HRT Medication Review: Could you Prescribe Femoston®?

estradiol/dydrogesterone

My Way

by Viatris Women's Healthcare

The only HRT range with dydrogesterone

femoston® estradiol/dydrogesterone

femoston®-conti estradiol/dydrogesterone

Key points to consider if switching women from other HRT products to Femoston®

Transdermal to **Femoston®**

Venous Thromboembolism (VTE)

The baseline risk of VTE is **16 per 10,000** women years and the addition of oral hormone replacement therapy (HRT) increases the risk **by 9 in 10,000** women years.[1] If a woman is at increased risk of venous thromboembolism (VTE), the British Menopause Society (BMS) and NICE guideline recommend a transdermal HRT.[2,3]

Observational studies suggest that dosage, route of administration, and types of estrogen and **progestogen may impact the associated VTE risk**. In a case-control study from 2019, amongst the oral combined preparations, **Femoston®** and **Femoston®-conti** (oral estradiol with dydrogesterone) was associated with the **lowest risk of VTE** (1.18, 0.98 to 1.42).[1]

Breast Cancer

With regards to breast cancer risk, observational studies have demonstrated there are **no differences between the route of administration: transdermal vs. oral.**[4-6]

However, observational studies have shown that **different progestogens** in HRT are associated with different levels of risks.[4-6]

Individualised Approach

BMS and NICE guideline highlight the importance of considering **a woman's personal choice and preferences.**[2,3]

Other Oral HRT to **Femoston®**

VTE

The occurrence of VTE associated with Femoston® and Femoston® conti is uncommon (between 1/100 and 1/1,000).[7-10] In a case-control study from 2019, amongst the oral combined preparations, **Femoston®** and **Femoston®-conti** (oral estradiol with dydrogesterone) was associated with the **lowest risk of VTE** (1.18, 0.98 to 1.42).[1]

Breast Cancer

Whilst all systemic HRT increases the risk of breast cancer,[5] observational studies have shown that **estradiol + dydrogesterone** may be associated with a **lower risk of breast cancer compared** with **other synthetic progestogens.**[4-6]

Side-Effects

Femoston® and Femoston®-conti contains 17β-estradiol and dydrogesterone.[7-10] **Dydrogesterone does not stimulate** the following receptors: **oestrogenic, androgenic, or glucocorticoid.**[11-13]

For a lower dose preparation, Femoston® Conti 0.5 mg contains the **lowest oral estradiol dose available on the market.**[14]

Progestogenic Side-Effect Profiles[13]

Progestogen	Progestogenic	Estrogenic	Androgenic	Antiandrogenic	Glucocorticoid	Anti-mineralocorticoid
Progesterone	+	-	-	±	+	+
Dydrogesterone	+	-	-	±	-	±
MPA*	+	-	±	-	+	-
Norethisterone	+	+	+	-	-	-
Levonorgestrel	+	-	+	-	-	-

+ Effective; ± Weakly effective; - Not effective

*MPA: Medroxyprogesterone acetate.

Dydrogesterone is highly selective for the progestogenic receptor and does not bind to oestrogenic, androgenic and glucocorticoid receptors.

Femoston® is indicated for oestrogen deficiency symptoms in postmenopausal women at least 6 months since last menses[7,8] and Femoston®-conti is indicated for estrogen deficiency symptoms in postmenopausal women at least 12 months since last menses.[9,10]

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Consider the progestogen…

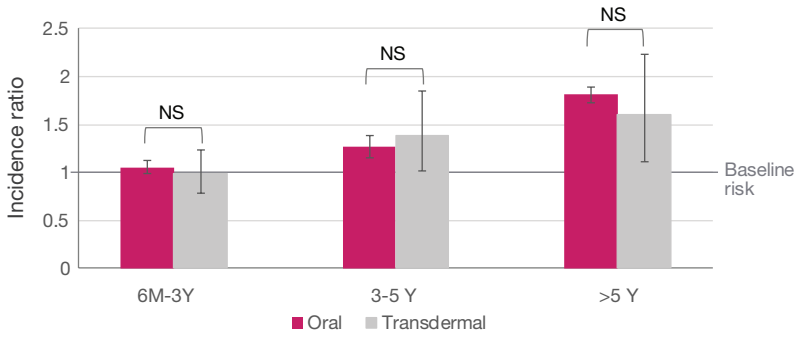
Breast Cancer

The 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 taking HRT.[7-10]

The Women's Health Initiative study (WHI), and a meta-analysis from 2019 are consistent in finding an increased risk of breast cancer in women taking combined oestrogen-progestogen for HRT which becomes apparent after about 3 (1-4) years.[7-10]

Additional results of observational studies and meta-analysis show that different progestogens may have different risk profiles when it comes to breast cancer risk.[4-6]

Finnish Data: Standardised incidence ratio of invasive breast cancer among women using oestrogen-progestogen therapy according to the route of administration and duration of use[4]



NS: non-significant

Finnish Conclusion: A Finnish Cohort study, which included 221,551 postmenopausal women, reported that there was **no difference between the route of administration (oral vs. transdermal)** when it comes to **breast cancer risk.**

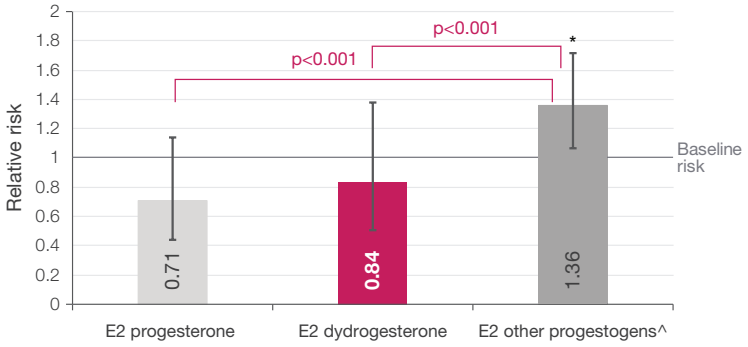
French study[6]

A French cohort study which included 80,377 postmenopausal women between 40-65 years of age, assessed and compared the risk of breast cancer with an average follow-up of 8.1 years.

Result:

- There are no differences between the route of administration: transdermal vs. oral.
- The increased risk of breast cancer became significant with the use of E2+other progestogens at <2 years of use.
- At the same time point, the risk was significantly lower with E2+dydrogesterone, (Femoston® and Femoston® Conti) compared to HRTs containing other synthetic progestogens.

French cohort study: Relative risks for breast cancer by type of HRT with <2 years of use



Adapted from: Fournier A. *Breast Cancer Res Treat.* 2008, Table 3.

*p=0.01 vs. no HRT

^nomegestrol, norethisterone acetate, medroxyprogesterone acetate

Venous Thromboembolism (VTE)

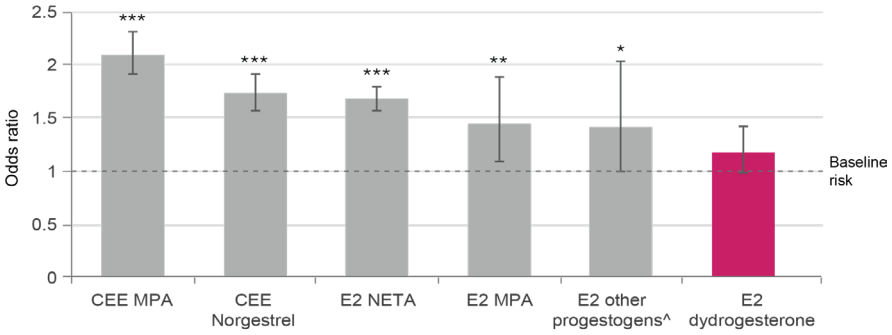
Vinogradova et al. 2019 study[1]

Two nested case-control analysis using UK-based Clinical Practice Research Datalink and QResearch to assess the association between risk of VTE and use of different types of HRT. Study included 80,396 women aged 40–79 with a primary diagnosis of VTE between 1998 and 2017, matched to 391,494 female controls.

Result:

In this analysis, amongst the oral combined preparations, Femoston® and Femoston®-conti (oral estradiol with dydrogesterone) was associated with the lowest risk of VTE (1.18, 0.98 to 1.42).

Odds ratio of VTE for different types of oral HRT



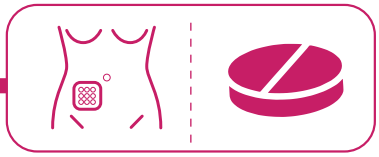
*P=0.05, **P=0.01, ***P<0.001 vs. no HRT

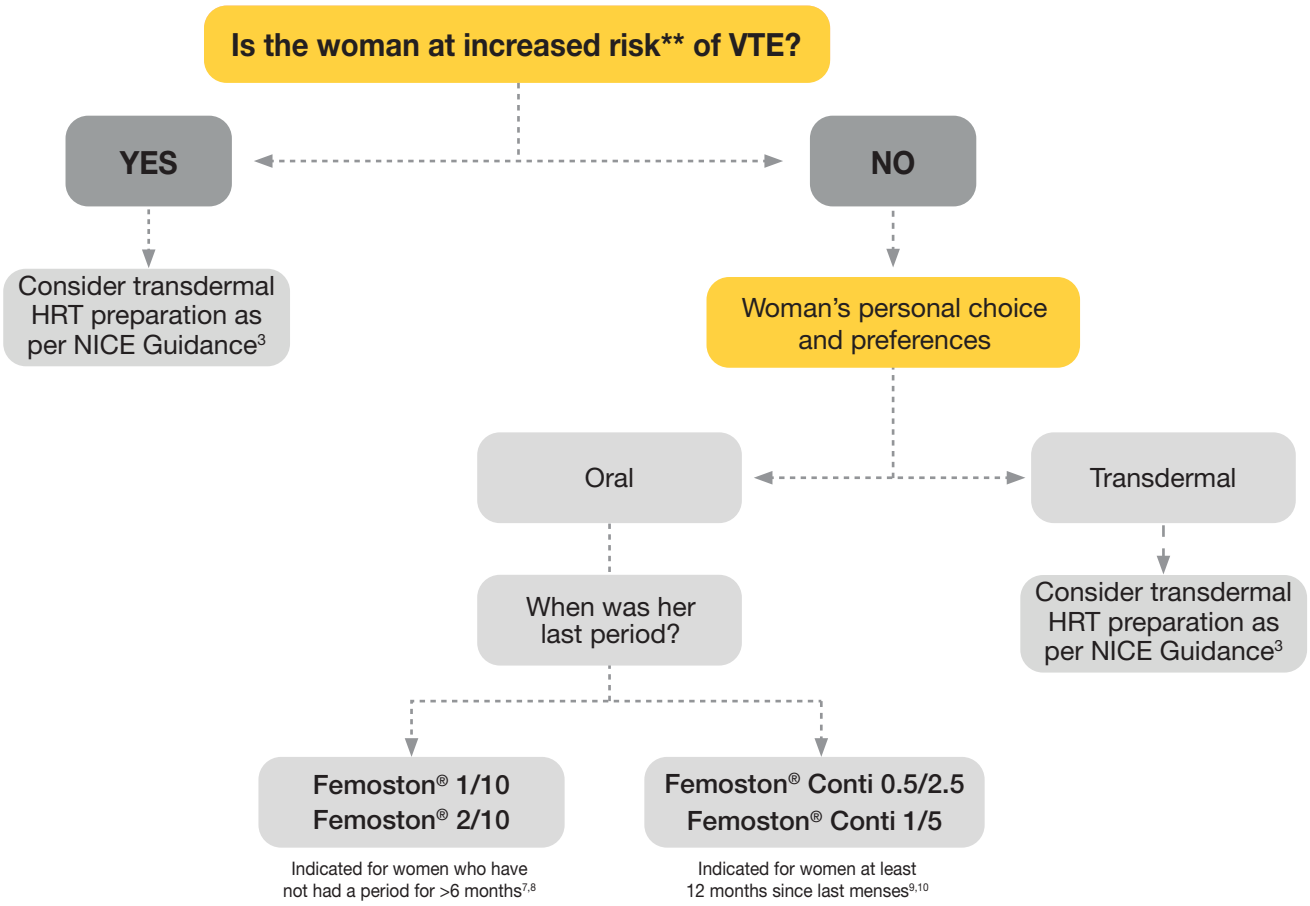
^HRTs containing norgestrel and drospirenone

E2: Estradiol
NETA: Norethisterone acetate
MPA: Medroxyprogesterone acetate
CEE: Conjugated equine oestrogen

Decision Aid for prescribing the Femoston® range

A progestin is required in women with an intact uterus. The decision aid applies to women with an intact uterus.





**Risk factors for VTE include:[2,15]

- Previous VTE
- Obesity
- Strong family history
- Major surgery
- Multiple trauma
- Immobilisation
- Increasing age
- Thrombophilia (e.g. Factor V Leiden)
- Malignancy

Product Name	17ß estradiol dose	Dydrogesterone dose	Pack
femoston® estradiol/dydrogesterone	1 mg	10 mg	3 x 28
femoston® estradiol/dydrogesterone	2 mg	10 mg	3 x 28
femoston®-conti estradiol/dydrogesterone	0.5 mg	2.5 mg	3 x 28
femoston®-conti estradiol/dydrogesterone	1 mg	5 mg	3 x 28

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References

1. Vinogradova Y, *et al. BMJ* 2019; 364:k4810 Use of hormone replacement therapy and risk of venous thromboembolism: nested case-control studies using the Qresearch and CPRM databases.
2. Hamoda H, Panay N, Pedder H, *et al.* The British Menopause Society & Women's Health Concern 2020 recommendations on hormone replacement therapy in menopausal women. *Post Reprod Health.* 2020:2053369120957514. doi: 10.1177/2053369120957514. Epub ahead of print. PMID: 33045914.
3. NICE Guideline [NG23] Menopause: diagnosis and management – https://www.nice.org.uk/guidance/ng23 (Last accessed August 2022).
4. Lyytinen H, *et al.* ObstetGynecol 2009;113:65-73 Breast cancer risk in postmenopausal women using oestradiol-progestogen therapy.
5. Collaborative Group on Hormonal Factors in Breast Cancer. *Lancet 2019*; published online: August 29, 2019. https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(19)31709-X/fulltext (Last accessed August 2022).
6. Fournier A, *et al. Breast Cancer Res Treat.* 2008;107:103–11.
7. Femoston® 1/10 mg Summary of Product Characteristics.
8. Femoston® 2/10 mg Summary of Product Characteristics.
9. Femoston®-conti 0.5 mg/2.5 mg Summary of Product Characteristics.
10. Femoston®-conti 1 mg/5 mg Summary of Product Characteristics.
11. Menopause Matters – https://www.menopausematters.co.uk/sideeffects.php. (Last accessed July 2021)
12. Panay N, *et al. Human Reproduction Update.*1997;3(2):159–71.
13. Schindler AE, Campagnoli C, Druckmann R, *et al.* Classification and pharmacology of progestins. *Maturitas.* 2008;61(1–2):171–80.
14. Mylan, data on file 2021.
15. Anderson FA, Spencer FA. *Circulation.* 2003;107(Suppl.1):1–9.

femoston®
estradiol/dydrogesterone

femoston®-conti
estradiol/dydrogesterone

PRESCRIBING INFORMATION (combined)

Femoston® 1/10 mg film-coated tablets **Femoston®-conti 0.5 mg/2.5 mg film-coated tablets**
Femoston® 2/10 mg film-coated tablets **Femoston®-conti 1 mg/5 mg film-coated tablets**

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 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