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Guidelines

summarising clinical guidelines for primary care

Prescribing combined hormone replacement therapy (HRT) containing dydrogesterone

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Femoston® (estradiol/dydrogesterone) is indicated for oestrogen deficiency symptoms in postmenopausal women at least 6 months since last menses;
Femoston®-conti (estradiol/dydrogesterone) is indicated for oestrogen deficiency symptoms in postmenopausal women at least 12 months since last menses.

ALGORITHM

This promotional algorithm has been commissioned and funded by Viatris and developed in partnership with *Guidelines*. Viatris reviewed and approved the scope and pre-meeting documents, suggested a Chair and experts for the group, and carried out full medical approval on all materials to ensure compliance with regulations. Viatris staff also attended the development meeting. Viatris contracted the participants and paid their honoraria. The views and opinions of the participants are not necessarily of Viatris, *Guidelines*, its publisher, advisers, or advertisers. No part of this publication may be reproduced in any form without the permission of the publisher.

Prescribing information can be found on pages 11 and 12.

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Prescribing combined hormone replacement therapy (HRT) containing dydrogesterone

Professor John Stevenson (Chair), Professor Serge Rozenberg, Dr Diana Mansour, Dr Joanne Hobson

Guidance background

- Hormone replacement therapy (HRT) is first-line treatment for menopausal symptoms:[1–3]
  - although all forms of systemic HRT have proven benefits in terms of vasomotor symptom control, other risk–benefit profiles depend on the type of HRT regimen and the woman's characteristics[2,4]
  - the current NICE guideline on menopause management (NG23) recommends an individualised approach for diagnosing and treating women with menopausal symptoms based on their specific needs[1]
- Little guidance is currently available on prescribing the progestogen component of combined HRT:
  - an expert panel was established to identify the different progestogens used in HRT that are available in the UK; their formulations and delivery routes; and their profiles in terms of breast cancer and venous thromboembolism (VTE) risk, metabolic effects, and side effects
  - this guidance focuses on use of the combined preparation containing oestradiol plus the progestogen, dydrogesterone (Femoston® and Femoston® -conti) for menopausal women with an intact uterus, who are suitable for oral HRT and have no pre-existing increased risk of VTE or breast cancer.

When to use HRT

- Prescribe HRT for women:
  - to treat vasomotor symptoms after discussing with them the short-term (up to 5 years) and longer-term benefits and risks[1]
  - to prevent osteoporosis in women with premature ovarian insufficiency (POI) and to be used until at least the age of natural menopause[1]
  - to prevent osteoporosis as a second line agent in menopausal women <60 years, particularly in those with oestrogen deficiency symptoms[1,4,6]
  - with oestrogen deficiency symptoms post-hysterectomy (those with endometriosis should be prescribed a continuous combined HRT for the first few years after surgery[5])
  - with menopausal symptoms, including premenstrual symptoms, anxiety, memory problems and difficulty concentrating (brain fog), and mood disturbances[1,2,4]
    - women who present with psychological symptoms may also have undisclosed symptoms of hot flushes and night sweats
- No specific blood tests are required before starting HRT. It is good practice to document blood pressure (BP) and body mass index (BMI) at baseline, women should be breast aware and attend check ups with the NHS Breast Cancer Screening Programme (depending on age)
  - diagnose menopausal symptoms without blood tests in otherwise healthy women >45 years with typical symptoms
  - consider FSH levels in women aged 40–45 years with menopausal symptoms or changes in their menstrual cycle, and in women <40 years in whom menopause is suspected.[1]

Adding a progestogen to oestrogen

- The addition of a progestogen greatly reduces the risk of oestrogen-associated endometrial hyperplasia in non-hysterectomised women[6–9]
- Progestogen-containing HRT should therefore be used in women with an intact uterus (including women with suspected residual endometrium after subtotal hysterectomy, after endometrial ablation, and in women with endometriosis and possible residual endometriosis lesions)[5]

Table 1. Progestogens available for hormone replacement therapy

Characteristic	Androgenic			Non-androgenic	
	Norethisterone acetate	Levonorgestrel	Medroxyprogesterone acetate	Dydrogesterone	Micronised progesterone
Route of administration	■ Oral ■ Transdermal	■ Oral ■ Transdermal ■ Intrauterine	■ Oral	■ Oral	■ Oral

- A variety of progestogens are available for combined HRT:
  - **Table 1** summarises the progestogens available to prescribe as part of HRT in the UK
  - dydrogesterone is the progestogen in the oral HRT combinations Femoston® and Femoston® -conti.[6–9]

Risk-based selection of progestogen-containing HRT formulations

- Good history is key to selecting the optimal HRT for each patient:
  - The Primary Care Women's Health Forum has produced a guide to support provision of HRT through telephone and virtual consultations (see **Useful resources** box)
- The main risks associated with HRT are breast cancer and VTE. Although these are very uncommon, they may vary depending on the type of progestogen combination (**Table 2** and **Table 3**)
  - when selecting progestogen-containing HRT consider patient's individual benefits and risks profile, including whether they have a uterus, their risk factors for breast cancer, VTE, and cardiovascular disease (including BMI)
  - the lowest effective dose of HRT for the individual should be chosen following informed discussion with the patient.[4]

Breast cancer and progestogens

- A personal history of breast cancer is a contraindication to HRT. For those with no personal history of breast cancer, but have a concerning family history, seek specialist secondary care advice[1,10]
  - overall evidence shows an increased risk of breast cancer in women taking combined oestrogen–progestogen or oestrogen-only HRT that is dependent on the duration of HRT use[6–9]
    - the Women's Health Initiative (WHI) study and a meta-analysis from 2019 are consistent in finding an increased risk of breast cancer in women taking combined oestrogen-progestogen for HRT that becomes apparent after about three (range 1–4) years[6–9]
  - the progestogen component of combined HRT has a differential effect on the risk of breast cancer:
    - observational studies have shown that oestradiol + dydrogesterone may be associated with a lower risk of breast cancer diagnosis than some other combined progestogen preparations[2,4,11–14]
      - the rate of increased breast cancer risk with HRT differs by type of progestogen used
      - dydrogesterone appears to increase this risk at a slower rate than some other progestogen preparations (**Figure 1**)[14]
  - consider seeking specialist advice if breast cancer risk is a particular concern.

VTE and progestogens

- The risk of VTE is increased by oral HRT preparations. Transdermal HRT at standard doses does not increase this risk[1]
  - the type of progestogen can differentially affect the risk of VTE with micronised progesterone and dydrogesterone conferring a lower risk compared to that with other synthetic progestogens[4]
  - in a large UK based case-control study conducted in 2019; amongst the oral combined preparations oestradiol with dydrogesterone was associated with the lowest risk of VTE 1.18 (0.98 to 1.42, **Table 3** and **Figure 2**).[15]

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Table 2. Side effects and breast cancer risk considerations when selecting the progestogen as part of combined HRT

Risk/side effect profile	Effect of progestogen with combined HRT				
	Androgenic progestogen			Non-androgenic progestogen	
	Norethisterone acetate[a]	Levonorgestrel[b]	Medroxyprogesterone acetate[c]	Dydrogesterone[a]	Micronised progesterone
Side effects[16–18]	■ Progestogenic* ■ Acne ■ Greasy skin ■ Hirsutism	■ Progestogenic* ■ Acne ■ Greasy skin ■ Hirsutism	■ Progestogenic* ■ Acne ■ Greasy skin ■ Hirsutism	■ Progestogenic*	■ Progestogenic* *Please note: May cause drowsiness. Should not be taken with food and should be taken at bedtime[18]*
Breast cancer risk (Figure 1)[14]	++	++	++	+	*Not included in this clinical study, other data may be available*

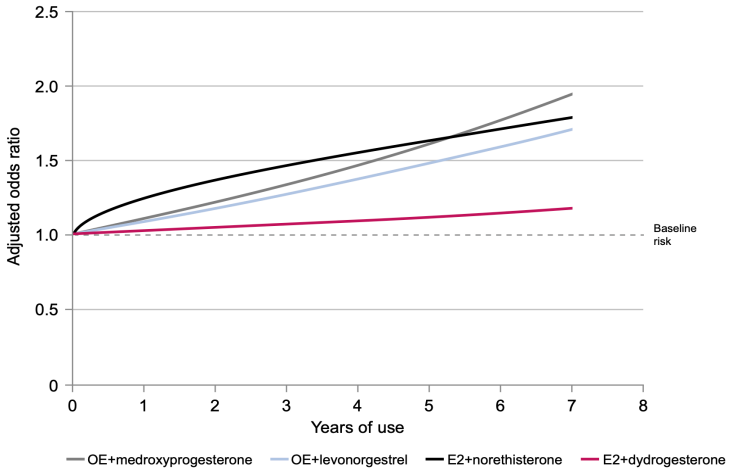
E2 = oestradiol, OR = odds ratio (with reference to non-users), SE = side effects
*Progestogenic SE = bloating, breast tenderness, premenstrual type symptoms;
+ increase statistically significant (OR = 1.0-1.5) ; ++ increase statistically significant (OR = 1.5-2.0);
[a]for breast cancer risk OR reflects both norethisterone and dydrogesterone combined with E2; [b]for breast cancer risk, the OR reflects levonorgestrel combined with conjugated equine oestrogen (CEE) in 95% of prescriptions; [c]for breast cancer risk, the OR reflects MPA combined with CEE in 84% of prescriptions; Results for breast cancer risks are adapted from figure 3, taken from Vinogradova Y et al 2020 for >5 years of use (*Data represents recent users women receiving HRT prescription >1 yr but <5 yrs before the index date*);

Table 3. Risk of venous thromboembolism and considerations when selecting oral oestradiol with dydrogesterone

Risk profile of VTE (Figure 2)[15]	CEE + MPA	CEE + Norgestrel	E2 + Norethisterone acetate	E2 + MPA	E2 + dydrogesterone
	+++	++	++	+	+*

E2 = oestradiol, CEE = conjugated equine estrogens, MPA = medroxyprogesterone acetate, OR = odds ratio (with reference to non-users); results for VTE risks are adapted from Table 2, taken from Vinogradova Y et al 2019. Data represents OR from the combined analysis.
+* increase, not statistically significant (OR = 1.0-1.5); + increase statistically significant (OR = 1.0-1.5); ++ increase statistically significant (OR = 1.5-2.0); +++ increase, statistically significant (OR>2)

Figure 1. Adjusted odds ratios for different durations of recent exposure^ to HRT in association with breast cancer risks[14]

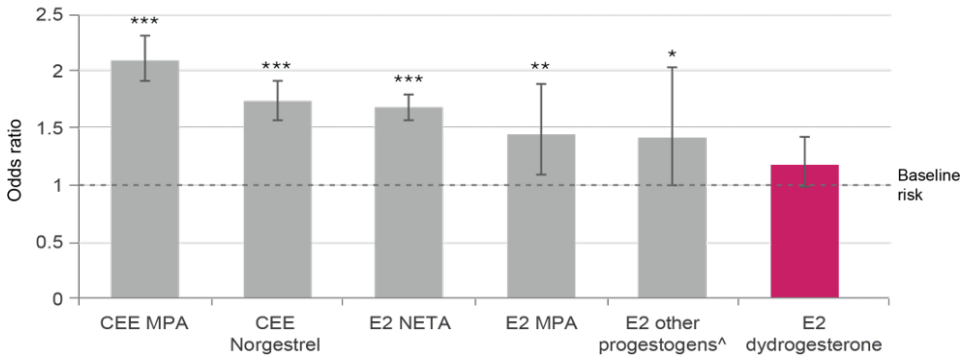


OE - Oestrogen
E2 - Estradiol

^Recent users is defined as those with prescriptions more than one year and less than five years before the index date.

Adapted from: Vinogradova Y, BMJ. 2020 Fig 4.

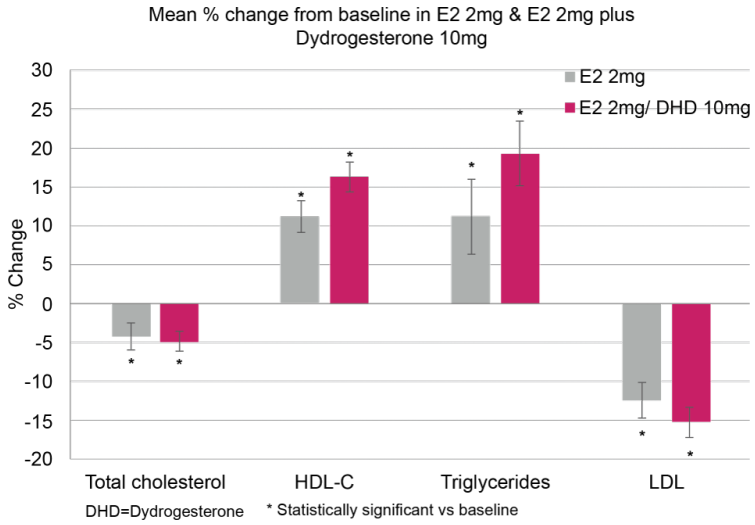
Figure 2. Odds ratio of VTE for different types of oral HRT[15]



*P=0.05, **P=0.01, ***P<0.001 vs. no HRT

^HRTs containing norgestrel and drospirenone

Figure 3. Pooled analysis of prospective studies to establish the effects of different HRTs on lipid and lipoprotein levels[19]



DHD=Dydrogesterone

* Statistically significant vs baseline

14 studies using E2 2mg and 6 studies using Femoston® 2/10 were included.

Compared to E2 2mg alone, the addition of dydrogesterone did not oppose:

- Reduction in total cholesterol
- Increase in HDL-C
- Reduction in LDL-C

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Metabolic effects of different progestogens

- For overweight women and those with type 2 diabetes or prediabetes, consider the metabolic effects of different progestogen-containing HRTs:[21]
  - oestradiol + dydrogesterone may have metabolic advantages over other combinations in terms of insulin resistance and lipid profiles[19–21]
    - oestrogen increases HDL, but this beneficial effect is blunted by medroxyprogesterone acetate and norethisterone acetate[19,21]
      - this blunting effect is not seen with dydrogesterone (**Figure 3**)[19,21]
    - oestrogen reduces insulin resistance, but the beneficial effect of the oestrogen on insulin sensitivity may be blunted by the addition of a progestogen[21,22]
      - dydrogesterone has a neutral effect on glucose metabolism, and may be considered to be used in women with insulin resistance or diabetes[21]
  - Randomised controlled trials have found no difference in weight gain between placebo and HRT[23]
    - differences between progestogens in terms of weight gain are not known.

Endometrial hyperplasia and progestogens

- The addition of a progestogen to oestrogen greatly reduces the risk of endometrial hyperplasia:[6–9]
  - women with a history of endometriosis should receive continuous combined HRT for at least the first few years after surgery, or until asymptomatic before moving onto oestrogen-replacement therapy[5]
  - the risk of endometrial hyperplasia with progestogen-containing HRT is higher when progestogen is given for fewer than 10 days.[24,25]

Side effects and progestogens

- Side effects differ for androgenic and non-androgenic progestogens due to their differential effects on steroid receptors:
  - norethisterone acetate, levonorgestrel, and medroxyprogesterone acetate are androgenic and result in side effects such as acne, greasy skin, and hirsutism[16,17]
  - dydrogesterone and micronised progesterone are non-androgenic and do not produce these side effects (**Table 2**) and should be considered in patients prone to acne or with a history of polycystic ovarian syndrome
  - micronised progesterone can cause drowsiness, which is not reported with dydrogesterone.[6–9,18]

Other considerations

- Lifestyle and behavioural factors should be taken into account when choosing the route of delivery. For example:
  - consider transdermal HRT in those who choose it as an option, where there is poor symptom control with oral HRT, gastrointestinal (GI) disorder affecting oral absorption, previous history of VTE, BMI >30, migraines, current use of hepatic medication (inducing enzymes), and gall bladder disease
  - oral HRT may be preferred in younger women who do not smoke.

Selecting the regimen and dose for Femoston® and Femoston® -conti

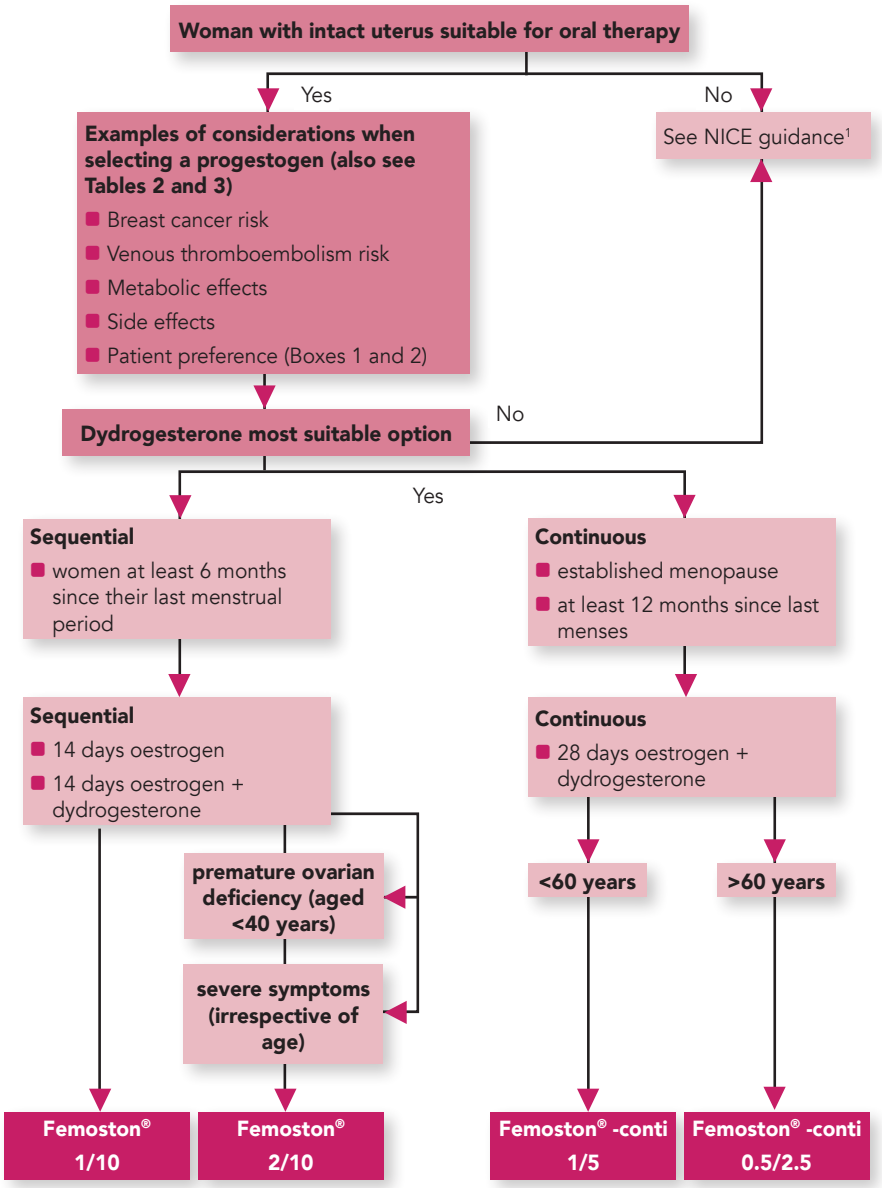
- Oestrogen + dydrogesterone is available as sequential (Femoston®)[6,7] or continuous combined (Femoston® -conti)[8,9]
- **Figure 4** provides an algorithm to guide prescribing of the Femoston® range
- **Boxes 1 and 2** illustrate key questions when selecting hormone therapy, patient considerations before and during HRT.

Sequential HRT with Femoston®

- Use sequential HRT for:
  - oestrogen deficiency symptoms in postmenopausal women at least 6 months since last menses[6,7]
- Initial dose selection should be Femoston® 1/10. However, other factors should also be taken into consideration when choosing the starting dose:
  - for women with POI (aged <40 years), a higher dose may be required such as Femoston® 2/10
  - for women sensitive to oestrogens, start with Femoston® 1/10

The benefits and risks of HRT must be assessed and tailored to each individual patient. Below is an example algorithm for prescribing the Femoston® range. This is an illustrative guide only and not intended to replace clinical decision making.

Figure 4. An algorithm for prescribing the Femoston® range[6–9]



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The benefits and risks of HRT must be assessed and tailored to each individual patient. Below are some examples of other factors which should be considered when prescribing HRT. This is not intended to replace clinical decision making.

Box 1. Key questions when selecting hormone therapy

- Does the woman want to take hormone replacement therapy?
- Does she have an intact uterus or cervix?
- Does she need progestogen with oestrogen?
- Does she have any risk factors such as a history of breast cancer or endometriosis that need to be taken into account?
- Does she have any lifestyle risk factors that need to be taken into account?
- Is sequential or continuous combined HRT most appropriate?
- Does she prefer oral or non-oral HRT?
- Does she still require contraception?

Box 2. Patient considerations before and during HRT

- Patient preference and concerns should be taken into account. For example:
  - concerns about perceived side effects with different progestogens
  - patients may be likely to adhere with HRT administered according to their preference for tablets, patches, or gel, and straight forward regimens where the oestrogen and progestogen are in one tablet or patch
- Patients should be counselled on potential side effects and follow up
  - dydrogesterone may be better tolerated in terms of side effects and may have a more favourable breast cancer and VTE risk profile than other progestogens
- Sequential therapy invokes two prescription charges, while continuous combined therapy invokes only one prescription charge (may differ depending on region)
- Lower doses of oestrogen produce less erratic bleeding in continuous combined HRT
- Changing the progestogen may be required in patients who develop progestogenic side effects.

HRT, hormone replacement therapy.

  - for women with severe symptoms, start the higher dose of Femoston® 2/10
  - for women who have been oestrogen deficient for some time, start with the lower dose of Femoston® 1/10
- Advise women that side effects are likely to have settled by 3 months.

Continuous combined HRT with Femoston® -conti

- Use continuous combined HRT for:
  - women with established menopause, whose last period was more than 12 months ago
- Initial dose selection can be based on the woman's age:
  - for women <60 years, start with the higher dose of Femoston® -conti 1/5
  - for women >60 years, start with the lower dose of Femoston® -conti 0.5/2.5
- Advise women that side effects are likely to have settled by 3 months.

Monitoring and follow up

- Monitoring of oestrogen levels is generally not required while taking HRT
- Review the patient after 3 months
  - check whether symptoms are controlled and whether any side effects have settled
    - increase the dose after 3 months if symptom relief with the lower dose is insufficient
    - if side effects are troublesome, taper down the dose rather than stopping HRT completely
    - if women still experience vaginal atrophy or dryness, prescribe a vaginal oestrogen in addition
  - check BP
    - BP increase is uncommon with HRT
  - reduce the dose if the patient develops breast tenderness
- HRT prescribing is generally reviewed three months after initiation then on an annual basis.

Frequency of review depends on individual clinical need. There are no arbitrary limits to the duration of use. Treatment should be guided by the balance of the benefits and risks for each individual patient
- consider reducing the dose of HRT once women turn 60 years of age.

Switching from sequential to continuous combined therapy

- After 1–2 years, consider switching women on sequential HRT to continuous combined therapy:
  - for each woman, the increased endometrial protection with continuous combined HRT must be balanced against the slightly increased risk of breast cancer
  - patient preference should be considered when switching from sequential to continuous combined therapy:
    - some women may prefer to remain on sequential therapy to maintain their monthly bleed, while others may prefer the amenorrhoea with continuous combined
- Start on continuous combined therapy after the withdrawal bleed
  - women may experience spotting or bleeding during the first few months after the switch:
    - if bleeding persists, consider switching back to sequential or reduce the oestrogen dose
    - refer women whose bleeding becomes heavy and/or painful or who start bleeding after 6 months of amenorrhoea to a gynaecologist for investigations
- Taper down the dose in women who want to stop HRT rather than stopping abruptly, unless treatment is being withdrawn due to a major event such as VTE.

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Useful resources

For healthcare professionals
- NICE guidance:
  - www.nice.org.uk/guidance/ng23
- International Menopause Society (IMS) guidance:
  - www.tandfonline.com/doi/abs/10.3109/13697137.2015.1129166?journalCode=icmt20
- British Menopause Society:
  - https://thebms.org.uk/wp-content/uploads/2020/07/04-BMS-TfC-HRT-Guide-JULY2020-01D.pdf
  - https://thebms.org.uk/education/menopause-education-for-nurses/
  - https://thebms.org.uk/education/impart-online-learning-for-health-care-professionals/
  - https://thebms.org.uk/education/bms-rcog-advanced-training-skills-module/
- Primary Care Women's Health Forum guide to providing HRT through telephone and virtual consultations:
  - https://pcwhf.co.uk/resources/how-to-manage-hrt-provision-without-face-to-face-consultations-during-covid-19-healthcare-restrictions/

For patients
- Menopause Support:
  - https://menopausesupport.co.uk/
- Women's Health Concern:
  - www.womens-health-concern.org
- Menopause and Me:
  - www.menopauseandme.co.uk/

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Group members–Professor John Stevenson (Chair), Professor Serge Rozenberg, Dr Diana Mansour, Dr Joanne Hobson.

PRESCRIBING INFORMATION (combined)
Femoston-conti 0.5 mg/2.5 mg film-coated tablets
Femoston-conti 1 mg/5 mg film-coated tablets
Femoston 1/10 mg film-coated tablets
Femoston 2/10 mg film-coated tablets
(Estradiol and dydrogesterone)

Refer to the Summary of Product Characteristics for full information.
Indication: Femoston-conti 0.5 mg/2.5 mg and 1 mg/5 mg film-coated tablets; Hormone replacement therapy (HRT) for oestrogen deficiency symptoms in postmenopausal women at least 12 months since last menses.
Femoston 1/10 mg and 2/10 mg film-coated tablets; Hormone replacement therapy (HRT) for oestrogen deficiency symptoms in postmenopausal women at least 6 months since last menses. Femoston-conti 1 mg/5 mg, Femoston 1/10 mg and 2/10 mg film-coated tablets are also indicated for the prevention of osteoporosis in postmenopausal women at high risk of future fractures who are intolerant of, or contraindicated for, other medicinal products approved for the prevention of osteoporosis.

Presentation: Femoston-conti 0.5 mg/2.5 mg film-coated tablets containing 0.5 mg estradiol (as hemihydrate) and 2.5 mg dydrogesterone. Femoston-conti 1 mg/5 mg film-coated tablets containing 1 mg estradiol (as hemihydrate) and 5 mg dydrogesterone. Femoston 1/10 mg film-coated tablets containing 1 mg estradiol (as hemihydrate) or a combination of 1 mg estradiol (as hemihydrate) and 10 mg dydrogesterone. Femoston 2/10 mg film-coated tablets containing 2 mg estradiol (as hemihydrate) or a combination of 2 mg estradiol (as hemihydrate) and 10 mg dydrogesterone.

Dosage and administration: Femoston-conti 0.5 mg/2.5 mg and 1 mg/5 mg film-coated tablets; given as a continuous combined HRT every day without a break between packs. Dosage is one tablet per day for a 28 day cycle. Continuous combined treatment may be started depending on the time since menopause and severity of symptoms. Women experiencing a natural menopause should commence treatment not earlier than at least 12 months after their last natural menstrual bleed. For surgically induced menopause, treatment may start immediately. Femoston 1/10 mg and 2/10 mg film-coated tablets; given as a continuous sequential HRT without a break between packs. For first 14 days of 28-day cycle, one tablet containing estradiol taken daily; during the following 14 days one tablet containing estradiol and dydrogesterone is taken. Women who are not taking HRT and who are amenorrhoeic, or those who switch from a continuous combined HRT treatment can start on any day. If transferring from a cyclic or continuous sequential HRT regimen, treatment should begin the day following completion of prior regimen. For initiation and continuation of treatment of postmenopausal symptoms, the lowest effective dose for the shortest duration should be used. Depending on the clinical response, the dosage can subsequently be adjusted. For oral use. Can be taken before or after food. *Paediatric population:* No relevant indication.

Contraindications: Known, past or suspected breast cancer, known or suspected oestrogen-dependent malignant tumours, known or suspected progestogen-dependent neoplasms, undiagnosed genital bleeding, untreated endometrial hyperplasia, venous thromboembolism, known thrombophilic disorders, arterial thromboembolic disease, acute liver disease or a history of liver disease, porphyria, known hypersensitivity to the active substances or to any of the excipients.

Warning and precautions: HRT should only be initiated for symptoms that adversely affect quality of life. In all cases, a careful appraisal of the risks and benefits should be undertaken at least annually and HRT should only be continued as long as the benefit outweighs the risk. Before initiating or re-instituting HRT, a complete physical and family medical history should be taken. Physical (including pelvic and breast) examination should be guided by this and by the contraindications and warnings for use. During treatment, periodic check-ups are recommended of a frequency and nature adapted to the individual woman. Women should be advised what changes in their breasts should be reported to their doctor or nurse. Carefully supervise if leiomyoma or endometriosis, risk factors for thromboembolic disorders or oestrogen-dependent tumours, hypertension, liver disorders, diabetes mellitus, cholelithiasis, migraine or severe headaches, systemic lupus erythematosus, history of endometrial hyperplasia, epilepsy, asthma, otosclerosis and meningioma conditions are present or have previously occurred and/or have been aggravated during pregnancy or previous hormone treatment. Therapy should be discontinued in case a contraindication is discovered and in the following situations: jaundice or deterioration in liver function, significant increase in blood pressure, new onset of migraine-type headache, pregnancy. Investigate breakthrough bleeding. An increased risk of breast cancer has been reported that is dependent on the length of treatment. HRT can increase the density of mammographic images which may affect radiological detection of breast cancer. The use of oestrogen-only or combined oestrogen-progestogen HRT has been associated with a slightly increased risk of ovarian cancer. HRT is associated with an increased relative risk of venous thromboembolism (VTE) i.e. deep vein thrombosis or pulmonary embolism. Patients with known thrombophilic states have an increased risk of VTE and HRT may add to this risk. HRT is therefore contraindicated in these patients Generally recognised risk factors for VTE include: use of oestrogens, older age, major surgery, prolonged immobilisation, obesity (BMI>30 kg/m2), pregnancy/postpartum period, systemic lupus erythematosus (SLE), and cancer. If VTE develops after initiating therapy, the drug should be discontinued. Oestrogens may cause fluid retention, and therefore patients with cardiac or renal dysfunction should be carefully observed. Relative risk of coronary artery disease is raised with oestrogen-progestogen therapy, but randomised controlled trials have not shown an increase with oestrogen-only therapy. The use of oestrogen-only and oestrogen-progestogen therapy

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is associated with an up to 1.5-fold increased relative risk of ischaemic stroke. Women with pre-existing hypertriglyceridemia should be followed closely (risk of pancreatitis). Exogenous estrogens may induce or exacerbate symptoms of hereditary and acquired angioedema. Certain endocrine tests may be affected. No evidence for improvement in cognitive function. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine. Oestrogen-progestogen combination treatment is not a contraceptive.

Interaction with other medicinal products: The metabolism of oestrogens and progestogens may be increased by concomitant use of P450 enzymes such as anticonvulsants and anti-infectives. Ritonavir, nelfinavir and herbal preparations containing St. John's Wort may induce the metabolism of oestrogens and progestogens. caution is warranted for co-administration with the combination drug regimen ombitasvir/paritaprevir/ritonavir with or without dasabuvir and also the regimen with glecaprevir/pibrentasvir. Clinically, an increased metabolism of oestrogens and progestogens may lead to decreased effect and changes in the uterine bleeding profile. Femoston 1/10 mg and 2/10 mg film-coated tablets; Oestrogens may inhibit CYP450 drug-metabolising enzymes via competitive inhibition particularly substances such as tacrolimus and cyclosporine A, fentanyl and theophylline. This may lead to an increased plasma level of the affected substances up to toxic levels. Careful drug monitoring might be indicated and a dosage decrease of tacrolimus, fentanyl, cyclosporine A and theophylline may be necessary.

Pregnancy, Lactation and Fertility: Not recommended. If pregnancy occurs withdraw treatment immediately.

Effects on ability to drive and use machines: No influence on the ability to drive and/or to use machines.

Undesirable effects: *Very Common:* Headache, abdominal pain, back pain, breast pain/tenderness. *Common:* Vaginal candidiasis, depression, nervousness, migraine, dizziness, nausea, vomiting, flatulence, allergic skin reactions (e.g. rash, urticaria, pruritus), menstrual disorders (including postmenopausal spotting, metrorrhagia, menorrhagia, oligo-/amenorrhoea, irregular menstruation, dysmenorrhoea), pelvic pain, cervical discharge, asthenic conditions (asthenia, fatigue, malaise), peripheral oedema, increased weight. *Uncommon:* Cystitis-like syndrome, increase in size of leiomyoma, hypersensitivity, influence on libido, venous thromboembolism, hypertension, peripheral vascular disease, varicose vein, dyspepsia, abnormal hepatic function, occasionally with jaundice, asthenia or malaise, and abdominal pain, gall bladder disorder, breast enlargement, premenstrual syndrome, decreased weight. *Rare:* Haemolytic anaemia, meningioma, steepening of corneal curvature, contact lenses intolerance, myocardial infarction, stroke, angioedema, vascular purpura, erythema nodosum, chloasma or melasma, which may persist when drug is discontinued, leg cramps. *Possible* risk factors: Breast cancer, ovarian and endometrial cancer, venous thromboembolism, coronary artery disease and ischaemic stroke. *Other adverse reactions:* Oestrogen dependent neoplasms both benign and malignant, e.g. endometrial cancer, ovarian cancer, increase in size of progestogen dependent neoplasms, e.g. meningioma, haemolytic anaemia, systemic lupus erythematosus, hypertriglyceridemia, probable dementia over the age of 65,chorea, exacerbation of epilepsy, steepening of corneal curvature, contact lenses intolerance, arterial thromboembolism, pancreatitis (in women with pre-existing hypertriglyceridemia), erythema multiforme, erythema nodosum, chloasma or melasma, which may persist when drug is discontinued, leg cramps, urinary incontinence, fibrocystic breast disease, uterine cervical erosion, aggravated porphyria, total thyroid hormones increased.

Legal Category: POM **Marketing Authorisation Number:** Femoston 1/10 mg film-coated tablets PL 46302/0035; Femoston 2/10 mg film-coated tablets PL 46302/0036; Femoston-conti 0.5 mg/2.5 mg film-coated tablets PL 46302/0037; Femoston-conti 1 mg/5 mg film-coated tablets PL 46302/0038 **MAH:** Mylan Products Ltd., 20 Station Close, Potters Bar, Herts, EN6 1TL, **UK NHS Price:** Femoston-conti £24.43 (84 tablets) & Femoston £16.16 (84 tablets) **Date of Revision of Prescribing Information:** June 2022 **Veeva Reference:** FEM-2022-0062

The SmPC for this product, including adverse reactions, precautions, contra-indications, and method of use can be found at: http://www.mhra.gov.uk/Safetyinformation/Medicinesinformation/SPCandPILs/index.htm and from Viatris Medical Information, Building 4, Trident Place, Hatfield Business Park, Mosquito Way, Hatfield, Hertfordshire, AL10 9UL, phone no. 01707 853000, Email: info.uk@viatris.com.

Please continue to report suspected adverse drug reactions with any medicine or vaccine to the MHRA through the Yellow Card Scheme. It is easiest and quickest to report adverse drug reactions online via the Yellow Card website: https://yellowcard.mhra.gov.uk/ or search for MHRA Yellow Card in the Google Play or Apple App Store. Alternatively, you can report via some clinical IT systems (EMIS/SystmOne/Vision/MiDatabank) or by calling the Commission on Human Medicines (CHM) free phone line: 0800-731-6789. Adverse reactions/events should also be reported to MAH at e-mail address: pv.uk@viatris.com.