AUSTRALIAN PRODUCT INFORMATION

FEMOSTON® 2/10

(estradiol (as hemihydrate) and dydrogesterone) tablets

WARNING

Estrogens 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 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 estrogens (0.625 mg) combined with medroxyprogesterone acetate (2.5 mg) relative to placebo (see Section 5.1 PHARMACODYNAMIC PROPERTIES – Clinical Trials and Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

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 estrogens (0.625 mg) relative to placebo (see Section 5.1 PHARMACODYNAMIC PROPERTIES – Clinical Trials and Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Other doses of conjugated estrogens and medroxyprogesterone acetate, and other combinations and dosage forms of estrogens 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, estrogens 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.

1 NAME OF THE MEDICINE

Estradiol (as hemihydrate) and dydrogesterone

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

FEMOSTON 2/10 tablets are immediate-release film-coated tablets for oral use, with each tablet containing 2 mg estradiol (as hemihydrate) and 10 mg dydrogesterone or 2 mg estradiol (as hemihydrate).

Excipients with known effect: sugars as lactose.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

Each blister strip contains:

- 14 round, biconvex, brick-red, film-coated tablets, each containing 2 mg estradiol (as hemihydrate) bearing the inscriptions "379" on one side, and
- 14 round, biconvex, yellow, film-coated tablets, each containing 2 mg estradiol (as hemihydrate) combined with 10 mg dydrogesterone bearing the inscriptions "379" on one side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Hormone replacement therapy (HRT) in estrogen 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 Section 4.2 DOSE AND METHOD OF ADMINISTRATION and Section 5.1 PHARMACODYNAMIC PROPERTIES – 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-estrogen products approved for prevention of osteoporosis. Lifestyle 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 Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

4.2 DOSE AND METHOD OF ADMINISTRATION

One tablet administered orally daily without interruption (see Section 4.1 THERAPEUTIC INDICATIONS and Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE 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 estradiol tablets for the first 14 days of a 28-day cycle, followed by 14 days administration of the yellow 2 mg estradiol/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.

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.

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.

4.3 CONTRAINDICATIONS

- Women who have had a hysterectomy
- Known or suspected carcinoma of the breast, endometrium or other estrogen 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 estrogen use
- Previous idiopathic or current venous thromboembolism (deep venous thrombosis, pulmonary embolism) or cerebrovascular accident
- Known thrombophilic disorders (e.g. protein C, protein S or antithrombin deficiency, see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE)
- 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

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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

Medical Examination/ Follow up

Before initiating or reinstituting 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 estrogens 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). Women should be advised what changes in their breasts should be reported to their doctor or nurse (see "Breast cancer" below). 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

Estrogen/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, estrogen/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 estrogen 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 conjugated equine estrogen (CEE) plus medroxyprogesterone acetate (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 Section 5.1 PHARMACODYNAMIC PROPERTIES – Clinical Trials).

In the same sub-study of WHI, an increased risk of stroke was observed in women receiving estrogen 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. 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 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

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 CEE plus MPA demonstrated no cardiovascular benefit. During an average follow-up of 4.1 years, treatment with CEE 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 estrogen/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 estrogen/ progestogen-treated group and the placebo group in HERS, HERS II, and overall.

A Cochrane meta-analysis including 19 trials with a total of 40,410 post-menopausal women found evidence that hormone therapy in both primary and secondary prevention conferred no protective effects for all-cause mortality, cardiovascular death, non-fatal myocardial infarction, angina, or re-vascularisation. There was an increased risk of stroke in those in the hormone therapy arm for primary prevention (RR 1.32; 95% CI 1.12 to 1.56). The absolute risk increase for stroke was 6 per 1000 women (number needed to treat for an additional harmful outcome (NNTH) =165; mean length of follow-up: 4.21 years (range: 2.0 to 7.1)).

In a nested case control study of the UK-based General Practice Research Database which included data from 69 412 women: 4658 estradiol/dydrogesterone (E/D) users, 30 048 users of other MHT, and 34 706 women who never used MHT. The incidence rates of MI and thrombotic stroke in E/D users were 0.40 (95% confidence interval (CI) 0.18–0.76) and 0.27 (95% CI 0.10–0.58) per 1000 person-years, respectively. As compared to non-users of HRT, the adjusted relative risk estimates (odds ratios) in the nested case–control analysis for ED users or users of other HRT were 1.06 (95% CI 0.48–2.36) and 1.12 (95% CI 0.84–1.51) for MI and 0.50 (95% CI 0.21–1.22) and 1.18 (95% CI 0.94–1.48) for thrombotic stroke.

Venous Thromboembolism (VTE)

In the estrogen 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 CEE + MPA compared to women receiving placebo. The rate of VTE was 34 per 10,000 women-years in the estrogen 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 Section 5.1 PHARMACODYNAMIC PROPERTIES – Clinical Trials).

A Cochrane meta-analysis including 19 trials with a total of 40,410 post-menopausal women found an increased risk of venous thromboembolic events (RR 1.92, 95% CI 1.36 to 2.69), as were pulmonary emboli (RR 1.89, 955 CI 1.17 to 3.04) on hormone therapy relative to placebo. The absolute risk increased for venous thromboembolism 8 per 1000 women (NNTH = 118; mean length of follow-up: 5.95 years (range: 1.0 to 7.1)); and for pulmonary embolism 4 per 1000 (NNTH = 242; mean length of follow-up: 3.13 years (range: 1.0 to 7.1)).

Data from two large, nested case-control studies in a UK population of 80,396 with primary diagnosis of VTE (1998-2017) showed for oral MHT therapy compared with no use a significantly increased risk of venous thromboembolism (adjusted odds ratio 1.58, 95% confidence interval 1.52 to 1.64). The risk was increased for both, oestrogen only preparations (1.40, 1.32 to 1.48) and combined oestrogen-progestin preparations (1.73, 1.65 to 1.81). Estradiol had a lower risk than conjugated equine oestrogen for oestrogen only preparations (0.85, 0.76 to 0.95) and combined preparations (0.83, 0.76 to 0.91). Compared with no exposure, conjugated equine oestrogen plus medroxyprogesterone acetate had the highest risk (2.10, 1.92 to 2.31), and estradiol plus dydrogesterone had the lowest risk (1.18, 0.98 to 1.42). The risk non-significantly increased with higher doses of estradiol (E2): E2 ≤1 mg/dydrogesterone 1.12 (0.90 to 1.40) and E2 >1 mg/dydrogesterone 1.34 (0.94 to 1.90). The risk of cyclical compared to continuous regimen of dydrogesterone was non-significantly higher (1.21, 0.95 to 1.53 compared to 1.13, 0.84 to 1.53).

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 CONTRAINDICATIONS).

Generally recognised risk factors for VTE include: use of estrogens, older age, major surgery, prolonged immobilisation, 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 feasible, estrogens 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. Treatment should not be restarted until the woman is completely mobilised.

In women with no personal history of VTE but with a close relative with a history of thrombosis at a 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 doctor immediately they are aware of a potential thromboembolic symptom (e.g. painful swelling of a leg, sudden pain in the chest, dyspnoea).

Malignant Neoplasms

Breast cancer

The overall evidence shows an increased risk of breast cancer in women taking combined estrogen/progestogen HRT or estrogen-only HRT, that is dependent on the duration of taking HRT.

Combined estrogen/progestogen therapy:

- The randomised placebo-controlled trial, the Women's Health Initiative study (WHI), and a meta-analysis of prospective epidemiological studies are consistent in finding an increased risk of breast cancer in women taking combined estrogen/progestogen for HRT that becomes apparent after about 3 (1-4) years (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

Estrogen-only therapy:

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

After a mean follow-up of 5.6 years, the WHI trial reported an increased risk of breast cancer in women who took estrogen plus progestogen. Results from a large meta-analysis showed that after stopping treatment, the excess risk will decrease with time and the time needed to return to baseline depends on the duration of prior HRT use. When HRT was taken for more than 5 years, the risk may persist for 10 years or more. In the meta-analysis, the risk of breast cancer with estrogen plus dydrogesterone was lower than that noted with other synthetic progestogens, although the meta-analysis only included a relatively small number of women on dydrogesterone. Less than 5 years of use of estrogen plus dydrogesterone was not associated with a statistically significant increased risk of breast cancer (RR 1.21; 95% CI 0.90 to 1.61). The risk, however, was increased with 5-14 years (RR 1.41; 95% CI 1.17 to 1.71) and ≥ 15 years of use of estrogen plus dydrogesterone (RR 2.23; 95% CI 1.32 to 3.26), although this appeared lower than that noted with other synthetic progestogens. The meta-analysis also noted that risk was reduced when progestogen was administered intermittently (10-14 days/month). During years 5–14 of use of an oestrogen-progestagen combination, the RR was greater for oestrogen plus daily progestagen than for oestrogen plus intermittent progestagen (which usually involved 10–14 days of progestogen per month); RR 2·30 (2·21–2·40) and RR 1·93 (1·84–2·01), respectively, heterogeneity p<0·0001

In the French E3N cohort study that assessed and compared the association between different HRT and breast cancer risk, during follow-up (mean duration 8.1 postmenopausal years), 2,354 cases of invasive breast cancer occurred among 80,377 postmenopausal women were reported. Compared with HRT never-use, the association of estrogen/progestogen combinations with breast cancer risk varied significantly according to the type of progestagen: the relative risk was 1.00 (0.83–1.22) for estrogen/progesterone, 1.16 (0.94–1.43) for estrogen/dydrogesterone, and 1.69 (1.50–1.91) for estrogen combined with other progestogens (which included MPA).

The use of estrogen 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 estrogen-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 estrogen users is about 2- to 12-fold greater than in nonusers, and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with the use of estrogens 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 estrogen 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 estrogen administration, or daily with estrogen in a continuous regimen, have reported a lowered incidence of endometrial hyperplasia than would be induced by estrogen 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 estrogens compared with estrogen-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 estrogen/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 estrogens results in a different endometrial risk profile than synthetic estrogens of equivalent estrogen 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 CEE plus MPA or placebo. A population of 2,947 hysterectomised women, aged 65 to 79 years, was randomised to CEE alone or placebo. In the planned analysis, pooling the events in women receiving CEE alone or CEE 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 estrogen-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 estrogen-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 Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and 'Use in the Elderly').

Gallbladder Disease

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

Hypercalcaemia

Estrogen 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 estrogens. 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, estrogens 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 estrogens. In a large, randomised, placebo-controlled clinical trial, a generalised effect of estrogen therapy on blood pressure was not seen. Blood pressure should be monitored at regular intervals with estrogen use.

Hypertriglyceridaemia

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

Impaired Liver Function and Past History of Cholestatic Jaundice

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

Hypothyroidism

Estrogen administration leads to increased thyroid-binding globulin (TBG) levels, leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 levels (by column or by radioimmunoassay) 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-I-antitrypsin, ceruloplasmin). 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 estrogens 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 estrogens/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 estrogens are prescribed.

Hypocalcaemia

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

Ovarian Cancer

Ovarian cancer is much rarer than breast cancer. Epidemiological evidence from a large meta-analysis suggests a slightly increased risk in women taking estrogen-only or combined estrogen-progestogen HRT, which becomes apparent within 5 years of use and diminishes over time after stopping. Some other studies, including the WHI trial suggest that use of combined HRTs may be associated with a similar, or slightly smaller risk (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

Exacerbation of Endometriosis

Endometriosis may be exacerbated with administration of estrogen therapy.

Exacerbation of other Conditions

Estrogen 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.

<u>Conditions which need supervision</u>

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

Estrogens 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.

Published literature has reported an increased risk of inflammatory bowel disease (ulcerative colitis and Crohn's disease) in association with HRT use.

Patients with rare hereditary problems of galactose intolerance, the total 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.

Exogenous oestrogens may induce or exacerbate symptoms of hereditary and acquired angioedema.

ALT elevations

ALT elevations have been observed in studies of women treated for hepatitis C virus (HCV) infections with combination of anti-viral regimens and concomitant use of ethinylestradiol containing medications such as CHCs (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Use in the Elderly

Of the total number of subjects in the estrogen 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 Section 5.1 PHARMACODYNAMIC PROPERTIES – 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 equine estrogens 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 equine estrogens (CEE 0.625 mg) alone or placebo. In the planned analysis, pooling the events in women receiving CEE or CEE 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 estrogen-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 estrogen-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 Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Dementia).

With respect to efficacy in the approved indications, there have not been sufficient numbers of geriatric patients involved in studies utilising estrogens and progestogens to determine whether those over 65 years of age differ from younger subjects in their response to estrogens and progestogens.

Paediatric Use

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

Effects on Laboratory Tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No interaction studies have been performed.

The efficacy of estrogen and progestogens may be impaired:

The concomitant use of drugs known to induce drug metabolising enzymes, specifically P450 enzymes 2B6, 3A4, 3A5, 3A7, such as anticonvulsants (e.g. phenobarbital, carbamazepine, phenytoin) and anti-infectives (e.g., rifampicin, rifabutin, nevirapine, efavirenz), may increase the metabolism of estrogen resulting in decreased estrogenic activity.

Ritonavir and nelfinavir, although known as strong inhibitors of CYP450 3A4, A5, A7, by contrast, exhibit inducing properties when used concomitantly with steroid hormones.

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

Herbal preparations containing St John's Wort (*Hypericum perforatum*) may induce the metabolism of estrogens and progestogens via the CYP450 3A4 pathway.

Interactions with HCV combination drug regimen

During clinical trials with the HCV combination drug regimen ombitasvir/paritaprevir/ritonavir with and without dasabuvir, ALT elevations greater than 5 times the upper limit of normal (ULN) were significantly more frequent in women using ethinylestradiol-containing medicinal products such as CHCs. Women using medicinal products containing oestrogens other than ethinylestradiol, such as estradiol, had a rate of ALT elevation similar to those not receiving any oestrogens; however, due to the limited number of women taking

these other oestrogens, caution is warranted for co-administration with the combination drug regimen ombitasvir/paritaprevir/ritonavir with or without dasabuvir and also the regimen with glecaprevir/pibrentasvir (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Estrogens might interfere with the metabolism of other drugs:

Estrogens 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 ciclosporin A (CYP450 3A4, 3A3)
- Fentanyl (CYP450 3A4)
- Theophylline (CYP450 1A2)

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, ciclosporinA and theophylline may be necessary.

Effect of HRT with oestrogens on other medicinal products:

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

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

No data available.

Use in Pregnancy – Category B3

FEMOSTON 2/10 is contraindicated during pregnancy. If pregnancy occurs during medication with FEMOSTON 2/10, treatment should be withdrawn immediately.

In animal studies, maternal administration of high doses of estradiol and dydrogesterone (as individual agents) produced urogenital malformations in the offspring. The clinical relevance of these findings is unclear.

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

Use in Lactation

Estrogen administration to nursing mothers has been shown to decrease the quantity and quality of milk. Detectable amounts of estrogens 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 estrogens and progestogens should not be taken by nursing mothers.

4.7 EFFECTS ON 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.

4.8 ADVERSE EFFECTS (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.

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

MedDRA system organ class	**Very common >1/10**	**Common >1/100, <1/10**	**Uncommon >1/1,000, <1/100**	**Rare >1/10,000, <1/1,000**
Infections and infestations		Vaginal candidiasis		
Neoplasms benign, malignant and unspecified			Increase in size of leiomyoma	
Immune system disorders			Hypersensitivity reactions	
Psychiatric disorders		Depression, nervousness	change in libido,	
Nervous system disorders	Headache	Migraine, dizziness		
Cardiac disorders				Myocardial infarction
Vascular disorders			Venous thrombo-embolism	
Gastro-intestinal disorders	Abdominal pain	Nausea, flatulence, vomiting		
Hepatobiliary disorders			Gall bladder disorders, alterations in liver function, sometimes with asthenia or malaise, jaundice and abdominal pain	
Skin and subcutaneous tissue disorders		Allergic skin reactions, rash, urticaria, pruritus		Vascular purpura, angioedema
Musculoskeletal and connective tissue disorders	Back pain			
Reproductive system and breast disorders	Breast pain/tenderness	Breakthrough bleeding and spotting, pelvic pain, menstrual disorders (including postmenopausal spotting, metrorrhagia, menorrhagia, oligo-/amenor-rhoea, irregular menstruation, dysmenorrhoea, change in cervical secretion,	Breast enlargement, premenstrual-like syndrome	
General disorders and administration site reactions		Asthenic conditions (asthenia, fatigue, malaise), peripheral oedema		
Investigations		Increase/decrease in weight		

For the most serious adverse reactions associated with hormone replacement therapy see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE.

Breast Cancer

- 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.
- The increased risk in users of oestrogen-only therapy is 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 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).
- The absolute risk estimations based on results from the largest meta-analysis of prospective epidemiological studies and the WHI trials are presented below.

Table 1. Estimated additional risk of breast cancer after 5 years' use in women with BMI 27 (kg/m^2) - from the largest meta-analysis of prospective epidemiological studies

Age at start HRT (years)	Incidence per 1000 never-users of HRT over a 5 year period (50-54 years)*	Risk ratio	Additional cases per 1000 HRT users after 5 years
		Estrogen only HRT	
50	13.3	1.2	2.7
		Combined estrogen/progestogen	
50	13.3	1.6	8.0
*Taken from baseline incidence rates in England in 2015 in women with BMI 27 (kg/m^2) Note: Since the background incidence of breast cancer differs by country, the number of additional cases of breast cancer will also change proportionately.			

Table 2. Estimated additional risk of breast cancer after 10 years' use in women with BMI 27 (kg/m^2) - from the largest meta-analysis of prospective epidemiological studies

Age at start HRT (years)	Incidence per 1000 never-users of HRT over a 10 year period (50-59 years)*	Risk ratio	Additional cases per 1000 HRT users after 10 years
		Estrogen only HRT	
50	26.6	1.3	7.1
		Combined estrogen/progestogen	
50	26.6	1.8	20.8
*Taken from baseline incidence rates in England in 2015 in women with BMI 27 (kg/m^2) Note: Since the background incidence of breast cancer differs by country, the number of additional cases of breast cancer will also change proportionately.			

Table 3. Additional risk of breast cancer after 5 years' use - from the WHI trial

Age range (years)	Incidence per 1000 women in placebo arm over 5 years	Risk ratio & 95% CI	Additional cases per 1000 HRT users over 5 years (95% CI)
		CEE estrogen-only	
50-79	21	0.8 (0.7 – 1.0)	-4 (-6 – 0)*
		CEE+MPA estrogen & progestogen‡	
50-79	17	1.2 (1.0 – 1.5)	+4 (0 – 9)
* WHI study in women with no uterus, which did not show an increase in risk of breast cancer ‡ When the analysis was restricted to women who had not used HRT prior to the study there was no increased risk apparent during the first 5 years of treatment: after 5 years the risk was higher than in non-users.			

See Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Malignant Neoplasms – Breast Cancer.

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, the risk of endometrial hyperplasia and endometrial cancer increases with increasing duration of use of unopposed estrogens (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). 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 estrogen-only or combined estrogen-progestogen HRT has been associated with a slightly increased risk of having ovarian cancer diagnosed (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). 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 (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 50-54 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 'PRECAUTIONS'). Results of the WHI studies are presented:

Table 4: 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 user
Oral oestrogen-only*			
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)

*Study in women with no uterus

Risk of Coronary Artery Disease

The risk of coronary artery disease is slightly increased in users of combined estrogen-progestogen HRT over the age of 60 (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Risk of Ischaemic Stroke

The use of estrogen-progestogen therapy is associated with an up to 1.5-fold increased relative risk of ischaemic stroke. The risk of haemorrhagic stroke is not increased during use of HRT. This relative risk is not dependent on age or on duration of use, but as the baseline risk is strongly age-dependent, the overall risk of stroke in women who use HRT will increase with age (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Table 5: WHI studies combined – Additional risk of ischaemic stroke[2] over 5 years' use

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

Other Adverse Effects

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

Neoplasms benign, malignant and unspecified: Estrogen dependent neoplasms both benign and malignant, e.g. endometrial cancer, ovarian cancer. Increase in size of progestogen dependent neoplasms, e.g. meningioma.

Blood and lymphatic system disorders: Haemolytic anaemia (very rare)

Immune system disorders: Systemic lupus erythematosus

Metabolism and nutrition disorders: Hypertriglyceridemia

Nervous system disorders: Probable dementia, chorea (very rare), exacerbation of epilepsy

Eye disorders: Intolerance to contact lenses (rare), steepening of corneal curvature (rare)

Reproductive system and breast disorders: Fibrocystic breast changes, change in cervical erosion (uncommon)

Vascular disorders: Arterial thromboembolism, stroke (very rare)

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

Skin and subcutaneous tissue disorders: Chloasma or melasma, which may persist when drug is discontinued (very rare), erythema multiforme (very rare), erythema nodosum (very rare)

Musculoskeletal and connective tissue disorders: Leg cramps (common)

Congenital and familial/genetic disorders: Aggravation of porphyria (very rare)

Investigations: Total thyroid hormones increased

Renal and urinary disorders: Urinary incontinence

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

No acute serious medical effects have been reported in association with an overdosage of either estradiol or dydrogesterone. Possible symptoms following overdosage are similar to the adverse reactions. 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. There are no specific therapeutic recommendations for the management of overdosage. In the event of a large overdose treatment should be symptomatic. For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

The estrogenic agent, estradiol, is chemically and biologically identical to endogenous human estradiol and has pharmacological actions similar to the physiological effects of the endogenous hormone. Estradiol is the primary estrogen and the most active of the ovarian hormones. The FEMOSTON estradiol preparation relieves the vasomotor symptoms arising from the decrease in the ovarian estrogen production, resulting from natural or artificially induced menopause. In addition to relieving or eliminating these symptoms, estrogen 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 estrogen treatment has been reported to increase the risk of endometrial carcinoma. The inclusion of dydrogesterone in the combination of estradiol/dydrogesterone tablets to be used for 14 days of each 28-day treatment cycle, induces a secretory endometrium in an estrogen-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.

Clinical Trials

In two double blind, prospective, randomised dydrogesterone dose finding studies, non-hysterectomised postmenopausal women (n = 271) were treated from day 1 to 28 with 2 mg estradiol daily (one estrogen cycle) and from day 15 to day 28 with dydrogesterone for a total of six estrogen 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 postmenopausal women, the effects of 1 mg and 2 mg estradiol sequentially combined with 5 mg 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 1 mg estradiol and 2.5% (±4.99) with 2 mg estradiol, and the increase at the lumbar vertebrae was 5.2% (±3.76) with 1 mg estradiol and 6.7% (±3.83) with 2 mg estradiol.

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 estradiol sequentially combined with 5 mg 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 estradiol combined with 5 and 10 mg dydrogesterone was 16% and 19% respectively, and for 2 mg estradiol combined with 10 and 20 mg dydrogesterone were 21% and 24% respectively. The change in LDL levels with 1 mg estradiol combined with 5 and 10 mg dydrogesterone were –9% and –6% respectively, and for 2 mg estradiol 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 dependent on the estradiol 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 estradiol 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 estrogens.

As reported in observational studies, an improvement of the lipid profile may be a factor contributing to the beneficial effect of estrogens 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 equine estrogens (CEE) 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 CEE plus MPA on menopausal symptoms. The estrogen 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 6 below:

TABLE 6. RELATIVE AND ABSOLUTE RISK SEEN IN THE ESTROGEN PLUS PROGESTOGEN (CEE+MPA) SUBSTUDY OF WHI[a]

Event[c]	**Relative Risk CEE+MPA vs Placebo at 5.2 Years (Nominal 95% CI*)**	**Placebo n = 8102**	**CEE+MPA n = 8506**
		Absolute Risk per 10,000 Women-years	
CHD events	1.29 (1.02-1.63)	30	37
Non-fatal MI	*1.32 (1.02-1.72)*	*23*	*30*
CHD death	*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 CEE + 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 Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

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 CEE 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 estrogen/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 Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Dementia and Use in the Elderly).

Guidelines on menopause and MHT

The International Menopause Society (IMS) and the British Menopause Society (BMS) provide recommendations on MHT in menopausal women. Their Recommendations and Consensus Statements include assessments of the long-term risks of thrombosis and breast cancer associated with dydrogesterone compared to other progestogens. For full details, please refer to the most recent guidance provided by the IMS and the BMS.

Other resources available to clinicians include a Joint Statement from these organisations, BMS, IMS, European Menopause and Andropause Society (EMAS), Royal College of Obstetricians and Gynaecologists (RCOG) and Australasian Menopause Society (AMS) on menopausal hormone therapy (MHT) and breast cancer risk in response to EMA Pharmacovigilance Risk Assessment Committee recommendations (May 2020).

5.2 PHARMACOKINETIC PROPERTIES

Micronised estradiol is rapidly and efficiently absorbed from the gastrointestinal tract. Following oral administration, estradiol is metabolised. The major unconjugated and conjugated metabolites are estrone and estrone sulfate. These metabolites may contribute to the estrogenic activity, either directly or following conversion to estradiol. Conjugates of the various estrogens and their metabolites are excreted in the urine, whilst unconjugated metabolites appear in the faeces. Estrogens 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 20α-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 17α-hydroxylation. This accounts for the lack of estrogenic 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 estradiol and dydrogesterone.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Genotoxicity assays with estradiol 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*.

Carcinogenicity

Supra-physiological doses of estradiol have been associated with the induction of tumours in estrogen-dependent target organs in all rodent species tested. The relevance of these findings with respect to humans has not been established. Unopposed estrogen 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.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Lactose monohydrate, hypromellose, maize starch, colloidal anhydrous silica and magnesium stearate. The colours used in the FEMOSTON 2/10 tablet are OPADRY complete film coating system OY-6957 pink (ARTG PI No. 4158) (for the 2 mg brick-red tablets) and OPADRY complete film coating system 02B22764 yellow (ARTG PI No. 4148) (for the 2 mg/10 mg yellow tablets).

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30ºC.

6.5 NATURE AND CONTENTS OF CONTAINER

Each pack contains one, two or three PVC/Al blister strips of 28 tablets (14 brick-red tablets and 14 yellow tablets).

Some pack sizes may not be marketed.

Australian Register of Therapeutic Goods (ARTG)

AUST R 75889 – FEMOSTON 2/10 estradiol 2mg and estradiol 2mg with dydrogesterone 10mg tablet blister pack composite pack

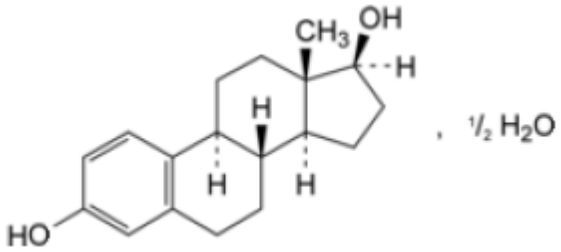
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Structure

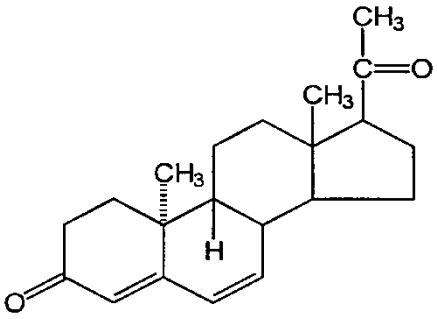
Estradiol hemihydrate
Chemical Name: Estra-1,3,5(10)-triene-3, 17β-diol hemihydrate.



$C_{18}H_{24}O_2.½H_2O$, MW: 281.4

It is a white or almost white, crystalline powder or colourless crystals. Melting point: approximately 175°C to 180ºC. Solubility: Practically insoluble in water, soluble in acetone, sparingly soluble in ethanol (96 per cent), slightly soluble in methylene chloride.

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



$C_{21}H_{28}O_2$, MW: 312.5

It is a white to pale yellow crystalline powder; odourless to almost odourless. Melting point: approximately 167°C to 171ºC. 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.

CAS Number

Estradiol hemihydrate: 35380-71-3
Dydrogesterone: 152-62-5

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

Viatris Pty Ltd

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Millers Point NSW 2000

www.viatris.com.au

Phone: 1800 274 276

9 DATE OF FIRST APPROVAL

08/09/2000

10 DATE OF REVISION

17/11/2023

Summary Table of Changes

Section Changed	Summary of New Information
All	Minor editorial changes.
4.5	Added interaction with Lamotrigine under section "Effect of HRT with oestrogens on other medicinal products".

FEMOSTON® is a Viatris company trade mark

FEMOSTON 2/10_pi\Nov23/00 (CCDS 21-Aug-2023)