Femoston® 2/10, film-coated tablets

2 mg estradiol, and a combination of 2 mg estradiol and 10 mg dydrogesterone

Abbott

Read this entire leaflet carefully before you start taking this medicine.
Keep this leaflet. You may need to read it again. If you have questions not answered by this pamphlet, please ask your doctor or pharmacist. This medicine has been prescribed to you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

Femoston 2/10 is a round, film-coated tablet for oral administration.

Femoston 2/10 contains 14 brick red tablets, each of which contains 2 mg estradiol and 14 yellow tablets, each of which contains 2 mg estradiol and 10 mg dydrogesterone.

All tablets bear the inscription 379 on one side and S on the other side.

Excipients (non-medicinal ingredients):

Tablet core (all tablets): Lactose monohydrate, hypromellose, maize starch, colloidal anhydrous silica, magnesium stearate

Brick red tablet film-coating contains: titanium dioxide (E171), iron oxide red (E172), iron oxide black (E172), iron oxide yellow (E172), hypromellose, Macrogol 400, talc

Yellow tablet film-coating contains: titanium dioxide (E171), iron oxide yellow (E172), hypromellose, Macrogol 400, talc

Indications

Femoston 2/10 is used as a *Hormone Replacement Therapy (HRT)* to treat symptoms of estrogen deficiency, which are experienced by women in the years following menopause. These symptoms vary from woman to woman and can include: hot flashes, night sweats, sleeping problems, vaginal dryness and urinary problems.

Femoston 2/10 is also used to prevent bone thinning *(osteoporosis)* in post-menopausal women who are at high risk for bone fractures and who are intolerant of, or contraindicated for, other medicinal products approved for the prevention of osteoporosis.

Dosage and administration

Always take Femoston 2/10 exactly as your doctor has prescribed. If you have any questions, you should ask your doctor or pharmacist.

Do not start taking Femoston until at least 12 months after your last natural period.

If you are currently not taking any HRT product or are switching from a continuous combined preparation (i.e.: both oestrogen and progesterone are taken daily in one tablet) you can start taking Femoston 2/10 on any convenient day. If you are still menstruating or have menstrual spotting, start taking Femoston 2/10 on the first day of your menstruation.

If you are switching from a 'cyclic' or 'sequential' HRT product (this is when you take an oestrogen tablet or use a patch for the first part of your cycle, followed by a daily tablet containing both an oestrogen and a progestogen for up to 14 days) start taking Femoston 2/10 the day after you finish the previous pack (i.e.: at the end of the progestogen phase).

If you are changing from a previous sequential hormone replacement therapy, your menopausal status may not be known. Also, in some women endogenous oestrogens may still be produced. This could result in unpredictable bleeding patterns, i.e. you may experience breakthrough bleeding or spotting.

The sequence in which to take your tablets is clearly indicated on the blister. Specifically, take one brick red tablet daily for the first 14 days of a 28 day cycle and one yellow tablet daily for the remaining 14 days of the cycle.

Always take Femoston 2/10 continuously without a break between packs

Femoston 2/10 can be taken with or without food; however the tablet should be swallowed with water.

Try to take your tablet at the same time each day. This will ensure that there is a constant amount of the product in your body. This will also help you to remember to take your tablets.

If you have forgotten to take a tablet it should be taken as soon as possible. If more than 12 hours have elapsed, you should take the next tablet without taking the forgotten one. Do not take a double dose. Be advised that breakthrough bleeding or spotting may occur if you miss a tablet.

Regardless of whether you are starting or continuing therapy for postmenopausal symptoms, your doctor will always prescribe the lowest possible dose for the shortest period of time (see section "Warnings and special precautions for use").

In general, your doctor will start your treatment with Femoston 1/10. Your dosage may be adjusted thereafter depending on your response to the therapy. If your (post-menopausal) symptoms are not sufficiently relieved, your doctor may increase the dosage by prescribing you Femoston 2/10.

If you are taking Femoston to prevent osteoporosis, your doctor will adjust the dose individually according to your bone mass.

Do not stop taking Femoston without first talking to your doctor.

The experience in treating women older than 65 is limited.

Femoston 2/10 is not indicated for the use in children.

Contraindications

Do not take Femoston 2/10 if:
- you are allergic (hypersensitive) to estradiol, dydrogesterone or to any of the other ingredients of Femoston (see "Excipients" above)
- you have, have had or your doctor suspects you may have breast cancer
- you have or your doctor suspects you may have a tumour that is
  - oestrogen-dependent (such as cancer of the uterine lining *(endometrial cancer)*)
  - or that is progestogen-dependent (such as *meningioma*)
- you have undiagnosed genital bleeding (i.e. unclear cause)
- you have abnormal thickening of the lining of the uterus *(endometrial hyperplasia)* for which you have not yet started treatment
- you have or have had a blood clot(s) in your leg(s) or lungs, for which no obvious cause has been found (*venous thromboembolism* i.e.: deep venous thrombosis, pulmonary embolism)
- you have or recently have had a disease caused by blood clots in the arteries *(arterial thromboembolic disease)*, such as angina or a heart attack *(myocardial infarction)*
- you have or have had a liver disease, and your liver function test values have not yet returned to normal
- you have a rare blood pigment disorder called "porphyria "which may be either passed down in families (inherited) or acquired.

Warnings and special precautions for use

For the treatment of postmenopausal symptoms, treatment with Femoston 2/10 should only be started if your symptoms seriously affect your quality of life. In all cases, your doctor will carefully consider both the risks and benefits of treatment with Femoston 2/10. Treatment should only be continued as long as the benefits outweigh the risks. Annual re-evaluations are recommended.

Medical examination and follow-up

Before you start or restart Hormone Replacement Therapy (HRT), your doctor will ask you for a complete personal and family medical history. According to the findings, your doctor will perform a full examination, possibly including a pelvic and breast examination. Your doctor will also take into account any contraindications and warnings for use that apply to you.

During treatment, you should have regular check-ups, including regular breast screenings (mammography) according to your doctor's recommendations and depending on your personal situation, but at least once a year.

Important note: Do regular self-breast examinations. If you notice any changes in your breasts tell your doctor immediately. If you are not sure how to do a self-breast examination or what changes to look for ask your doctor. For more information, see "Breast Cancer" below.

Conditions which need supervision

Your doctor will closely supervise you if you have or have had any of the following conditions, or if pregnancy or previous hormone treatment has worsened the condition. It is possible for these conditions to recur or to be aggravated during treatment with Femoston 2/10, in particular:
- aberrant growth of the lining of the uterus (uterine fibroids (*leiomyoma*)) or of uterine tissues outside the uterus *(endometriosis)*
- a history of, or risk factors for, blood clots or other disorders caused by the blockage of blood vessels *(thrombo-embolic disorders)* (see "Venous thromboembolism" below)
- an increased risk for oestrogen-dependent tumours, e.g. a direct (1st degree, such as a mother or a sister) relative with breast cancer
- high blood pressure *(hypertension)*
- liver disorders, e.g. adenoma, which is a benign tumour
- diabetes mellitus, with or without concurrent vascular complications
- gall stones *(cholelithiasis)*
- Migraine or severe headache
- an immune system disorder affecting many organs of the body *(systemic lupus erythematosus)*
- a history of abnormal thickening of the uterine lining *(endometrial hyperplasia)* (see below)
- seizures *(epilepsy)*
- asthma
- inner ear disease *(otosclerosis)*

Reasons to stop taking Femoston immediately:

Your doctor will stop your therapy with Femoston 2/10 if any of the contraindications apply to you or if he notices any of the following:
- yellowing of the skin and/or whites of your eyes (jaundice)
- worsening of liver function
- significant increase in your blood pressure
- new onset of migraine-type headache
- pregnancy

Important note: If you notice any of the above listed conditions *stop taking Femoston immediately* and talk to your doctor.

Endometrial hyperplasia

The risk of developing abnormal overgrowth of the tissues lining the uterus *(endometrial hyperplasia)* and cancer (carcinoma) is increased when oestrogens are administered alone for prolonged periods (see section "Undesirable effects"). The addition of a progestogen (separately or in a combined tablet) for at least 12 days per cycle greatly reduces this risk in women with an intact uterus *(non-hysterectomised)*.

Bleeding patterns

Unexpected bleeding (breakthrough bleeding) and spotting may occasionally occur during the first months of treatment. If you experience breakthrough bleeding or spotting after you have been on the therapy for some time, or if bleeding continues after the treatment has been stopped, inform your doctor immediately. Your doctor will investigate the cause of the bleeding and may perform tests (e.g. a uterine *(endometrial)* biopsy) to rule out uterine cancer *(endometrial malignancies)*.

Breast cancer

Several studies have been performed to investigate the possible link between treatment of women with hormones and the development of breast cancer. Results are as follows:

A randomised placebo-controlled trial, the Women's Health Initiative study (WHI), and epidemiological studies, including the Million Women Study (MWS), have reported an increased risk of breast cancer in women taking oestrogens, oestrogen-progestogen combinations or tibolone for HRT for several years (see section "Undesirable effects").

For all types of HRT, there is an increased risk of developing breast cancer after several years of continuous use. This extra risk increases the longer HRT is continued, but returns to normal levels within a few (at most five) years after stopping treatment.

The MWS reported an increased risk of developing breast cancer when a combined (oestrogen-progestogen) product was used regardless of the type of progestogen used, the method of administration (sequential or continuous) or the route of administration.

In the WHI study, the continuous combined conjugated equine oestrogen and medroxyprogesterone acetate (CEE+MPA)) product used was associated with breast cancers that were slightly larger in size and more frequently had local lymph node metastases compared to women not taking HRT.

HRT, especially oestrogen-progestogen combined products, increases the density of mammographic images which may make the detection of breast cancer more difficult.

Venous thromboembolism

HRT may increase your risk of developing blood clots in the veins of the legs or lungs (*venous thromboembolism* (VTE)).

One randomised controlled trial and epidemiological studies found the risk to be two to three times higher for women taking HRT compared to women not taking HRT. For non-users it is estimated that the number of cases of VTE that will occur over a 5 year period is about 3 per 1000 women aged 50-59 years; and 8 per 1000 women aged between 60-69 years. It is estimated that in healthy women who have used HRT for at least 5 years, the number of additional cases of VTE over a 5 year period will be between 2 and 6 (best estimate= 4) per 1000 women aged 50-59 years; and between 5 and 15 (best estimate= 9) per 1000 women aged 60-69 years. The probability of such a thromboemblism occurring is higher during the first year of HRT as opposed to later.
- In general the risk of developing VTE while on Femoston 2/10 is increased if you are severely obese (Body Mass Index > 30 kg/m^2) or if you have the immune system disorder "systemic lupus erythematosus".
- It is unclear whether varicose veins contribute to the risk of VTE. If you have varicose veins please inform your doctor before starting HRT.
- You may be predisposed to develop VTE if you, or a family member, have or have had a history of VTE or other known disease which causes blood clots. HRT may increase this risk. Your doctor will investigate any personal or strong family history of blood clot disorders *(thrombo-embolism)* or recurrent miscarriages in order to be sure you are not predisposed to VTE or, alternatively, to assess the potential risks of VTE to you. You will not be started on Femoston 2/10 until a thorough evaluation of these factors has been made or you have started taking blood thinning medicines *(anticoagulants)*. Also, if you are already taking an anticoagulant, talk to your doctor. You will only be prescribed Femoston 2/10 if the benefits of HRT far outweigh the risks of developing VTE.
- The risk of VTE may be temporarily increased if you have been immobile (e.g. bed ridden or in a wheelchair) for a prolonged period, if you have suffered a major trauma or have had a major surgery. As is always done following surgery, your doctor will do everything possible to help prevent a VTE from occurring. If you are scheduled for an elective surgery which is likely to result in prolonged immobilization, such as belly (abdominal) or leg (orthopaedic) surgery, your doctor may temporarily stop your HRT four to six weeks before the procedure. The treatment should not be restarted until you are fully recovered from the surgery and have regained your mobility.
- If you develop a VTE after starting therapy with Femoston 2/10, your doctor will stop your therapy. Furthermore, stop taking Femoston 2/10 and contact your doctor immediately if you develop any potentially thromboembolic symptoms such as: painful leg swelling, sudden chest pain, and/or difficulty breathing (dyspnea).

Coronary artery disease (CAD)

Investigative studies (randomised controlled trials) showed no benefits with the use of a specific type of HRT (continuous combined conjugated oestrogens and medroxy progesterone acetate (MPA)) to the cardiovascular (heart/vessel) system. Two large clinical trials (WHI and HERS, i.e. Heart and Oestrogen/progestin Replacement Study) showed that the risk of suffering (morbidity) from a cardiovascular disease may be higher in the first year of use and that there are no overall cardiovascular benefits. There is not enough information concerning other types of HRT to determine if these findings also extend to other HRT products (including Femoston 2/10).

Stroke

According to the Women's Health Initiative trial (WHI-trial) the risk to healthy women for ischaemic stroke (resulting from a deficiency of blood supplied to the brain) is higher when taking HRT which contains continuous combined conjugated oestrogens and MPA.

As comparison: for those women *not treated* with hormones, it is estimated that the number of cases of stroke that will occur over a 5 year period is about 3 per 1000 women aged 50-59 years; and 11 per 1000 women aged 60-69 years. In women who have been *treated* with conjugated oestrogens and MPAs for 5 years, the number of *additional* cases of stroke will be between 0 and 3 (best estimate= 1) per 1000 users aged 50-59 years and between 1 and 9 (best estimate= 4) per 1000 users aged 60-69 years. It is unknown whether the increased risk also extends to other HRT products (including Femoston 2/10).

Ovarian cancer

Long-term (at least 5-10 years) use of oestrogen-only HRT products in women whose uterus has been removed *(hysterectomised)* has been associated with an increased risk of ovarian cancer in some epidemiological studies. It is uncertain whether long-term use of combined HRT (such as Femoston 2/10) confers a different risk than oestrogen-only products.

Other conditions
- Oestrogens may cause fluid retention, so your doctor will monitor you carefully if you have any type of heart or kidney disease. Furthermore, if you have severe kidney disease *(terminal renal insufficiency)* you should be monitored closely by your doctor, since this condition can cause an increase of circulating active ingredients of Femoston 2/10 in your blood.
- If you have a high concentration of lipids in your blood *(hypertriglyceridemia)*, you should visit your doctor more frequently while on HRT (whether you take an oestogen-only or combined product). In rare cases large increases of blood lipid levels *(triglycerides)* leading to inflammation of the pancreas have been reported with oestrogen therapy in patients with this condition.
- Oestrogens may affect thyroid gland function. Talk to your doctor if you have a thyroid gland disease or problem before you start taking HRT.
  [*Information for the doctor:* Specifically, oestrogens increase thyroid binding globulin (TBG), leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 levels (by column or by radio-immunoassay) or T3 levels (by radio-immuno-assay). 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 biologically active hormone concentrations are unchanged. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-I-antitrypsin, ceruloplasmin).]
- There is no conclusive evidence that HRT improves the ability to think clearly (cognitive function). There is some evidence from the WHI trial of an increased risk of dementia in women who start using a specific type of HRT (continuous combined CEE and MPA) after the age of 65. It is unknown whether the findings apply to younger post-menopausal women or other HRT products (including Femoston 2/10).
- Do not take this medicine if you have any of the following rare hereditary problems: galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.

Femoston 2/10 is not a contraceptive and is not intended to be used by women who could become pregnant. In case of doubt, use a non-hormonal contraceptive.

Interactions with other medications

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines including medicines obtained without a prescription and herbal preparations.

Please make sure to read the leaflet of any other medicine you are taking at the same time as Femoston.

No studies have been performed to investigate the interactions between Femoston 2/10 and other medicinal products.

The following may reduce the effects of Femoston and give rise to bleeding or spotting:
- Medicines for the treatment of:
  - epilepsy (such as phenobarbital, carbamazepine and phenytoin).
  - HIV infection [AIDS] (such as ritonavir, nelfinavir)
- herbal remedies containing St John's wort (the extract of the plant called St. John's wort is included in certain herbal preparations used particularly for menopausal symptoms).

Oestrogens might slow the breakdown of other drugs which may lead to dangerously high levels of such drugs in the blood. Therefore, careful drug monitoring and possibly a dosage decrease may be necessary, particularly for the following medicines: tacrolimus, fentanyl, cyclosporin A, and theophylline.

Information for the doctor:

The efficacy of oestrogens and progestogens might be impaired:
- The metabolism of oestrogens and progestogens may be increased by concomitant use of substances known to induce drug-metabolising enzymes, specifically the P450 enzymes 2B6, 3A4, 3A5, 3A7, such as anticonvulsants (e.g. phenobarbital, carbamazepine and phenytoin) and anti-infectives (e.g. rifampicin, rifabutin, nevirapine, efavirenz).
- Ritonavir and nelfinavir, although known as strong inhibitors of CYP450 3A4, A5, A7, by contrast exhibit inducing properties when used concomitantly with steroid hormones.
- Herbal preparations containing St. John's Wort (Hypericum perforatum) may induce the metabolism of oestrogens and progestogens via the CYP450 3A4 pathway.
- Clinically, an increased metabolism of oestrogens and progestogens may lead to decreased effect and changes in the uterine bleeding profile.

Oestrogens might interfere with the metabolism of other drugs:

Oestrogens per se may inhibit CYP450 drug-metabolising enzymes via competitive inhibition. This is in particular to be considered for substrates with a narrow therapeutic index, such as
- tacrolimus and cyclosporine A (CYP450 3A4, 3A3)
- fentanyl (CYP450 3A4)
- theophylline (CYP450 1A2).

Clinically this may lead to 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, cyclosporin A, and theophylline may be necessary.

Pregnancy and lactation

Ask your doctor or pharmacist for advice before taking any medicine during pregnancy.

Important: Do not take Femoston 2/10 if you are pregnant or breast-feeding.

Femoston 2/10 is for use in post-menopausal women only. If you become (or think you are) pregnant while being treated with Femoston 2/10, stop taking the medicine immediately and tell your doctor.

The results of most epidemiological studies concerning the accidental exposure of a foetus to oestrogen/progestogen combinations show no negative effects to the developing baby (no teratogenic or foetotoxic effects).

Effects on ability to drive and use machines

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

Important information about the ingredients

Femoston 2/10 contains lactose monohydrate. If you have been told by your doctor that you have an intolerance to some sugars, especially lactose, contact your doctor before taking this medicinal product.

Undesirable effects

Like all medicines, Femoston 2/10 can cause side effects, although not everybody experiences them.

If you notice any side effects not mentioned in this leaflet, or if any of the side effects gets serious, please inform your doctor or pharmacist.

Undesirable effects reported in clinical trials and in post-marketing experience are the following:

The frequencies of study related side effects are ranked according to the following: common (frequency 1-10%), uncommon (frequency 0.1-1%), rare (frequency 0.1-0.01%), very rare (frequency <0.01%, including isolated reports).

Undesirable Effects by System Organ Class:

Infections and infestations
Uncommon: Vaginal yeast infections *(vaginal candidiasis)*

Neoplasms benign, malignant and unspecified
Uncommon: Increase in size uterine fibroids *(leiomyoma)*

Blood and lymphatic system disorders
Very rare: Illness due to the destruction of red blood cells *(haemolytic anaemia)* symptoms may include paleness of the skin, generalized weakness and/or difficulty breathing

Immune system disorders
Very rare: Allergic reactions *(hypersensitivity)*

Psychiatric disorders
Uncommon: Depression, changes in sex drive, nervousness

Nervous system disorders
Common: Migraine, headache
Uncommon: Dizziness
Very rare: Involuntary muscle twitches *(chorea)*

Eye disorders
Rare: Flexion/bending of the membrane covering the eye *(steepening of corneal curvature)*, intolerance to contact lenses

Cardiac disorders
Very rare: Heart attack *(myocardial infarction)*

Vascular disorders
Uncommon: Blood clots in the legs or lungs (venous thromboembolism (see below for further information))
Very rare: Stroke

Gastrointestinal disorders
Common: Nausea, abdominal pain, flatulence
Very rare: Vomiting

Hepatobiliary disorders
Uncommon: Gall bladder disease
Rare: Abnormal liver function, occasionally with yellowing of the skin, gums and/or inner eye membrane *(jaundice)*, weakness *(asthenia)* or general malaise, and abdominal pain

Skin and subcutaneous tissue disorders
Uncommon: Allergic skin reactions (e.g. rash, hives *(urticaria)*, itching *(pruritus)*)
Very rare: Swelling of the limbs, face or throat, which may cause difficulty breathing *(angioedema)*, red or brown patches on the skin *(erythema multiforme/nodosum)*, purplish patches or spots on the skin *(vascular purpura)*, skin discolouration, which may persist when drug is discontinued *(chloasma or melasma)*

Musculoskeletal and connective tissue disorders
Common: Leg cramps
Uncommon: Back pain

Reproductive system and breast disorders
Common: Breast pain/tenderness, non-menstrual uterine bleeding or spotting *(metrorrhagia)* and post-menopausal spotting, pelvic pain
Uncommon: Erosion of the lining of the cervix *(uterine cervical erosion)*, cervical discharge, painful menstruation *(dysmenorrhoea)*
Rare: Breast enlargement, pre-menstrual syndrome

Congenital and familial/genetic disorders
Very rare: Worsening of a rare blood pigment disorder called porphyria

General disorders and administration site reactions
Common: Muscle weakness (asthenia)
Uncommon: Swelling of the limbs *(peripheral oedema)*

Investigations
Common: Increase or decrease in weight

Breast cancer

Based on results of a large number of epidemiological studies and one randomised placebo-controlled trial, the Women's Health Initiative (WHI), the overall risk of breast cancer increases the longer a woman is on HRT. This is true, both for women currently using HRT and those having used HRT recently.

*Below, you will find detailed information concerning the risks associated with using HRT and developing breast cancer. For clarifications or further information, please consult your doctor.

For *oestrogen-only* HRT, estimates of relative risk (RR) from a reanalysis of original data from 51 epidemiological studies (in which more than 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– .40), respectively.

For *oestrogen-progestogen* combined HRT, several epidemiological studies have reported an overall higher risk for breast cancer than with oestrogens alone.

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 WHI trial reported a risk estimate of 1.24 (95% CI: 1.01–1.54) after 5.6 years of use of oestrogen-progestogen combined HRT (CEE + MPA) in all users compared with placebo.

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 1000 are expected to have breast cancer diagnosed between the ages of 50 and 64 years.
- for 1000 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-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 (CEE + MPA) per 10,000 women years.

According to calculations from the trial data, it is estimated that:
- For 1000 women in the placebo group, about 16 cases of invasive breast cancer would be diagnosed in 5 years.
- For 1000 women who used oestrogen-progestogen combined HRT (CEE + 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) (see section "Warnings and special precautions for use").

Endometrial cancer

In women with an intact uterus, the risk of developing an abnormal growth of the lining of the uterus *(endometrial hyperplasia)* and cancer of the inner lining of the uterus *(endometrial cancer)* increases the longer a woman takes unopposed oestrogens. Results of epidemiological studies show that, for women not using HRT, approximately 5 in every 1000 are expected to have endometrial cancer diagnosed between the ages of 50 and 65. Depending on the duration of treatment and oestrogen dose, the reported increased risk for endometrial cancer among unopposed oestrogen users varies from 2- to 12-fold greater compared with non-users. Adding a progestogen to oestrogen-only therapy greatly reduces this increased risk.

Venous thromboembolism, i.e. blood clots in the legs, pelvic or lungs (deep leg or pelvic venous thrombosis and pulmonary embolism), is more frequent among HRT users than among non-users. For further information, see sections "Contraindications" and "Warnings and special precautions for use".

Other adverse reactions that have been reported in association with oestrogen-progestogen treatment:
- *Tumors/neoplasms, benign, malignant and unspecified:*
  - Oestrogen-dependent neoplasms both self-limiting (benign) and invasive (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:* Possibility of developing dementia, worsening of epileptic symptoms
- Vascular disorders: blood clots in the arteries (arterial thromboembolism)
- Renal and urinary disorders: loss of bladder control (urinary incontinence)

Overdose

No case of overdose has been reported for Femoston 2/10.

Both estradiol and dydrogesterone are substances with low toxicity. If you take too many Femoston tablets, they are unlikely to do any harm. However, symptoms of overdose may include: nausea, vomiting, sleepiness and dizziness. It is unlikely that any treatment will be necessary, however if you (or someone else) take too many tablets inform your doctor immediately.

The above information is also applicable to cases of overdose in children.

Pharmacodynamics

Pharmacotherapeutic group: Genito urinary sytem and sex hormones, progestogens and oestrogens, sequential preparations.

The following is a detailed description of how the active ingredients (estradiol and dydrogesterone) of Femoston 2/10 work. For clarifications or further information please consult your doctor.

Estradiol

The active ingredient, estradiol, is chemically and biologically identical to the endogenous human estradiol and is, therefore classified as a human oestrogen. Estradiol is the primary oestrogen and the most active of the ovarian hormones. Endogenous oestrogens are involved in certain functions of the uterus and accessory organs, including the proliferation of the endometrium and the cyclic changes in the cervix and vagina.

Oestrogens are known to play an important role on bone and fat metabolism. Furthermore, oestrogens also affect the autonomic nervous system and may have indirect positive psychotropic actions.

Dydrogesterone

Dydrogesterone is an orally-active progestogen having an activity comparable to parenterally administered progesterone.

In the context of HRT, dydrogesterone produces a complete secretory endometrium in an oestrogen-primed uterus thereby providing protection for oestrogen-induced increased risk for endometrial hyperplasia and/or carcinogenesis, without androgenic side-effects.

As oestrogens promote the growth of the endometrium, unopposed oestrogens increase the risk of endometrial hyperplasia and cancer. The addition of a progestogen greatly reduces the oestrogen-induced risk of endometrial hyperplasia in non-hysterectomised women.
- Below find information on the results of clinical trials for Femoston products, for clarifications or further information please consult your doctor.

Clinical trial Information
- *Relief of oestrogen-deficiency symptoms and bleeding patterns:*
  Relief of menopausal symptoms was achieved during the first few weeks of treatment. Regular withdrawal bleeding with Femoston 2/10 occurred in approximately 90% of women with a mean duration of 5 days. Withdrawal bleeding usually started on the day of the last tablet of the progestogen phase. Breakthrough bleeding and/or spotting appeared in approximately 10% of the women. Amenorrhoea (no bleeding or spotting) occurred in 5 - 15% of the women per cycle during the first year of treatment.
  With Femoston 1/10, 75 - 80% of women had regular withdrawal bleeding. The start day and duration of bleeding, and the number of women with intermittent bleeding was the same as with Femoston 2/10, but there were more women without any bleeding per cycle (10 - 25% per cycle).
- *Prevention of osteoporosis:*
  Oestrogen deficiency at menopause is associated with an increasing bone turnover and decline in bone mass. The effect of oestrogens on the bone mineral density is dose-dependent. Protection appears to be effective for as long as treatment is continued. After discontinuation of HRT, bone mass is lost at a rate similar to that in untreated women.
  Evidence from the WHI trial and meta-analysed trials shows that current use of HRT, alone or in combination with a progestogen – given to predominantly healthy women – reduces the risk of hip, vertebral, and other osteoporotic fractures. HRT may also prevent fractures in women with low bone density and/or established osteoporosis, but the evidence for that is limited.
  After two years of treatment with Femoston 2/10, the increase in lumbar spine bone mineral density (BMD) was 6.7% ± 3.9 % (mean ± SD). For Femoston 1/10 the percentage of women who maintained or gained BMD in lumbar zone during treatment was 94.5%. For Femoston 1/10 the increase in lumbar spine BMD was 5.2%+ 3.8% (mean +SD), and the percentage of women with no change or an increase in lumbar spine BMD was 93.0%. Femoston also had an effect on hip BMD. The increase after two years of treatment with 1 mg estradiol was 2.7% ± 4.2 % (mean ± SD) at femoral neck, 3.5% ± 5.0% (mean ± SD) at trochanter and 2.7%±6.7% (mean ± SD) at Wards triangle, after two years of treatment with 2 mg estradiol these figures where respectively 2.6% ± 5.0%; 4.6% ± 5.0% and 4.1% ± 7.4%. The percentage of women who maintained or gained BMD in the 3 hip areas after treatment with 1 mg estradiol was 67-78% and 71-88% after treatment with 2 mg estradiol.

Pharmacokinetics
- The following is a detailed description of how the active ingredients (estradiol and dydrogesterone) of Femoston 2/10 are processed by your body. For clarifications or further information please consult your doctor.

Estradiol

Following oral administration, micronized estradiol is readily absorbed, but extensively metabolised. The major unconjugated and conjugated metabolites are estrone and estrone sulphate respectively. These metabolites can contribute to the oestrogen activity, either directly or after conversion to estradiol. Estrone sulphate may undergo enterohepatic circulation. In urine, the major compounds are the glucuronides of estrone and estradiol.

Oestrogens are secreted in the milk of nursing mothers.

Dydrogesterone

After oral administration of labelled dydrogesterone, on average 63% of the dose is excreted into the urine. Within 72 hours excretion is complete. In man, dydrogesterone is completely metabolised.

The main metabolite of dydrogesterone is 20 α-dihydrodydrogesterone (DHD) and is present in the urine predominantly as the glucuronic acid conjugate. A common feature of all metabolites characterized is the retention of the 4,6 diene-3-one configuration of the parent compound and the absence of 17α-hydroxylation. This explains the lack of oestrogenic and androgenic effects of dydrogesterone.

After oral administration of dydrogesterone, plasma concentrations of DHD are substantially higher as compared to the parent drug. The AUC and C_{max} ratios of DHD to dydrogesterone are in the order of 40 and 25, respectively.

Dydrogesterone is rapidly absorbed. The T_{max} values of dydrogesterone and DHD vary between 0.5 and 2.5 hours. Mean terminal half lives of dydrogesterone and DHD vary between 5 to 7 and 14 to 17 hours, respectively.

Dydrogesterone is not excreted in urine as pregnanediol, like progesterone. Analysis of endogenous progesterone production based on pregnanediol excretion therefore remains possible.

After oral administration, the T_{max} values for dydrogesterone and DHD were 1.25 hours and 1.21 hours respectively. The mean terminal half times of dydrogesterone and DHD were was 6.56 hours and 17.62 hours respectively.

Incompatibilities

Not applicable

Shelf life and storage conditions

3 years.

Do not store above 30°C.

Store in the original package.

Do not use this medicine after the expiry date stated on the carton.

Keep this medicine out of the reach and sight of children.

Pack sizes

28, 84 or 280 (10 x 28) film-coated tablets per pack (not all pack sizes may be marketed).

The blisters are made of PVC/PVDC or PVC with a covering of aluminium foil.

Further information

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

The information in this leaflet is limited. For further information, please contact your doctor or pharmacist.

Date of information
April, 2009

Manufactured by
Abbott Biologicals B.V.,
The Netherlands
for
Abbott Healthcare Products B.V.,
The Netherlands

THIS MEDICATION

is a product which affects your health and its use contrary to instructions is dangerous to you.
Strictly follow the doctor's prescription, the method of use and the instructions of the pharmacist who sold you the medication.
- The doctor and the pharmacist are the experts in medicines, their benefits and risks.
- Do not interrupt the period of treatment prescribed without talking to your doctor first.
- Do not repeat the same prescription without first consulting your doctor.
- Keep all medications out of reach of children.

Council of Arab Health Ministers,
Union of Arab Pharmacists.

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