

Data Sheet

FEMOSTON® 2/10 TABLETS

WARNING

Oestrogens and progestogens should not be used for the prevention of cardiovascular disease or dementia.

The Women's Health Initiative (WHI) study reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis in postmenopausal women (50 to 79 years of age) during 5 years of treatment with conjugated oestrogens (0.625 mg) combined with medroxyprogesterone acetate (2.5 mg) relative to placebo (See 'Clinical Trials' and 'Precautions')

The WHI study reported increased risks of stroke and deep vein thrombosis in postmenopausal women (50 to 79 years of age) during 6.8 years of treatment with conjugated oestrogens (0.625 mg) relative to placebo (See 'Clinical Trials' and 'Precautions').

The Women's Health Initiative Memory Study (WHIMS), a sub-study of WHI, reported increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 to 5.2 years of treatment with conjugated oestrogens, with or without medroxyprogesterone acetate, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women (See 'Clinical Trials' and 'Precautions').

Other doses of conjugated oestrogens and medroxyprogesterone acetate, and other combinations and dosage forms of oestrogens and progestogens were not studied in the WHI clinical trials and, in the absence of comparable data, these risks should be assumed to be similar. Because of these risks, oestrogens with or without progestogens should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

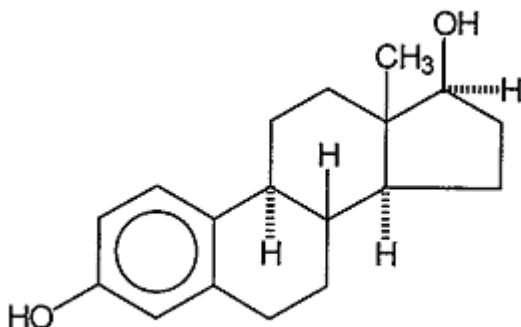
Name of the Medicine

Oestradiol and Dydrogesterone

Chemical Structure:

Oestradiol

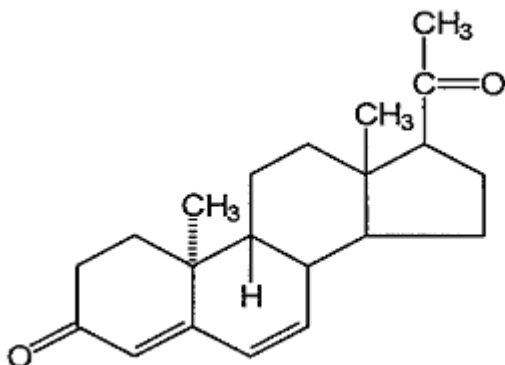
Chemical Name: Estra-1,3,5(10)-triene-3, 17 β -diol.



C₁₈H₂₄O₂, MW: 272.4

Dydrogesterone

Chemical Name: 9 β , 10 α -pregna-4, 6 diene-3, 20 dione.



C₂₁H₂₈O₂, MW: 312.5

CAS Number

Oestradiol : 50-28-2 (anhydrous)

Dydrogesterone: 152-62-5

Description

Oestradiol

It is a white, or creamy-white, odourless, hygroscopic crystals or crystalline powder.

Melting point: approximately 175°C to 180°C.

Solubility: Practically insoluble in water; slightly soluble in alcohol and in fixed oils; sparingly soluble in acetone.

Dydrogesterone

It is a white to pale yellow crystalline powder; odourless to almost odourless.

Melting point: approximately 167°C to 171°C.

Solubility: Practically insoluble in water; freely soluble in chloroform; soluble in acetone; slightly soluble in ethanol (96%) and in methanol; and slightly in ether and in fixed oils.

Femoston 2/10 tablets are immediate-release film-coated tablets for oral use containing 2 mg oestradiol and 10 mg dydrogesterone.

Femoston tablets also contain the following excipients; lactose, hypromellose, maize starch, colloidal anhydrous silica and magnesium stearate. The colours used in the Femoston 2/10 tablet are OPADRY OY-6957 pink (for the 2 mg brick-red tablets) and OPADRY OY-02B22764 (for the 2 mg/10 mg yellow tablets).

Pharmacology

Pharmacodynamics

The oestrogenic agent, oestradiol, is chemically and biologically identical to endogenous human oestradiol and has pharmacological actions similar to the physiological effects of the endogenous hormone.

Oestradiol is the primary oestrogen and the most active of the ovarian hormones.

The Femoston oestradiol preparation relieves the vasomotor symptoms arising from the decrease in the ovarian oestrogen production, resulting from natural or artificially induced menopause. In addition to relieving or eliminating these symptoms, oestrogen replacement therapy has also been demonstrated to retard or halt postmenopausal bone mass loss (osteoporosis) and to play an important role in fat metabolism.

Dydrogesterone given orally has progestational effects similar to parenterally administered progesterone. Unopposed oestrogen treatment has been reported to increase the risk of endometrial carcinoma. The inclusion of dydrogesterone in the combination of oestradiol/dydrogesterone tablets to be used for 14 days of each 28-day treatment cycle, induces a secretory endometrium in an oestrogen-primed uterus. A withdrawal bleed usually follows the completion of the progestogen component of each treatment cycle. This reduces the risk of the endometrium being hyperstimulated. Dydrogesterone does not cause androgenic side-effects.

Pharmacokinetics

Micronised oestradiol is rapidly and efficiently absorbed from the gastrointestinal tract. Following oral administration, oestradiol is metabolised. The major unconjugated and conjugated metabolites are oestrone and oestrone sulphate. These metabolites may contribute to the oestrogenic activity, either directly or following conversion to oestradiol. Conjugates of the various oestrogens and their metabolites are excreted in the urine, whilst unconjugated metabolites appear in the faeces. Oestrogens are also secreted in the milk of nursing mothers.

Following oral administration, dydrogesterone is completely metabolised, with an average 63% of the dose excreted into the urine. Excretion is complete within 72 hours. The major metabolite of dydrogesterone is 20 α -dihydrodydrogesterone (DHD), excreted predominantly in the urine as the glucuronic acid conjugate.

A common feature of all metabolites of dydrogesterone characterised is the retention of the 4,6 diene-3-one configuration of the parent compound and the absence of 17 α -hydroxylation. This accounts for the lack of oestrogenic and androgenic effects of dydrogesterone.

Plasma concentrations of DHD following oral administration of dydrogesterone are substantially higher in comparison to the parent drug. The AUC and C_{max} ratios of DHD to dydrogesterone are in the order of 40 and 25, respectively. The T_{max} values of dydrogesterone and DHD vary between 0.5 and 2.5 hours. The mean terminal half

lives of dydrogesterone and DHD vary between 5 to 7 and 14 to 17 hours, respectively.

Unlike progesterone, dydrogesterone is not excreted in urine as pregnanediol. It therefore remains possible to analyse endogenous progesterone production based on pregnanediol excretion.

No clinically relevant pharmacokinetic interactions occur between oestradiol and dydrogesterone.

Clinical Trials

In two double blind, prospective, randomised dydrogesterone dose finding studies, non hysterectomised post menopausal women (n = 271) were treated from day 1 to 28 with 2 mg oestradiol daily (one oestrogen cycle) and from day 15 to day 28 with dydrogesterone for a total of six oestrogen cycles. The doses were 5 mg, 10 mg, 15 mg and 20 mg. At dydrogesterone doses in excess of 10 mg, there was a shift from insufficient endometrium to secretory endometrium without significant endometrial proliferation/hyperplasia/carcinoma. The incidence of cyclic bleeding was 91%, with a mean severity of bleeding per day was slight to normal. Non-cyclic bleeding was reported in 5% of these patients and was classified as slight and of short duration. In a separate open label study the incidence of cyclic bleeding exceeds 85% from the first cycle and was regular, both for the day of onset and duration of an individual patient. The incidence of non-cyclic bleeding varied from 4.6% to 9.8% per evaluable cycle.

Bone mineral density effects

In a two year randomised, double blind, placebo controlled study in post menopausal women, the effects of 1 mg and 2 mg oestradiol sequentially combined with 5mg to 20 mg dydrogesterone was investigated. A clinically relevant and statistically significant ($p < 0.001$) mean increase in BMD was observed in the lumbar spine and femoral neck after 1 and 2 years, in both the 1 and 2 mg groups of the evaluable patient sample (n=409). At 2 years, the mean increase in BMD at the femoral neck were 2.7% (± 4.24) with 1mg oestradiol and 2.5% (± 4.99) with 2 mg oestradiol, and the increase at the lumbar vertebrae was 5.2% (± 3.76) with 1 mg oestradiol and 6.7% (± 3.83) with 2 mg oestradiol.

Lipid effects

During treatment with Femoston an increase in HDL, reduction in LDL and an increase in triglycerides were observed. In a two year randomised, double blind, placebo controlled study in post menopausal women, the effects of 1 mg and 2 mg oestradiol sequentially combined with 5mg to 20 mg dydrogesterone, on lipid levels was investigated. The results for the evaluable patient sample (n=384) indicated a significant effect ($p < 0.005$) on increase in HDL and decrease in LDL after 2 years in comparison with placebo. The mean change in HDL for 1 mg oestradiol combined with 5 and 10 mg dydrogesterone was 16% and 19% respectively, and for 2 mg oestradiol combined with 10 and 20 mg dydrogesterone were 21% and 24% respectively. The change in LDL levels with 1 mg oestradiol combined with 5 and 10 mg dydrogesterone were -9% and -6% respectively, and for 2 mg oestradiol combined with 10 and 20 mg dydrogesterone were -15% and -18% respectively over 2 years. The results suggest that the magnitude of these effects is dependant on the oestradiol dose.

In two open trials conducted for 1 year (n = 146) and two years (n = 58) respectively, non hysterectomised post menopausal women received 2 mg oestradiol from day 1 to 28 and 10 mg dydrogesterone from day 15 to day 28. There was an observed lowering of total cholesterol and LDL-cholesterol and an increase in HDL cholesterol.

The addition of dydrogesterone does not appear to interfere with lipid changes induced by oestrogens.

As reported in observational studies, an improvement of the lipid profile may be a factor contributing to the beneficial effect of oestrogens in reducing the risk of coronary heart disease in postmenopausal women. However, the long term effects of these changes on the cardiovascular system are unknown.

Women's Health Initiative Studies

A sub-study of the Women's Health Initiative (WHI) enrolled 16,608 predominantly healthy postmenopausal women (average age of 63 years, range 50 to 79; 83.9% White, 6.5% Black, 5.5% Hispanic) to assess the risks and benefits of the use of a continuous combined regimen of conjugated oestrogens (CE) 0.625 mg plus medroxyprogesterone acetate (MPA) 2.5 mg per day compared to placebo in the prevention of certain chronic diseases. The primary endpoint was the incidence of coronary heart disease (CHD) (nonfatal myocardial infarction and CHD death), with invasive breast cancer as the primary adverse outcome studied. A "global index" included the earliest occurrence of CHD, invasive breast cancer, stroke, pulmonary embolism (PE), endometrial cancer, colorectal cancer, hip fracture, or death due to other cause. The study did not evaluate the effects of CE plus MPA on menopausal symptoms. The oestrogen plus progestogen sub-study was stopped early because, according to the predefined stopping rule, the increased risk of breast cancer and cardiovascular events exceeded the specified benefits included in the "global index." Results are presented in Table 1 below:

TABLE 1. RELATIVE AND ABSOLUTE RISK SEEN IN THE OESTROGEN PLUS PROGESTOGEN (CE+MPA) SUBSTUDY OF WHI^a			
Event^c	Relative Risk CE+MPA vs Placebo at 5.2 Years (Nominal 95% CI*)	Placebo n = 8102	CE+MPA n = 8506
		Absolute Risk per 10,000 Women-years	
CHD events	1.29 (1.02-1.63)	30	37
<i>Non-fatal MI</i>	1.32 (1.02-1.72)	23	30
<i>CHD death</i>	1.18 (0.70-1.97)	6	7
Invasive breast cancer ^b	1.26 (1.00-1.59)	30	38
Stroke	1.41 (1.07-1.85)	21	29
Pulmonary embolism	2.13 (1.39-3.25)	8	16
Colorectal cancer	0.63 (0.43-0.92)	16	10
Endometrial cancer	0.83 (0.47-1.47)	6	5
Hip fracture	0.66 (0.45-0.98)	15	10
Death due to causes other than the events above	0.92 (0.74-1.14)	40	37
Global Index ^c	1.15 (1.03-1.28)	151	170
Deep vein thrombosis ^d	2.07 (1.49-2.87)	13	26
Vertebral fractures ^d	0.66 (0.44-0.98)	15	9
Other osteoporotic fractures ^d	0.77 (0.69-0.86)	170	131

a: adapted from JAMA, 2002; 288:321-333
b: includes metastatic and non-metastatic breast cancer with the exception of in situ breast cancer

c: a subset of the events was combined in a "global index", defined as the earliest occurrence of CHD events, invasive breast cancer, stroke, pulmonary embolism, endometrial cancer, colorectal cancer, hip fracture, or death due to other causes
d: not included in Global Index
*: nominal confidence intervals unadjusted for multiple looks and multiple comparisons. Except for deep vein thrombosis and other osteoporotic fractures, based on adjusted confidence intervals, the relative risks were not statistically significant.

For those outcomes included in the "global index", the absolute excess risks per 10,000 women-years in the group treated with CE + MPA were 7 more CHD events, 8 more strokes, 8 more PEs, and 8 more invasive breast cancers, while the absolute risk reductions per 10,000 women-years were 6 fewer colorectal cancers and 5 fewer hip fractures. The absolute excess risk of events included in the "global index" was 19 per 10,000 women-years. There was no difference between the groups in terms of all-cause mortality. (See 'Boxed Warning', and 'Precautions'.)

Women's Health Initiative Memory Study

The Women's Health Initiative Memory Study (WHIMS), a sub-study of WHI, enrolled 4,532 predominantly healthy postmenopausal women 65 years of age and older (47% were age 65 to 69 years, 35% were 70 to 74 years, and 18% were 75 years of age and older) to evaluate the effects of CE plus MPA on the incidence of probable dementia (primary outcome) compared with placebo.

After an average follow-up of 4 years, 40 women in the oestrogen/progestogen group (45 per 10,000 women-years) and 21 in the placebo group (22 per 10,000 women-years) were diagnosed with probable dementia. The relative risk of probable dementia in the hormone therapy group was 2.05 (95% CI, 1.21 to 3.48) compared to placebo. Differences between groups became apparent in the first year of treatment. It is unknown whether these findings apply to younger postmenopausal women. (See 'Boxed 'Precautions - Dementia' and 'Use in the Elderly')

Indications

Hormone replacement therapy (HRT) in oestrogen deficiency associated with natural or artificial menopause in women with an intact uterus. Prevention of postmenopausal bone mineral density loss in women. For initiation and continuation of treatment of postmenopausal symptoms, the lowest effective dose for the shortest duration should be used with the goal being short term use (See 'Dosage and Administration' and 'Clinical Trials').

When prescribed solely for the prevention of postmenopausal bone mineral density loss in women, therapy should only be prescribed for women who are at high risk of osteoporosis and future fracture and who are intolerant of, or contraindicated for non-oestrogen products approved for prevention of osteoporosis. Life style modifications and the risk benefit profile of Femoston should be taken into careful consideration and discussed with the patient, to allow the patient to make an informed decision prior to prescribing (see 'Precautions' and 'Dosage and Administration').

Contraindications

- Women who have had a hysterectomy
- Known or suspected carcinoma of the breast, endometrium or other oestrogen dependent neoplasia.
- Known or suspected progestogen dependent neoplasms
- Untreated endometrial hyperplasia
- Active or chronic liver disease or a history of liver disease where the liver function tests have failed to return to normal.

- Cerebrovascular accident or a past history of these conditions associated with previous oestrogen use.
- Previous idiopathic or current venous thromboembolism (deep venous thrombosis, pulmonary embolism) or cerebrovascular accident
- Active or recent arterial thromboembolic disease (e.g. angina, myocardial infarction)
- Abnormal genitourinary tract bleeding of unknown aetiology.
- Porphyria
- Known or suspected pregnancy.
- Lactation.
- Known hypersensitivity to any ingredients contained in Femoston tablets.

Precautions

The benefits and risks of oestrogen/progestogen therapy must always be carefully weighed including consideration of the emergence of risks as therapy continues.

Medical Examination/ Follow up

Before initiating therapy, a complete medical and family history should be taken and a physical examination performed. Pre-treatment and subsequent physical examinations should include special reference to blood pressure, breasts, abdomen and pelvic organs. Mammography is advisable. Patients who are being, or have previously been treated with unopposed oestrogens should be examined with special care to exclude endometrial stimulation before commencing Femoston therapy.

As a general rule, hormone replacement therapy (HRT) should not be prescribed for longer than one year without another physical examination including gynaecological examination being performed. Women on HRT should have regular breast examinations, and regular mammography (every 1-2 years). In all cases of undiagnosed, persistent or recurring abnormal vaginal bleeding, adequate diagnostic measures, including endometrial sampling, should be undertaken to rule out malignancy. The benefits and risks of HRT should be carefully considered. HRT should be dosed at the lowest effective dose to relieve symptoms and for the shortest duration for control of symptoms.

Cardiovascular disorders

Oestrogen/progestogen therapy has been associated with an increased risk of cardiovascular events such as myocardial infarction and stroke, as well as venous thrombosis and pulmonary embolism (venous thromboembolism or VTE). Should any of these occur or be suspected, oestrogen/progestogen therapy should be discontinued immediately.

Risk factors for arterial vascular disease (e.g., hypertension, diabetes mellitus, tobacco use, hypercholesterolaemia, and obesity) and/or venous thromboembolism (e.g., personal history or family history of VTE, obesity, and systemic lupus erythematosus) should be managed appropriately.

Coronary heart disease and stroke

In the oestrogen plus progestogen sub-study of the Women's Health Initiative (WHI) study, an increased risk of coronary heart disease (CHD) events (defined as nonfatal myocardial infarction and CHD death) was observed in women receiving CE plus MPA compared to women receiving placebo (37 vs 30 per 10,000 women-years). The increase in risk was observed in year one and persisted. (See 'Clinical trials'.)

In the same sub-study of WHI, an increased risk of stroke was observed in women receiving oestrogen plus progestogen compared to women receiving placebo (29 vs

21 per 10,000 women-years). The increase in risk was observed after the first year and persisted.

In postmenopausal women with documented heart disease (n = 2,763, average age 66.7 years) a controlled clinical trial of secondary prevention of cardiovascular disease (Heart and Estrogen/progestin Replacement Study; HERS) treatment with CE plus MPA demonstrated no cardiovascular benefit. During an average follow-up of 4.1 years, treatment with CE plus MPA did not reduce the overall rate of CHD events in postmenopausal women with established coronary heart disease. There were more CHD events in the oestrogen/progestogen-treated group than in the placebo group in year 1, but not during the subsequent years. Two thousand three hundred and twenty one women from the original HERS trial agreed to participate in an open label extension of HERS, HERS II. Average follow-up in HERS II was an additional 2.7 years, for a total of 6.8 years overall. Rates of CHD events were comparable among women in the oestrogen/ progestogen-treated group and the placebo group in HERS, HERS II, and overall.

Venous thromboembolism (VTE)

In the oestrogen plus progestogen sub-study of WHI, a 2-fold greater rate of VTE, including deep venous thrombosis and pulmonary embolism, was observed in women receiving CE + MPA compared to women receiving placebo. The rate of VTE was 34 per 10,000 women-years in the oestrogen plus progestogen-treated group compared to 16 per 10,000 women-years in the placebo group. The increase in VTE risk was observed during the first year and persisted. (See 'Clinical trials'.)

If feasible, oestrogens should be discontinued at least 4 to 6 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilisation.

Malignant neoplasms

Breast cancer

The use of oestrogens and progestogens by postmenopausal women has been reported to increase the risk of breast cancer. The most important randomised clinical trial providing information about this issue is the Women's Health Initiative (WHI) trial of oestrogen plus progestogen (see 'Clinical trials'). The results from observational studies are generally consistent with those of the WHI clinical trial.

After a mean follow-up of 5.6 years, the WHI trial reported an increased risk of breast cancer in women who took oestrogen plus progestogen. Observational studies have also reported an increased risk for oestrogen/progestogen combination therapy, and a smaller increased risk for oestrogen alone therapy, after several years of use. For both findings, the excess risk increased with duration of use, and appeared to return to baseline over about five years after stopping treatment (only the observational studies have substantial data on risk after stopping). In these studies, the risk of breast cancer was greater, and became apparent earlier, with oestrogen/progestogen combination therapy as compared to oestrogen alone therapy. However, these studies have not found significant variation in the risk of breast cancer among different oestrogens or among different oestrogen/progestogen combinations, doses, or routes of administration.

In the WHI trial of oestrogen plus progestogen, 26% of the women reported prior use of oestrogen alone and/or oestrogen/progestogen combination hormone therapy. After a mean follow-up of 5.6 years during the clinical trial, the overall relative risk of invasive breast cancer was 1.24 (95% confidence interval 1.01-1.54), and the overall absolute risk was 41 vs. 33 cases per 10,000 women-years, for oestrogen plus progestogen compared with placebo. Among women who reported prior use of hormone therapy, the relative risk of invasive breast cancer was 1.86, and the

absolute risk was 46 vs. 25 cases per 10,000 women-years, for oestrogen plus progestogen compared with placebo. Among women who reported no prior use of hormone therapy, the relative risk of invasive breast cancer was 1.09, and the absolute risk was 40 vs. 36 cases per 10,000 women-years for oestrogen plus progestogen compared with placebo. In the WHI trial, invasive breast cancers were larger and diagnosed at a more advanced stage in the oestrogen plus progestogen group compared with the placebo group. Metastatic disease was rare with no apparent difference between the two groups. Other prognostic factors such as histologic subtype, grade and hormone receptor status did not differ between the groups.

The observational Million Women Study in Europe reported an increased risk of mortality due to breast cancer among current users of oestrogens alone or oestrogens plus progestogens compared to never users, while the oestrogen plus progestogen sub-study of WHI showed no effect on breast cancer mortality with a mean follow-up of 5.6 years.

The use of oestrogen plus progestogen has been reported to result in an increase in abnormal mammograms requiring further evaluation. All women should receive yearly breast examinations by a healthcare provider and perform monthly breast self-examinations. In addition, mammography examinations should be scheduled based on patient age, risk factors, and prior mammogram results.

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

Endometrial cancer

The reported endometrial cancer risk among unopposed oestrogen users is about 2- to 12-fold greater than in nonusers, and appears dependent on duration of treatment and on oestrogen dose. Most studies show no significant increased risk associated with the use of oestrogens for less than one year. The greatest risk appears associated with prolonged use, with increased risks of 15- to 24-fold for five to ten years or more, and this risk has been shown to persist for at least 8 to 15 years after oestrogen therapy is discontinued.

Addition of a progestogen when a woman has not had a hysterectomy

Studies of the addition of a progestogen for 10 or more days of a cycle of oestrogen administration, or daily with oestrogen in a continuous regimen, have reported a lowered incidence of endometrial hyperplasia than would be induced by oestrogen treatment alone. Endometrial hyperplasia may be a precursor to endometrial cancer.

There are, however, possible risks that may be associated with the use of progestogens with oestrogens compared with oestrogen-alone regimens. These include a possible increased risk of breast cancer, adverse effects on lipoprotein metabolism (e.g., lowering HDL, raising LDL) and impairment of glucose tolerance.

Clinical surveillance of all women taking oestrogen/progestogen combinations is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. There is no evidence that the use of natural oestrogens results in a different endometrial risk profile than synthetic oestrogens of equivalent oestrogen dose.

Dementia

In the Women's Health Initiative Memory Study (WHIMS), an ancillary study of WHI, a population of 4,532 women aged 65 to 79 years was randomised to CE plus MPA or placebo. A population of 2,947 hysterectomised women, aged 65 to 79 years, was randomised to CE alone or placebo. In the planned analysis, pooling the events in

women receiving CE alone or CE plus MPA in comparison to those in women on placebo, the overall relative risk (RR) for probable dementia was 1.76 (95% CI 1.19-2.60). In the oestrogen-alone group, after an average follow-up of 5.2 years a RR of 1.49 (95% CI 0.83-2.66) for probable dementia was observed compared to placebo. In the oestrogen-plus-progestogen group, after an average follow-up of 4 years, a RR of 2.05 (95% CI 1.21-3.48) for probable dementia was observed compared to placebo. Since this study was conducted in women aged 65 to 79 years, it is unknown whether these findings apply to younger postmenopausal women. (See 'Precautions', 'Use in the Elderly'.)

Gallbladder Disease

A 2- to 4-fold increase in the risk of gallbladder disease requiring surgery in postmenopausal women receiving oestrogens has been reported.

Hypercalcaemia

Oestrogen administration may lead to severe hypercalcaemia in patients with breast cancer and bone metastases. If hypercalcaemia occurs, use of the drug should be stopped and appropriate measures taken to reduce the serum calcium level.

Visual Abnormalities

Retinal vascular thrombosis has been reported in patients receiving oestrogens. Discontinue medication pending examination if there is sudden partial or complete loss of vision, or a sudden onset of proptosis, diplopia, or migraine. If examination reveals papilloedema or retinal vascular lesions, oestrogens should be discontinued.

Elevated blood pressure

In a small number of case reports, substantial increases in blood pressure have been attributed to idiosyncratic reactions to oestrogens. In a large, randomised, placebo-controlled clinical trial, a generalised effect of oestrogen therapy on blood pressure was not seen. Blood pressure should be monitored at regular intervals with oestrogen use.

Hypertriglyceridaemia

In patients with pre-existing hypertriglyceridaemia, oestrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis and other complications.

Impaired liver function and past history of cholestatic jaundice

Oestrogens may be poorly metabolised in patients with impaired liver function. For patients with a history of cholestatic jaundice associated with past oestrogen use or with pregnancy, caution should be exercised and in the case of recurrence, medication should be discontinued.

Hypothyroidism

Oestrogen administration leads to increased thyroid-binding globulin (TBG) levels. Patients with normal thyroid function can compensate for the increased TBG by making more thyroid hormone, thus maintaining free T₄ and T₃ serum concentrations in the normal range. Patients dependent on thyroid hormone replacement therapy who are also receiving oestrogens may require increased doses of their thyroid replacement therapy. These patients should have their thyroid function monitored in order to maintain their free thyroid hormone levels in an acceptable range.

Fluid retention

Because oestrogens/progestogens may cause some degree of fluid retention, patients with conditions that might be influenced by this factor, such as cardiac or renal dysfunction, warrant careful observation when oestrogens are prescribed.

Hypocalcaemia

Oestrogens should be used with caution in individuals with severe hypocalcaemia.

Ovarian cancer

The oestrogen plus progestogen sub-study of WHI reported that, after an average follow-up of 5.6 years, the relative risk of ovarian cancer for oestrogen plus progestogen versus placebo was 1.58 (95% confidence interval 0.77 - 3.24) but was not statistically significant. The absolute risk for oestrogen plus progestogen versus placebo was 4.2 versus 2.7 cases per 10,000 women-years. In some epidemiologic studies, the use of oestrogen-only products, in particular for ten or more years, has been associated with an increased risk of ovarian cancer. Other epidemiologic studies have not found these associations.

Exacerbation of endometriosis

Endometriosis may be exacerbated with administration of oestrogen therapy.

Exacerbation of other conditions

Oestrogen therapy may cause an exacerbation of asthma, diabetes mellitus, epilepsy, migraine, porphyria, systemic lupus erythematosus, and hepatic haemangiomas and should be used with caution in women with these conditions.

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 also may recur or be aggravated during treatment with Femoston, in particular:

- Leiomyoma (uterine fibroids) or endometriosis
- Hypertension
- Liver disorders (eg: liver adenoma)
- Diabetes mellitus with or without vascular involvement
- Cholelithiasis
- Otosclerosis

Reasons for immediate withdrawal of therapy

Therapy should be discontinued in case a contraindication is discovered and in the following situations:

- Jaundice or deterioration in liver function
- Significant increase in blood pressure
- New onset of migraine-type headache, sudden partial or complete loss of vision, sudden onset of proptosis.
- Pregnancy

Bleeding Patterns

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

investigated, which may include endometrial biopsy to exclude endometrial malignancy.

Other conditions

Oestrogens may cause fluid retention, and therefore patients with cardiac or renal dysfunction should be carefully observed. Patients with terminal renal insufficiency should be closely observed, since it is expected that the level of circulating active ingredients in Femoston is increased.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Femoston is not an oral contraceptive. Patients in the perimenopausal phase should be advised to use non-hormonal contraceptive methods.

Use in pregnancy

Category D

Oestradiol has teratogenic actions on the genital tract and possibly on other organs. Animal data on the reproductive toxicity of dydrogesterone are inadequate. Use of combination oestrogen and progestogen therapy in pregnancy is contraindicated.

Use in lactation

Oestrogen administration to nursing mothers has been shown to decrease the quantity and quality of milk. Detectable amounts of oestrogens and progestogens have been found in the milk of lactating mothers receiving these compounds, but the effects on the breastfed infant have not been determined. Hormones, such as oestrogens and progestogens should not be taken by nursing mothers.

Paediatric Use

Femoston 2/10 is not recommended for use in children below age 18 due to insufficient data on safety and efficacy.

Use in the Elderly

Of the total number of subjects in the oestrogen plus progestogen sub-study of the Women's Health Initiative study, 44% (n = 7,320) were 65 years and over, while 6.6% (n = 1,095) were 75 years and over (see 'Clinical Trials'). There was a higher incidence of stroke and invasive breast cancer in women 75 and over compared to women less than 75 years of age.

In the Women's Health Initiative Memory Study (WHIMS), an ancillary study of WHI, a population of 4,532 women aged 65 to 79 years was randomised to a continuous combined regimen of conjugated oestrogens 0.625 mg/day plus medroxyprogesterone acetate 2.5 mg/day or placebo. A population of 2,947 hysterectomised women, aged 65 to 79 years, was randomised to conjugated oestrogens (CE 0.625 mg) alone or placebo. In the planned analysis, pooling the events in women receiving CE or CE plus MPA in comparison to those in women on placebo, the overall relative risk (RR) for probable dementia was 1.76 (95% CI 1.19-2.60). In the oestrogen-alone group, after an average follow-up of 5.2 years a RR of 1.49 (95% CI 0.83-2.66) for probable dementia was observed compared to placebo. In the oestrogen-plus-progestogen group, after an average follow-up of 4 years, a RR of 2.05 (95% CI 1.21-3.48) for probable dementia was observed compared to placebo. Since this study was conducted in women aged 65 to 79 years, it is unknown whether these findings apply to younger postmenopausal women. (See "Precaution – Dementia")

With respect to efficacy in the approved indications, there have not been sufficient numbers of geriatric patients involved in studies utilising oestrogens and

progestogens to determine whether those over 65 years of age differ from younger subjects in their response to oestrogens and progestogens.

Carcinogenicity

Supra-physiological doses of oestradiol have been associated with the induction of tumours in oestrogen-dependent target organs in all rodent species tested. The relevance of these findings with respect to humans has not been established. Unopposed oestrogen therapy is associated with an increased incidence of endometrial carcinoma, particularly with prolonged use. Concurrent progestogen therapy for a minimum of 12 to 14 days reduces the risk of endometrial hyperplasia.

Genotoxicity

Genotoxicity assays with oestradiol have shown no changes in the incidence of sister chromatid exchanges, but have shown increased frequency of gene mutation in transformed mouse cells *in vitro*, chromosomal aberrations in Chinese Hamster Ovary cells *in vitro*, and increased aneuploidy in Syrian Hamster Embryo cells and cultured human fibroblasts *in vitro*.

Dydrogesterone did not exhibit any evidence of genotoxicity in gene mutation studies in bacteria or in tests for clastogenic effects in mammalian cells *in vitro* or *in vivo*.

Effects on the ability to drive and use machines

Femoston 2/10 has no or negligible influence on the ability to drive and use machines.

Note: Femoston tablets do not cause drowsiness.

Interactions with other drugs

The concomitant use of drugs known to induce drug metabolising enzymes, specifically P450 enzymes, such as anticonvulsants (e.g. Phenobarbital, carbamazepine, phenytoin) and anti-infectives (e.g., rifampicin, rifabutin, nevirapine, efavirenz), may increase the metabolism of oestrogen resulting in decreased oestrogenic activity.

Ritonavir and nelfinavir, although known as strong inhibitors, by contrast exhibit inducing properties when used concomitantly with steroid hormones.

Clinically, an increased metabolism of oestrogens and progestogens may lead to decreased effect and changes in the uterine bleeding profile.

No drug interactions are known for dydrogesterone.

Herbal preparations containing St. John's Wort (*Hypericum perforatum*) may induce the metabolism of oestrogens.

Oestrogens might interfere with the metabolism of other drugs:

Oestrogens may inhibit CYP450 drug metabolising enzymes via competitive inhibition. This is in particular to be considered for substances with a narrow therapeutic index, such as

- Tacrolimus and cyclosporine A
- Fentanyl
- Theophylline

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

Adverse Effects

Side effects data available from the premarketing clinical trial program and in post marketing experience are tabulated according to each body system and in descending order of frequency.

MedDRA system organ class	Common >1/100, <1/10	Uncommon >1/1,000, <1/100	Rare >1/10,000, <1/1,000	Very rare <1/10,000 incl. isolated reports
Infections and infestations		Vaginal candidiasis		
Neoplasms benign, malignant and unspecified		Increase in size of leiomyoma		
Blood and the lymphatic system disorders				Haemolytic anaemia
Immune system disorders				Hypersensitivity reactions
Psychiatric disorders		Depression, change in libido, nervousness		
Nervous system disorders	Headache, migraine	Dizziness		Chorea
Eye disorders			Intolerance to contact lenses, steepening of corneal curvature	
Cardiac disorders				Myocardial infarction
Vascular disorders		Venous thrombo-embolism		Stroke
Gastro-intestinal disorders	Nausea, abdominal pain, flatulence			Vomiting
Hepatobiliary disorders		Gall bladder disease	Alterations in liver function, sometimes with asthenia or malaise, jaundice and abdominal pain	
Skin and subcutaneous tissue disorders		Allergic skin reactions, rash, urticaria, pruritus		Chloasma or melasma, which may persist when drug is discontinued, erythema multiforme, erythema nodosum, vascular purpura, angioedema

Musculoskeletal and connective tissue disorders	Leg cramps	Back pain		
Reproductive system and breast disorders	Breast pain/tenderness, breakthrough bleeding and spotting, pelvic pain	Change in cervical erosion, change in cervical secretion, dysmenorrhoea	Breast enlargement Premenstrual-like syndrome	
Congenital and familial/genetic disorders				Aggravation of porphyria
General disorders and administration site reactions	Asthenia	Peripheral oedema		
Investigations	Increase/decrease in weight			

Skin reactions have also been reported. For the most serious adverse reactions associated with hormone replacement therapy see Precautions.

Breast cancer (See 'Precautions- Breast cancer')

For oestrogen-only HRT, estimates of relative risk (RR) from a reanalysis of original data from 51 epidemiological studies (in which >80% of HRT use was oestrogen-only HRT) and from the epidemiological Million Women Study (MWS) are similar at 1.35 (95% CI 1.21-1.49) and 1.30 (95% CI 1.21-1.40), respectively.

The MWS reported that, compared to never users, the use of various types of oestrogen-progestogen combined HRT was associated with a higher risk of breast cancer (RR=2.00, 95% CI 1.88-2.12) than use of oestrogens alone (RR=1.30, 95% CI 1.21-1.40) or use of tibolone (RR=1.45, 95% CI 1.25-1.68).

The absolute risks calculated from the MWS and the WHI trials are presented below:

The MWS has estimated, from the known average incidence of breast cancer in developed countries, that:

For women not using HRT, about 32 in every 1,000 are expected to have breast cancer diagnosed between the ages of 50 and 64 years.

For 1,000 current or recent users of HRT, the number of additional cases during the corresponding period will be

- For users of oestrogen-only replacement therapy
Between 0 and 3 (best estimate = 1.5) for 5 years' use
Between 3 and 7 (best estimate = 5) for 10 years' use
- For users of oestrogen plus progestogen combined HRT
Between 5 and 7 (best estimate = 6) for 5 years' use
Between 18 and 20 (best estimate = 19) for 10 years' use

The WHI trial estimated that after 5.6 years of follow-up of women between the ages of 50 and 79 years, an additional 8 cases of invasive breast cancer would be due to oestrogen-progestogen combined HRT (CE plus MPA) per 10,000 women years. According to calculations from the trial data, it is estimated that:

- For 1,000 women in the placebo group about 16 cases of invasive breast cancer would be diagnosed in 5 years.

- For 1,000 women who used oestrogen + progestogen combined HRT (CE plus MPA), the number of additional cases would be between 0 and 9 (best estimate = 4) for 5 years' use.

The number of additional cases of breast cancer in women who use HRT is broadly similar for women who start HRT irrespective of age at start of use (between the ages of 45-65).

Endometrial cancer

In women with an intact uterus, the risk of endometrial hyperplasia and endometrial cancer increases with increasing duration of use of unopposed oestrogens (See 'Precautions').

Other adverse reactions have been reported in association with oestrogen/progestogen treatment:

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

Nervous system disorders: Probable dementia, exacerbation of epilepsy

Vascular disorders: Arterial thromboembolism

Dosage and Administration

One tablet administered orally daily without interruption (See 'Indications' and 'Precautions' for treatment duration advice).

The mainstays for decreasing the risk of postmenopausal osteoporosis are weight bearing exercise, adequate calcium and vitamin D intake, and when indicated, pharmacological therapy. Postmenopausal women require an adequate daily intake of elemental calcium. Therefore, when not contraindicated, calcium supplementation may be helpful for women with sub-optimal dietary intake. Vitamin D supplementation may also be required to ensure adequate daily intake in postmenopausal women.

Femoston 2/10: Treatment should begin with the administration of the brick red, 2 mg oestradiol tablets for the first 14 days of a 28 day cycle, followed by 14 days administration of the yellow 2 mg oestradiol/10 mg dydrogesterone combination tablets. This sequence is also indicated on the blister strip. When all 28 tablets in the pack have been taken, another pack is started without interruption.

In menstruating women, treatment with Femoston should be started on the first day after onset of menstruation.

In patients with oligomenorrhoea, treatment is advised to begin following 10-14 days monotherapy with progestogen such as dydrogesterone ("chemical curettage").

In postmenopausal non hysterectomised women, with at least 12 months of amenorrhoea, treatment may be commenced at any time.

A withdrawal bleed usually occurs following completion of the progestogen component (yellow tablets) of each 28-day treatment cycle.

Overdosage

No acute serious medical effects have been reported in association with an overdosage of either oestradiol or dydrogesterone. Possible symptoms following overdosage are similar to the adverse reactions. There are no specific therapeutic recommendations for the management of overdosage. In the event of a large overdose treatment should be symptomatic.

Contact the Poisons Information Centre on 0800 764 766 for management of overdose.

Presentation and Storage Conditions

Femoston 2/10: Each pack contains one, two or three* blister strips of:

14 round, biconvex, brick-red, film-coated tablets, each containing 2 mg oestradiol bearing the inscriptions "379" on one side and "S" on the other, and

14 round, biconvex, yellow, film-coated tablets, each containing 2 mg oestradiol combined with 10 mg dydrogesterone bearing the inscriptions "379" on one side and "S" on the other.

* Not available in New Zealand

Store below 30°C, protect from light.

Further Information

Nil

Name and Address of the Sponsor

Abbott Laboratories NZ Ltd

4 Pacific Rise

Mt Wellington

Auckland

New Zealand

Medicine Schedule

Prescription Medicine

Date of Preparation

01 July 2011