NHS
South Yorkshire
Integrated Care Board

Progestogens for endometrial protection when using HRT
Guidance for Sheffield Primary Care

This guidance is summarised from the British Menopause Society (BMS) guidelines[1,2] and local recommendations. Primary care clinicians are advised to consult the full BMS guidelines for more detailed information.

Key points

- Oestrogen alone HRT will increase the risk of endometrial hyperplasia over 1-3 years.
- Women with an intact uterus need either sequential (cyclical) progestogen for 12-14 days per cycle, if less than 12 months since last LMP, or continuous (combined) if more than 12 months since LMP. The dose of progestogen should be in proportion to the oestrogen dose.
- If women stay on sequential HRT for more than 5 years there is a small increased risk of endometrial hyperplasia therefore it is better to switch to continuous combined after a minimum of 1 year, depending on the age of the patient when starting HRT and the duration of amenorrhoea prior to it (can do sooner rather than later if older women with more months of amenorrhoea).
- For the vast majority of women with unscheduled bleeding, increasing the progestogen dose or using an alternative type will settle things, especially in the first few months of use. For detailed guidance on when patients should be assessed to exclude endometrial pathology, refer to the SYB Cancer Alliance Guidance for patients on HRT with unscheduled bleeding and the BMS joint guideline Management of unscheduled bleeding on HRT[2,3].

Standard dose progestogen regimes:

Progestogens, licensed for HRT, are available as single oral preparations or in combination with oestrogen as oral preparations or transdermal patches or as intrauterine devices. Refer to Appendix 1 for recommended standard dose progestogen regimens and Sheffield Formulary choices.

Vaginal micronised progesterone: Oral capsules are not licensed for vaginal administration; whereas Utrogestan® 200 mg vaginal pessary, Cyclogest® 200 mg vaginal pessary and Lutigest® 100 mg vaginal pessary are not licensed for endometrial protection. Off label use may be considered where there are prostogenic side effects with oral use and other progestogens are not suitable. Local recommendation is to use the oral capsules by the vaginal route, in preference to the pessary products, at the same dose regimen as oral regimens. See below for recommendations for unscheduled bleeding.

Body identical compounded preparations from private providers are not recommended as the purity/potency and safety is unknown. Progesterone gel or cream has variable absorption and fluctuating levels so can't guarantee endometrial protection.

Higher dose progestogen regimes:
These may be required for unscheduled bleeding or for a higher oestrogen dose – see Appendix 2.

Options for unscheduled bleeding:

- Increasing the dose or changing the progestogen type.
- If taking oral micronised progesterone, increase dose to 300mg for 12-14 days for sequential or 200mg every night or on days 1 to 25 for continuous combined; these are unlicensed regimens. There is no evidence that vaginal micronised progesterone (off-licence use of oral capsules) reduces unscheduled bleeding episodes compared with oral use or other progestogens. Consider a 3 month trial of 200 mg micronised progesterone vaginally[2] if other progestogens are not tolerated; dosage is 200mg for 14 days for sequential or 200mg daily for continuous combined regimens.
- Offer all women a Mirena® 52 mg LNG-IUD; this preparation reduces episodes of unscheduled bleeding when compared with other preparations. Mirena® is licensed for endometrial protection for 4 years; studies have shown it to offer sufficient endometrial protection up to 5 years. Other 52mg LNG-IUD preparations are not licensed but are also recommended outside the licence by the BMS and FSRH.
- If using a combined patch or Mirena® or other 52mg LNG-IUD, then oral micronised progesterone or an alternative oral progestogen can be added in (unlicensed use).
- Oral preparations provide higher rates of amenorrhoea compared with transdermal oestrogen preparations and may be offered as an alternative, if BMI <30kg/m^2 and low risk of thrombosis [2,4].
- If bleeding occurs when starting or switching to continuous combined HRT, then switch back to cyclical for another year and then try again.

Licensed oestrogen dose and proportionate progestogen dose
The BMS recommends that the dose of the progestogen should be proportionate to the dose of oestrogen. Women who require high dose oestrogen intake should consider having their progestogen dose increased to ensure adequate endometrial protection (BMS 2021[1])

The BMS 2024[2] unscheduled bleeding on HRT guidance classifies the dose of oestrogen from ultra-low to high dose regimens for the different oestrogen products and gives the corresponding dose of progestogen for each. This has been reproduced in Appendix 2.

HRT and subtotal hysterectomy – use a sequential product for 3 months and if no bleeding can assume no endometrial tissue in cervical stump and switch to oestrogen alone. For existing individuals on oestrogen only HRT where this guidance has not been followed, a local recommendation is to consider an ultrasound of the pelvis to exclude any collection/mass and give the 3 month trial of cyclical HRT. If there is any abnormality on scan, refer to specialist. If there is no bleed on the cyclical therapy, it is safe to return to the current oestrogen-only regimen.

HRT and endometriosis – there is limited evidence to guide practice, however, continuous combined regimes should be considered following surgery for severe endometriosis to prevent reactivation and malignant transformation of any deposits/residual disease.

HRT and endometrial ablation - need progestogenic cover, not just oestrogen, as the uterus is intact and it cannot be assumed that all endometrial tissue has gone.

References:

1. BMS guideline Progestogens and endometrial protection (Oct 2021) https://thebms.org.uk/wp-content/uploads/2021/10/14-BMS-TfC-Progestogens-and-endometrial-protection-01H.pdf
2. BMS joint guideline Management of unscheduled bleeding on HRT (April 2024) https://thebms.org.uk/publications/bms-joint-guidelines/management-of-unscheduled-bleeding-on-hormone-replacement-therapy-hrt/
3. NHSE Getting It Right First Time (GIRFT) summary guide Management of unscheduled bleeding on HRT (June 2024) https://gettingitrightfirsttime.co.uk/wp-content/uploads/2024/06/Summary-Guide-Management-of-Unscheduled-Bleeding-on-HRT-June-2024.pdf
4. Sheffield Formuary Chapter 6.4.1.1 Oestrogens and Hormone Replacement Therapy (HRT) www.intranet.sheffieldccg.nhs.uk/Downloads/Medicines%20Management/Sheffield%20Formulary/Current%20Formulary%20Chapters/6_Endocrine.pdf

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Appendix 1: Standard dose progestogens licensed or with an evidence base for endometrial protection

Progestogen	Dose	Sheffield Formulary Product*	Notes
Micronised progesterone	Sequential regimen: 200mg po daily at bedtime from day 15 to day 26 of cycle (12 days/cycle) **or** 100mg po at bedtime from day 1 to day 25 of cycle (less withdrawal bleeding) Off label sequential regimen: 200mg po daily at bedtime for 2 out of 4 weeks (easier for women to remember) Continuous combined regimen: 100mg po daily, at bedtime – off label except for combination product Bijuve®	Utrogestan®, Gepretix®: 100 mg oral caps** No combined sequential product available. Continuous combined product: Bijuve® caps** (estradiol 1mg/progesterone 100mg) 1 po daily **caps contain gelatin	Consider generic prescribing to mitigate supply problems with Utrogestan®caps. **Vaginal use (unlicensed):** Oral capsules are not licensed for vaginal administration. Off label use, at the same doses as given orally, may be considered to reduce progestogenic side-effects where other progestogens are not suitable.
Medroxyprogesterone acetate (MPA)	Sequential regimen: 10mg po daily from day 15 to day 28 of cycle (14 days/cycle) Continuous combined regimen: 2.5mg/5mg po daily	MPA tabs 2.5mg, 5mg, 10mg tabs (generic); off label prescribing see notes. No combined sequential formulary choice product#. Continuous combined product: no formulary choice; cost-effective option Indivina® tabs (estradiol 1mg/MPA 2.5mg; estradiol 1mg/MPA 2.5mg; estradiol 2mg/MPA 5mg) 1 po daily.	Climanor® was the only brand of MPA licensed for the progestogenic opposition of oestrogen only HRT but this has been discontinued. # Combined sequential product (non-formulary): Tridestra® – a 3 monthly bleed product with 20mg MPA taken 14 days in every 91.
Dydrogesterone	Sequential regimen: 10 mg daily for 12-14 days a month	Combined sequential product: Femoston® (2 separate tabs)	Only available in combination products. Closest to micronised progesterone.

	Continuous combined regimen: 2.5mg/5 mg po daily	Estradiol 1mg or 2mg 1 po daily x 14 days then combined with dydrogesterone 10mg 1 po daily x 14 days. Continuous combined product: Femoston® conti tabs Estradiol 0.5mg/dydrogesterone 2.5mg 1 po daily. Estradiol 1mg/dydrogesterone 5mg 1 po daily	
Norethisterone	5mg tablets Sequential regimen: 1mg po daily from day 15 to day 26 of cycle (12 days/cycle) Continuous combined regimen: 0.5 to 1mg daily	Not licensed for endometrial protection. Combined sequential product oral: Elleste Duet® (2 separate tabs) Estradiol 1mg or 2mg 1 po daily x 16 days then combined with norethisterone 1mg 1 po daily x 12 days. Combined sequential product transdermal: Evorel® Sequi (2 separate patches) Estradiol 50mcg per 24 hours 1 patch twice weekly x 2 weeks then combined with norethisterone 170mcg per 24 hours 1 patch twice weekly x 2 weeks. Continuous combined products: Elleste Duet® Conti tabs Estradiol 2mg/norethisterone 1mg 1 po daily	Norethisterone alone is only available in 5mg tabs and therefore is less suitable for routine use outside low dose combination products. It should only be considered as an add on (i.e. outside combination products) for individuals with a BMI <30kg/m^2 due to thromboembolic risk (see Women's Health Concern, Statement regarding progestogens). If norethisterone is the preferred add on progestogen, an alternative to the 5mg tabs is to use the oral contraceptive norethisterone 350 micrograms and give 3 tabs (1.05mg); this is unlicensed.

		Kliovance® tabs Estradiol 1mg/norethisterone 500mcg 1 po daily Continuous combined product transdermal: Evorel® Conti patches Estradiol 50mcg/norethisterone 170mcg per 24 hours 1 patch twice weekly	
Levonorgestrel Intrauterine system (LNG-IUS)	52mg (20mcg/24 hours) for 4 years; off label for 5 years	Mirena® 52mg (20mcg/24 hours)	Mirena® 52mg is the only LNG-IUS that is licensed for endometrial protection. It is licensed for 4 years but can be used off label for 5 years. Levosert® and Benilexa® are also 52mg strength preparations and may be considered to provide adequate endometrial protection for up to 5 years. (BMS , FSRH guideline). There is a lack of evidence regarding Jaydess® (13.5mg strength and Kyleena® (19.5mg strength) and these are not recommended.

* For full range of HRT products and prescribing information see:

PrescQIPP HRT products table (as of Feb 22) – registration required

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Note: there is no evidence to support use of contraceptives such as combined oral contraceptives, standard dose progestogen only pills, Implanon®, or medroxyprogesterone acetate depo injection.

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Appendix 2: Licensed oestrogen dose and proportionate progestogen dose

The tables below are reproduced from BMS 2024 for educational purposes only.

Prescribed oestrogen dose for ultra-low, low, standard, moderate and high dose regimens

	Ultra-low dose	Low dose	Standard dose	Moderate dose	High dose
Oestrogel®	½ pump	1 pump	2 pumps	3 pumps	4 pumps
Sandrena® gel	0.25 mg	0.5 mg	1 mg	1.5 to 2 mg	3 mg*
Lenzetto® spray	1 spray	2 sprays	3 sprays	4 to 5 sprays*	6 sprays*
Patch	12.5 mcg	25 mcg	50 mcg	75 mcg	100 mcg
Oral estradiol	0.5 mg	1 mg	2 mg	3 mg^	4 mg^

*off licence use ^Off-licence use – rarely required to achieve symptom control

mg = milligrams mcg = micrograms

Progestogen dose per licensed oestrogen dose in the baseline population

Oestrogen dose	Micronised progesterone		Medroxyprogesterone		Norethisterone		LNG-IUD 52mg
	continuous	sequential	continuous	sequential	continuous	sequential	
Ultra-low / low	100 mg	200 mg	2.5 mg	10 mg	5mg*	5mg*	One up to 5years of use
Standard	100mg	200mg	2.5 to 5mg	10mg	5 mg*	5 mg*	
Moderate	100 mg	200 mg	5 mg	10 mg	5 mg	5 mg	
High	200 mg+	300 mg+	10 mg^	20 mg^	5 mg	5 mg	

*1 mg provides endometrial protection for ultra-low to standard dose oestrogen but the lowest stand-alone dose currently available in the UK is 5 mg (off-licence use of three Noriday® POP i.e 1.05 mg, could be considered if 5 mg is not tolerated).

^There is limited evidence in relation to optimal MPA dose with high dose oestrogen; the advised dose is based on studies reporting 10 mg providing protection with up to moderate dose oestrogen.

+There is limited evidence in relation to optimal micronised progesterone dose for moderate or high dose oestrogen; until evidence is available to guide practice, the advised dose is based on studies reporting 100 mg/day providing protection with up to standard dose oestrogen. If unscheduled bleeding occurs with ultra-low to moderate dose oestrogen, and other progestogens are not acceptable, offer micronised progesterone at the dosage recommended for high dose oestrogen.