with the patient.

### 8.2 Migraine and HRT

- Migraine aura **does not contraindicate** the use of HRT unlike with combined contraceptive pill use.
- Changing oestrogen levels and menstrual disorders are linked with increased migraine prevalence during the menopause. Effective management of vasomotor symptoms is a recognised way of improving migraines.
- Detailed guidance on how to manage migraine and HRT is available from the BMS which includes preferred medicines and routes of administration as well as non-pharmacological measures.
- General advice includes:
  - Use the lowest topical oestrogen dose that effectively controls vasomotor symptoms
  - Where progestogen is required, continuous delivery is recommended, with preparations such as:
    - levonorgestrel intrauterine system
    - transdermal norethisterone (as in combined patches)
    - micronised progesterone
  - Women with migraine and vasomotor symptoms who do not wish to use HRT or in whom oestrogens are contraindicated may benefit from escitalopram (unlicensed) or venlafaxine (licensed to treat menopausal symptoms, particularly hot flushes, in women with breast cancer).

### 8.3 Premature Ovarian Insufficiency (POI)

- Premature ovarian insufficiency is a condition defined by loss of ovarian activity before the age of 40. It is characterised by menstrual disturbance such as amenorrhea or oligomenorrhea, with raised gonadotropins and low oestradiol.
- POI can occur spontaneously or from iatrogenic causes (as a result of surgery or medication etc.). Establish the cause, if unclear or unknown refer to the specialist menopause clinic for further investigation.
- Offer patient the choice of HRT or a combined hormonal contraceptive, unless contraindicated.
- HRT should be continued until at least the age of natural menopause (average age is 51 years in the UK). After this point reassess and offer therapy as needed.
- Consider/offer an early DXA scan utilising results to calculate FRAX score and to assess fragility risk.
- Counselling points:
  - The baseline population risk of diseases such as breast cancer and cardiovascular disease increases with age and is very low in women aged under 40.
  - HRT may have a beneficial effect on blood pressure when compared with a combined oral contraceptive.
  - Both HRT and combined oral contraceptives offer bone protection.
  - HRT is not a contraceptive- see section 13 for further advice on contraception.

## 9. HRT Product Lists

Multiple stock supply disruptions can impact choice of HRT products. For up-to-date alternatives see guidance from the British Menopause Society. Prescribe HRT products by brand for continuity and to comply with licensing.

Table 6 has been drawn up by the British Menopause Society as a practical guide to dose equivalents based on a combination of pharmacokinetics, clinical trials and clinical experience. These are subject to significant individual variation in absorption and metabolism so patients should be reviewed 3- 4 months after any changes are made.

**Table 6:** Estradiol equivalent doses for initiation and titration

| | Ultra-Low dose | Low dose | Medium dose | High dose | Above licensed dose |
|---|---|---|---|---|---|
| **Oral** | 0.5mg | 1mg | 2mg | 3-4mg | Consider changing to an alternative product if patient on max dose and still experiencing symptoms, see trouble shooting (section 10). Use "Advice and Refer service if required. |
| **Patch** | Half a 25 microgram patch | 25 micrograms | 50 micrograms | 75-100 micrograms | |
| **Gel-pump** | Half a pump | 1 pump | 2 pumps | 3-4 pumps | |
| **Sachet** | Half of 0.5mg sachet | 0.5mg | 1-1.5mg | 2-3mg | |

**Ref:** BMS-HRT Practical Prescribing Tool For Clinicians

| Key to medication status | |
|---|---|
| First line treatment option<br>Second line treatment option<br>Continuation in primary care after specialist initiation - see comments for detailed advice on transfer to primary care | Hospital only<br>No longer considered preferred therapy. During routine review consider change to alternative treatment option where appropriate. |

| **9.1 Sequential Combined HRT:** Suitable for sub-total hysterectomy (progestogen challenge), POI, peri-menopausal women, women who have undergone endometrial ablation | | | | |
|---|---|---|---|---|
| **Brand** | **Oestrogen content** | **Progestogen content** | **Dose frequency** | **Comments** |
| **Patches** | | | | |
| Evorel Sequi® | Estradiol 50mcg | Norethisterone 170mcg | Twice weekly | |
| FemSeven Sequi® | Estradiol 50mcg | Levonorgestrel 10mcg | Weekly | Preferred option for patients experiencing progestogenic side effects - see Table 9 |
| **Oral** | | | | |
| Femoston® | Estradiol 1mg or 2mg | Dydrogesterone 10mg | Daily | Preferred option for patients experiencing progestogenic side effects - see Table 9 |
| Elleste Duet | Estradiol 1mg or 2mg | Norethisterone 1mg | Daily | |
| Clinorette® | Estradiol 2mg, 2mg | Norethisterone 1mg | Daily | |
| Novofem® | Estradiol 1mg | Norethisterone 1mg | Daily | |
| Trisequens® | Estradiol 1mg, 2mg, 2mg | Norethisterone 1mg | Daily | |
| Tridestra® | Estradiol valerate 2mg | Medroxyprogesterone 20mg | Daily | |

| **9.2 Continuous Combined HRT:** Suitable for TH+BSO, POI & peri-menopausal women after 1 year sequential combined therapy, women in the post-menopausal period, women who have undergone endometrial ablation | | | | |
|---|---|---|---|---|
| **Brand** | **Oestrogen content** | **Progestogen content** | **Dose frequency** | **Comments** |
| **Patches** | | | | |
| Evorel® Conti | Estradiol 50mcg | Norethisterone 170mcg | Twice weekly | |
| FemSeven® Conti | Estradiol 50mcg | Levonorgestrel 7mcg | Weekly | Preferred option for patients experiencing progestogenic side effects - see Table 9 |
| **Oral** | | | | |
| Femoston® Conti | Estradiol 0.5mg or 1mg | Dydrogesterone 2.5mg or 5mg | Daily | Preferred option for patients experiencing progestogenic side effects - see Table 9 |
| Bijuve® | Estradiol 1 mg | Progesterone 100mg | Daily in the evening with food | Contains gelatin |
| Kliovance® | Estradiol 1mg | Norethisterone 0.5mg | Daily | |
| Kliofem® | Estradiol 2mg | Norethisterone 1mg | Daily | |
| Elleste Duet® Conti | Estradiol 2mg | Norethisterone 1mg | Daily | |
| Indivina® | Estradiol valerate 1mg or 2mg | Medroxyprogesterone 2.5mg or 5mg | Daily | |
| Premique low dose | Conjugated oestrogen 300micrgram | Medroxyprogesterone 1.5mg | Daily | During routine review consider change to alternative treatment option where appropriate. |

| **9.3 Oestrogen Only HRT:** Suitable for total hysterectomy, sub-total hysterectomy (after progestogen challenge), Mirena® IUS in place, can be used as an alternative to sequential or continuous combined HRT along with adjunctive progesterone<br>**NB: When using with adjunctive progestogen annotate prescription with "only to be used in conjunction with <INSERT PROGESTOGEN NAME>" to avoid risk of endometrial hyperplasia.** | | | | |
|---|---|---|---|---|
| **Brand** | **Oestrogen content** | **Progestogen content** | **Dose frequency** | **Comments** |
| **Patches** | | | | |
| Evorel® | Estradiol 25, 50, 75 or 100mcg | None | Twice weekly | Evorel® 25 not licensed for the prevention of post- menopausal osteoporosis. |
| Estradot® | Estradiol 25, 37.5, 50, 75 or 100mcg | None | Twice weekly | Estradot® 25 and 37.5 are not indicated for osteoporosis.<br>Patches are smaller in size than other brands which may be beneficial when prescribing higher doses. |
| Estraderm® MX | Estradiol 25, 50, 75 or 100mcg | None | Twice weekly | |
| Femseven® | Estradiol 50, 75 or 100mcg | None | Weekly | |
| Progynova® TS | Estradiol 50 or 100mcg | None | Weekly | |
| **Gel** | | | | |
| Oestrogel® | Estradiol 0.06% w/w<br>Each pump actuation delivers 1.25 g of gel which contains 0.75 mg of Estradiol | None | Daily | For patients unable to tolerate patches. |
| Sandrena® | Estradiol hemihydrate 0.5mg or 1mg per single-dose sachet | None | Daily | |
| **Transdermal Spray** | | | | |
| Lenzetto® | Estradiol 1.53mg per actuation (equivalent to 1.58mg estradiol hemihydrate) | None | Daily | For patients unable to tolerate or comply with other topical products such as patches or gels. |
| **Oral Tablets** | | | | |
| Elleste Solo® | Estradiol 1mg or 2mg | None | Daily | |
| Bedol® | Estradiol 2mg | None | Daily | |
| Zumenon ® | Estradiol 1mg or 2mg | None | Daily | |
| Progynova® | Estradiol valerate 1mg or 2mg | None | Daily | |

| **9.4 Adjunctive Progestogen:** Use alongside either oral or transdermal oestrogen for women with uterus to provide endometrial protection. | | | | |
|---|---|---|---|---|
| **Brand** | **Oestrogen content** | **Progestogen content** | **Dose frequency** | **Comments** |
| **Intrauterine Delivery System** | | | | |
| Mirena® | None | Levonorgestrel 20mcg/24hrs | | Licensed for 4 years in UK for progestogenic opposition of oestrogen HRT but may be used for up to 5 years off-label. |
| **Oral Tablets/Capsules** | | | | |
| Utrogestan® | None | Micronised progesterone 100mg | Sequential combined dose is 200mg daily at bedtime, for twelve days in the last half of each therapeutic cycle (day 15-26).<br>Continuous combined dose is 100 mg at bedtime from day 1-25. | |
| Climanor® | None | Medroxyprogesterone acetate 5mg | In women with an intact uterus, a cyclic regimen of 10mg a day for the last 14 days of each 28 day cycle to reduce the risk to the endometrium. | |
| Provera® | None | Medroxyprogesterone acetate 2.5mg, 5mg or 10mg | Suggested dose of progestogen in a continuous combined HRT regimen would be a minimum 2.5 mg/day of medroxyprogesterone acetate.<br>For low-dose sequential regimens medroxyprogesterone acetate 10 mg/day for 10–14 days a month. | Provera® is not licensed for use as a progestogenic component of HRT but is widely used and supported by SWL Gynaecology Network |
| Noriday®<br><br>**AMBER 1** | None | Noresthisterone 350microgram | For continuous combined HRT regimen dose recommended is 3 tablets daily | Not licensed for progestogenic opposition of HRT.<br>**Can be initiated in primary care on specialist advice only.** |
| **Vaginal Pessary** | | | | |
| Utrogestan® vaginal capsules<br>**AMBER 2** | None | Micronised progesterone 200mg | 200mg daily at bedtime for 12 days a month | For patients who are unable to tolerate oral route.<br>Unlicensed for this indication.<br>**For specialist initiation then continuation in primary care** |

| **9.5 Vaginal Oestrogen Only:** Suitable for women with genitourinary syndrome of menopause only. Consider dexterity issues and patient preference. | | | | |
|---|---|---|---|---|
| **Brand** | **Oestrogen content** | **Progestogen content** | **Dose frequency** | **Comments** |
| **Vaginal Cream** | | | | |
| Ovestin® | Estriol 0.1% | None | 1 applicator (0.5mg estriol per application) Daily for 2 weeks followed by twice weekly | 15g tube (1 applicator = 0.5g therefore 30 doses in a pack). |
| Generic prep | Estriol 0.01% | None | 1 applicator (0.5mg estriol per application) Daily for 2 weeks followed by twice weekly | 80g tube (1 applicator = 5g therefore 16 doses in a pack). Second-line for patients unable to tolerate Ovestin®. |
| **Vaginal Tablets/Pessaries** | | | | |
| Vagirux® vaginal tablets | Estradiol 10microgram | None | 10microgram daily for 2 weeks followed by twice weekly | Applicator is reusable. |
| Vagifem® vaginal tablets | Estradiol 10microgram | None | 10microgram daily for 2 weeks followed by twice weekly | |
| Imvaggis® pessary | Estriol 0.03mg | None | One pessary daily for 3 weeks followed by twice weekly | Does not include applicator. |
| **Vaginal Ring** | | | | |
| Estring® | Estradiol hemihydrate released at an average amount of 7.5 micrograms per 24 hours over a period of 90 days | None | Remove and replace every 90 days. | Only licensed for 2 years continuous use.<br>Consider in patients with allergies to other topical products. |

| **9.6 Tibolone** | | |
|---|---|---|
| **Brand** | **Dose frequency** | **Comments** |
| Tibolone | 2.5mg tablets daily | During routine review consider change to alternative treatment option where appropriate. |

- The risk benefit profile of this agent differs to that of other forms of HRT (section 7.3) and should not be routinely used.
- This was traditionally offered as an alternative no-bleed regimen for postmenopausal women, more than 12 months after their last natural bleed. It was given as an alternative to combined HRT for postmenopausal women who wished to have amenorrhoea.
- In patients older than about 60 years, the risks associated with tibolone start to outweigh the benefits because of the increased risk of stroke as per MHRA guidance.

| **9.7 Testosterone :** Suitable for menopausal women experiencing low sex drive. | | | |
|---|---|---|---|
| **Brand** | **Testosterone content** | **Dose frequency** | **Comments** |
| | | **Gel** | |
| Testogel® sachets<br><br>**AMBER 2** | 40.5mg in 2.5g | Apply 1/8th (5mg) of a sachet daily. Apply a small pea sized amount once daily to clean and dry skin on either the lower abdomen, buttock or outer thighs. Rotate the site of application. Use at the same time each day. One 2.5g sachet should last 8 days, seal with a clip between uses. | • Unlicensed for use in women<br>• Do not use Testogel 16.2mg/g gel (pump version) preparation as the dispenser delivers supraphysiological levels.<br>• One pack should last approximately 8 months with usual use.<br>• Offer SWL Testosterone patient information leaflet<br>**For specialist initiation then continuation in primary care** |
| Tostran® pump dispenser<br><br>**AMBER 2** | 20mg in 1g. One press of the canister piston delivers 0.5g of gel containing 10mg testosterone. | One press delivers 0.5g of gel containing 10mg of testosterone for administration three times a week. Apply to clean and dry skin on either the lower abdomen, buttock or outer thighs. Rotate the site of application. | • Unlicensed for use in women<br>• One dispenser lasts 6-8 months with usual use.<br>• Offer SWL Testosterone patient information leaflet<br>**For specialist initiation then continuation in primary care** |

- Topical therapy may be useful for menopausal women with low sexual desire if standard HRT dose is not effective.
- There are currently no licensed treatments available for women in the UK.
- There are many issues affecting libido, so if testosterone replacement is being considered, consider ruling out other causes.
- Do not refer asymptomatic patients purely based on low systemic testosterone levels
- Testosterone should not be used in patients currently being treated with tibolone due to increased risk of androgenic side effects.
- In South West London, this medication has been approved for formulary use as an AMBER 2 medication. If clinically appropriate, a referral can be made to a menopause specialist.
- It can be useful to request baseline blood tests. See BMS guidance for current details.
- The specialist will initiate therapy issuing the first prescription. If the patient demonstrates clear benefits, prescribing and monitoring will occur in primary care.

**Monitoring of benefits and adverse effects testosterone:**

- An initial review to assess compliance, efficacy and tolerability should be done around 2-3 months from initiation.
- It may take 3-6 months to fully evaluate the efficacy of treatment.
- Check patients are correctly using product – this includes rotating sites of administration and checking that each pack is lasting roughly the expected durations indicated above.
- There should be at least an annual re-evaluation of ongoing usage based on the same criteria that would be used for standard hormone therapy i.e. carefully weighing up the pros and cons of long term usage.
- If any issues are identified, please use “Advice and Refer” for further guidance.

## 10. Trouble shooting and Management of side effects

### 10.1 Poor symptom control

**Table 7:** Suggested changes to combat poor symptom control

| Suspected problem | Advice |
|---|---|
| **Compliance** | Allow 3-6 months on treatment for the full effect & counsel on the importance of compliance. |
| **Oestrogen dose** | Increase dose or change route of administration. If the patient is already on high-dose (see table 6) consider changing to alternative product. Blood test to check levels may also be considered. |
| **Poor patch adhesion / skin irritation** | Ensure that patient is rotating the application site. Switch to alternative brand or to oestrogen gel. |
| **Incorrect diagnosis** | Review indications (e.g. thyroid disease) or refer. |
| **Poor absorption** | Consider change to route of administration. |
| **Unrealistic expectations** | Counsel patient. |
| **Drug Interactions** | Enzyme inducers lower the circulating levels of hormones e.g. phenytoin, carbamazepine, rifampicin – change to a non-oral route or increase the oral dose (specialist advice may be required). Intrauterine systems are not affected. |

### 10.2 Management of side effects

In all patients encourage them where possible to persevere with treatment for 3 months as side effects may resolve.

**Table 8:** Oestrogen-related adverse events-these may occur continuously or randomly throughout the cycle

| Side effects | Management |
|---|---|
| **Breast tenderness or enlargement** | • evening primrose oil or starflower oil purchased OTC<br>• wearing a well fitted bra or sports bra<br>• topical or oral Non-steroidal anti-inflammatory (NSAIDs) if not contra-indicated<br>• can be alleviated by a low-fat, high carbohydrate diet<br>• reduce the dose of oestrogen |
| **Nausea, bloating or dyspepsia** | • may be helped by adjusting the timing of the oestrogen dose or taking with food<br>• change the route of administration to a non-enteral formulation<br>• if caused by Utrogestan® consider vaginal use (off license) rather than oral |
| **Headaches or migraines** | • these may be triggered by fluctuating oestrogen levels – try switching to a transdermal route as this produces more stable oestrogen levels |
| **Angioedema** | • symptoms of angioedema can be exacerbated or caused by oestrogens. This is particularly relevant in patients with hereditary angioedema. Consider a referral to menopause expert |

**Table 9**: Progestogen-related adverse events – tend to occur in a cyclical pattern during the progestogen phase of cyclical HRT

| Side effects | Management |
|---|---|
| **Fluid retention**<br>**Breast tenderness**<br>**Lower abdominal pain**<br>**Back pain**<br>**Headaches or migraines**<br>**Mood swings**<br>**Depression**<br>**Acne** | • **Type:** Changing the progestogen type, for example from a more androgenic one (such as norethisterone and norgestrel) to a less androgenic one (Utrogestan®, medroxyprogesterone or dydrogesterone).<br>• **Route:** Changing the route of progestogen delivery, for example from oral to transdermal, vaginal, or intrauterine (IUS). This may be most beneficial for women who experience nausea with oral HRT.<br>• **Regimen:** Reducing the regimen of progestogen administration. Progestogens can be taken for 10–14 days of each monthly sequential regimen, so swapping from a 14-day to a 10-day product may provide benefit.<br>• **Product:** Changing to a product with a lower dose of progestogen.<br>• **Frequency:** Reducing the frequency of progestogen dosing. This can be achieved by switching to a long-cycle regimen of administering progestogen for 14 days every 3 months (but this strategy is only suitable for women without natural regular periods). Continuous progestogen provides better long-term protection than cyclical.<br>• **Changing to continuous combined therapy** often reduces progestogenic adverse effects with established use. However, this option is only suitable for postmenopausal women. |
| **NB: Treatment changes may need to be checked against the licensed indications and discussed with the patient as appropriate. See HRT Product lists for further details.** | |

## 11. Unscheduled bleeding on HRT

- Exclude 2 week rule criteria for referral
- Take a careful history to determine:
  - Type of HRT
  - Severity and extent of bleeding
  - Length of use of HRT
  - Compliance with HRT
- For the majority of cases changing progestogen intake will control the bleeding especially in women who experience unscheduled bleeding in the first few months after commencing HRT. For suggestions on how to do this see Table 10 below:

**Table 10:** Bleeding – troubleshooting advice

| Type of HRT | Management |
|---|---|
| **For sequential HRT regimens** | 1) Increase dose of progestogen:<br>• Micronised progesterone 300mg or medroxyprogesterone acetate 20mg for 12-14 days a month<br>2) Increase duration of progestogen intake to 21 days out of a 28-day HRT cycle.<br>3) Change type e.g. medroxyprogesterone acetate has good endometrial affinity and may provide the best bleed control |
| **For continuous combined HRT regimens** | 1) Increase dose of progestogen:<br>• If using micronised progesterone 100 mg daily increase to 200 mg daily on continuous basis.<br>• Medroxyprogesterone acetate 5mg to 10mg<br>• If using continuous combined HRT or oestrogen plus Mirena® consider adding micronised progesterone/ medroxyprogesterone acetate or norethisterone to their HRT regimen.<br>2) Change type to e.g. medroxyprogesterone acetate<br>3) Change to a sequential regimen for another 12 months OR<br>4) Add desogestrel 75mcg if the bleeding is 'period-like' suggesting ongoing ovulation.<br>If bleeding or spotting becomes heavier despite changes or occurs after a spell of amenorrhoea endometrial pathology should be excluded. Consider examination, transvaginal ultrasound and ensure cervical screening is up to date to exclude other causes and refer.<br>For further details see Primary Care Women's Health Forum documents:<br>• How to manage women presenting with abnormal uterine bleeding in primary care without face to face contact during COVID-19<br>• How to manage HRT provision without face to face consultations during COVID-19 |
| **NB: Treatment changes may need to be checked against the licensed indications and discussed with the patient as appropriate. See HRT Product lists for further details.** | |

## 12. Stopping HRT

- Stop HRT when risks outweigh benefits and the patient agrees to stop. Consider a gradual withdrawal of HRT to limit a recurrence of symptoms.
- Depending on clinical judgement, pending investigation, consider stopping HRT temporarily if the following occur:
  - Sudden breathlessness or cough with blood-stained sputum
  - Sudden severe chest pain (even if not radiating to left arm)
  - Blood pressure above systolic 160mmHg or diastolic 95mmHg
  - Serious neurological effects, including unusually severe, prolonged headache, especially:
    - If it is the first time, or getting progressively worse,
    - There is sudden partial or complete loss of vision,
    - Sudden disturbance of hearing or other perceptual disorders,
    - Dysphasia,
    - Vasovagal episode or collapse,
    - First unexplained epileptic seizure,
    - Weakness, motor disturbances, or very marked numbness suddenly affecting one side or one part of the body
  - Hepatitis, jaundice, or liver enlargement
  - Unexplained swelling or severe pain in calf of one leg
  - New contraindication to treatment
  - Prolonged immobility after surgery or leg injury – if oral HRT

## 13. Contraception

See the Faculty of Sexual and Reproductive Healthcare guidance on 'Contraception for Women Over 40 Years' for detailed guidance.

A woman is potentially considered to be fertile for 2 years after her last menstrual period if she is younger than 50 years of age, and for 1 year if she is over 50 years of age.[1]

In patients requiring contraception and free of all contraindications consider offering the following HRT/contraceptive options:

- Oestrogen-only pill, patch or gel and Mirena® coil (other intrauterine systems are not licensed for endometrial protection)
- Combined hormonal contraception (if eligible but only up until age 50)
- Sequential combined HRT (pill or patch) and progestogen-only contraception (tablet, implant, injection)
- If hormonal contraception is declined: advise barrier methods with sequential combined HRT

***When to stop contraception:***

- <50 years - 2 years after last period
- >50 years - 1 year after last period
- 45- 55 years - Mirena® after 45 years can stay in till age 55 for contraception and as part of HRT for 5 years only (unlicensed use)
- Stop hormonal contraception at 55 years of age
- Do not check FSH if on HRT / combined hormonal contraception
- If >50 years with amenorrhoea due to progestogen only method- check FSH: if FSH level >30 IU/L stop after 1 year, if <30 IU/L repeat again in 12 months
- On sequential HRT –contraception required until 55 years
- Detailed advice on when to stop contraception can be found on the CKS 'Contraception Assessment'.

## 14. Referral Criteria

### 14.1 Referral to menopause clinic

- Difficulty diagnosing menopause.
- Contraindication to HRT such as previous idiopathic or current VTE or history of recurrent VTE (unless the woman is already on anticoagulant treatment), active or recent arterial thromboembolic disease, thrombophilic disorder, active liver disease with abnormal liver function tests, acute porphyria.
- Carriers of faulty genes such as BRCA1 or BRCA2, known to increase risk of cancer or current, past or suspected breast cancer or other oestrogen-dependent cancer.
- Ineffectiveness or persistent side effects despite logical therapy changes.
- Low libido not improving on HRT – specialist advice required for consideration of testosterone therapy.
- Premature ovarian insufficiency (POI) - for further advice and management (if primary concern is fertility refer directly to fertility clinic). The following baseline tests should be done prior to referral for POI and included in referral letter:
- Thyroid function & TPO antibodies
- Prolactin levels
- Pelvic ultrasound
- DXA
- FSH/LH (2 levels done 6 weeks apart >30IU)

### 14.2 Referral to other clinics

Abnormal bleeding: exclude two week rule criteria and consider referral according to local management pathway on abnormal uterine bleeding:

- for those with normal physical exam but risk factors of irregular menstrual bleed, short cycle <24 days or prolonged bleeding ≥10 days and over the age of 40 years
- for patients taking:
  - **Sequential HRT** referral may be appropriate if there is an increase in heaviness or duration of bleeding, after attempt of adjustment of HRT (see Table 10) or if bleeding irregular
  - **Continuous combined HRT**: if bleeding beyond six months of therapy (despite adjustment of HRT – section 11), or if it occurs after spell of amenorrhoea

## 15. Further Information

- British Menopause Society contains up-to-date information on product shortages as well as useful guidelines including Tools for clinicians
- Royal College of Obstetricians & Gynaecologists (RCOG) information leaflet on alternative treatments to manage menopausal symptoms
- Women's Health Concern; provides a confidential, independent service to advise, inform and reassure women about their gynaecological, sexual and post reproductive health.

## 16. References & Acknowledgements


British Menopause Society. HRT Guide. July 2020. (Accessed 16.05.22)

British Menopause Society. Progestogens and Endometrial Protection. October 2021. (Accessed 16.05.22)

British Menopause Society. Testosterone replacement in menopause. July 2020. (Accessed 16.05.22)

British Menopause Society. BMS Consensus Statements. July 2020. (Accessed 16.05.22)

British National Formulary Online (Accessed 16.05.22)

Croydon Clinical Commissioning Group (CCG). Hormone Replacement Therapy (HRT) Guidance and Treatment Pathway. September 2018.

Medicines and Healthcare products Regulatory Agency. Hormone replacement therapy (HRT): further information on the known increased risk of breast cancer with HRT and its persistence after stopping. August 2019. (Accessed 16.05.22)

NHS Health A-Z. Menopause (Accessed 16.05.22)

National Institute for Health and Clinical Excellence. Clinical Guideline 23: Menopause: diagnosis and management. Updated December 2019 (Accessed 16.05.22)

National Institute for Health and Clinical Excellence. Clinical Knowledge Summaries: Menopause. Revised March 2022 (Accessed 16.05.22)

PrescQIPP Menopause B299. April 2022. (Accessed 16.05.22. Requires subscription to access)

Red Whale. Menopause and HRT. Updated January 2021. (Accessed 16.05.22)

Summary of Product Characteristics (SmPC). (Accessed 16.05.22)


## Document History

Version: V 1.0
Author: SWL ICS
Approved by: Integrated medicines committee (IMOC)
Approval date: Sept 2022
Review Date: 2 years or sooner where appropriate

### Updates

Version: 1.1 (28/11/2022)
Updates:

1. Correction: Table 9.2 (page 7) for Biiuve, progesterone content changed to progesterone 100mg.
2. Correction: Table 9.4 (page 9) for Utrogestan, vaginal pessaries changed vaginal capsules.