SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Femoston 1/10 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Blister of 28 tablets: 14 white tablets contains 1 mg estradiol and 14 grey tablets contains 1 mg estradiol 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 section 6.1

3. PHARMACEUTICAL FORM

Estradiol Film-coated tablets:
Round, biconvex, white film-coated tablets marked on one side with '379'

Estradiol/Dydrogesterone film-coated Tablet: 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 paediatric patients.

4.3 Contra-indications

- Presence or suspicion of breast cancer; history of breast cancer;
- Presence or suspicion of estrogen-sensitive tumours (for example endometrial cancer);
- Vaginal bleeding of which the cause has not been determined;
- Untreated endometrial hyperplasia;
- History of active venous thromboembolism (deep vein thrombosis, pulmonary embolism);
- Presence of a thrombophilic condition (e.g. protein C, protein S or antithrombin deficiency, see section 4.4);
- Active or recent arterial thromboembolic disease (angina pectoris, myocardial infarction);
- Acute liver disease or history of liver disease as long as the liver function values have not returned to normal;
- Porphyry;
- Known hypersensitivity to the active ingredients or one of excipients listed in section 6.1;

4.4 Special warnings and precautions for use

For the treatment of symptoms of estrogen deficiency in postmenopausal women, treatment with hormone replacement therapy (HRT) should only be initiated if these symptoms adversely affect the quality of life. A careful appraisal of the advantages and disadvantages of HRT should be carried out regularly, at least annually, and the treatment should only be continued if the advantages outweigh the disadvantages.

Evidence relating to the risks associated with HRT in the treatment of premature menopause is limited. But because of the low absolute risk in young women the balance of advantages and disadvantages for these women are more positive than for older women.

Medical examination / follow up
Before starting HRT or if its use is to be reinstated the use after an interruption, a full medical history (including family history) should be taken. Physical examination (including

gynaecological and breast examination) should be carried out guided by the history, contra-indications and warnings. During the treatment period regular 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 immediately (see the section “Breast cancer” below).

Regular examination of the breasts, including imaging techniques such as mammography, should be carried out in accordance with the current guidelines for healthy women, taking into account here the medical need of the individual woman.

Conditions which need supervision
If one of the following conditions is present, was present in the past and/or has 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 the treatment with Femoston 1/10 mg, in particular in case of:
- Leiomyoma (uterine fibroma) or endometriosis
- Risk factors for thromboembolic disorders (see below)
- Risk factors for estrogen-sensitive tumours (breast cancer in first degree family member)
- Hypertension
- Liver disease (liver adenoma)
- Diabetes mellitus with or without vascular symptoms
- Cholelithiasis
- Migraine or (severe) headache
- Systemic Lupus Erythematodes
- A history of endometrial hyperplasia (see below)
- Epilepsy
- Asthma
- Otosclerosis
- Meningioma

Reasons for immediate discontinuance of treatment
Hormone replacement therapy should be discontinued immediately where a contra-indication is discovered and in the following situations:
- Jaundice or deterioration in the liver function
- Significant increase in blood pressure
- New onset of migraine-type headache
- Pregnancy

Endometrial hyperplasia and carcinoma
- In women whose uterus has not been removed the risk of endometrial hyperplasia and endometrial cancer is increased if over a prolonged period estrogen-only HRT is taken. The reported increased risk of endometrial cancer in users of estrogen preparations varies from 2 to 12 times as great compared with non-users, depending on the treatment period and the estrogen dose (see section 4.8). After stopping the treatment the risk remains high for at least 10 years.
- The cyclical combination of an estrogen preparation with a progestagen for at least 12 days per month/per 28-day cycle or continuous combined estrogen-progestagen treatment in women with a uterus protects against the increased risk associated with estrogen preparations.
- Breakthrough bleeding and spotting may occur during the first months of the treatment. If breakthrough bleeding or spotting appears after some time on therapy or continues after treatment has been discontinued, further investigation is indicated. This may mean that an endometrial biopsy must be taken to exclude malignancy.

Breast cancer
All the available data indicate an increased risk of breast cancer if women are using combined estrogen and progestagen as HRT and possibly also if they are using estrogen-only as HRT. This risk depends on the duration of use.

Combined estrogen-progestagen treatment:
- Both a randomised placebo-controlled study, the Women's Health Initiative Study (WHI), and epidemiological studies have consistently demonstrated an increased risk of breast cancer in women using combined estrogen-progestagen HRT. The increased risk is apparent after around 3 years (see section 4.8).

Estrogen monotherapy:

- In the WHI study no increased risk of breast cancer was found in hysterectomised women using estrogen-only HRT. Observational studies have predominantly reported a small increase in the risk of the diagnosis of breast cancer that is substantially lower than found in users of combined estrogens and progestagens (see section 4.8).

The increased risk becomes apparent within a few years of use and increases as the duration of use increases but falls again to the initial value within a few (at the most 5) years after stopping the treatment.

Treatment with HRT, especially combined estrogen-progestagen treatment, increases the density of the mammography images increases, which may adversely effect on 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 the 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 times higher risk of developing venous thromboembolism (VTE), i.e. deep vein thrombosis or pulmonary embolism. This is greater during the first year of HRT treatment than afterwards (see section 4.8).

- Patients with a known thrombophilic status have an increased risk of VTE and HRT may increase the risk further. HRT is therefore contra-indicated in these patients (see section 4.3).

- General risk factors for the occurrence of VTE are: the use of estrogens, greater age, major surgical intervention, prolonged immobilisation, obesity (Body Mass Index > 30 kg/m^2), pregnancy/ postpartum period, systemic lupus erythematodes (SLE) and carcinoma.
  There is no consensus about the possible role of varicosis in VTE. As in all postoperative patients, precautions should be taken after surgery to prevent VTE. Where prolonged immobilisation is anticipated after elective surgery, consideration should be given to stopping the HRT 4 to 6 weeks before the operation and only restarting it when the woman is completely mobilised again.

- Women without a history of VTE, but with a first degree family member with a history of thrombosis at a young age, should be offered screening after careful information relating to the limitations of such screening (only a proportion of thrombophilic conditions are identified in screening). If a congenital thrombophilic condition is identified, which is accompanied in a family with thrombosis or if the condition is serious (e.g. antithrombin, protein S or protein C deficiencies or a combination of conditions) HRT is contra-indicated.

- In women already treated chronically with anticoagulation therapy, careful consideration should be given to the advantages and disadvantages of the treatment.

- If VTE develops after initiating therapy, the administration of medication should be discontinued immediately. Patients must be informed that they should contact their doctor immediately if potential thromboembolic symptoms occur (e.g.: painful swelling of a leg, sudden pain in the chest, shortness of breath).

Coronary artery disease (CAD)
There is no evidence from randomised controlled studies of a protective effect against myocardial infarction in women with or without existing coronary artery disease who receive combined estrogen-progestagen or estrogen-only HRT.

Combined estrogen-progestagen therapy:
The relative risk of coronary artery disease during combined estrogen-progestagen HRT is slightly increased. Since the absolute risk of coronary artery disease in the initial situation is greatly age-dependent, the number of extra cases of coronary artery disease as a result of estrogen-progestagen use is very low in healthy women who are close to the menopause. This number will however increase as they get older.

Estrogen monotherapy
In randomised controlled studies no increased risk of coronary artery disease was found in hysterectomised women using estrogen monotherapy.

Ischemic Stroke
Combined estrogen-progestagen therapy and estrogen monotherapy are associated with an up to 1.5 times higher risk of an ischemic stroke. The relative risk does not change with age or with the time after the menopause. However, because the absolute risk of a CVA in the initial situation is strongly dependent on age, the overall risk of a CVA in women using HRT will increase with age (see section 4.8).

Other conditions
- Estrogens may cause fluid retention. For this reason patients with a reduced cardiac or renal function must therefore be carefully observed.
- Women with a pre-existing hypertriglyceridaemia should be closely followed during estrogen replacement or hormone replacement therapy, since in rare cases in women with this abnormality, the plasma triglycerides increased considerably during estrogen therapy, and have led to pancreatitis.
  Estrogens cause an increase in the thyroid binding globulin (TBG), which leads to increased circulating thyroid hormone, measured as the protein bound iodine (PBI), T4 levels (column or RIA) or T3 levels (RIA). The T3-resin uptake is decreased as a result of the increased TBG levels. The free T3 and T4 concentrations remain unchanged. Other binding proteins may also be elevated in the serum, such as corticoid binding globulin (CBG) and the sex-hormone binding globulin (SHBG), leading to increased blood levels of corticosteroids and sex hormones. Free and/or biologically active hormone concentrations remain unchanged. Other plasma proteins may be increased (angiotensin-renin substrate, alpha-1-antitrypsin, ceruloplasmin).
- HRT does not improve cognitive functions. There is no evidence of increased risk of possible dementia in women who start using treatment of combined preparations or estrogen preparations after the age of 65 years.
- Patients with rare hereditary conditions, such as galactose intolerance, Lapp-lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.
- This combined estrogen-progestagen is not a contraceptive product.

4.5 Interactions with other medicinal products and other forms of interaction

No interaction studies have been carried out.

The efficacy of estrogens and progestagens may be disrupted:

- The metabolism of estrogens (and progestagens) may be increased by concomitant use of substances known to induce enzymes which are involved in the metabolism of medicinal products. This applies particularly for P450 enzymes. These substances include anti-epileptics (phenobarbital, phenytoin, carbamazepine) and antibacterials /antivirals (for example rifampicin, rifabutin, nevirapine, efavirenz).
- Ritonavir and nelfinavir, although known as strong inhibitors do in fact have an inducing effect when used concomitantly with steroid hormones.
- Herbal preparations containing St. John's wort (*Hypericum perforatum*) may also increase the metabolism of estrogens (and progestagens).
- Clinically an increased metabolism of estrogens and progestagens may lead to a reduced efficacy and changes in the bleeding pattern.

4.6 Fertility, pregnancy and lactation

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

There are no adequate data available on the use of estradiol/dydrogesterone during pregnancy. The results of most epidemiological studies to date that are relevant for the assessment of effects of inadvertent foetal exposure to combined estrogens and progestagens indicate no teratogenic or toxic effect for the foetus.

Lactation
Femoston 1/10 mg is not indicated in women who are breastfeeding.

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

4.7 Influence on the ability to drive or to operate machinery

Femoston 1/10 mg has no or a negligible effect on the ability to drive and/or to operate machinery.

4.8 Undesirable effects

The most commonly indicated undesirable effects in patients that were treated in clinical trials with estradiol/dydrogesterone, are headache, abdominal pain, breast pain/tenderness and back pain.
The following undesirable effects were observed during clinical trials (n=4929) with the frequencies indicated below. *Undesirable effects from spontaneous reports that were not observed in clinical trials have been added to the frequency "rare":

Organ system	**Very common ≥1/10**	**Common ≥1/100, <1/10**	**Uncommon ≥1/1,000 to <1/100**	**Rare ≥1/10,000 to <1/1,000**
Infections and parasitic infestations		Vaginal candidiasis	Cystitis-like syndrome	
Neoplasms, benign, malignant and unspecified			Increase in size of myoma	
Blood and lymphatic system disorders				Haemolytic anaemia*

Organ system	Very common ≥1/10	Common ≥1/100, <1/10	Uncommon ≥1/1,000 to <1/100	Rare ≥1/10,000 to <1/1,000
Immune system disorders			Hypersensitivity	
Psychiatric disorders		Depression; Nervousness	Change in libido	
Central nervous system disorders	Headache	Migraine; Dizziness		Meningioma*
Eye disorders				Steepening of the cornea*; Intolerance to contact lenses*
Cardiac disorders				Myocardial infarction
Vascular disorders			Venous thrombo-embolism*; Hypertension; Peripheral vascular disease; Varicosis	Stroke*
Gastrointestinal disorders	Abdominal pain;	Nausea; Vomiting; Flatulence	Dyspepsia	
Hepatobiliary disorders			Abnormal liver function (sometimes combined with jaundice, asthenia or malaise and abdominal pain); Gall bladder problems	
Skin and sub-cutaneous tissue disorders		Allergic skin reactions (e.g. rash, urticaria, pruritus)		Angioedema; Erythema nodosum*; Vascular purpura; Chloasma or melasma which may persist when the treatment is discontinued*;
Musculoskeletal and connective tissue disorders	Back pain			Leg cramps*
Reproductive system and breast disorders	Breast pain/ tenderness	Menstruation disorders (including postmenopausal	Breast enlargement; Premenstrual syndrome	

Organ system	Very common ≥1/10	Common ≥1/100, <1/10	Uncommon ≥1/1,000 to <1/100	Rare ≥1/10,000 to <1/1,000
		spotting; metrorrhagia; menorrhagia; oligo/ amenorrhoea, irregular menstruation; dysmenorrhoea) ; Pelvic pain; Cervical erosion	(PMS)	
General disorders and administration site reactions		Asthenic disorders (asthenia, fatigue, malaise); Peripheral oedema		
Investigations		Increase in weight	Decrease in weight	

Risk of breast cancer

- An up to 2 times higher risk of the diagnosis of breast cancer is reported in women who have used combined estrogen-progestagen HRT for more than 5 years.
- For users of estrogen monotherapy the increased risk is substantially lower than for users of combined estrogen-progestagen therapy.
- The level of the risk depends on the duration of use (see section 4.4).
- The results of the biggest randomised placebo-controlled study (WHI) and the biggest epidemiological study (MWS) are set out below.

Million Women Study (MWS) – estimated extra risk of breast cancer after 5 years use

Age group (years)	Extra cases per 1,000 non-HRT users over a period of 5 years*	Risk ratio#	Extra cases per 1,000 HRT users over a period of 5 years (95%CI)
		Estrogen mono HRT	
50-65	9-12	1.2	1-2 (0-3)
		Combined estrogen-progestagen therapy as HRT	
50-65	9-12	1.7	6 (5-7)
#Overall risk ratio. The risk ratio is not constant, but will rise with a longer duration of use N.B.: Since the background incidence of breast cancer differs for each EU country, the number of extra cases of breast cancer will also be proportionately different. *Deduced from the baseline incidence in developed countries.			

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

Age group (years)	Incidence per 1,000 women in the placebo group over a period of 5	Risk ratio & 95% Confidence interval (CI)	Extra cases per 1,000 HRT users over a period of 5 years (95%CI)

	years		
EEC estrogen mono HRT			
50-79	21	0.8 (0.7 – 1.0)	-4 (-6 – 0)*
EEC+ MPA combined estrogen-progestagen HRT ‡			
50-79	17	1.2 (1.0 – 1.5)	+4 (0 – 9)

‡if the analysis was limited to women who did not use HRT before the start of the study no increased risk was observed during the first 5 years of treatment: after 5 years the risk was higher than for non-users.
*WHI study in women with no uterus, in which no increased risk of breast cancer was observed.

Risk of endometrial cancer
Postmenopausal women with a uterus:
The risk of endometrial cancer is around 5 in every 1,000 women with a uterus not using HRT.

In women with a uterus the use of estrogen monotherapy is not recommended, because this increases the risk of endometrial cancer (see section 4.4).
Depending on the duration of use of estrogen monotherapy and the estrogen dose used, the increase in the risk of endometrial cancer in epidemiologic studies varied between 5 and 55 extra cases diagnosed per 1,000 women aged between 50-65 years.

The addition of a progestagen to the estrogen monotherapy for at least 12 days per cycle may prevent this increased risk. In the Million Women Study the risk of endometrial cancer did not increase for 5 years of combined (sequential or continuous) HRT (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 to 3 times higher relative risk of developing venous thromboembolism (VTE), i.e. deep vein thrombosis or pulmonary embolism. The chance of this is greater during the first year of HRT treatment (see section 4.4). The results of the WHI are set out below:

WHI Studies – extra risk of VTE during 5 years use

Age group (years)	Incidence per 1,000 women in the placebo group over a period of 5 years	Risk ratio and 95% CI	Extra cases per 1,000 HRT users over a period of 5 years (95% CI)
Oral estrogen mono HRT*			
50-59	7	1.2 (0.6-2.4)	1 (-3 – 10)
Oral combined estrogen-progestagen HRT			
50-59	4	2.3 (1.2 – 4.3)	5 (1 - 13)

* Study in women with no uterus.

Risk of coronary artery disease
The risk of coronary artery disease is slightly increased in users aged over 60 years for combined estrogen-progestagen HRT (see section 4.4).

Risk of an ischemic stroke
The use of estrogen monotherapy and combined estrogen-progestagen HRT is associated with up to a 1.5 times higher relative risk of an ischemic stroke. The risk of a haemorrhagic stroke is not increased during use of HRT.

This relative risk does not depend on the age or the duration of use, but because the risk in the initial situation is strongly dependent on age, the risk of a stroke in users of HRT generally increases with the increase in age (see section 4.4).

Combined WHI studies – extra risk of an ischemic stroke* during 5 years use

Age group (years)	Incidence per 1,000 women in the placebo group over a period of 5 years	Risk ratio and 95% CI	Extra cases per 1,000 HRT users over a period of 5 years (95% CI)
50-59	8	1.3 (1.1-1.6)	3 (1-5)

*No distinction is made between ischemic and haemorrhagic stroke

Other reported undesirable effects associated with treatment with estrogen/progestagen:
Neoplasms, benign, malignant and unspecified:
Benign and malignant estrogen-dependent neoplasms, for example endometrial cancer and ovarian cancer. Increase in size of meningioma.

Immune system disorders:
Systemic Lupus Erythematodes (SLE).

Nutritional and metabolic disorders:
Hypertriglyceridaemia.

Central nervous system disorders:
Possible dementia, chorea, aggravation of epilepsy.

Vascular disorders:
Arterial thromboembolism.

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

Skin and sub-cutaneous disorders
Erythema multiforme.

Renal and urinary tract disorders:
Urine incontinence.

Reproductive system and breast disorders:
Fibrocystic breast disorder, uterine cervical erosion.

Congenital, familial and genetic disorders:
Aggravation of porphyria

Investigations:
Increased level of total thyroid hormone.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization 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://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il

4.9 Overdose

Both estradiol and dydrogesterone are substances with a low toxicity. Symptoms such as nausea, vomiting, breast tenderness, dizziness, abdominal pain, drowsiness/fatigue and withdrawal bleeding may occur in case of overdose. Specific or symptomatic treatment is probably not necessary.

The information described above also applies after overdose in children.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic category: urogenital system and sex hormones, progestagens and estrogens, sequential products.
ATC code: G03FB08.

Estradiol
The active ingredient, synthetic 17β-estradiol is chemically and biologically identical to the natural human female sex hormone estradiol. It substitutes for the loss of own estrogen production in postmenopausal women and alleviates menopausal symptoms. Estrogens prevent loss of bone mass following menopause or ovarectomy.

Dydrogesterone
Dydrogesterone is an orally active progestagen that has an activity comparable with parenterally administered progesterone.

As estrogens promote the growth of the endometrium, if no progestagen is used, they will lead to an increased risk of endometrial hyperplasia and carcinoma. The addition of a progestagen largely reduces the estrogen-induced risk in women with a uterus.

Information from clinical studies
- Alleviation of estrogen-deficiency symptoms and the bleeding pattern:
- Alleviation of menopausal symptoms was achieved in the first few weeks of therapy.

76% of women treated with Femoston 1/10 mg suffered from regular withdrawal bleeding that lasted on average 5 days. The withdrawal bleeding usually started on the last day of the

progestagen phase (on average day 28 of the cycle). 23% of the women suffered from breakthrough bleeding or spotting during the first 3 months treatment; for 15% of the women this was during the 10^{th} to 12^{th} month of treatment. Amenorrhoea (no bleeding or spotting) occurred in 21% of cycles during the first year of treatment.

Osteoporosis prevention
Estrogen deficiency after the menopause is associated with an increase in bone turnover and decline in bone mass. The effect of estrogens on bone density is dose-related. Protection seems to be effective as long as the treatment continues. After discontinuation of the HRT the rate of bone mass loss is the same as that in untreated women.

The WHI study and meta-analyses of other studies showed that use of HRT (estrogen preparations or combined preparations) by predominantly healthy women leads to a reduction in the risk of hip, vertebral and other osteoporotic fractures. HRT may possibly also lead to prevention of fractures in women with a low bone density and/or in whom osteoporosis is established, but the available data relating to this patient group is limited.

For Femoston 1/10 mg, the increase for the lumbar spine was 5.2% ± 3.8% (mean ± SD) and the percentage of women without change or increase in the lumbar spine was 93.0%.

Femoston 1/10 mg also had an effect on the bone density of the hip. After two years treatment with Femoston 1/10 mg the bone density of the femoral neck increased by 2.7% ± 4.2% (mean ±SD), at the trochanter by 3.5% ± 5.0% (mean ±SD) and at the Ward's triangle 2.7% ± 6.7% (mean ±SD). The percentage of women in whom after treatment with Femoston 1/10 mg the bone density in the 3 hip areas was maintained or increased, was 67-78%.

5.2 Pharmacokinetic properties

Estradiol
Absorption
Absorption of estradiol depends on the particle size: micronized estradiol is readily absorbed from the gastrointestinal tract.

The following table gives the average steady-state pharmacokinetic parameters of estradiol (E2), estrone (E1) and estrone sulphate (E1S) for each dose of micronized estradiol. Data are presented as averages (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 may occur bound or unbound. Approx. 98-99% of the estradiol dose binds to plasma proteins, with approx. 30-52% to albumin and approx. 46-69 % to sex-hormone binding globulin (SHBG).

Biotransformation:
Following oral administration estradiol is metabolised on a large scale. The main unconjugated and conjugated metabolites are estrone and estrone sulphate. These metabolites may contribute to

estrogen activity, either directly, or after conversion into estradiol. Estrone sulphate may undergo enterohepatic circulation.

Elimination:
Glucuronides are the main components of estrone and estradiol in the urine. The elimination half-life is between 10 and 16 hours.
Estrogens are secreted in the breast milk.

Dose and time dependencies:
Following daily oral administration of Femoston estradiol concentrations reach a steady state after around 5 days.
Generally steady state concentrations appear to be reached within 8 to 11 days of dosing.

Dydrogesterone
Absorption:
Following oral administration dydrogesterone is quickly absorbed with a T_{max} between 0.5 and 2.5 hours. The absolute biological availability of dydrogesterone (20 mg oral dose versus 7.8 mg intravenous infusion) is 28%.

The following table gives the average pharmacokinetic parameters of dydrogesterone (D) and dihydrodydrogesterone (DHD). Data are presented as averages (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)
$AUC_{0-\tau}$ (ng·h/ml)	9.14 (6.43)	311.17 (114.35)

Distribution:
Following intravenous administration of dydrogesterone the steady-state distribution volume is around 1400 l. More than 90% of dydrogesterone and DHD is bound to plasma proteins.

Biotransformation:
Following oral administration dydrogesterone is quickly metabolized to DHD. The levels of the main active metabolite 20α-dihydrodydrogesterone (DHD) show a peak around 1.5 hours after administration. The plasma levels of DHD are substantially higher than those of the related medicinal product. The AUC and C_{max} ratios of DHD and dydrogesterone are of the order of magnitude of respectively 40 and 25. The mean terminal half-life of dydrogesterone and DHD varies from respectively 5 to 7 and 14 to 17 hours. A common feature of all metabolites described is the retention of the 4,6-diene-3-one configuration of the original molecule and the absence of 17α-hydroxylation. This explains the absence of estrogenic and androgenic effects of dydrogesterone.

Elimination:
Following oral administration of labelled dydrogesterone on average 63% of the dose is excreted in the urine. The total plasma clearing is 6.4 l/minute. Excretion is complete within 72 hours. DHD is predominantly present in the urine as the conjugated glucuronic acid.

Dose and time dependencies:
The pharmacokinetics of single and multiples doses are linear in the oral dosage range of 2.5 to 10 mg. Comparison of the kinetics of single and multiple doses shows that the

pharmacokinetics of dydrogesterone and DHD do not change as a result of repeated doses. Steady state was reached after 3 days treatment.

5.3 Preclinical safety data

There are no relevant preclinical data for the prescriber that are in addition to data already stated in other sections of this Product Information

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Estradiol only tablets:
Lactose monohydrate, Maize starch, Hypromellose , Colloidal anhydrous silica, Magnesium stearate,
Opadry® Y-1-7000 white: Hypromellose , Titanium dioxide (E171), Macrogol 400

Estradiol/dydrogesterone tablets:
Lactose monohydrate, Maize starch, Hypromellose , Colloidal anhydrous silica, Magnesium stearate,
Opadry® II Grey 85F27664: Polyvinyl alcohol, Titanium dioxide (E171), Macrogol 3350, Talc, Iron Oxide Black (E 172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Femoston 1/10 mgThe 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 the packs listed are marketed.

6.6 Special precautions for disposal and other instructions

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MANUFACTURER

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8. MARKETING AUTHORISATION HOLDER

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9. MARKETIN AUTHORISATION NUMBER

161 66 35128 00

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