Femoston® film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

Femoston® Conti 1/5 film-coated tablets
Femoston® 1/10 film-coated tablets
Femoston® 2/10 film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Femoston® Conti 1/5 Tablet
28 tablets, each containing 1 mg 17ß-estradiol (as hemihydrate) and 5 mg dydrogesterone.

Femoston® 1/10 Tablet
14 tablets, each containing 1 mg 17ß-estradiol (as hemihydrate) and 14 tablets, each containing 1 mg 17ß-estradiol (as hemihydrate) and 10 mg dydrogesterone.

Femoston® 2/10 Tablet
14 tablets, each containing 2 mg 17ß-estradiol (as hemihydrate) and 14 tablets, each containing 2 mg 17ß-estradiol (as hemihydrate) and 10 mg dydrogesterone.

Excipient with known effect: lactose monohydrate
For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Film-coated tablet
Round, biconvex tablets marked 379 on one side.

Femoston® Conti 1/5
Salmon-coloured 1/5 mg tablets.

Femoston® 1/10
White 1 mg tablets and grey 1/10 mg tablets.

Femoston® 2/10
Brick red 2 mg tablets and yellow 2/10 mg tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

For continuous combined HRT regimen: Femoston® Conti 1 /5
Hormone Replacement Therapy (HRT) for oestrogen deficiency symptoms in postmenopausal women with a uterus, at least 12 months since last menses.

Prevention of osteoporosis in postmenopausal women with a uterus, at high risk of future fractures who are intolerant of, or contraindicated for, other medicinal products approved for the prevention of osteoporosis.

For continuous sequential HRT regimen: Femoston® 1/10
Hormone Replacement Therapy (HRT) for oestrogen deficiency symptoms in postmenopausal women at least 6 months since last menses.

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.

For continuous sequential HRT regimen: Femoston® 2/10
Hormone Replacement Therapy (HRT) for oestrogen deficiency symptoms in postmenopausal women at least 6 months since last menses.

All Formulations
Elderly population
The experience in treating women older than 65 years is limited.

4.2 Posology and method of administration

For oral use

Femoston® Conti 1/5: Continuous combined
Femoston® should be taken continuously without a break between packs.

The oestrogen and the progestogen are given every day without interruption.
One tablet to be taken daily for a 28 day cycle.

Femoston® conti is intended to prevent stimulation of the endometrium in postmenopausal women, usually resulting in amenorrhoea.
Before initiating treatment, pregnancy must be excluded.

Changing from other HRT:
Patients changing from a continuous combined preparation may start therapy at any time. Patients changing from another continuous sequential or cyclical preparation should complete the 28 day cycle and then change to Femoston®.

Femoston® conti should be used only in postmenopausal women more than 12 months after menopause. If the menopausal status is not known (e.g. because of previous use of sequential HRT or oral combination contraceptives) the endogenous estrogen may still be high. This could result in unpredictable bleeding.

If a dose has been forgotten, it should be taken as soon as possible. If more than 12 hours have elapsed, treatment should be continued with the next tablet without taking the forgotten tablet. The likelihood of breakthrough bleeding or spotting may be increased.

Femoston® may be taken irrespective of food intake.

Femoston® 1/10: Continuous sequential
Femoston® should be taken continuously without a break between packs.

The oestrogen is dosed continuously. The progestogen is added for the last 14 days of every 28 day cycle, in a sequential manner.

For initiation and continuation of treatment of postmenopausal symptoms, the lowest effective dose for the shortest duration (see also **section 4.4**) should be used.

1. Treatment of postmenopausal symptoms
In general, sequential combined treatment should start with Femoston® 1/10. Depending on the clinical response, the dosage can afterwards be adjusted to individual need. If the complaints linked to estrogen

deficiency are not ameliorated, the dosage can be increased by using Femoston® 2/10.

2. Osteoporosis prevention
Hormone replacement therapy for the prevention of postmenopausal osteoporosis must take into account the expected effects on bone mass, which are dose-related (see **section 5.1**) and the individual tolerability of treatment.

Treatment commences with one white tablet daily for the first 14 days followed by one grey tablet daily for the next 14 days, as directed on the 28 days calendar pack.

Changing from other HRT:
Patients changing from a continuous combined preparation may start therapy at any time. Patients changing from another continuous sequential or cyclical preparation should complete the 28 day cycle and then change to Femoston®.

If a dose has been forgotten, it should be taken as soon as possible. If more than 12 hours have elapsed, treatment should be continued with the next tablet without taking the forgotten tablet. The likelihood of breakthrough bleeding or spotting may be increased.

Femoston® may be taken irrespective of food intake.

Femoston® 2/10: Continuous sequential
Femoston® should be taken continuously without a break between packs.
The oestrogen is dosed continuously. The progestogen is added for the last 14 days of every 28 day cycle, in a sequential manner.

Treatment commences with one brick red tablet daily for the first 14 days followed by one yellow tablet daily for the next 14 days, as directed on the 28 day calendar pack.

Changing from other HRT:
Patients changing from a continuous combined preparation may start therapy at any time. Patients changing from another continuous sequential or cyclical preparation should complete the 28 day cycle and then change to Femoston®.

If a dose has been forgotten, it should be taken as soon as possible. If more than 12 hours have elapsed, treatment should be continued with the next tablet without taking the forgotten tablet. The likelihood of breakthrough bleeding or spotting may be increased.

Femoston® may be taken irrespective of food intake.

Paediatric population:
There is no relevant indication for the use of Femoston® in the paediatric population.

4.3 Contraindications
- Known past or suspected breast cancer
- Known or suspected oestrogen-dependent malignant tumours (e.g. endometrial cancer)
- Known or suspected progestogen-dependent neoplasms (e.g. meningioma)
- Undiagnosed genital bleeding
- Untreated endometrial hyperplasia
- Previous or current venous thromboembolism (deep venous thrombosis, pulmonary embolism)
- Known thrombophilic disorders (e.g. protein C, protein S or antithrombin deficiency, see **section 4.4**)
- Active or recent arterial thromboembolic disease (e.g. angina, myocardial infarction)
- Acute liver disease, or a history of liver disease, as long as the liver function tests have failed to return to normal
- Porphyria
- Known hypersensitivity to the active substances or to any of the excipients

4.4 Special warnings and precautions for use

For the treatment of postmenopausal symptoms, 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.

Evidence regarding the risks associated with HRT in the treatment of premature menopause is limited. Due to the low level of absolute risk in younger women, however, the balance of benefits and risks for these women may be more favourable than in older women.

Medical examination / follow-up

Before initiating or re-instituting HRT, a complete personal 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 (see "Breast cancer" below). Investigations, including appropriate imaging tools, e.g. mammography, should be carried out in accordance with currently accepted screening practices, modified to the clinical needs of the individual.

Conditions which need supervision

If any of the following conditions are present, have occurred previously, and/or have been aggravated during pregnancy or previous hormone treatment, the patient should be closely supervised. It should be taken into account that these conditions may recur or be aggravated during treatment with Femoston®, in particular:

- Leiomyoma (uterine fibroids) or endometriosis
- Risk factors for thromboembolic disorders (see below)
- Risk factors for oestrogen-dependent tumours, e.g. 1st degree heredity for breast cancer
- Hypertension
- Liver disorders (e.g. liver adenoma)
- Diabetes mellitus with or without vascular involvement
- Cholelithiasis
- Migraine or (severe) headache
- Systemic lupus erythematosus
- A history of endometrial hyperplasia (see below)
- Epilepsy
- Asthma
- Otosclerosis

Reasons for immediate withdrawal of therapy:

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

Endometrial hyperplasia and carcinoma

- In women with an intact uterus the risk of endometrial hyperplasia and carcinoma is increased when oestrogens are administered alone for prolonged periods. The reported increase in endometrial cancer risk among oestrogen-only users varies from 2- to 12-fold greater compared with non-users, depending on the duration of treatment and oestrogen dose (see **section 4.8**). After stopping treatment, risk may remain elevated for at least 10 years.

- The addition of a progestogen cyclically for at least 12 days per month / 28 day cycle or continuous combined oestrogen-progestogen therapy in non-hysterectomised women can prevent the excess risk associated with oestrogen-only HRT.

- Breakthrough bleeding and spotting may occasionally occur during the first months of treatment. If breakthrough bleeding or spotting appears after some time on therapy, or continues after treatment has

been discontinued, the reason should be investigated, which may include endometrial biopsy to exclude endometrial malignancy.

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.

Combined oestrogen-progestogen therapy

- The randomized placebo-controlled trial, the Women's Health Initiative study (WHI), and a meta-analysis of prospective epidemiological studies are consistent in finding an increased risk of breast cancer in women taking combined oestrogen-progestogen for HRT that becomes apparent after about 3(1-4) years (see **section 4.8)**.

Oestrogen-only therapy

- The WHI trial found no increase in the risk of breast cancer in hysterectomised women using oestrogen-only HRT. Observational studies have mostly reported a small increase in risk of having breast cancer diagnosed that is substantially lower than that found in users of oestrogen-progestogen combinations (see **section 4.8**)

Results from a large meta-analysis showed that after stopping treatment the excessive risk will decrease with time and the time needed to return to baseline depends on duration of prior HRT use. When HRT was taken for more than 5 years, the risk may persist for 10 years or more.

HRT, especially oestrogen-progestogen combined treatment, increases the density of mammographic images which may adversely affect the radiological detection of breast cancer.

Ovarian cancer

Ovarian cancer is much rarer than breast cancer. Epidemiological evidence from a large meta-analysis suggests a slightly increased risk in women taking oestrogen-only or combined oestrogen-progestogen HRT, which becomes apparent within 5 years of use and diminishes over time after stopping. Some other studies, including the WHI trial suggest that use of combined HRTs may be associated with a similar, or slightly smaller, risk (see **section 4.8**).

Venous thromboembolism

- HRT is associated with a 1.3 to 3 fold risk of developing venous thromboembolism (VTE), i.e. deep vein thrombosis or pulmonary embolism. The occurrence of such an event is more likely in the first year of HRT than later (see **section 4.8**).
- 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 (see **section 4.3**). Personal or strong family history of thromboembolism or recurrent spontaneous abortion should be investigated in order to exclude a thrombophilic predisposition.
- Generally recognized risk factors for VTE include: a personal history or family history, use of oestrogens, older age, major surgery, prolonged immobilization, obesity (Body Mass Index (BMI) > 30 kg/m^2), pregnancy / postpartum period, systemic lupus erythematosus (SLE), and cancer. There is no consensus about the possible role of varicose veins in VTE. The risk of VTE may be temporarily increased with major trauma.
- As in all postoperative patients, prophylactic measures need be considered to prevent VTE following surgery. If prolonged immobilization is to follow elective surgery, temporarily stopping HRT 4 to 6 weeks earlier is recommended. Treatment should not be restarted until the woman is completely mobilized.
- In women with no personal history of VTE but with a first degree relative with a history of thrombosis at a young age, screening may be offered after careful counseling regarding its limitations (only a proportion of thrombophilic defects are identified by screening).
- If a thrombophilic defect is identified which segregates with thrombosis in family members or if the defect is 'severe' (e.g. antithrombin, protein S or protein C deficiencies or a combination of defects) HRT is contraindicated.

- Women already on anticoagulant treatment require careful consideration of the benefit-risk of use of HRT.
- If VTE develops after initiating therapy, the drug should be discontinued. Patients should be told to contact their doctors immediately when they are aware of a potential thromboembolic symptom (e.g. painful swelling of a leg, sudden pain in the chest, dyspnoea).

Coronary artery disease (CAD)
There is no evidence from randomised controlled trials of protection against myocardial infarction in women with or without existing CAD who received combined oestrogen-progestogen or oestrogen-only HRT. Two large clinical trials (WHI and HERS i.e. Heart and Estrogen/progestin Replacement Study) showed a possible increased risk of cardiovascular morbidity in the first year of use and no overall benefit.

Combined oestrogen-progestogen therapy
The relative risk of CAD during use of combined oestrogen-progestogen HRT is slightly increased. As the baseline absolute risk of CAD is strongly dependent on age, the number of extra cases of CAD due to oestrogen-progestogen use is very low in healthy women close to menopause, but will rise with more advanced age.

Oestrogen-only
Randomised controlled data found no increased risk of CAD in hysterectomised women using oestrogen-only therapy.

Ischemic Stroke
Combined oestrogen-progestogen and oestrogen-only therapy are associated with an up to 1.5-fold increase in risk of ischaemic stroke. The relative risk does not change with age or time since menopause. However, as the baseline risk of stroke is strongly age-dependent, the overall risk of stroke in women who use HRT will increase with age (see **section 4.8**).

Other conditions
- Oestrogens may cause fluid retention and therefore patient with cardiac or renal dysfunction should be carefully observed.
- Women with pre-existing hypertriglyceridemia should be followed closely during oestrogen replacement or hormone replacement therapy, since rare cases of large increases of plasma triglycerides leading to pancreatitis have been reported with oestrogen therapy in this condition.
- Exogenous estrogens may induce or exacerbate symptoms of hereditary and acquired angioedema
- Oestrogens increase thyroid binding globulin (TBG), leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 levels (by column or by radio-immunoassay) or T3 levels (by radio-immunoassay). T3 resin uptake is decreased, reflecting the elevated TBG. Free T4 and free T3 concentrations are unaltered. Other binding proteins may be elevated in serum, i.e. corticoid binding globulin (CBG), sex-hormone binding globulin (SHBG) leading to increased circulating corticosteroids and sex steroids, respectively. Free or biologically active hormone concentrations are unchanged. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-I-antitrypsin, ceruloplasmin).
- HRT use does not improve cognitive function. There is some evidence of increased risk of probable dementia in women who start using continuous combined or oestrogen-only HRT after the age of 65.
- Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.
- This product contains Lactose monohydrate. Patients who have known intolerance to some sugars should check with their physician before taking this medicinal product.

This oestrogen-progestogen combination treatment is not a contraceptive.

ALT elevations
During clinical trials with patients treated for hepatitis C virus (HCV) infections with the combination regimen ombitasvir/paritaprevir/ritonavir with and without dasabuvir, ALT elevations greater than 5 times the upper limit of normal (ULN) were significantly more frequent in women using ethinylestradiol-containing medicinal products such as CHCs. Additionally, also in patients treated with glecaprevir/pibrentasvir, ALT elevations were observed in women using ethinylestradiol-containing

medicinal products such as CHCs. Women using medicinal products containing oestrogens other than ethinylestradiol, such as estradiol, had a rate of ALT elevation similar to those not receiving any oestrogens; however, due to the limited number of women taking these other oestrogens, caution is warranted for co-administration with the combination drug regimen ombitasvir/paritaprevir/ritonavir with or without dasabuvir and also the regimen glecaprevir/pibrentasvir. (See **section 4.5**)

4.5 Interaction with other medicinal product and other forms of interaction

No interaction studies have been performed.

The efficacy of oestrogens and progestogens might be impaired:

- The metabolism of oestrogens and progestogens may be increased by concomitant use of substances known to induce drug-metabolizing enzymes, specifically P450 enzymes 2B6, 3A4, 3A5, 3A7, such as anticonvulsants (e.g. phenobarbital, carbamazepine, phenytoin) and anti-infectives (e.g. rifampicin, rifabutin, nevirapine, efavirenz).
- Ritonavir and nelfinavir, although known as strong inhibitors of CYP450 3A4, A5, A7, by contrast, exhibit inducing properties when used concomitantly with steroid hormones
- Herbal preparations containing St. John's Wort (*Hypericum perforatum*) may induce the metabolism of oestrogens and progestogens via the CYP450 3A4 pathway.
- Clinically, an increased metabolism of oestrogens and progestogens may lead to decreased effect and changes in the uterine bleeding profile.

Pharmacodynamic Interactions

During clinical trials with the HCV combination drug regime ombitasvir/paritaprevir/ritonavir with and without dasabuvir, ALT elevations greater than 5 times the upper limit of normal (ULN) were significantly more frequent in women using ethinylestradiol-containing medicinal products such as CHCs. Women using medicinal products containing oestrogens other than ethinylestradiol, such as estradiol, had a rate of ALT elevation similar to those not receiving any oestrogens; however, due to the limited number of women taking these other oestrogens, 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 (see **section 4.4**)

Oestrogens might interfere with the metabolism of other drugs:

Oestrogens per se many inhibit CYP450 drug-metabolising enzymes via competitive inhibition. This is in particular to be considered for substrates with a narrow therapeutic index, such as

- Tacrolimus and cyclosporine A (CYP450 3A4, 3A3)
- Fentanyl (CYP450 3A4)
- Theophylline (CYP450 1A2)

Clinically this may lead to an increased plasma level of the affected substances up to toxic concentrations. Thus, careful monitoring for an extended period of time might be indicated and a dosage decrease of tacrolimus, fentanyl, cyclosporine A and theophylline may be necessary.

4.6 Fertility, pregnancy and lactation

Femoston® is not indicated during pregnancy. If pregnancy occurs during medication with Femoston®, treatment should be withdrawn immediately.

The results of most epidemiological studies to date relevant to inadvertent fetal exposure to combinations of oestrogens with progestogens indicate no teratogenic or foetotoxic effect. There are no adequate data from the use of estradiol/dydrogesterone in pregnant women.

Lactation

Femoston® is not indicated during lactation.

4.7 Effects on ability to drive and use machines

Femoston® has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

The most commonly reported adverse drug reactions of patients treated with estradiol/dydrogesterone in clinical trials are headache, abdominal pain, breast pain/tenderness and back pain.

The following undesirable effects have been observed with the frequencies indicated below during clinical trials (n = 5108):

MedDRA system organ class	**Very Common ≥ 1/10**	**Common ≥ 1/100 to <1/10**	**Uncommon ≥ 1/1,000 to <1/100**	**Rare ≥ 1/10,000 to <1/1,000**
Infections and infestations		Vaginal candidiasis		
Neoplasms benign, malignant and unspecified			Increase in size of leiomyoma	
Immune system disorders			Hypersensitivity	
Psychiatric disorders		Depression, nervousness	Influence on libido	
Nervous system disorders	Headache	Migraine, dizziness		
Cardiac disorders				Myocardial infarction
Vascular disorders			Venous thromboembolism*	
Gastrointestinal disorders	Abdominal pain	Nausea, vomiting, flatulence		
Hepatobiliary disorders			Abnormal hepatic function, occasionally with jaundice, asthenia or malaise, and abdominal pain, gall bladder disorders	
Skin and subcutaneous tissue disorders		Allergic skin reactions (e.g. rash, urticaria, pruritus)		Angioedema, vascular purpura,
Musculoskelatal and connective tissue disorders	Back pain			
Reproductive system and breast disorders	Breast pain/tenderness	Menstrual disorders (including postmenopausal spotting,	Breast enlargement, Premenstrual syndrome	

		metrorrhagia, menorrhagia, oligo-/amenorrhoea, irregular menstruation, dysmenorrhoea), pelvic pain, cervical discharge		
General disorders and administration site reactions		Asthenic conditions (asthenia, fatigue, malaise), peripheral oedema		
Investigations		Increased weight	Decreased weight	

*see below for further information

Breast cancer risk

- An up to 2-fold increased risk of having breast cancer diagnosed is reported in women taking combined oestrogen-progestogen therapy for more than 5 years.
- The increased risk in users of oestrogen-only therapy is lower than that seen in users of oestrogen-progestogen combinations.
- The level of risk is dependent on the durations of use (see **section 4.4**).
- Absolute risk estimations based on results of the largest randomized placebo-controlled trial (WHI-study) and the largest meta-analysis of prospective epidemiological studies are presented.

Largest meta-analysis of prospective epidemiological studies
Estimated additional risk of breast cancer after 5 years' use in women with BMI 27 (kg/m^2)

Age at start HRT (years)	Incidence per 1000 never-users of HRT over a 5 year period (50-54 years)[1]	Risk ratio	Additional cases per 1000 HRT users after 5 years
Oestrogen only HRT			
50	13.3	1.2	2.7
Combined oestrogen-progestogen			
50	13.3	1.6	8.0

[1] Taken from baseline incidence rates in England in 2015 women with BMI 27 (kg/m^2)
Note: Since the background incidence of breast cancer differs by EU country, the number of additional cases of breast cancer will also change proportionately.

Estimated additional risk of breast cancer after 10 years' use in women with BMI 27 (kg/m^2)

Age at start HRT (years)	Incidence per 1000 never-users of HRT over a 10 year period (50-59 years)*	Risk ratio	Additional cases per 1000 HRT users after 10 years
Oestrogen only HRT			
50	26.6	1.3	7.1
Combined oestrogen-progestogen			
50	26.6	1.8	20.8

*Taken from baseline incidence rates in England in 2015 in women with BMI 27 (kg/m^2)
Note: Since the background incidence of breast cancer differs by EU country, the number of additional cases of breast cancer will also change proportionately.

US WHI studies – additional risk of breast cancer after 5 years' use

Age range (years)	Incidence per 1000 women in placebo arm over 5 years	Risk ratio & 95% CI	Additional cases per 1000 HRT users over 5 years
CEE oestrogen-only			
50-79	21	0.8 (0.7 – 1.0)	-4 (-6 – 0)[2]
CEE+MPA oestrogen & progestogen*			
50-79	17	1.2 (1.0 – 1.5)	+4 (0 – 9)

[2] WHI study in women with no uterus, which did not show an increase in risk of breast cancer
* When the analysis was restricted to women who had not used HRT prior to the study there was no increased risk apparent during the first 5 years of treatment: after 5 years the risk was higher than in non-users.

Endometrial cancer risk
Postmenopausal women with a uterus
The endometrial cancer risk is about 5 in every 1000 women with a uterus not using HRT.

In women with a uterus, use of oestrogen-only HRT is not recommended because it increases the risk of endometrial hyperplasia and endometrial cancer (see **section 4.4**).

Depending on the duration of oestrogen-only use and estrogen dose, the increase in risk of endometrial cancer in epidemiology studies varied from between 5 and 55 extra cases diagnosed in every 1000 women between the ages of 50 and 65.

Adding a progestogen to oestrogen-only therapy for at least 12 days per cycle can prevent this increased risk. In the Million Women Study the use of five years of combined (sequential or continuous) HRT did not increase the risk of endometrial cancer (RR of 1.0 (0.8 – 1.2))

Ovarian Cancer
Use of oestrogen-only or combined oestrogen-progestogen HRT has been associated with a slightly increased risk of having ovarian cancer diagnosed (see **section 4.4**). A meta-analysis from 52 epidemiological studies reported an increased risk of ovarian cancer in women currently using HRT compared to women who have never used HRT (RR 1.43, 95% CI 1.31-1.56). For women aged 50 to 54 years taking 5 years of HRT, this results in about 1 extra case per 2000 users. In women aged 50 to 54 who are not taking HRT, about 2 women in 2000 will be diagnosed with ovarian cancer over a 5-year period.

Risk of venous thromboembolism
HRT is associated with a 1.3-3-fold increased relative risk of developing venous thromboembolism (VTE), i.e. deep vein thrombosis or pulmonary embolism. The occurrence of such an event is more likely in the first year of using HRT (see **section 4.4**). Results of the WHI studies are presented:

WHI Studies – Additional risk of VTE over 5 years' use

Age range (years)	Incidence per 1000 women in placebo arm over 5 years	Risk ratio & 95% CI	Additional cases per 1000 HRT users
Oral oestrogen-only[3]			
50-59	7	1.2 (0.6 – 2.4)	1 (-3 – 10)
Oral combined oestrogen-progestogen			
50-59	4	2.3 (1.2 – 4.3)	5 (1 – 13)

[3] Study in women with no uterus

Risk of coronary artery disease
The risk of coronary artery disease is slightly increased in users of combined oestrogen-progestogen HRT over the age of 60 (see **section 4.4**).

Risk of ischaemic stroke
The use of oestrogen-only and oestrogen-progestogen therapy is associated with an up to 1.5-fold increased relative risk of ischaemic stroke. The risk of haemorrhagic stroke is not increased during use of HRT.

This relative risk is not dependent on age or on duration of use, but as the baseline risk is strongly age-dependent, the overall risk of stroke in women who use HRT will increase with age (see **section 4.4**).

WHI studies combined – Additional risk of ischaemic stroke[4] over 5 years' use

Age range (years)	Incidence per 1000 women in placebo arm over 5 years	Risk ratio & 95% CI	Additional cases per 1000 HRT users over 5 years
50-59	8	1.3 (1.1 – 1.6)	3 (1 - 5)
[4] No differentiation was made between ischaemic and haemorrhagic stroke			

Other adverse reactions have been reported in association with oestrogen/progestogen treatment (including estradiol/dydrogesterone):

Neoplasms benign, malignant and unspecified:
Oestrogen dependent neoplasms both benign and malignant, e.g. endometrial cancer, ovarian cancer.
Increase in size of progestogen dependent neoplasms, e.g. meningioma.

Blood and lymphatic system disorders:
Haemolytic anaemia

Immune system disorders:
Systemic lupus erythematous

Metabolism and nutrition disorders:
Hypertriglyceridemia

Nervous system disorders:
Probable dementia, chorea, exacerbation of epilepsy

Eye disorders:
Steepening of corneal curvature, contact lenses intolerance

Vascular disorders:
Arterial thromboembolism

Gastrointestinal disorders:
Pancreatitis (in women with pre-existing hypertriglyceridemia)

Skin and subcutaneous tissue disorders:
Erythema multiforme, erythema nodosum, chloasma or melasma, which may persist when drug is discontinued.

Musculoskeletal and connective tissue disorders:
Leg cramps

Renal and urinary disorders:
Urinary incontinence

Reproductive system and breast disorders:
Fibrocystic breast disease, uterine cervical erosion

Congenital, familial and genetic disorders:
Aggravated porphyria

Investigations:
Total thyroid hormones increased

4.9 Overdose

Both oestradiol and dydrogesterone are substances with low toxicity. Symptoms such as nausea, vomiting, breast tenderness, dizziness, abdominal pain, drowsiness/fatigue, and withdrawal bleeding could occur in cases of overdosing. It is unlikely that any specific symptomatic treatment will be necessary. Aforementioned information is also applicable for overdosing in children.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Femoston® Conti 1/5
Pharmacotherapeutic group: Genito urinary system and sex hormones, progestogens and oestrogens, fixed combinations. The ATC code is G03FA14.

Femoston® 1/10 and Femoston® 2/10
Pharmacotherapeutic group: Genito urinary system and sex hormones, progestogens and oestrogens, sequential preparations. The ATC code is G03FB08.

Estradiol
The active ingredient, 17ß-estradiol, is chemically and biologically identical to the endogenous human estradiol.
It substitutes for the loss of oestrogen production in menopausal women, and alleviates menopausal symptoms.
Femoston® Conti 1/5 and Femoston® 1/10 oestrogens prevent bone loss following menopause.

Dydrogesterone
Dydrogesterone is an orally-active progestogen having an activity comparable to parenterally administered progesterone.

As oestrogens promote the growth of the endometrium, unopposed oestrogens increase the risk of endometrial hyperplasia and cancer. The addition of a progestogen greatly reduces the oestrogen-induced risk of endometrial hyperplasia in non-hysterectomised women.

Clinical trial Information
- Relief of oestrogen-deficiency symptoms and bleeding patterns
- Relief of menopausal symptoms was achieved during the first few weeks of treatment.

Femoston® Conti 1/5
Amenorrhoea was seen in 88% of the women during months 10-12 treatment. Irregular bleeding and/or spotting appeared in 15% of the women during the first 3 months of treatment and in 12% during months 10-12 of treatment.

Femoston® 1/10
Regular withdrawal bleeding occurred in 76% of the women with a mean duration of 5 days. Withdrawal bleeding usually started at mean day 28 of the cycle. Breakthrough bleeding and/or spotting appeared in 23% of the women during the first three months of therapy and in 15% of the women during months 10-12 of treatment. Amenorrhea (no bleeding or spotting) occurred in 21% of the cycles during the first year of treatment.

Femoston® 2/10
Regular withdrawal bleeding occurred in 89% of the women with a mean duration of 5 days. Withdrawal bleeding usually started at mean day 28 of the cycle. Breakthrough bleeding and/or spotting appeared in 22% of the women during the first three months of therapy and in 19% of the women during months 10-12 of treatment. Amenorrhoea (no bleeding or spotting) occurred in 12% of the cycles during the first year of treatment.

Femoston® Conti 1/5, Femoston® 1/10 and Femoston® 2/10

Relief of climacteric complaints was achieved during the first weeks of treatment.

Femoston® Conti 1/5 and Femoston® 1/10

- Prevention of osteoporosis:
  Oestrogen deficiency at menopause is associated with an increase in bone turnover and a decline in bone mass. The effect of oestrogens on the bone mineral density is dose-dependent. Protection appears to be effective for as long as treatment is continued. After discontinuation of HRT, bone mass is lost at a rate similar to that in untreated women.
  Evidence from the WHI trial and meta-analysed trials shows that current use of HRT, alone or in combination with a progestogen – given to predominantly healthy women – reduces the risk of hip, vertebral, and other osteoporotic fractures. HRT may also prevent fractures in women with low bone density and/or established osteoporosis, but the evidence for that is limited.

Femoston® Conti 1/5

After one year of treatment the bone mineral density in the lumbar vertebrae increased about 4.0% ± 3.4% (mean ± SD). In 90% of the subjects the bone mineral density increased or stayed the same during treatment. Femoston® 1/5 also had an effect on hip BMD.

The increase after one year of treatment with Femoston® Conti 1/5 was 1.5% ± 4.5% (mean ± SD) at femoral neck, 3.7% ± 6% (mean ± SD) at trochanter and 2.1% ± 7.2% (mean ± SD) at Wards triangle.

The percentage of women who maintained or gained BMD in the 3 hip areas after treatment with Femoston® Conti 1/5 was 71%, 66% and 81% respectively.

Femoston® 1/10

For Femoston® 1/10, the increase in lumbar spine BMD was 5.2% ± 3.8% (mean ± SD), and the percentage of women with no change or an increase in lumbar spine BMD was 93.0%. Femoston® 1/10 also had an effect on hip BMD.
The increase after two years of treatment with Femoston® 1/10 was 2.7% ± 4.2% (mean ± SD) at femoral neck, 3.5% ± 5% (mean ± SD) at trochanter and 2.7% ± 6.7% (mean ± SD) at Wards triangle.
The percentage of women who maintained or gained BMD in the 3 hip areas after treatment with Femoston® 1/10 was 67-78%.

Femoston® 2/10

After two years of treatment with Femoston® 2/10, the increase in lumbar spine bone mineral density (BMD) was 6.7% ± 3.9 % (mean ± SD). For Femoston® 2/10 the percentage of women who maintained or gained BMD in lumbar zone during treatment was 94.5%. Femoston® 2/10 also had an effect on hip BMD.
The increase after two years of treatment with Femoston® 2/10 was 2.6% ± 5.0% (mean ± SD) at femoral neck; 4.6% ± 5.0% (mean ± SD) at trochanter and 4.1% ± 7.4% (mean ± SD) at Wards triangle.
The percentage of women who maintained or gained BMD in the 3 hip areas after treatment with Femoston® 2/10 was 71-88%.

5.2 Pharmacokinetic properties

Estradiol

- Absorption

Absorption of estradiol is dependent on the particle size, micronized estradiol is readily absorbed from the gastrointestinal tract.

The following tables provide the mean steady state pharmacokinetic parameters of estradiol (E2), estrone (E1) and estrone sulphate (E1S) for each dose of micronized estradiol. Data is presented as mean (SD).

Estradiol 1 mg				
Parameters	E2	E1	Parameters	E1S
C_{max} (pg/mL)	71 (36)	310 (99)	C_{max} (ng/mL)	9.3 (3.9)
C_{min} (pg/mL)	18.6 (9.4)	114 (50)	C_{min} (ng/mL)	2.099 (1.340)

C_{av} (pg/mL)	30.1 (11.0)	194 (72)	C_{av} (ng/mL)	4.695 (2.350)
AUC_{0-24} (pg.h/mL)	725 (270)	4767 (1857)	AUC_{0-24} (ng.h/mL)	112.7 (55.1)

Estradiol 2 mg				
Parameters	E2	E1	Parameters	E1S
C_{max} (pg/mL)	103.7 (48.2)	622.2 (263.6)	C_{max} (ng/mL)	25.9 (16.4)
C_{min} (pg/mL)	48 (30)	270 (138)	C_{min} (ng/mL)	5.7 (5.9)
C_{av} (pg/mL)	68 (31)	429 (191)	C_{av} (ng/mL)	13.1 (9.4)
AUC_{0-24} (pg.h/mL)	1619 (733)	10209 (4561)	AUC_{0-24} (ng.h/mL)	307.3 (224.1)

- Distribution

Oestrogens can be found either unbound or bound. About 98-99% of the estradiol dose binds to plasma proteins, from which about 30-52% on albumin and about 46-69% on the sex hormones-binding globulin (SHBG).

- Metabolism

Following oral administration, estradiol is extensively metabolized. The major unconjugated and conjugated metabolites are estrone and estrone sulphate. These metabolites can contribute to the oestrogen activity, either directly or after conversion to estradiol. Estrone sulphate may undergo enterohepatic circulation.

- Elimination

In urine, the major compounds are the glucuronides of estrone and estradiol. The elimination half-life is between 10 to 16 hours.
Oestrogens are secreted in the milk of nursing mothers.

- Dose and time dependencies

Following daily oral administration of Femoston®, estradiol concentrations reached a steady-state after about five days.
Generally, steady state concentrations appeared to be reached for within 8 to 11 days of dosing.

Dydrogesterone

- Absorption

Following oral administration, dydrogesterone is rapidly absorbed with a T_{max} between 0.5 and 1.5 hours.

The following tables provide the mean pharmacokinetic parameters of dydrogesterone (D) and dihydrodydrogesterone (DHD) after single dose (5 mg dydrogesterone) and at steady state (10 mg dydrogesterone). Data is presented as mean (SD).

Dydrogesterone 5 mg		
Parameters	*D*	*DHD*
C_{max} (ng/mL)	0.90 (0.59)	24.68 (10.89)
AUC_{0-t} (ng.h/mL)	1.55 (1.08)	98.37 (43.21)
AUC_{inf} (ng.h/mL)	-	121.36 (63.63)

Dydrogesterone 10 mg		
Parameters	*D*	*DHD*
C_{max} (ng/mL)	2.54 (1.80)	62.50 (33.10)
C_{min} (ng/mL)	0.13 (0.07)	3.70 (1.67)
C_{av} (ng/mL)	0.42 (0.25)	13.04 (4.77)
AUC_{τ} (ng.h/mL)	10.17 (5.96)	312.90 (114.54)

After a single dose, food delays the peak plasma concentration of dydrogesterone with approximately 1 hour, resulting in approximately 20% lower dydrogesterone peak plasma concentrations without affecting the extent of exposure to dydrogesterone and DHD.

- Distribution

After oral administration of dydrogesterone the apparent volume of distribution is large, being approximately 22000L. Dydrogesterone and DHD are more than 90% bound to plasma proteins.

- Metabolism

Following oral administration, dydrogesterone is rapidly metabolized to 20 α-dihydrodydrogesterone (DHD). The levels of the main active metabolite DHD peak at similar times as dydrogesterone. The plasma concentrations of DHD are substantially higher as compared to the parent drug. The AUC and Cmax ratios of DHD to dydrogesterone are approximately 25 and 20, respectively. The mean terminal half-lives of dydrogesterone and DHD is about 15 hours. A common feature of all metabolites characterized is the retention of the 4,6 diene-3-one configuration of the parent compound and the absence of 17α-hydroxylation. This explains the lack of oestrogenic and androgenic effects of dydrogesterone.

Dydrogesterone is not excreted in urine as pregnanediol, like progesterone. Analysis of endogenous progesterone production based on pregnanediol excretion therefore remains possible.

- Elimination

After oral administration of labelled dydrogesterone, on average 63% of the dose is excreted into the urine. The apparent total body clearance of dydrogesterone from plasma is high at approximately 20 L/min. Within 72 hours excretion is complete. DHD is present in the urine predominantly as the glucuronic acid conjugate.

- Dose and time dependencies

The single and multiple dose pharmacokinetics are linear in the oral dose range 2.5 to 20 mg. Comparison of the single and multiple dose kinetics shows that the pharmacokinetics of dydrogesterone and DHD are not changed as a result of repeated dosing. Steady state conditions are generally reached after 3 days of treatment.

5.3 Preclinical safety data

There are no preclinical safety data of relevance to the prescriber in the target population that are additional to those already included in other sections of the leaflet.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:
Lactose monohydrate
Hypromellose
Maize starch
Colloidal anhydrous silica
Magnesium stearate

Film-coating

Formulation	Tablet Colour	Composition of Colouring Agents
Femoston® Conti 1/5		
1 mg estradiol and 5 mg dydrogesterone	Salmon	Titanium dioxide (E171) Iron oxide yellow (E172) Iron oxide red (E172) Hypromellose Macrogol 400
Femoston® 1/10		
1 mg estradiol	White	Titanium dioxide (E171) Hypromellose Macrogol 400

1 mg estradiol and 10 mg dydrogesterone	Grey	Titanium dioxide (E171) Iron oxide black (E172) Polyvinyl alcohol Macrogol 3350 Talc
Femoston® 2/10		
2 mg estradiol	Brick red	Titanium dioxide (E171) Iron oxide red (E172) Iron oxide black (E172) Iron oxide yellow (E172) Hypromellose Macrogol 400 Talc
2 mg estradiol and 10 mg dydrogesterone	Yellow	Titanium dioxide (E171) Iron oxide yellow (E172) Hypromellose Macrogol 400 Talc

6.2 Incompatibilities
Not applicable

6.3 Shelf life
Please refer to the product carton for expiry.

6.4 Special precautions for storage
Do not store above 30°C.
Store in the original package.
Do not use this medicine after the expiry date stated on the carton.
Keep this medicine out of the reach and sight of children.

6.5 Nature and contents of container
The tablets are packed in blister packs of 28 or 84 (3 x 28) tablets. Not all pack sizes may be marketed.
The blister packs are made of PVC/PVDC or PVC film with a covering aluminium foil.

6.6 Manufactured by
Abbott Biologicals B.V.,
The Netherlands

Revision date: 22 February 2022 (RDCCDS000421/13)