Prescribing Information

Femoston® 1/10 mg

1 NAME OF THE MEDICINAL PRODUCT

Femoston® 1/10 mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Blister of 28 tablets: 14 white tablets contain 1 mg estradiol (as hemihydrate) and 14 grey tablets contain 1 mg estradiol (as hemihydrate) and 10 mg dydrogesterone.
Also contains: lactose monohydrate 119.1 mg (white film-coated tablets) and 110.2 mg (grey film-coated tablets).

For the full list of excipients see 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablets

Estradiol film coated tablet 1 mg: Round, biconvex, white film-coated tablets with inscription '379' on one side.

Estradiol/dydrogesterone film coated tablet 1/10mg: Round, biconvex, grey film-coated tablets with inscription '379' on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Hormone replacement therapy (HRT) for estrogen deficiency symptoms in postmenopausal women at least 6 months since last menses.

Prevention of osteoporosis in postmenopausal women at high risk of future fractures. Femoston 1/10 mg should only be used in patients who are intolerant of other products, approved for the prevention of osteoporosis or for whom these products are contra-indicated (See also section 4.4).

Femoston is indicated for women with an intact uterus.

Experience with treatment of women older than 65 years is limited.

4.2 Posology and method of administration

Femoston 1/10 mg is indicated for the treatment of symptoms and not for prevention.

Femoston 1/10 mg is taken orally daily according to a continuous sequential regimen, as described below.

For each cycle of 28 days for the first 14 days one white tablet with estradiol is taken once a day and for the following 14 days one grey tablet with estradiol and dydrogesterone is taken once a day, as indicated on the calendar pack for 28 days.

After a cycle of 28 days on the 29th day a new cycle of 28 days begins. The treatment cycles therefore follow one another without a break.

For the treatment of estrogen deficiency in postmenopausal women as an initial and maintenance dose the lowest effective dose should be used and the duration of treatment period should be kept as short as possible (see also section 4.4). In case of no improvement of symptoms within 3 months, treatment should be stopped.

In general sequential combined treatment should be started with Femoston 1/10 mg. Depending on the clinical response the dose can be adjusted accordingly.

In women who are not taking hormone replacement therapy or in women switching from continuous combined hormone replacement therapy, the treatment can be started on any convenient day. In women switching from cyclical or continuous sequential hormone replacement therapy, treatment should start on the day immediately after completion of the previous cycle.

If a tablet is missed it is recommended to take the next tablet without taking the forgotten tablet. Forgetting a tablet may increase the chance of breakthrough bleeding or spotting.

Femoston 1/10 mg can be taken both with and without food.

Paediatric patients:

There are no relevant indications for the use of Femoston 1/10 mg in the paediatric patients.

4.3 Contraindications

- Known, past or suspected breast cancer;
- Known or suspected estrogen-dependent malignant tumours (e.g. endometrial cancer);
- Known or suspected progestogen-dependent neoplasms;
- Undiagnosed genital bleeding;
- Untreated endometrial hyperplasia;
- Previous idiopathic or current venous thromboembolism (deep vein 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 liver function tests have failed to return to normal;
- Porphyria;
- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1;.
- Meningioma or history of meningioma;

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 reinstituting 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) immediately. 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 1/10 mg, in particular:

- Leiomyoma (uterine fibroids) or endometriosis
- Risk factors for thromboembolic disorders (see below)
- Risk factors for estrogen 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
- Meningioma
  The occurrence of meningiomas (single and multiple) has been reported in association with use of Femoston. Patients should be monitored for signs and symptoms of meningiomas in accordance with clinical practice. If a patient is diagnosed with meningioma, any oestradiol/dydrogesterone containing treatment must be stopped (see section 4.3). Tumour shrinkage has been observed after treatment discontinuation.

Reasons for immediate withdrawal of therapy:

Therapy should be discontinued in cases where a contra-indication 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 estrogens are administered alone for prolonged periods. The reported increase in endometrial cancer risk among estrogen-only users varies from 2- to 12-fold greater compared with non-users, depending on the duration of treatment and

estrogen 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 estrogen-progestogen therapy in non-hysterectomised women prevents the excess risk associated with estrogen-only HRT.
- Break-through bleeding and spotting may occur during the first months of treatment. If break-through 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 estrogen-progestogen or estrogen-only HRT, that is dependent on the duration of taking HRT.

Combined estrogen-progestogen therapy

The randomised 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 estrogen-progestogen for HRT that becomes apparent after about 3 (1-4) years (see Section 4.8).

Estrogen-only therapy

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

Results from a large meta-analysis showed that after stopping treatment, the excess risk will decrease with time and the time needed to return to baseline depends on the 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 estrogen-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 estrogen-only or combined estrogen-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 1.3-3 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.
- 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)
- Generally recognised risk factors for VTE include, use of estrogens, older ages, major surgery, prolonged immobilisation, severe obesity (BMI>30 kg/m2), pregnancy/postpartum period, systemic lupus erythematosus (SLE), and cancer. There is no consensus about the possible role of varicose veins in VTE.
  As in all postoperative patients, prophylactic measures need to be considered to prevent

VTE following surgery. If prolonged immobilisation 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 mobilised.

- In women with no personal history of VTE but with a first degree relative with a history of thrombosis at young age, screening may be offered after careful counselling 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 chronic anticoagulant treatment require careful consideration of the benefit-risk 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 estrogen-progestogen or estrogen-only HRT.

Combined estrogen-progestogen therapy

The relative risk of CAD during use of combined estrogen+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 estrogen+progestogen use is very low in healthy women close to menopause, but will rise with more advanced age.

Estrogen-only

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

Ischaemic stroke

Combined estrogen-progestogen and estrogen-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

- Estrogens may cause fluid retention, and therefore patients with cardiac or renal dysfunction should be carefully observed.
- Women with pre-existing hypertriglyceridemia should be followed closely during estrogen replacement or hormone replacement therapy, since rare cases of large increases of plasma triglycerides leading to pancreatitis have been reported with estrogen therapy in this condition.
- Exogenous estrogens may induce or exacerbate symptoms of hereditary and acquired angioedema.
- Estrogens 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 biological active hormone concentrations are unchanged. Other plasma proteins may be increased

(angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin).

- HRT use does not improve cognitive function. There is some evidence of increased risk of possible dementia in women who start using continuous combined or estrogen-only HRT after the age of 65.
- Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.
- Women who may be at risk of pregnancy should be advised to adhere to non-hormonal contraceptive methods.

ALT elevations

During clinical trials with patients treated for hepatitis C virus (HCV) infections with the combination regimen ombitasvir/paritaprevir/ritonavir and dasabuvir with and without ribavirin 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, or sofosbuvir/velpatasvir/voxilaprevir, ALT elevations were observed in women using ethinylestradiol-containing medications such as CHCs. Women using medicinal products containing estrogens other than ethinylestradiol, such as estradiol and ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin, had a rate of ALT elevation similar to those not receiving any estrogens; however, due to the limited number of women taking these other estrogens, caution is warranted for co-administration with the following combination drug regimens ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin, glecaprevir/pibrentasvir or sofosbuvir/velpatasvir/voxilaprevir.. See section 4.5.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

The efficacy of estrogens and progestogens might be impaired:

- The metabolism of estrogens and progestogens may be increased by concomitant use of substances known to induce drug-metabolising enzymes, specifically the P450 enzymes 2B6, 3A4, 3A5, 3A7, such as anticonvulsants (e.g. phenobarbital, phenytoin, carbamezapin) 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 estrogens and progestogens via the CYP450 3A4 pathway.
- Clinically an increased metabolism of estrogens and progestogens may lead to decreased effect and changes in the uterine bleeding profile.

Effect of HRT with estrogens on other medicinal products

Hormone contraceptives containing estrogens have been shown to significantly decrease plasma concentrations of lamotrigine when co-administered due to induction of lamotrigine glucuronidation. This may reduce seizure control. Although the potential interaction between hormone replacement therapy and lamotrigine has not been studied, it is expected that a similar interaction exists, which may lead to a reduction in seizure

control among women taking both medicinal products together.

Pharmacodynamic interactions

During clinical trials with the HCV combination drug regimen ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin, 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 with glecaprevir/pibrentasvir or sofosbuvir/velpatasvir/voxilaprevir, ALT elevations were observed in women using ethinylestradiol-containing medications such as CHCs.

Women using medicinal products containing estrogens other than ethinylestradiol, such as estradiol, and ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin had a rate of ALT elevation similar to those not receiving any estrogens; however, due to the limited number of women taking these other estrogens, caution is warranted for co-administration with the following combination drug regimens ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin glecaprevir/pibrentasvir or sofosbuvir/velpatasvir/voxilaprevir (see section 4.4).

Estrogens might interfere with the metabolism of other drugs:
Estrogens per se may 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 drug monitoring for an extended period of time might be indicated and a dosage decrease of tacrolimus, fentanyl, cyclosporin A and theophylline may be necessary.

4.6 Fertility, pregnancy and lactation

Pregnancy:
Femoston 1/10 mg is not indicated during pregnancy. If pregnancy occurs during medication with Femoston 1/10 mg, treatment should be withdrawn immediately.

The results of most epidemiological studies to date relevant to inadvertent foetal exposure to combinations of estrogens and progestogens indicate no teratogenic or foetotoxic effect.

There are no adequate data from the use of estradiol/dydrogesterone in pregnant women.

Breast feeding:
Femoston 1/10 mg is not indicated during lactation.

Fertility:
Femoston 1/10 mg is not indicated in women of child-bearing age.

4.7 Effects on ability to drive and use machines

Femoston 1/10 mg does not affect 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=4929):

MedDRA system organ class	**Very common ≥1/10**	**Common ≥1/100, <1/10**	**Uncommon ≥1/1,000, <1/100**	**Rare ≥1/10,000, <1/1,000**
Infections and infestations		Vaginal candidiasis	Cystitis-like syndrome	
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			Hypertension, Peripheral vascular disease, Varicose vein, Venous thromboembolism	
Gastrointestinal disorders	Abdominal pain	Nausea, Vomiting, Flatulence	Dyspepsia	
Hepatobiliary disorders			Abnormal hepatic function, occasionally with jaundice asthenia or malaise, and abdominal pain, Gall bladder disorder	
Skin and subcutaneous tissue disorders		Allergic skin reactions (e.g. rash, urticaria, pruritus)		Angioedema, Vascular purpura

Musculoskeletal and connective tissue disorders	Back pain			
Reproductive system and breast disorders	Breast pain/ tenderness	Menstrual disorders (including postmenopausal spotting, metrorrhagia, menorrhagia, oligo-/amenorrhoea, irregular menstruation, dysmenorrhoea), Pelvic pain, Cervical discharge	Breast enlargement, Premenstrual syndrome	
General disorders and administration site reactions		Asthenic conditions (asthenia, fatigue, malaise), Peripheral oedema		
Investigations		Increased weight	Decreased weight	

Breast Cancer risk

- An up to 2-fold increased risk of having breast cancer diagnosed is reported in women taking combined estrogen-progestogen therapy for more than 5 years.
- The increased risk in users of estrogen-only therapy is lower than that seen in users of estrogen-progestogen combinations.
- The level of risk is dependent on the duration of use (see section 4.4).
- Absolute risk estimations based on results of the largest randomised 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/m2)

Age at the start of HRT (years)	Incidence per 1000 never-users of HRT over a 5 year period (50-54 years)*	Risk ratio	Additional cases per 1000 HRT users after 5 years
Estrogen only HRT			
50	13.3	1.2	2.7
Combined estrogen-progestogen			
50	13.3	1.6	8.0
*Taken from baseline incidence rates 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.			

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

Age at the start of 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
Estrogen only HRT			
50	26.6	1.3	7.1
Combined estrogen-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 (95%CI)
CEE estrogen-only			
50-79	21	0.8 (0.7 – 1.0)	-4 (-6 – 0)*
CEE+MPA estrogen & progestogen‡			
50-79	17	1.2 (1.0 – 1.5)	+4 (0 – 9)

*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
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 estrogen-only HRT is not recommended because it increases the risk of endometrial cancer (see section 4.4). Depending on the duration of estrogen-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 between the ages of 50 and 65.
Adding a progestogen to estrogen-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 risk of endometrial cancer (R.R of 1 .0 (0.8-1.2)).

Ovarian cancer
Use of estrogen-only or combined estrogen-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 HT (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 and 95%CI	Additional cases per 1000 HRT users
Oral estrogen-only*[1]			
50-59	7	1.2 (0.6-2.4)	1 (-3 – 10)
Oral combined estrogen-progestogen			
50-59	4	2.3 (1.2 – 4.3)	5 (1 - 13)

[1]*Study in women with no uterus*

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

Risk of ischaemic stroke

- The use of estrogen-only and estrogen + 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*[2] over 5 years' use

Age range (years)	Incidence per 1000 women in placebo arm over 5 years	Risk ratio and 95%CI	Additional cases per 1000 HRT users
50-59	8	1.3 (1.1-1.6)	3 (1–5)

[2]*No differentiation was made between ischaemic and haemorrhagic stroke*

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

Neoplasms benign, malignant and unspecified:
Estrogen 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 erythematosus

Metabolism and nutrition disorders:
Hypertriglyceridemia

Nervous system disorders:

Probable dementia over the age of 65 (see section 4.4), 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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form:
https://sideeffects.health.gov.il /

4.9 Overdose

Both estradiol 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 or symptomatic treatment will be necessary.

Aforementioned information is applicable for overdosing by children also.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

The ATC code is G03FB08. (Estrogens: urogenital system and sex hormones)

Sequential hormone replacement therapy (combined estradiol and dydrogesterone).

Estradiol

The active ingredient, synthetic 17β-estradiol, is chemically and biologically identical to endogenous human oestradiol. It substitutes for the loss of estrogen production in menopausal women, and alleviates menopausal symptoms. Estrogens prevent bone loss following menopause or ovariectomy.

Dydrogesterone

Dydrogesterone is an orally-active progestogen having an activity comparable to parenterally administered progesterone. As estrogens promote the growth of the endometrium, unopposed estrogens increase the risk of endometrial hyperplasia and cancer. The addition of a progestogen greatly reduces the estrogen-induced risk of endometrial hyperplasia in non-hysterectomised women.

Clinical trial information

Relief of estrogen-deficiency symptoms and bleeding patterns.

- Relief of menopausal symptoms was achieved during the first few weeks of treatment.
- Regular withdrawal bleeding with Femoston 1/10 mg occurred in approximately 75-80% of women with a mean duration of 5 days.

Withdrawal bleeding usually started on the day of the last pill of the progestogen phase. Break-through bleeding and/or spotting occurred in approximately 10% of the women; amenorrhoea (no bleeding or spotting) occurred in 21-25% of the women for months 10 to 12 of treatment.

Prevention of osteoporosis

- Estrogen deficiency at menopause is associated with an increasing bone turnover and decline in bone mass.
- The effect of estrogens 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.

- For Femoston 1/10 mg 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%.
- Femoston 1/10 mg also had an effect on hip BMD. The increase after two years of treatment with Femoston 1/10 mg was 2.7% ± 4.2% (mean ± SD) at femoral neck, 3.5% ± 5.0% (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 mg was 67-78%.

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 table provides 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)

- Distribution

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

- Metabolism

Following oral administration, estradiol is extensively metabolised. The major unconjugated and conjugated metabolites are estrone and estrone sulphate. These metabolites can contribute to the estrogen 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 oestradiol. The elimination half-life is between 10-16 h.

Estrogens are secreted in the milk of nursing mothers.

- Dose and time dependencies

Following daily oral administration of Femoston 1/10 mg, 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 2.5 hours. The absolute bioavailability of dydrogesterone (oral 20 mg dose versus 7.8 mg intravenous infusion) is 28%.

The following table provide the mean steady state pharmacokinetic parameters of dydrogesterone (D) and dihydrodydrogesterone (DHD). Data is presented as mean (SD).

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_{0-t} (ng.h/mL)	9.14 (6.43)	311.17 (114.35)

- Distribution

After intravenous administration of dydrogesterone the steady-state volume of distribution is approximately 1400 L. Dydrogesterone and DHD are more than 90% bound to plasma proteins.

- Metabolism

Following oral administration, dydrogesterone is rapidly metabolised to DHD. The levels of the main active metabolite 20 α-dihydrodydrogesterone (DHD) peak about 1.5 hours post dose. The plasma levels of DHD are substantially higher as compared to the parent drug. The AUC and C_{max} ratios of DHD to dydrogesterone are in the order of 40 and 25, respectively. Mean terminal half-lives of dydrogesterone and DHD vary between 5 to 7 and 14 to 17 hours, respectively. A common feature of all metabolites characterised 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 estrogenic and androgenic effects of dydrogesterone.

- Elimination

After oral administration of labelled dydrogesterone, on average 63% of the dose is excreted into the urine. Total plasma clearance is 6.4 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 10 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 was 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 this Product information.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Estradiol only tablets:

Lactose monohydrate, Maize starch, Hypromellose (HPMC 2910), Colloidal anhydrous silica, Magnesium stearate

Opadry® Y-l-7000 white: Hypromellose (HPMC 2910), Titanium dioxide (E171), Macrogol 400

Estradiol/dydrogesterone tablets:

Lactose monohydrate, Maize starch, Hypromellose (HPMC 2910), Colloidal anhydrous silica, Magnesium stearate

Opadry® II grey 85F27664: Polyvinyl alcohol, Titanium dioxide (E171), Macrogol 3350, Talc (E553b), Iron oxide black (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials

6.4 Special precautions for storage

Store below 30°C. Store in original pack.

6.5 Nature and contents of container

PVC/Aluminium blister packs in a printed cardboard carton.

Blister pack:
28 film-coated tablets (14 white tablets with estradiol and 14 grey tablets with estradiol and dydrogesterone)
84 (3 x 28) film-coated tablets
280 (10 x 28) film-coated tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

This medicinal product may pose a risk to the aquatic environment. Medicines no longer required should not be disposed of via wastewater or household waste. Any unused product or waste material should be disposed of in accordance with local requirements or returned to the pharmacy.

7 MANUFACTURER

Abbott Healthcare Products B.V.
1381 CP Weesp, The Netherlands

8 MARKETING AUTHORISATION HOLDER

Abbott Medical Laboratories Ltd.
Kiriat Atidim, POB 58099, Tel-Aviv 6158002, Israel

9 MARKETING AUTHORISATION NUMBER

161 66 35128 00

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