## 1 NAME OF THE MEDICINAL PRODUCT

Femoston® 1/10 , 1mg/10mg film-coated tablets

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Femoston® 1/10, 1mg/10mg film-coated tablets

14 tablets, each containing 1 mg 17β -estradiol (as hemihydrate) and 14 tablets, each containing 1 mg 17β -estradiol (as hemihydrate) and 10 mg dydrogesterone.

## 3 PHARMACEUTICAL FORM

Film-coated tablet

Round, biconvex tablets marked 379 on one side.

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

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

- Hormone replacement therapy (HRT) for symptoms of oestrogen deficiency in women in perimenopause (not earlier than 6 months after the last menstruation) or in postmenopause;
- 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.

The experience in treating women older than 65 years is limited.

### 4.2 Posology and Method of Administration

Femoston 1/10 is continuous sequential hormone replacement therapies. For oral use.

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

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

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.

In general, sequential combined treatment should start with Femoston® 1/10.

Depending on the clinical response, the dosage can subsequently be adjusted.

Patients changing from another continuous sequential or cyclical preparation should complete the 28 day cycle and then change to Femoston® 1/10.

Patients changing from a continuous combined preparation may start therapy at any time. 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® 1/10 can be taken irrespective of food intake.

*Pediatric population:*

There is no relevant indication for the use of Femoston® 1/10 in the pediatric 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 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;
- 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 Trademark, 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
- Meningioma

**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 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 suggests an increased risk of breast cancer in women taking combined oestrogen-progestogen and possibly also oestrogen-only HRT, that is dependent on the duration of taking HRT.
Combined oestrogen-progestogen therapy

- The randomised placebo-controlled trial, the Women's Health Initiative study (WHI), and 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 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).

The excess risk becomes apparent within a few years of use but returns to baseline within a few (at most five) years after stopping treatment.

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 metaanalysis 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 1.3-3 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).
- Generally recognised risk factors for VTE include: use of oestrogens, older age, major surgery, prolonged immobilisation, obesity (BMI > 30 kg/m2), pregnancy/postpartum period, systemic lupus erythematosus (SLE), and cancer. There is no consensus about the possible role of varicose veins in VTE.
- As in all postoperative patients, prophylactic measures need 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 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 oestrogenprogestogen or oestrogen-only HRT.

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.

**Ischaemic 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 patients with cardiac or renal dysfunction should be carefully observed.
- Women with pre-existing hypertriglyceridaemia 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.
- 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), sexhormone-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-Iantitrypsin, 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, Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.
- This oestrogen-progestogen combination treatment is not contraceptive.

## 4.5 Interaction with Other Medicinal Products 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-metabolising enzymes, specifically the 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.

Oestrogens might interfere with the metabolism of other drugs:

- Oestrogens 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

Femoston® 1/10 is not indicated during pregnancy.
If pregnancy occurs during medication with Femoston® 1/10 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.
Femoston® 1/10 is not indicated during lactation.

## 4.7 Effects on Ability to Drive and Use Machines

Femoston® 1/10 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=4929):

| 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, gallbladder disorders | |
| Skin and subcutaneous tissue disorders | | Allergic skin reactions (e.g. rash, urticarial, pruritus) | | Angioedema, vascular purpura |
| Musculoskeletal and connective tissue disorders | Back pain | | | |
| Reproductive system and breast | Breast pain/tenderness | Menstrual disorders | Breast enlargement, | |

| 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 |
|---|---|---|---|---|
| disorders | | (including postmenopausal spotting, metrorrhagia, menorrhagia, oligo/ amenorrhoea, irregular menstruation, dysmenorrhoea), pelvic pain, cervical discharge | premenstrual syndrome | |
| 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.
- Any increased risk in users of oestrogen-only therapy is substantially lower than that seen in users of oestrogen-progestogen combinations.
- The level of risk is dependent on the duration of use (see section 4.4).

Results of the largest randomised placebo-controlled trial (WHI-study) and largest epidemiological study (MWS) are presented.

**Million Women study– Estimated additional risk of breast cancer after 5 years' use:**

| Age range (years) | Additional cases per 1000 never-users of HRT over a 5 year period[1] | Risk ratio & 95%CI[#] | Additional cases per 1000 HRT users over 5 years (95%CI) |
|---|---|---|---|
| Oestrogen only HRT | | | |
| 50-65 | 9-12 | 1.2 | 1-2 (0-3) |
| Combined oestrogen-progestogen | | | |
| 50-65 | 9-12 | 1.7 | 6 (5-7) |

[#]Overall risk ratio. The risk ratio is not constant but will increase with increasing duration on use
Note: Since the background incidence of breast cancer differs by EU country, the number of additional cases of breast cancer will also change proportionately.

[1] Taken from baseline incidence rates in developed countries

**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 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 cancer (see Section 4.4).
Depending on the duration of oestrogen-only use and oestrogen 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. 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 over 5 years (95%CI) |
|---|---|---|---|
| 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 oestrogenprogestogen 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 (95%CI) |
|---|---|---|---|
| 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 erythematosus.

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 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 symptomatic treatment will be necessary.
Aforementioned information is also applicable for overdosing in children.

## 5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Genito urinary system and sex hormones, progestogens and oestrogens, sequential preparations. The ATC code is G03FB08.

**Estradiol**

The active ingredient, 17β-estradiol, is chemically and biologically identical to endogenous human estradiol.

It substitutes for the loss of oestrogen production in menopausal women, and alleviates menopausal symptoms.

Femoston® 1/10 Oestrogens prevent bone loss following menopause or ovariectomy.

**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.*

Regular withdrawal bleeding occurred 76% of the women with a mean duration of 5 days. Withdrawal bleeding usually started at mean day 28 of the cycle. Break through 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. Amenorrhoea (no bleeding or spotting) occurred in 21% of the cycles during the first year of treatment.

*Prevention of osteoporosis*

Oestrogen deficiency at menopause is associated with 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.

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% ± 5.0% (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 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 |
|---|---|---|---|---|
| Cmax (pg/mL) | 71 (36) | 310 (99) | Cmax (ng/mL) | 9.3 (3.9) |
| Cmin (pg/mL) | 18.6 (9.4) | 114 (50) | Cmin (ng/mL) | 2.099 (1.340) |
| Cav (pg/mL) | 30.1 (11.0) | 194 (72) | Cav (ng/mL) | 4.695 (2.350) |
| AUC0-24(pg.h/mL) | 725 (270) | 4767 (1857) | AUC0-24 (ng.h/mL) | 112.7 (55.1) |

- 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 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 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 10-16 h.
Oestrogens are secreted in the milk of nursing mothers.

- Dose and time dependencies

Following daily oral administration Femoston® 1/10, estradiol concentrations reached a steadystate 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 Tmax 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 provides the mean single dose pharmacokinetic parameters of dydrogesterone (D) and dihydrodydrogesterone (DHD). Data is presented as mean (SD).

**Dydrogesterone 10 mg**

| | D | DHD |
|---|---|---|
| Cmax (ng/mL) | 2.54 (1.80) | 62.50 (33.10) |
| Cmin (ng/mL) | 0.13 (0.07) | 3.70 (1.67) |

| | | |
|---|---|---|
| Cav (ng/mL) | 0.42 (0.25) | 13.04 (4.77) |
| AUC0-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 metabolized 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 Cmax 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 oestrogenic 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 the Summary of Product Characteristics (SmPC).

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 List of Excipients

Femoston® 1/10 contains:
Core: Lactose monohydrate; Hypromellose, Maize starch; Colloidal anhydrous silica; Magnesium stearate.
Film-coating: 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.

## 6.2 Incompatibilities

Not applicable

## 6.3 Shelf Life

3 years

## 6.4 Special Precautions for Storage

Store in original package at temperatures not above 30° C.
Keep of reach of children.

## 6.5 Nature and Contents of Container

28 tablets (14 white tablets containing 1 mg estradiol and 14 grey tablets containing 1 mg estradiol and 10 mg dydrogesterone) is placed in a blister of PVC/al foil.
1 blister with leaflet in a carton pack.

## 6.6 Marketing Authorization Holder

**Abbott Healthcare Products B.V.**
C.J. van Houtenlaan 36,
1381 CP Weesp, The Netherlands.

## 6.7 Manufcturer

**Abbott Biologicals B.V.**
Veerweg 12,
8121 AA Olst, The Netherlands.