NHS
South Yorkshire
Integrated Care Board

HORMONE REPLACEMENT THERAPY (HRT)

Barnsley Formulary Treatment Options

Date Ratified by Barnsley Area Prescribing Committee:	**13th September 2023**
Date to be Reviewed:	**September 2026**

Useful links:

For healthcare-professionals-

https://thebms.org.uk/publications/tools-for-clinicians/

https://thebms.org.uk/wp-content/uploads/2019/11/HRT-alternatives-04.11.2019.pdf

For women-

https://www.nhs.uk/conditions/hormone-replacement-therapy-hrt/

ORAL TREATMENT OPTIONS

Oestrogen Only

(no uterus)
1 prescription charge

1st Line: Zumenon®
(1mg or 2mg estradiol)
OR Elleste Solo®
(1mg or 2mg estradiol)

2nd Line: Premarin®
0.625mg or 1.25mg conjugated oestrogen

Older women (60yrs plus) / low dose preparations
•For this group of patients, the following low oestrogen products may be more suitable:

Oestrogen only (includes transdermal options)
o **Premarin®** 300mcg (conjugated oestrogen)
o **Evorel®** 25 patch 25mcg/24hrs
o **Oestrogel®** (estradiol 0.75mg/measure, 1 measure= low dose)

Continuous combined
o **Premique®** low dose 300mcg (conjugated oestrogen and medroxyprogesterone acetate 1.5mg)
o **Kliovance®** (estradiol 1mg and norethisterone acetate 500mcg)

Sequential combined

(uterus - monthly bleed)
Perimenopausal, amenorrhoea <1 year
2 prescription charges

1st Line: Novofem ®
OR
Elleste Duet®
1mg or 2mg estradiol + 1mg norethisterone

2nd Line: Progestogenic side effects:
Femoston®
1mg or 2mg estradiol + dydrogesterone 10mg
OR
Tridestra 2mg estradiol + 20mg Medroxyprogestrone

Modifiable lifestyle factors - *ensure that these are addressed*
•Women should be advised to eat a healthy balanced diet, to maintain a healthy BMI, to ensure they eat sufficient dietary calcium (700mg/day) and undertake regular weight-bearing exercise.
•Ensure that a discussion occurs with the patient in order to address stopping smoking, reducing alcohol intake.
•Ensure optimum treatment of conditions such as diabetes and blood pressure as applicable in order to reduce the impact of such diseases on menopausal symptoms.

Progestogenic side effects:
e.g. PMS type symptoms, Breast tenderness, Lower abdominal pain, Backache, Depressed mood, Acne/greasy skin, headache).
If side effects are experience, a change of progestogen may be needed. See below

Continuous combined

(uterus – no bleed)
Postmenopausal,
Amenorrhea > 2 years
Age over 54 years old+
(uterus - no bleed) 1 prescription charge

1st Line: Kliofem® or Elleste Duet Conti®

2mg estradiol + 1mg norethisterone

2nd Line: **Progestogenic side effects:**

Femoston Conti® +
1mg estradiol + 5mg dydrogesterone
0.5mg estradiol +2.5mg dydrogesterone

OR

Indivina®
1mg or 2mg estradiol + 2.5mg or 5mg medroxyprogesterone acetate

OR

Bijuve®
1mg estradiol + 100mg micronized progesterone

Tibolone (Livial®)

(See text overleaf for full guidance)

Urogenital Atrophy
Ovestin® (0.1% estriol vaginal cream) or
Vagirux® (10mcg vaginal tablet)
To initiate (reducing course):
•Use once a night for 14 nights
•Twice per week thereafter
•Continue while therapeutic benefit
OR
Estring® (7.5mcg /24hrs vaginal delivery system) 3 month device

Consider transdermal rather than oral HRT for menopausal women who are at increased risk of VTE, including those with a BMI >30 kg/m2. https://www.nice.org.uk/guidance/ng23

TRANSDERMAL TREATMENT OPTIONS

Oestrogen only	Sequential combined	Continuous combined
1st line Evorel® patches Change TWICE per week 25, 50, 75, 100mcg estradiol **2nd line Estradot®** patches Change TWICE per week 25, 37.5, 50, 75, 100mcg oestradiol OR **Estraderm MX®** patches	**1st line Evorel Sequi®** patches Change TWICE per week 50mcg estradiol + 170mcg norethisterone	**1st line Evorel Conti®** patches Change TWICE per week 50mcg estradiol + 170mcg norethisterone
Oestrogel® 0.06% oestradiol gel, 0.75mg estradiol per measure, 2 measures= standard regime OR **Sandrena®** gel 0.5mg or 1mg estradiol individual sachets	If prostogenic side effects: **2nd line FemSeven Sequi®** patches Change ONCE weekly 50mcg estradiol + 10mcg levonorgestrel Alternative: Use oestrogen only transdermal therapy with micronised progesterone (**Utrogestan®**) 200mg at night for 12 days per cycle (usually from days 12-26) *	If progestogenic side effects: **FemSeven Conti®** patches Change ONCE weekly 50mcg estradiol + 7mcg levonorgestrel Alternative (also see below): Use oestrogen only transdermal therapy with micronised progesterone 100mg at night continuously**

*Provera (medroxyprogesterone) 10mg daily for 12 days per cycle can be used as an alternative

**Provera (medroxyprogesterone) 2.5mg-5mg daily continuously can be used as an alternative

Topical Oestrogen Treatment Options	Offer to women with urogenital atrophy (including those on systemic HRT) and continue at maintenance dose for as long as needed to relieve symptoms. **1st line Ovestin®** cream (0.1% estriol cream) once daily for 2 weeks, then use one application twice weekly **2nd line Vagirux®** tablets (10microg tablets) use one tablet at night for 2 weeks, then one twice weekly **3rd line Estring®** vaginal ring 7.5microg/24 hours reapply every 90 days. Max continuous duration of use – 2 years. Reserved for women with dexterity issues or allergies which prevent use of cream or vaginal tabs.

Alternative Progestogens

In the case of side effects or treatment shortages, alternative treatments may become necessary. Topical oestrogen treatment in combination with oral progesterones may also be used. In this case, micronised progesterone (Utrogestan®) or medroxyprogesterone (Provera®) can be used in the doses stated above.

Micronised progesterone is the only body identical progesterone and may be a helpful alternative option if the progestogenic side effects are experienced. If oral progestogens are not suitable or cause side effects, Levonorgestrel Intrauterine System (LNG-IUS) (Mirena®) can be used (see below).

Off-license Prescribing and High Dose Treatment

The BMS has published guidance on the appropriate doses of progestogens and endometrial protection, including unlicensed regimes. The dose of the progestogen should be proportionate to the dose of oestrogen and women who require high dose oestrogen intake should consider having their progestogen dose increased to ensure adequate endometrial protection. However, such use remains unlicensed, and it is up to individual clinicians to decide if they are willing to take on such prescribing, on the recommendation of private or NHS specialists.

14-BMS-TfC-Progestogens-and-endometrial-protection-NOV2022-A.pdf (thebms.org.uk)

HRT Formulary Treatment Options Additional information:

Choice of HRT

- Oestrogen only therapy should be used for women who have had a hysterectomy or have a Mirena Coil in place (see below).
- Unopposed oestrogen is associated with an increased risk of endometrial hyperplasia and with this comes an increased risk of endometrial cancer. Non- hysterectomised women require progestogens for 12-14 days per month (sequential combined) or daily (continuous combined).
- Sequential combined therapy should be given if perimenopausal, still having periods or LMP <1 year ago and age <54 years.
- Continuous combined therapy should be given if post-menopausal, LMP>1 year ago or age 54 and over.
- HRT may be oral or transdermal (patches, gels), depending on patient preference and risk factors. The risk of VTE and stroke is increased by oral HRT. Consider transdermal HRT for women who are at increased risk of VTE.
- Transdermal therapy should be considered if poor symptom control with oral therapy, GI disorders affecting oral absorption, personal or family history of VTE, BMI >30, poor BP control, migraines, use of hepatic inducing enzyme medication, gall bladder disease.
- Topical oestrogens can be used to manage symptoms of vaginal atrophy. Symptoms of vaginal atrophy include itching, dryness, burning, frequent urination and recurrent UTIs. When these symptoms predominate, consider topical treatment. This can also be used in addition to systemic HRT if necessary, as absorption is minimal. First line treatment is with vaginal tablets or cream used nightly for 2 weeks then twice weekly for maintenance treatment. E-string is reserved for patients who are unable to apply the first line options due to dexterity issues or allergies.

Levonorgestrel Intrauterine System (LNG-IUS) (Mirena® Coil)

- This is an intra-uterine hormone delivery system and can be a useful treatment option if progestogenic side effects are an issue with systemic treatment. It is licensed as a contraceptive, to treat menorrhagia and to give endometrial protection during oestrogen replacement therapy, as part of HRT. Mirena® has a green classification on the Barnsley Formulary and is for use by healthcare professionals who have received the appropriate training.
- Once the IUS is in place, if being used as part of a HRT regime, only additional oestrogen HRT is needed as a tablet, patch or topical gel. In a HRT regime, it has a 5 year license. Other IUS products (e.g.Levosert®) are not licensed for use as part of a HRT regime.
- Irregular bleeding is common in the first few months of use. An IUS should only be inserted into a perimenopausal woman, after an appropriate gynaecological/menstrual history and after appropriate assessment/investigation. Once in-situ, periods may be reduced by >95% by 6 months, and approximately 20% of users will be completely amenorrheic.

Tibolone (gonadomimetic)

- Tibolone is a synthetic steroid with oestrogenic, progestogenic and androgenic activity. As such, it is a type of continuous combined HRT and so is a no bleed preparation. Because of its androgenic activity, it has been shown to have a positive effect on libido.
- Tibolone has been shown to be as/or more effective than estradiol in controlling menopausal symptoms.
- Although 85% of tibolone users are amenorrhoeic, there is an 11% chance of irregular bleeding, so this may require gynaecological investigation.
- Long-term use of tibolone is thought to be associated with a similar increased risk of breast cancer to that of oestrogen alone, which is less than that of oestrogen plus progestogen.

Herbal Medicines

There are non-hormonal alternatives for menopause treatment, but none are as effective as HRT. There is some evidence that some herbal remedies may relieve vasomotor symptoms, however long term safety and efficacy has not been established and these can interact with other drugs. Herbal treatments are included in the NHS England guidance 'Items which should not routinely be prescribed in primary care' with no exceptions and should not be prescribed on a FP10. Further information and self-help advice can be found at: https://www.menopausematters.co.uk/what_to_do_at_menopause.php

Testosterone

- Although the British Menopause Society does recommend testosterone as a treatment option for loss of libido, there are no licensed treatments available for women in the UK.
- Locally, testosterone for this indication is shared care and should be initiated by an appropriate specialist. A shared care protocol exists to enable the continuation of care by primary care clinicians of women initiated on topical testosterone preparations for the management of menopausal symptoms by the menopause clinic at STHFT, where this is appropriate and in the patients' best interests.
- A copy is available at the link below, or on the BEST website:

  Topical Testosterone Therapy in Post-Menopausal Women Shared care guideline (barnsleyccg.nhs.uk)

Follow-up/Annual Review/Duration of treatment

- See patient after 3/12 of treatment to assess effect, enquire about side effects & bleeding pattern.
- Unscheduled vaginal bleeding is a common side-effect of HRT within the first 3 months of treatment, but should be reported promptly if it occurs after the first 3 months (see recommendations on endometrial cancer in the NICE guideline on suspected cancer (see reference section below).
- **At annual review**: check efficacy, side-effects, ensure correct dose, optimal route of delivery and compliance. Also check:
  - Pros & cons of continuing HRT, increased risk of breast cancer with long-term use, do benefits outweigh risks? In September 2019 the MHRA advised of new data which shows that an excess risk of breast cancer persists for longer after stopping HRT than previously thought (see link and information below). This new information should be discussed with women using HRT.
  - Check blood pressure, encourage breast awareness/attendance of screening mammography.
  - Assess osteoporosis risk & consider the need for investigation/monitoring.
  - Ensure cervical screening is up to date.
  - Enquire about symptoms of urogenital atrophy.
- **DURATION of treatment:**
  - Most guidelines recommend that the use of HRT for around 5 years in women as they enter menopause (i.e. in late 40's/early 50's) is likely to confer benefit and not harm.
  - There are no reasons to place mandatory limitations on duration of HRT, which should be decided with a well-informed woman & her health professional, dependent on specific goals & objective estimate of risks & benefits.
  - Withdraw HRT slowly as this may reduce the chance of recurrent symptoms. It should be noted that 5% of women will have hot flushes for life.

Contra-indications (see individual products Summary of Product Characteristics for full information: http://www.medicines.org.uk/emc/)

- Active liver disease with abnormal liver function tests.
- Untreated or unstable hypertension
- Active or recent thromboembolic disease
- Dubin-Johnson and Rotor syndromes (or monitor closely).
- Acute porphyria
- Pregnancy
- Previous idiopathic or current VTE unless the woman is already on anticoagulant
- Current, past or suspected breast cancer
- Known or suspected oestrogen-sensitive cancer
- Undiagnosed abnormal vaginal bleeding.
- Untreated endometrial hyperplasia

When To Refer

- Contraindications to HRT
- Complex medical history
- History of hormone dependent cancer
- Ineffectiveness of HRT or persistent side effects
- Unexplained bleeding
- Sudden change in bleeding pattern (e.g. ***sequential***- increase in heaviness or duration, or irregular bleeding; ***continuous***- bleeding beyond 6 months or after a period of amenorrhoea)

RISKS OF HRT: The NICE clinical guideline on menopause from 2019 is the best source to look at the risks of long - term HRT use, in order to explain such risks to your patient. See section 1.5 (p11) and tables 1 to 4: https://www.nice.org.uk/guidance/ng23.

MHRA Drug Safety Update August 2019: Hormone replacement therapy (HRT): further information on the known increased risk of breast cancer with HRT and its persistence after stopping:

https://www.gov.uk/drug-safety-update/hormone-replacement-therapy-hrt-further-information-on-the-known-increased-risk-of-breast-cancer-with-hrt-and-its-persistence-after-stopping?UNLID=632615138201911261523 20

Advice for healthcare professionals:

- a new meta-analysis of more than 100,000 women with breast cancer has shown that some excess risk of breast cancer with systemic HRT persists for more than 10 years after stopping; the total increased risk of breast cancer associated with HRT is therefore higher than previous estimates.
- prescribers of HRT should inform women who use or are considering starting HRT of the new information about breast cancer risk at their next routine appointment (see resources in the full alert).
- only prescribe HRT to relieve post-menopausal symptoms that are adversely affecting quality of life and regularly review patients using HRT to ensure it is used for the shortest time and at the lowest dose.
- remind current and past HRT users to be vigilant for signs of breast cancer and encourage them to attend for breast screening when invited.

References:

- The British Menopause Society: http://www.thebms.org.uk/
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- Menopause. NICE Quality standard [QS143] Published date: February 2017 https://www.nice.org.uk/guidance/qs143
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- Suspected cancer: recognition and referral. NICE guideline [NG12] Published date: Dec 2021 https://www.nice.org.uk/guidance/ng12

Acknowledgements

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Development Process

This guideline was approved by the Area Prescribing Committee on 13th September 2023.