OFFICE of the DEPUTY PRIME MINISTER
MINISTRY for HEALTH
15, PALAZZO CASTELLANIA, MERCHANTS STREET, VALLETTA, MALTA

DH Circular 43/2019
DH 754/2019

15th May 2019

Attention All: Consultants
Medical Officers
Pharmacists
Pharmacy Technicians
Nurses

Re: Change in Hormone Replacement Therapy Tablets

Until recently, Hormone Replacement Therapy (HRT) Tablets were available on the Government Formulary List (GFL) as estradiol valerate 2mg and norgestrel 0.5mg tablets. However, due to sourcing issues, and following discussion with Consultants, the new stock of HRT tablets available will be estradiol (as hemihydrate) 2mg and dydrogesterone 10mg tablets (Femoston® 2/10mg). The differences in the preparations are highlighted in the table below.

	Previous Preparation Estradiol Valerate 2mg and Norgestrel 0.5mg Tablets	**New Preparation** Estradiol (as Hemihydrate) 2mg and Dydrogesterone 10mg Tablets
Qualitative and Quantitative Composition	White Tablets – 2mg estradiol valerate Pale Brown Tablets – 0.5mg norgestrel + 2mg estradiol valerate	Brick-Red Tablets – 2mg estradiol (as hemihydrate) Yellow Tablets – 10mg dydrogesterone + 2mg estradiol (as hemihydrate)
Administration	One tablet is to be taken orally once a day for 21 days, followed by a 7-day tablet free interval. Therefore, each new pack is started after a 28-day cycle. The white tablets should be taken from days 1 to 11 followed by the brown tablets from days 12 to 21. It is recommended that the tablets are taken at the same time every day.	For the first 14 days during a 28-cycle, one tablet containing estradiol is taken daily; during the following 14 days one tablet containing estradiol and dydrogesterone is taken. After a cycle of 28 days, on the 29th day, a new 28-day cycle begins. This means that the treatment should be taken continuously **without a break between packs**. Tablets can be taken with or without food. The days of the week are printed on the back of the blister strips. Firstly, the tablets from the part marked with arrow 1 should be taken, then all the tablets from the part marked with arrow 2 should be taken.

HRT tablets are regulated by protocol 234 (Annex 1) and used in Malignant Diseases and Hypopituitarism. More information on the new HRT tablets (Femoston® 2/10mg) is available on the Summary of Product Characteristics attached (Annex 2).

For your attention please.

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234

Estradiol (as Hemihydrate) and Dydrogesterone Tablets

Prescriber Criteria: Consultant Endocrinology & Diabetes
Consultant Haematologist
Consultant Oncologist

Out-patient and In-patient use:

1. Hypopituitarism
2. Malignant Diseases

1. Hypopituitarism

Reserved for patients of non-menopausal age with gonadotrophin deficiency due to hypopituitarism.

2. Malignant Diseases

Reserved for patients who experience early menopausal symptoms secondary to radiation or chemotherapy.

Duration of Approval:

1 year

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Femoston®

2/10 mg Film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2 mg oestradiol (as hemihydrate) or a combination of 2 mg oestradiol (as hemihydrate) and 10 mg dydrogesterone.

Excipient with known effect: lactose monohydrate

For a full list of excipients see 6.1

3. PHARMACEUTICAL FORM

Film-coated tablets

Oestradiol only tablets: Round, biconvex, brick-red film-coated tablets with inscription '379'.

Oestradiol/dydrogesterone combination tablets: Round, biconvex, yellow film-coated tablets with inscription '379'.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

Prevention of osteoporosis in postmenopausal women at high risk of future fractures who are intolerant of, or contraindicated for, other medicinal products approved for the prevention of osteoporosis. (See also section 4.4)

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

4.2 Posology and method of administration

Femoston 1/10, and Femoston 2/10, are continuous sequential hormone replacement therapies.

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, treatment should start with Femoston 1/10. Depending on the clinical response, the dosage can afterwards be adjusted to individual need. If the complaints linked to oestrogen deficiency are not ameliorated the dosage can be increased by using Femoston 2/10.

Starting Femoston
In women who are not taking hormone replacement therapy and who are amenorrhoeic, or women who switch from a continuous combined hormone replacement therapy, treatment may be started on any convenient day. In women transferring from a cyclic or continuous sequential HRT regimen, treatment should begin the day following completion of the prior regimen.

Administration

For the first 14 days during a 28-cycle, one tablet containing oestradiol is taken daily; during the following 14 days one tablet containing oestradiol and dydrogesterone is taken.
After a cycle of 28 days, on the 29th day, a new 28-day cycle begins. This means that the treatment should be taken continuously without a break between packs. Femoston can be taken with or without food.

The days of the week are printed on the back of the blister strips. Firstly the tablets from the part marked with arrow 1 should be taken, then all the tablets from the part marked with arrow 2 should be taken.

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

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

4.3. Contraindications

- Known, past or suspected breast cancer;
- Known or suspected oestrogen-dependent malignant tumours (e.g. endometrial cancer);
- 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 special 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). Investigations, including appropriate imaging tools, e.g. mammography, should be carried out in accordance with currently accepted screening practices, modified to the clinical needs of the individual.

Conditions which need supervision

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

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

Reasons for immediate withdrawal of therapy:

Therapy should be discontinued in 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 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 progestagen cyclically for at least 12 days per month/28 day cycle or continuous combined oestrogen-progestagen therapy in non-hysterectomised women prevents the excess risk associated with oestrogen-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 suggests an increased risk of breast cancer in women taking combined oestrogen-progestagen 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 Womens Health Initiative study (WHI) and epidemiological studies are consistent in finding an increased risk of breast cancer in women taking combined oestrogen-progestagen for HRT that becomes apparent after about 3 years (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-progestagen combined treatment, increases the density of mammographic images which may adversely affect the radiological detection of breast cancer.

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 braest 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-progestagen 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 oestrogens, older ages, major surgery, prolonged immobilisation, severe obesity (BMI>30 kg/m^2), pregnancy/postpartum period, systemic lupus erythematosus (SLE) and cancer. There is no consensus about the possible role of varicose veins in VTE. 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 oestrogen-progestagen or oestrogen-only HRT.

Combined oestrogen-progestagen therapy

The relative risk of CAD during use of combined oestrogen+progestagen 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+progestagen 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-progestagen 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 hypertriglyceridemia should be followed closely during oestrogen replacement or hormone replacement therapy, since rare cases of large increases of plasma triglycerides leading to pancreatitis have been reported with oestrogen therapy in this condition.
- Oestrogens increase thyroid binding globulin (TBG), leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 levels (by column or by radio-immunoassay) or T3 levels (by radio-immunoassay). T3 resin uptake is decreased, reflecting the elevated TBG. Free T4 and free T3 concentrations are unaltered. Other binding proteins may be elevated in serum, i.e. corticoid binding globulin (CBG), sex- hormone-binding globulin (SHBG) leading to increased circulating corticosteroids and sex steroids, respectively. Free or 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 oestrogen-only HRT after the age of 65.
- Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.
- Women who may be at risk of pregnancy should be advised to adhere to non-hormonal contraceptive methods

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 progestagens may be increased by concomitant use of substances known to induce drug-metabolising enzymes, specifically the P450 enzymes 2B6, 3A4, 3A7, such as anticonvulsants (eg. 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 progestagens may lead to decreased effect and changes in the uterine bleeding profile.

Oestrogens might interfere with the metabolism of other drugs:
Oestrogen 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, cyclosporine A and theophylline may be necessary.

4.6. Pregnancy and lactation

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

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

Lactation:
Femoston is not indicated during lactation.

4.7. Effects on ability to drive and use machines

Femoston does not affect the ability to drive or 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 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)		Vascular purpura, Angioedema

Musculoskeletal and connective tissue disorders	Back pain			
Reproductive system and breast disorders	Breast pain/tenderness,	Menstral disorders (including postmenopausal spotting, metrorrhagia, menorrhagia, oligo-/amenorrhoea, irregular menstruation, dysmennorrhoea), Pelvic pain, Cervical discharge	Breast enlargement, Premenstrual-like symptoms	
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 oestrogen-progestagen 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-progestagen 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-progestagen			
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 & progestagen‡			
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

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 an intact uterus, use of oestrogen-only HRT is not recommended because it increases the risk of endometrial cancer increases (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 between the ages of 50 and 65.
Adding a progestagen 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 risk of endometrial cancer (R.R 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 after 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 oestrogen-only*[3]			
50-59	7	1.2 (0.6-2.4)	1 (-3 – 10)
Oral combined oestrogen-progestagen			
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 oestrogenprogestagen HRT over the age of 60 (see section 4.4).

Risk of ischaemic stroke

- The use of oestrogen-only and oestrogen + progestagen 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 and 95%CI	Additional cases per 1000 HRT users
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.

Immune system disorders

Systemic lupus erythematosus

Metabolism and nutrition disorders:

Hypertriglyceridemia

Nervous system disorders:

Probable dementia, over the age of 65 (see section 4.40, 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 muliforme, erythema nodosum, chloasma or melisma, which may persist when drug is discontinued.

Musculoskeletal and connective tissue disorders:

Leg cramps

Renal and urinary disorders:

Urinary incontinence

Reproduction 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. Healthcare professionals are asked to report any suspected adverse reactions via ADR reporting system at www.medicinesauthority.gov.mt.

4.9. Overdose

Both oestradiol and dydrogesterone are substances with low toxicity. Symptoms such as nausea, vomiting, breast tenderness, dizziness, abdominal pain, drowsiness/fatigue, and withdrawal bleeding could occur in cases of overdosing. It is unlikely that any specific 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. (Oestrogens: urogenital system and sex hormones) Sequential hormone replacement therapy (combined oestradiol and dydrogesterone).

Oestradiol

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

Dydrogesterone

Dydrogesterone is an orally-active progestagen 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 progestagen 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 with Femoston 1/10 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 progestagen 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.

- With Femoston 2/10, approximately 90% of women had regular withdrawal

bleeding. The start day and duration of bleeding, and the number of women with intermittent bleeding was the same as with Femoston 1/10, amenorrhoea occurred in 7-11% of the women for months 10 to 12 of treatments.

• Prevention of osteoporosis

- Oestrogen deficiency at menopause is associated with an increasing boneturnover and 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 progestagen – 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.
- After two years of treatment with Femoston 2/10, the increase in lumbar spine bone mineral density (BMD) was 6.7% ± 3.9% (mean ± SD). The percentage of women who maintained or gained BMD in lumbar zone during treatment was 94.5%. 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%.
- Femoston also had an effect on hip BMD. The increase after two years of treatment with 1mg estradiol 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. After two years of treatment with 2mg estradiol these figures were respectively, 2.6% ± 5.0%; 4.6% ± 5.0% and 4.1% ± 7.4%. The percentage of women who maintained or gained BMD in the 3 hip areas after treatment with 1mg estradiol was 67-78% and 71-88% after treatment with 2mg estradiol.

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 single dose pharmacokinetic parameters of estradiol (E2), estrone (E1) and estrone sulphate (E1S) for each dose of micronized estradiol. Data is presented as mean (SD)

Estradiol 2mg				
Parameters	E2	E1	Parameters	EIS
Cmax (pg/mL)	103.7 (48.2)	622.2 (263.6)	Cmax (ng/mL)	25.9 (16.4)
Cmin (pg/mL)	48 (30)	270 (138)	Cmin (ng/mL)	5.7 (5.9)
Cav (pg/mL)	68 (31)	429 (191)	Cav (ng/mL)	13.1 (9.4)
AUC $_{0-24}$ (pg.h/mL)	1619 (733)	10209 (4561)	AUC_{0-24} (ng.h/mL)	307.3 (224.1)

- Distribution

Oestrogens can be found either unbound or bound. About 98-99% of the estradiol dose binds to plasma proteins, from which about 30-52% 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 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 of Femoston, estradiol concentrations reached a steady-state after about five days.
Generally, steady state concentrations appeared to be reached for within 8 to 11 days of dosing.

Dydrogesterone:

- Absorption

Following oral administration, dydrogesterone is rapidly absorbed with a 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 steady state pharmacokinetic parameters of dydrogesterone (D) and dihydrodydrogesterone (DHD). Data is presemted as mean (SD).

Dydrogesterone 10mg		
Parameters	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)
AUC_{0-1} (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 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

Oestradiol only tablets (brick-red):

Tablet core:
Lactose
Hypromellose
Maize starch
Colloidal anhydrous silica
Magnesium stearate

Film coat:
Hypromellose
Talc Macrogol
400
Titanium dioxide E171
Iron oxide red E171
Iron oxide black E172
Iron oxides yellow E172

Oestradiol/Dydrogesterone tablets (yellow):

Tablet core: Lactose
Hypromellose

Maize starch
Colloidal anhydrous silica
Magnesium stearate

Film coat:
Hypromellose
Talc Macrogol
400
Titanium dioxide (E171) Iron
oxide yellow (E172)

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

3 years.

6.4. Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5. Nature and contents of container

The tablets are packed in blister strips of 28. The blister packs are made of PVC/PVdC or PVC film with a covering aluminum foil. Each carton contains 28 or 84 tablets.

6.6. Instruction for use and handling

Not applicable.

7. MARKETING AUTHORISATION HOLDER

Mylan Products Ltd.
20 Station Close
Potters Bar
Herts
EN6 1TL
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

MA 1138/00404

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

7th April 2008

10. DATE OF REVISION OF THE TEXT

10th April 2017

Legal category

POM