

# Tayside Sexual & Reproductive Health Service (TSRHS)

## Complex Menopause Service

### “Prescribing HRT Support Information”



05/25

## Hormone Replacement Therapy- combined therapy: pharmacological content

Type	Route	Oestrogen	Progestogen	PV Bleed	Brand	Comment <sup>1</sup>
Sequential Combined Therapy	Patches	Estradiol 50 mcg/d	Norethisterone 170 mcg/d	Monthly	Evorel Sequi®	Twice weekly change 14d E/ 14d E&P
		Estradiol 50 mcg/d	Levonorgestrel 10 mcg/d	Monthly	FemSeven Sequi®	Weekly change 14d E/ 14d E&P Out of stock until ?later in 2025
	Tablets	Estradiol 1 mg	Norethisterone 1mg	Monthly	Elleste-Duet® 1 mg Novofem®	16d E/ 12d E&P
		Estradiol 1 mg	Dydrogesterone 10mg	Monthly	Femoston® 1/10	14d E/ 14d E&P CVD and breast friendly progestogen
		Estradiol 2 mg	Norethisterone 1mg	Monthly	Elleste-Duet® 2 mg Clinorette®	16d E/ 12d E&P
		Estradiol 2/2/1 mg	Norethisterone 1 mg	Monthly	Trisequens®	12d E/10d E&P/ 6d E Triphasic (reasoning?), only 10 days of progestogen ?safety
Estradiol 2 mg	Dydrogesterone 10mg	Monthly	Femoston® 2/10	14d E/ 14d E&P CVD and breast friendly progestogen		
Continuous Combined Therapy	Patches	Estradiol 50 mcg/d	Norethisterone 170 mcg/d	None	Evorel Conti®	Twice weekly change
		Estradiol 50 mcg/d	Levonorgestrel 7 mcg/d	None	FemSeven Conti®	Weekly change
	Tablets	Estradiol 0.5 mg	Dydrogesterone 2.5 mg	None	Femoston conti® 0,5/2,5	Ultralow oral dose CVD and breast friendly progestogen
		Estradiol 1 mg	Dydrogesterone 5 mg	None	Femoston conti® 1/5	CVD and breast friendly progestogen
		Estradiol 1 mg	Norethisterone 0.5 mg	None	Kliovance®	
		Estradiol 1 mg	Micronised progesterone 100 mg	None	Bijuve®	CVD and breast friendly progestogen Body-identical, well tolerated
		Estradiol 1 mg	Medroxyprogesterone 2.5 mg	None	Indivina® 1 mg/2.5 mg	"Strong progestogen" (↑risks, SE, bleeding control)
		Estradiol 1 mg	Medroxyprogesterone 5 mg	None	Indivina® 1 mg/5 mg	
		Estradiol 2 mg	Medroxyprogesterone 5 mg	None	Indivina® 2 mg/5 mg	"Strong progestogen" (↑risks, SE, bleeding control)
		Estradiol 2 mg	Norethisterone 1mg	None	Elleste Duet Conti® Kliofem®	
Conjugated oestrogen 300 mcg	Medroxyprogesterone 1.5 mg	None	Premique low dose®	Of equine origin		
Gonadomimetic	Tablets		Tibolone (2.5 mg)	None	Livial®	Higher CVD risk for patients >60. Only weakly estrogenic. Some androgenic effect.

<sup>1</sup> E= estrogen, P= progestogen, SE= side effects

## Hormone Replacement Therapy- oestrogen-only systemic therapy: pharmacological content

Type	Route	Estrogen	Brand	Comment
Unopposed Oestrogen*	Tablets	Estradiol 1 mg	Elleste- Solo® 1 mg Progynova® 1 mg Zumenon® 1 mg	
		Estradiol 2 mg	Bedol® Elleste-Solo® 2 mg Progynova® 2 mg Zumenon® 2 mg	
		Conj. oestrogen 300 mcg Conj. oestrogen 625 mcg Conj. oestrogen 1.25 mg	Premarin® 300 mcg Premarin® 625 mcg Premarin® 1.25 mcg	Of equine origin, low dose Of equine origin, medium dose Of equine origin, high dose dose
	Patches**	Estradiol 25 mcg	Estradot® Evorel® Estraderm MX®	Smallest patch on the market
		Estradiol 37.5 mcg	Estradot®	
		Estradiol 50 mcg	Estradot® Evorel® Estraderm MX® FemSeven® Progynova TS®	Smallest patch on the market Largest patch on the market Weekly change Weekly change
		Estradiol 75 mcg	Estradot® Evorel® Estraderm MX® FemSeven®	Smallest patch on the market Weekly change
		Estradiol 100 mcg	Estradot® Evorel® Estraderm MX® FemSeven® Progynova TS®	Smallest patch on the market Weekly change Weekly change
	Gel***	Estradiol (0.06%)	Oestrogel®	Pump: 1-4 pumps/day Use in two takes (AM, evening) if > 2 pumps
		Estradiol (0.1%) 500 mcg sachet Estradiol (0.1%) 1 mg sachet	Sandrena® Sandrena®	Sachets: 0.5-1.5 mg/day (up to 2 mg- unlicensed) More concentrated than Oestrogel®
	Spray	Estradiol 1.53 mg/spray	Lenzetto®	Max 3 sprays/d Low/medium dose product- max dose approx. equivalent to 40 mcg/d patch

\* In patients uterus: require additionally separate cyclical progesterone 12-14 d or continuously, or 52 mg LNG-IUD inserted under 5 years ago

\*\* All patches (except the weekly FemSeven® and ProgynovaTS® patches) should be used continuously, changed twice weekly and started within five days of period (or any time if cycle has ceased or periods infrequent). Recommended application sites are on clean, dry, healthy, intact skin and each application should be made to a slightly different area of skin on the trunk below waistline (abdomen, hip or buttock). Low dose patches or gel can be used as “top-ups”.

\*\*\* Apply to intact dry skin (lower trunk, thighs, arms, shoulders) over an area of 1-2 times size of hand. Avoid breast and vulval area. Let dry for 5 min before covering with clothing. No washing, use of other skin products or skin contact to another person for over an hour afterwards. Wash hands.

## Estradiol and conjugated estrogen equivalents

Route	Ultra-low dose	Low dose	Medium dose (Standard dose)	Moderate dose	High dose
Transdermal- patch	12.5 mcg/d (½ of a 25 mcg/d patch)	25 mcg/d	50 mcg/d*	75 mcg/d	100 mcg/d
Transdermal- gel (Oestrogel®) (estradiol 0.06%) (one squirt: 0.75 mg estradiol)	½ squirt (0.38 mg estradiol)	1 squirt (0.75 mg estradiol)	2 squirts ** (1.5 mg estradiol)	3 squirts ** (2.25 mg estradiol)	4 squirts ** (3 mg estradiol)
Transdermal- gel (Sandrena®) (estradiol 0.1%)	0.25 mg (½ of a 0.5 mg sachet)	0.5 mg	1 – 1.5 mg	2 mg ** off-license but can be considered	3 mg ** off-license but can be considered
Transdermal- spray (Lenzetto®)	na	1-2 sprays (21- 29 mcg/d)	3 sprays (40 mcg/d)	4-5 sprays- off-license but can be considered	6 sprays off-license but can be considered
Oral estradiol***	0.5 mg (1/2 of a 1 mg tablet or Femoston conti® 0.5/2.5)	1 mg	2 mg	3 mg off-license, rarely needed, indicated, or recommended- involve BMS approved menopause specialist	4 mg off license, rarely needed, indicated, or recommended- involve BMS approved menopause specialist
Conjugated equine estrogen (CEE)***	na	0.3 mg	0.625 mg	1.25 mg	Usually not needed, indicated, or recommended

\* All combined sequential and continuous HRT patches currently on the UK market contain 50 mcg/d estradiol

\*\* If using more than medium/standard dose- consider dividing application of estradiol gel into two takes- AM and evening.

\*\*\* Oral route is contraindicated in patients with a BMI ≥ 30 or with increased VTE or CVD risk factors.

## Progestogen dose per licensed estrogen dose (if combined preparations not suitable)

(adapted from the BMS/RCOG Guideline: Management of unscheduled bleeding on HRT- 04/24)

Estrogen dose	Micronised Progesterone (MP) (Utrogestan®, Gepletix®)		Medroxyprogesterone (MPA) (Provera®)		Norethisterone (NE) (unlicensed)		LNG-IUD (52mg) (Mirena®, Benilexa® or Levosert®)
	continuous	sequential* (minimum 12 days/ 28 days)	continuous	sequential* (minimum 10 days/ 28 days)	continuous	sequential* (minimum 10 days/ 28 days)	
Ultra-low dose	100 mg	200 mg	2.5 mg	10 mg	5 mg**	5 mg	One up to 5 years of use  (off label)
Low dose							
Medium dose (Standard dose)	100 mg	200 mg	5 mg	10 mg	5 mg**	5 mg	
Moderate dose	100 mg	200 mg	5 mg	10 mg	5 mg	5 mg	
High dose	200 mg	300 mg	10 mg***	20 mg***	5 mg	5 mg	

**Consider prescribing combined preparations as first line  
(if a 52 mg LNG-IUD is not acceptable or suitable) due to concerns about compliance with a separate progestogen for endometrial protection.  
The role and importance of the separate progestogen needs to be explained to the patient and the need of compliance emphasised.**

\* Prescribing a separate progestogen sequentially as 2 weeks on 2 weeks off will likely help compliance.

\*\* 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-license use of three Noriday® POP (350 mcg x 3) 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.

**See previous page with regards to the definition of oestrogen doses. Most regimes are off label.**

## HRT patches available in the UK

HRT patch	Estradot®	Progynova TS®	FemSeven®	Evorel®	Estraderm MX®
Change	Twice weekly	Weekly	Weekly	Twice weekly	Twice weekly
<b>Estradiol only</b>					
25 mcg/d	2.5 cm <sup>2</sup>	na	na	8 cm <sup>2</sup>	11 cm <sup>2</sup>
37.5 mcg/d	3.75 cm <sup>2</sup>	na	na	na	na
50 mcg/d	5 cm <sup>2</sup>	12.5 cm <sup>2</sup>	15 cm <sup>2</sup>	16 cm <sup>2</sup>	22 cm <sup>2</sup>
75 mcg/d	7.5 cm <sup>2</sup>	na	22.5 cm <sup>2</sup>	24 cm <sup>2</sup>	33 cm <sup>2</sup>
100 mcg/d	10 cm <sup>2</sup> (3.2 cm/side)	25 cm <sup>2</sup> (5 cm/side)	30 cm <sup>2</sup> (5.5 cm/side)	32 cm <sup>2</sup> (5.7 cm/side)	44 cm <sup>2</sup> (6.6 cm/side)
<b>Combined patches</b>					
50 mcg/d + NE	na	na	na	16 cm <sup>2</sup> Evorel® Sequi or Conti (4 cm/side)	na
50 mcg/d + LNG	na	na	15 cm <sup>2</sup> FemSeven® Sequi or Conti (3.9 cm/side)	na	na
	<b>Size increases</b>	➔	➔	➔	➔

### Comments:

- The estradiol concentration stays the same per patch brand- they only get bigger with increased strength.
- Every patch adhesive is different- if there is a mild skin reaction with one patch it might be worth trying a different patch before changing to other Transdermal preparation (gel, spray) or the route. Using a puff of Clenil® (beclometasone) steroid inhalers on the skin before applying the patch when dried has been used to reduce skin reactions (not evidence based).
- Smaller patches might adhere and therefore be absorbed better.
- Weekly patches might help compliance but might adhere less but cause more skin irritation.
- FemSeven® Sequi is out of stock- ?back in stock Q1 2024.

## Possible hormonal side effects: classification according to hormone class\*

Side effect	Estrogenic	Progestogenic
Acne +/- seborrhoea	- (can help)	+ (especially "older" generation progestogens)
Anxiety	- (can help)	+
Bloating	+/-	+
Breast swelling	+	+/-
Breast tenderness	+	+/-
Decreased sex drive	- (can help, but oral estradiol increases SHBG which inactivates testosterone)	+/- (assoc. with low mood)
Depression	- (can help)	+
Growth of uterine fibroids	++	+
Headaches	+	+
Hirsutism	- (can help)	+
Mood swings	- (can help)	+
Nausea	+	-
Raised BP	+	-
Weight gain	+/- (water retention: cyclical gain)	+/- (via increased appetite)

\* Similar side effects as hormones used in hormonal contraception but bodyidentical estradiol used in HRT often better tolerated than ethinylestradiol used in combined hormonal contraception (CHC)

## Difference between licensed progestogen options when prescribing oestrogen and progestogen separately as part of HRT

### Sequential HRT

Name	Progestogen	Dosage	Comment
Mirena <sup>®</sup> , Benilexa <sup>®</sup> or Levosert <sup>®</sup> LNG- IUD	Levonorgestrel	52 mg	<p>Allows continuous HRT in the perimenopause, provides contraception, good bleeding control, low systemic progestogen levels and fewer systemic side effects.</p> <p>Lack of data re. CV, VTE and breast ca risk compared to other combined HRT regimes.</p> <p>Not suitable in patients with submucosal fibroids.</p> <p>Can be used for up to 5 years. Unlicensed use &gt; 4 years with Mirena<sup>®</sup>, and overall unlicensed indication for Benilexa<sup>®</sup> and Levosert<sup>®</sup>, but supported by the FSRH (03/23).</p> <p>Risk of unopposed oestrogen px when LNG- IUD is not replaced on time- consider recall alert, pop up reminders etc.</p>
Provera <sup>®</sup>	Medroxy- progesterone acetate	10 mg	<p>Compliance is essential when prescribing separate oral progestogen: see further comments below</p> <p>10 mg/d 14 days on, 14 days off. Licensed for but simplified regime could help compliance.</p> <p>Good for bleeding control.</p> <p>Higher CV, VTE and breast ca risk than micronised progesterone</p> <p>Increase dose if px high dose estradiol (100 mcg/d estradiol patches or 4 pumps of oestrogen<sup>®</sup> etc.)- see table previous page.</p>
Utrogestan <sup>®</sup> / Gepretix <sup>®</sup>	Micronised progesterone	200 mg (2 x 100 mg oral capsule)	<p>Compliance is essential when prescribing separate oral progestogen: see further comments below</p> <p>200 mg/nocte 14 days on, 14 days off. Licensed 12 days per 28-day HRT cycle for but simplified regime could help compliance.</p> <p>Take at night as it can cause tiredness. Could help insomnia.</p> <p>Tends to be well tolerated. Safer with regards to breast ca, CVD and VTE risks.</p> <p>Oral capsules can be used vaginally, especially when getting systemic side effects (unlicensed in the UK but licensed widely used in the EU)- same dose as oral regime.</p> <p>Increase dose if px high dose estradiol (100 mcg/d estradiol patches or 4 pumps of oestrogen<sup>®</sup> etc.)- see table previous page.</p>

**Further comments:**

Sequential HRT is not contraceptive. Compliance with separately prescribed progestogen tablets is important and needs to be emphasised to the patient, to avoid unopposed or sub-optimally opposed oestrogen and therefore risk endometrial hyperplasia or cancer. Please recommend the use of reminders on physical or smart phone calendar or visual reminders to help compliance.

## Continuous HRT

Name	Progestogen	Dosage	Comment
Mirena®, Benilexa® or Levosert® LNG- IUD	Levonorgestrel	52 mg	<p>Allows continuous HRT in the perimenopause, provides contraception, good for bleeding control, low systemic progestogen levels and fewer systemic side effects.</p> <p>Lack of data re. CV, VTE and breast ca risk compared to other combined HRT regimes.</p> <p>Not suitable in patients with submucosal fibroids.</p> <p>Can be used for up to 5 years. Unlicensed use &gt; 4 years with Mirena®, and overall unlicensed indication for Benilexa® and Levosert®, but supported by the FSRH (03/23).</p> <p>Risk of unopposed oestrogen px when LNG-IUD is not replaced on time- consider recall alert, pop up reminders etc.</p>
Provera®	Medroxy-progesterone acetate	5 mg	<p>Compliance is essential when prescribing separate oral progestogen: see further comments below</p> <p>5mg/d- could consider 2.5 mg with low dose estradiol px only</p> <p>Good for bleeding control.</p> <p>Higher CV, VTE and breast ca risk than micronised progestogen.</p> <p>Increase dose if px high dose estradiol (100 mcg/d estradiol patches or 4 pumps of oestrogen® etc.)- see table previous page.</p>
Utrogestan®/ Gepretix®	Micronised progesterone	100 mg (oral capsule)	<p>Compliance is essential when prescribing separate oral progestogen: see further comments below</p> <p>100 mg/nocte as recommended by the BMS (British Menopause Society). Licensed for days 1–25 of each 28-day HRT cycle but continuous use/simplified regime could help compliance and is usually prescribed.</p> <p>Take at night as it can cause tiredness. Could help insomnia.</p> <p>Tends to be well tolerated.</p> <p>Safer with regards to breast ca, CVD and VTE risks.</p> <p>Oral capsules can be used vaginally, especially when getting systemic side effects (unlicensed in the UK but licensed widely used in the EU)- same dose as oral regime.</p> <p>Increase dose if px high dose estradiol (100 mcg/d estradiol patches or 4 pumps of oestrogen® etc.)- see table previous page.</p>

**Further comments:**

Compliance with a separate (oral or vaginal) progestogen is important and needs to be emphasised to the patient, to avoid unopposed or sub-optimally opposed oestrogen and risk endometrial hyperplasia or cancer. Please recommend the use of reminders on physical or smart phone calendar or visual reminders to help compliance.

## Main progestogen types used for endometrial protections (part of HRT)

Progestogen	HRT products	Type of HRT	Estradiol	Androgenic	Anti-androgenic	Anti-mineral-corticoid
<b>Norethisterone (NE)*</b>	Evorel Sequi® Elleste-Duet® 1 mg ≈ Novofem® Elleste-Duet® 2 mg ≈ Clinorette®	Sequential	50 mcg/d 1 mg 1 mg 2 mg 2 mg	+	-	-
	Evorel Conti® Kliovance® Elleste Duet Conti® ≈ Kliefem®	Continuous	50 mcg/d 1 mg 2 mg 2 mg			
<b>Levonorgestrel (LNG)</b>	FemSeven Sequi®	Sequential	50 mcg/d	+	-	-
	FemSeven Conti®	Continuous	50 mcg/d			
<b>Dydrogesterone</b>	Femoston® 1/10 Femoston® 2/10	Sequential	1 mg 2 mg	-	+/-	+/-
	Femoston conti® 0,5/2,5 Femoston conti® 1/5	Continuous	0,5 mg 1 mg			
<b>Medroxyprogesterone acetate (MPA)</b>	Provera®	Sequential	na	+/-	-	-
	Provera® Indivina® 1 mg/2.5 mg Indivina® 1 mg/5 mg Indivina® 2 mg/5 mg	Continuous	na 1 mg 1 mg 2 mg			
<b>Micronised progesterone (MP)</b>	Utrogestan® Gepetrix®	Sequential	na na	-	+/-	+
	Utrogestan® Gepetrix® Bijuve®	Continuous	na na 1 mg			

\* Norethisterone also has mild oestrogenic properties  
na= not applicable

# Unscheduled Bleeding on HRT

## History, investigations and potential HRT adjustments before or when referring to the Post Menopausal Bleeding Clinic (gynaecology)

*(adapted from from the BMS/RCOG Guideline: Management of unscheduled bleeding on HRT- 04/24)*

### General principles of HRT px

- At initiation of HRT, start low or medium estradiol dose preparation.
- Combined HRT products are first choice, or estradiol plus 52 mg LNG-IUD. Combined HRT products reduce the risk of unopposed or underopposed estradiol prescription due to poor compliance with a separate progestogen capsule/tablet, due to prescription errors etc.
- At initiation of HRT, offer a sequential preparation in patients who are still menstruating (LMP < 1 year ago).
- Time the start of sHRT to their natural cycle, starting with the oestrogen only part with their next period (if appropriate).
- Offer ccHRT if initiating HRT and patient is postmenopausal (last period  $\geq$  1 year ago) or has been using sHRT  $\geq$  5 years, especially when aged  $\geq$  50 years.
- Offer the 52 mg LNG-IUD for endometrial protection, if appropriate, to patients initiating HRT, particularly if contraception is also required.
- Offer ccHRT in patient with established amenorrhoea on progestogen-only contraception, after endometrial ablation or with expired 52 mg LNG-IUD (> 5 years) (3/12 trial-reverse to sHRT if getting bleeding issues).

### General principles when patient have unscheduled bleeding on HRT

- Check HRT prescription- correct type? correct amount of progestogen to provide endometrial protection with the px dose of estradiol?
- Assess when HRT was started and bleeding pattern before starting, current bleeding pattern (heaviness, pattern-random or cyclical, postcoital etc), associated symptoms (pain, dyspareunia, discharge, PMS symptoms), O&G history, smear history, sexual history.
- Assess compliance, skin adherence, absorption (oral estradiol or oral combined HRT), drug interaction + / - correct order of pills or patches if using sHRT.
- Check cervix (speculum), do a vaginal and abdominal examination.
- Take smear, do pregnancy test and sexual health screening if appropriate.
- Offer vaginal oestrogen if atrophic findings on clinical examination or patient have symptoms of the genitourinary syndrome of the menopause/ vulvovaginal atrophy), even in patients on systemic HRT.
- Recommend applying the estradiol gel when taking the oral progestogen.
- A 52 mg LNG-IUD for endometrial protection leads to the best bleeding control.
- Oral progestogen (especially medroxyprogesterone acetate) leads often to better bleeding control than transdermal progestogen.
- Synthetic progestogen (medroxyprogesterone acetate, norethisterone) leads often to better bleeding control than micronized progesterone.
- Consider reducing the oestrogen if acceptable and supplement with non-hormonal pharmaceutical and non-pharmaceutical treatment options if required.

### Non-combined HRT combinations (separate progestogen tablet or capsule)

- Check compliance and dosage.
- Educate patient and review early to recheck understanding and compliance.
- Offer the 52 mg LNG-IUD.
- Change to a combined HRT patch.
- Change to a combined oral HRT (if eligible- BMI < 30 and low VTE/CVD risk).
- Double check the BMS/RCOG Joint Guideline: Management of unscheduled bleeding on HRT (04/24) for their recommendations about the appropriate dose of progestogen in patients on higher dose estradiol (4 pumps of oestrogen<sup>®</sup> or a 100 mcg/d estradiol patch).
- Consider recommending using the oral micronized progesterone capsules vaginally (same timing and dosage, unlicensed in the UK but licensed in the EU).

**Fibroids**

- Offer the 52 mg LNG-IUD (if cavity  $\leq$  10 cm and uterine cavity is not distorted- contraindicated in submucosal fibroids).
- Switch to a synthetic progestogen or increase dose of synthetic progestogen. Increase micronized progesterone dose if this is not acceptable.
- Consider referral to gynae to discuss hysteroscopic resection of fibroids if fibroids submucosal and progestogen adjustments are not acceptable, or unscheduled bleeding continues.

**BMI  $\geq$  30**

- Offer weight management strategies.
- Offer the 52 mg LNG-IUD.
- Switch to a synthetic progestogen or increase dose of synthetic progestogen. Increase micronized progesterone dose if this is not acceptable.

**Unscheduled bleeding with sHRT**

- Consider adding a desogestrel POP to suppress endogenous ovarian activity.
- If  $<$  50 and low VTE and CVD risk, consider switching HRT to a COC if eligible according to the UKMEC.
- Change to a combined oral preparation (if BMI  $<$  30 and low risk of VTE/CVD).
- Offer the 52 mg LNG-IUD.
- Switch to a synthetic progestogen or increase dose of synthetic progestogen. Increase micronized progesterone dose if this is not acceptable.
- Consider 3-month trial of an additional progestogen on top of the current preparation.
- Reduce the oestrogen and supplement with non-hormonal pharmaceutical and non-pharmaceutical treatment options if required.

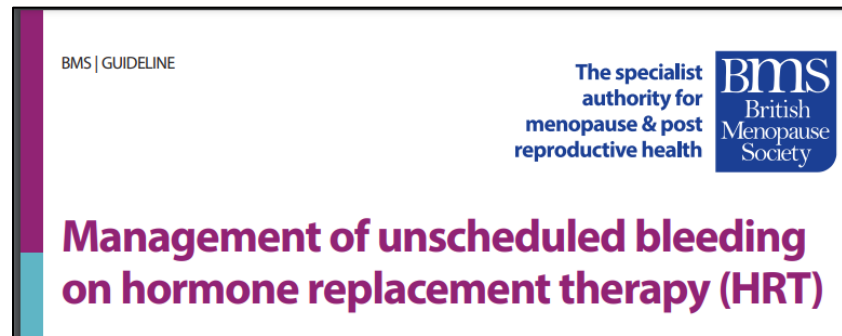
**Unscheduled bleeding with cHRT**

- Offer a 52 mg LNG-IUD.
- Change from combined patch to a combined oral preparation (if BMI  $<$  30 and low risk of VTE/CVD).
- Switch to a synthetic progestogen or increase dose of synthetic progestogen. Increase micronized progesterone dose if this is not acceptable.
- Offer a 3-month trial of an additional progestogen on top of the current preparation (including patients using a 52 mg LNG-IUD).
- Consider a 6-month trial of sHRT if recently postmenopausal, or in patients with premature ovarian insufficiency or early menopause (?transitional ovarian activity).
- Consider reducing the oestrogen and supplement with non-hormonal pharmaceutical and non-pharmaceutical treatment options if required.

**Unscheduled bleeding on 52 mg LNG-IUD**

- Any 52 mg LNG-IUD can be used for endometrial protection for up to 5 years (Mirena®, Benilexa®, Levosert®).
- Irregular due to a newly inserted LNG-IUD is common in the first 3-6/12 after insertion.
- Check type of LNG-IUD and insertion date.
- Check bleeding pattern before insertion and any previous pelvic USS results (?submucosal fibroids).
- Check any associated symptoms of infection or malposition.
- Check for threads and for threads length. An expected thread length (2-3 cm) does not exclude a malpositioned LNG-IUD as the device might have been inserted low.
- Offer an early change of 52 mg LNG-IUD (before 5 years) if new onset unscheduled bleeding after  $\geq$ 4 years of use and investigations are normal (esp. if BMI  $\geq$  40).
- Offer a 3-month trial of an additional progestogen on top of a 52 mg LNG-IUD (but exclude pathology and a malposition).

Check out the BMS/RCOG Joint Guideline “Unscheduled Bleeding on HRT” (04/24) about which patients to refer to the Postmenopausal Bleeding Clinic (Gynaecology): <https://thebms.org.uk/2024/04/joint-bms-bsge-bgcs-fsrh-girft-and-rcog-guideline-on-management-of-unscheduled-bleeding-on-hrt/>






## Topical (vaginal) treatment options for VVA/GSM (vulvovaginal atrophy/ genitourinary syndrome of the menopause)

Name	Topical (vaginal) oestrogen	Type	Use	Comments	Costs for 1/12 tx (maintenance dose) (MIMS 03/24)
<b>Estriol</b>					
<b>Ovestin<sup>®</sup> or generic equivalent</b>	<b>Estriol 0.1%</b> One applicator: 0.5 mg estriol	Intravaginal cream	One applicator nightly for 2-4/52, then 2 x /week maintenance	<b>First choice in TAF.</b> Most cost-effective topical HRT. Small volume (0.5 ml). Can be messy (vaginal leakage). Applicator reusable. Can be applied to external genitalia. Effect on condoms not known.	£1.18
<b>Estriol pessary (generic)</b>	<b>One pessary: 0.5 mg of estriol</b>	Intravaginal pessary	One pessary nightly for 3/52, then 2 x /week maintenance	<b>First choice in TAF but more expensive than Ovestin<sup>®</sup>, Vagirux<sup>®</sup> and Imvaggis<sup>®</sup>.</b> Waxy pessary- larger than vaginal tablet but no applicator needed. Less waste. Might be easier to use than products with applicator, especially in patients with visual impairment or reduced manual dexterity. Effect on condoms not detailed by the SPC.	£5.45
<b>Gynest<sup>®</sup> discontinued-generic equivalent</b>	<b>Estriol 0.01%</b> One applicator: 0.5 mg estriol	Intravaginal cream	One applicator nightly until improvement occurs, then 2 x /week maintenance	<b>Not on Tayside Formulary</b> Most expensive option. Diluted- large volume (5 ml)- same estriol content/application as 0.1% cream. Might be less irritant than other cream. Can be messy. <u>Includes peanut oil- avoid if allergic.</u> Applicator reusable. Can also be applied to vulva. Can damage condoms.	£12.50
<b>Blissel<sup>®</sup></b>	<b>Estriol 0.005%</b> One applicator: 0.05 mg estriol	Intravaginal gel	One applicator nightly for 3/52, then 2 x /week maintenance	<b>Not on Tayside Formulary</b> Low dose option. Reusable plastic applicator. Effect on condoms not detailed by the SPC.	£5.04
<b>Imvaggis<sup>®</sup></b>	<b>Estriol 0.003%</b> One pessary: 0.03 mg estriol	Intravaginal pessary	One pessary nightly for 3/52, then 2 x /week maintenance	<b>First choice in TAF but more expensive than Ovestin<sup>®</sup> and Vagirux<sup>®</sup>.</b> <u>Ultra-low dose option.</u> Waxy pessary- larger than vaginal tablet but no applicator needed. Less waste. Might be easier to use than products with applicator, especially in patients with visual impairment or reduced manual dexterity. Can damage condoms.	£4.46
<b>Estradiol</b>					
<b>Vagirux<sup>®</sup></b>	<b>Estradiol (10 mcg)</b>	Intravaginal tablet	One tablet nightly for 2/52, then 2 x /week maintenance	<b>First choice in TAF but more expensive than Ovestin<sup>®</sup> cream.</b> Same as Vagifem <sup>®</sup> but environmentally friendlier and cheaper option. One plastic applicator for 24 tablets- applicator needs to be washed after use. Can be used up to 5 x/week (unlicensed). Effect on condoms not detailed by the SPC.	£3.78
<b>Vagifem<sup>®</sup></b>	<b>Estradiol (10 mcg)</b>	Intravaginal tablet	One tablet nightly for 2/52, then 2 x /week maintenance	<b>First choice in TAF but more expensive than Ovestin<sup>®</sup>, Vagirux<sup>®</sup>, Imvaggis<sup>®</sup> and generic estriol pessaries.</b> One disposable plastic applicator for each tablet. Can be used up to 5 x/week (unlicensed). Compatible with condoms.	£5.57
<b>Estring<sup>®</sup></b>	<b>Estradiol (7.5 mcg/ 24 hours)</b>	Intravaginal ring	One ring in the upper third of vagina <u>every three months</u>	<b>Second choice on TAF.</b> Slightly stronger than other products- good effect as constant hormone release. Not messy. Can stay in situ during sex or be removed, if preferred. Can be used together with pessary rings for uterine prolapse tx. Effect on condoms not detailed by the SPC. Replaced by patients themselves every 3/12. Maximal licensed duration: two years but often used long-term (off label).	£10.47

Name	Topical (vaginal) product	Type	Use	Comments	Costs for 1/12 tx (maintenance tx) (MIMS 03/24)
<b>Prasterone (dehydroepiandrosterone- DHEA)</b>					
<b>Intrarosa®</b>	<b>Prasterone 6.5 mg</b>	Intravaginal pessary	One pessary <u>nightly</u>	<p><b>Not on Tayside Formulary. Not submitted to or approved by SMC</b></p> <p>DHEA is converted to oestrogens and androgens. Treatment should be reassessed at least every 6 months (BNF). Can be inserted with finder or applicator. Can damage condoms. Some patients experience better symptoms relief compared to twice weekly products as product used every day. <u>See also Estring® for the same advantage.</u> Could be consider via non-formulary request after several topical oestrogen (over 3/12- 6/12 each) and non-hormonal treatment options do not improve symptom. Could be started and then switched back to topical oestrogen once symptoms controlled.</p>	£15.94

*The therapeutical effectiveness of these products in treating the symptoms of the genitourinary syndrome of the menopause (vulvovaginal atrophy) has not been compared directly but is likely similar.*

**Characteristics of LNG-IUDs suitable for endometrial protection and available in the UK (all devices are on TAF)**

Device	Design	Levonorgestrel (LNG) - total amount - initial release rate	Minimum uterine depth	Maximum uterine depth	Inserter tube width + other info	LNG-IUD dimension	Licensed indications + duration of use	Comment	Price (BNF 05/2024)
Mirena®		52 mg 20.1 mcg/24h	6 cm (FDA advice only)	10 cm (FDA advice only)	One handed technique (EvoInserter®) Width 4,4 mm Not reloadable (Original inserter: 4,75 mm)	Width: 32 mm Length: 32 mm	4 years as part of HRT Licensed indications: contraception, HMB, endometrial protection (part of HRT/PMS tx) Brown retrieval threads	"Gold standard" LNG-IUD. <b>See note underneath regarding BMS/FSRH recommended extensions of use.</b>	£88 (£17.6 /year for 5 years use)
Benilexa®		52 mg 20.1 mcg/24h	5,5 cm	na	One handed technique Width 4,8 mm Reloadable Longer inserter	Width: 32 mm Length: 32 mm	Licensed indication: contraception and HMB (not part of HRT) Blue retrieval treads	<b>See note underneath regarding FSRH recommended unlicensed indication as part of HRT/PMS tx.</b> Larger inserter- consider if uterine sounding easy, or HCP able to dilate cervix. Distance from IUC tip to slider approx. 2 cm longer compared to EvoInserter® - might come handy in patients with a long vagina or requiring a long speculum (Winterton's).	£71 (£14.2/year for 5 years use)
Levosert®		52 mg 20.1 mcg/24h	5,5 cm	na	Two-handed technique Width 4,8 mm Reloadable	Width: 32 mm Length: 32 mm	Licensed indication: contraception and HMB (not part of HRT) Blue retrieval treads	<b>See note underneath regarding FSRH recommended unlicensed indication as part of HRT/PMS tx.</b> <b>Currently cheapest 52 mg LNG-IUD on the market (off label).</b> Larger "fiddly" two -handed inserter- consider especially if uterine sounding easy, or HCP able to dilate cervix.	£66 (£13.2/year for 5 years use)

## Notes:

- Any 52 mg LNG-IUD can be used for endometrial protection (as part of HRT or PMS/PMDD treatment) for up to 5 years (off label, supported by the Faculty of Sexual & Reproductive Healthcare and the British Menopause Society). There is no extension of their recommended use as part of HRT beyond 5 years.
- All three 52 mg LNG-IUDs are on the Tayside Area Formulary.
- **Forgetting to replace an LNG-IUD in time is a common prescription error, leading to prescribing unopposed or suboptimal opposed estradiol prescription which can cause endometrial hyperplasia and cancer. Please consider adding the expiry date to your repeat HRT prescribing system, or establishing a recall system.**
- WHO and FSRH now recommend calling hormone coils, previously called intrauterine systems (IUS), levonorgestrel containing intrauterine device (LNG-IUD)
- Even expired LNG IUD might their use in providing contraception and helping to prevent bleeding on HRT- change to combined HRT and consider keeping the LNG-IUD in for up to 10 years (off-label, good practice point).
- If the patient has amenorrhoea on an expired LNG-IUD and chooses not to replace it but to keep it in- please consider continuous combined HRT, at least to start with (off-label, good practice point).

## Abbreviations:

BMS+	British Menopause Society
ccHRT=	continuous combined HRT
FSRH=	Faculty of Sexual & Reproductive Healthcare
HMB=	heavy menstrual bleeding
HRT=	hormone replacement therapy
IUD=	intrauterine device
LNG=	levonorgestrel
LNG-IUD=	levonorgestrel containing intrauterine device (formerly know as intrauterine system- IUS= hormone coil)
MP=	micronised progesterone
MPA=	medroxyprogesterone acetate
na=	information not available or not applicable
NE=	norethisterone
px=	prescribed or prescription
sHRT=	sequential HRT
tx=	treatment