FEMOSTON CONTI 1/5

ESTRADIOL and DYDROGESTERONE

Composition

Femoston conti 1/5 film-coated tablets contain 1 mg estradiol and 5 mg dydrogesterone per tablet

Pharmacological Properties

Pharmacodynamic Properties

The ATC code is G03FA14

Pharmacotherapeutic group: Genito urinary system and sex hormones, progestogens and estrogens, fixed combinations.

Estradiol

The active ingredient, estradiol, is chemically and biologically identical to the endogenous human estradiol and is, therefore, classified as a human estrogen. Estradiol is the primary estrogen and the most active of the ovarian hormones. The endogenous estrogens 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. Estrogens are known to play an important role for bone and fat metabolism. Futhermore, estrogens also affect the autonomic nervous system and may have indirect positive psychotropic actions.

Dydrogesteone

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 estrogenprimed uterus thereby providing protection for estrogen-induced increased risk for endometrial hyperplasia and/or carcinogenesis, without androgenic side-effects. As estrogens promote the growth of the endometrium, unopposed estrogens increase the risk of endometrial hyperplasia and cancer. The addition of a progestogen greatly reduces the estrogen-induced risk of endometrial hyperplasia in non-hysterectomised women.

Clinical trial Information

- Relief of estrogen-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 pill of the progestogen phase. Break-through bleeding and/or spotting appeared in approx. 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 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

- Estrogen deficiency at menopause is associated with an increasing bone turnover and decline in bone mass. The effect of estrogens on the mineral density is dose-dependent. Protection appears to be effective for as long as treatment is continued. After discontinuation of HRT, bone mass is loast at a rate similar to that in untreated women.

- Evidence from WHI trail and meta-analyzed trail shows that current use of HRT, alone or in combination with a progestegen - given to predominantly healthy women - reduces the risk of hip, vertebra, and other osteoporotic fractures. HRT may also prevent fractures in women with low bone density and/or established osteoporosis, but the evidence for that is limited.

- After two years of treatment with Femoston 2/10, the increase in lumbar spine bone mineral density (BMD) was 6.7% ± 3.9% (mean ± SD). The Femoston 1/10 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 precentage 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.

Pharmacokinetic properties

Estradiol
Following oral administration, micronized estradiol is readily absorbed, but extensively metabolised. The major unconjugated and conjugated metabolites are estrone and estrone sulphate. There metabolites can contribute to the estrogen activity, either directly or after conversion to estradiol. Estrone sulphate may undergo enterohepatic circulation. In urine, the major compouds are glucurnides of estrone and estradiol.
Estrogens are secreted in the milk of nursing mothers.

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

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

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

Preclinical safety data

Supraphysiologically high doses (prolonged overdoses) of estradiol have been associated with the iducation of tumours in estrogen-dependent target organs for all rodent species tested. Pronounced species diffrences in toxicology, pharmacology and pharmacodynamics exist. The effects of progesterone-like compounds**.**
Doses administered to and mice sufficient to produce hormone mediated changes gave no evidence of carcinogenesis.

Indications

- Hormone replacement therapy (HRT) for relief of symptoms due to estrogen deficiency in women with uterus. Femoston conti 1/5 should be used only in postmenopausal women more than 12 months after menopause.
- Prevention of postmenopausal osteoporosis in women with uterus at high risk of future fractures

The experience of treatment of women older than 65 years is limited.

Posology and method of a administration
Femoston conti 1/5 is not recommended for use in the children below age 18 due to insufficient data on safety and efficacy.

The dosage is one table per day. femoston conti 1/5 should be taken continuously without a break between packs.

For initiation and continuation of tratment of postmenopausal symptoms, the lowest effective dose for the shortes duration (see also section Special warnings and precautions for use) should be used.

<u>Osteoporosis prevention</u>
Hormone replacement therapy for the prevention of postmenopausal osteoporosis must take into account the expected effects on bone mass, which are dose-related (see section Pharmacodynamic properties) and the individual tolerability of treatment.

Contraindications

Hypersensitivity to the active substances or to any of the excipients.
Known past or suspected breast cancer
Known or suspected estrogen-dependent malignant tumours (e.g. endometrial cancer)
Known or suspected progesterone dapendant neoplasms
Undiagnosed genital bleeding
Untreated edometrial hyperplasia

Previous idiopathic or current venous thromboembolism (deep venous thrombosis, pulmonary embolism)

Active or recent arterial thromboembolic disease (e.g. angina, myocardial infarction)

Acute liver disease, or a history of liver disease, as long as the liver function tests have failed to return to normal

Porphyria

Only when indication are <u>not</u> restricted to postmenopausal women:

^Known or suspected pregnancy.

Special warnings and special precautions for use

For the treatment of postmenopausal symptoms, HRT should only be initiated for symptoms that adversely affect quality of life. In all cases, a careful appraisal of the risks and benefits should be undertaken at least annually and HRT should only be continued as long as the benefit outweighs the risk.

<u>Medical examination/follow-up</u>

Before initiating or re-instituting HRT, a complete personal or family medical history should be taken. Physical (including pelvic and breast) examination should be guided by this and by the contraindication and warnings for use. During treatment, periodic check-ups are recommended of a frequency and nature adapted to the individual women. Women should be advised what changes in their breasts should be reported to their doctor or nurse. Investigations, including mammography, should be carried out in accordance with currenty accepted screeening practices, modified to the clinical needs of the individual.

<u>Conditions which need supervision</u>

If any of the following conditions are present, have occurred previously, and/or have been aggraved during pregnancy or previous hormone treatment, the patient should be closely supervised. It should be taken into account that these conditions may recur or be aggravated during treatment with Femoston conti 1/5 in particular:

- Leiomyoma (uterine fibroids) or endometriosis
- A history of, risk factors for, thromboembolic disorders (see below)
- Risk factors for estrogen dependent tumour, e.g. 1st degree heredity for breast cancer
- Hypertension
- Liver disorders (e.g. liver adenoma)
- Diabetes mellitus with or vascular involvement
- Cholelithiasis
- Migraine or (severe) headache
- Systemic lupus erythematosus

- A history of endometrial hyperplasia (see below)
- Epilepsy
- Asthma
- Otosclerosis

Reasons for immediate withdrawal of therapy:
Therapy should be discontinued in case a contraindication is discovered and in the following situations:

- Jaudice or deterioration in liver function
- Significant increase in blood pressure
- New onset or migraine-type headache
- Prenancy

Endometrial hyperplasia
The risk of endometrial hyperplasia and carcinoma is increased when estrogen are administered alone for prolonged periods (see section Undesirable effects). The addition of a progestagen for at least 12 days per cycle in non-hyterectomised women greatly reduces this risk.

Bleeding patterns
Breakthrough bleeding and spotting may occasionally occur during the first months of treatment. If break-through bleeding or spotting appears after some time on therapy, or continues after treatment has been discontinued, the reason should be investigated, which may include endometrial biopsy to exclude endometrial malignancy.

Breast cancer
A randomized 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 estrogens, estrogen-progestagen combinations or tibolone for HRT for several years (see section undesirable effects). For all HRT, an excess risk becomes apparent within a few years of use and increases with duration of intake but returns to baseline within a few (at most five) years after stopping treatment.

In the MWS, the relative risk of breast cancer with conjugated equine estrogens (CEE) or estradiol (E2) was greater when a progestagen was added, either sequentially or continuously, and regerdless of type of progestagen. There was no evidence of a different risk between the different routes of administration.

In the WHI study, the continuous combined conjugated equine estrogen 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 placebo.

HRT, especially estrogen-progestagen combined treatment, increases the density of mammographic images which may adversely affect the rediological detection of breast cancer.

Venous thromboembolism

HRT is associated with a higher relative risk of developing venous thromboembolism (VTE), i.e. deep vein thrombosis or pulmonary embolism. One randomized controlled trial and epidemiological studies found a two-to threefold higher risk for users compared with non-users. 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 100 women aged 50-59 years and 8 per 1000 women aged between 60-69 years. It is estimated that in healthy women who use HRT for 5 year, the number of additional cases of VTE over a 5 years 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 occurrence of such an event is more likely in the first year of HRT than later.

- Generally recognized risk factors for VTE include a personal history or family history, severe obesity (Body Mass Index > 30 kg/m^2) and systemic lupus erythematosus (SLE). There is no consensus about the possible role of varicose veins in VTE.
- Patients with a history of VTE or known thrombophilic states have an increased risk of VTE. HRT may add to this risk. Personal or strong family history of thromboembolism or recurrent spontaneous abortion should be investigated in order to exclude a thrombophilic predisposition. Until a thorough evaluation of thrombophilic factors has been made or anticoagulant treatment initiated, use of HRT in such patients should be viewed as contraindicated. Those women already on anticoagulant treatment require careful consideration of the benefit-risk of use of HRT.
- The risk of VTE may be temporarily increased with prolonged immobilization, major trauma or major surgery. As in all post-operative patients, scrupulous attention should be given to prophylactic measures to prevent VTE following surgery. Where prolonged immobilization is liable to follow elective surgery, particularly abdominal or orthopaedic surgery to the lower limbs, consideration should be given to temporarily stopping HRT four to six weeks earlier, if possible. Treatment should not be restarted until the woman is completely mobilised.
- If venous thromboembolism develops after initiating therapy, the drug should be discontinued. Patients should be told to contact their doctors immediately when they are aware of a potential thromboembolic symptom (e.g. painfull swelling of a leg, sudden pain in the chest, dyspnea).

Coronary artery disease (CAD)

There is no evidence from randomized controlled trials of cardiovascular benefit with continuous combined conjugated estrogens and medroxyprogesterone acetate (MPA). Two large clinical trials (WHI and HERS, i.e. Heart and Estrogen/progestin Replacement Study) showed a possible increased risk of cardiovascular morbidity in the first year of use and no overall benefit. For other HRT products there are only limited data from randomised controlled trials examining effects in cardiovascular morbidity or mortality. Therefore, it is uncertain whether these findings also extend to other HRT products.

Stroke

One large randomized clinical trial (WHI-trial) found, as a secondary outcome, an increased risk of ischaemic stroke in healthy women during treatment with continuous combined conjugated estrogens and MPA. For women who do not use HRT, 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. It is estimated that for women who use conjugated estrogens and MPA for 5 years, the number of additional cases will be between 0 and 3 (best estimate = 1) per 1000 years 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.

Ovarian cancer

Long-term (at least 5-10 years) use of estrogen-only HRT products in hysterectomised women has been associated with an increased risk of ovarian cancer in some epidemiological studies.

It is uncertain whether long-term use of combined HRT confers a different risk than estrogen-only products.

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 conti 1/5 is increased.
- Women with pre-existing hypertriglyceridemia should be followed closely during estrogen replacement or hormone replacement therapy, since rare cases of large increases of plasma triglycerides leading to pancreatitis have been reported with estrogen therapy in this condition.
- Estrogens 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 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 protein may be increased (angiotensin/renin substrate, alpha-l-antitrypsin, ceruloplasmin).
- There is no conclusive evidence for improvement of cognitive function. There is some evidence from the WHI trial of increased risk of probable dementia in women who start using 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.
- Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Only when indications are not restricted to postmenopausal women:

- This estrogen-progestogen combination treatment is not contraceptive. Patients in the perimenopausal phase should be advised to take non hormonal contraceptive precautions.

Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

The metabolism of estrogens may be increased by concomitant use of substances known to induce drug-metabolizing enzymes, specifically p450 enzymes, such as anticonvulsants (e.g. Phenobarbital, carbamazepine, phenytoin) and anti-infectives (e.g. rifampicin, rifabutin, nevirapine, efavirenz).

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

Herbal preparations containing St. John's Wort *{Hypericum perforatum)* may induce the metabolism of estrogens and progestagens.

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

Femoston conti 1/5 can be administered irrespective of food intake.

Pregnancy and lactation

Femoston conti 1/5 is not indicated during pregnancy. If pregnancy occurs during medication with Femoston conti 1/5 treatment should be withdrawn immediately.

Clinically, data on a large number of exposed pregnancies indicate no adverse effects of dydrogesterone on the fetus.

The results of most epidemiological studies to date relevant to inadvertent fetal exposure to combinations of estrogens with other progestagens indicate no teratogenic or fetotoxic effect.

Femoston conti 1/5 is not indicated during lactation.

Effects on ability to drive and use machines
Femoston conti 1/5 has no or negligible influence on the ability to drive or use machines.

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

MedDRA system organ class	**Common >1/100, <1/10**	**Uncommon >1/1,000, <1/100**	**Rare >1/10,000, <1/1,000**	**Very rare <1/10,000 incl isolated reports**
Infections and infestations		Vaginal candidiasis		
Neoplasms benign, malignant and unspecified		Increase in size of leiomyoma		
Blood and the lymphatic system disorders				Haemolytic anaemia
Immune system disorders				Hypersensitivity reactions
Psychiatric disorders		Depression, change in libido, nervousness		
Nervous system disorders	Headache, migraine	Dizziness		Chorea
Eye disorders			Intolerance to contact lenses, steepening of corneal curvature	
Cardiac disorders				Myocardial infarction
Vascular disorders		Venous thromboembolism*		Stroke
Gastrointestinal disorders	Nausea, abdominal **pain,** flatulence			Vomiting

Hepatobiliary disorders		Gall bladder disease	Alterations in liver function, sometimes with asthenia or malaise, jaundice and abdominal pain	
Skin and subcutaneous tissue disorders		Allergic skin reactions, rash, urticaria, pruritus		Chloasma or melasma, which may persist when drug is discontinued, erythema multiforme, erythema nodosum, vascular purpura, angioedema
Musculoskeletal and connective tissue disorders	Leg cramps	Back pain		
Reproductive system and breast disorders	Breast pain/tenderness, breakthrough bleeding and spotting, pelvic pain	Change in cervical erosion, change in cervical secretion, dysmenorrhoea	Breast enlargement, premenstrual -like syndrome	
Congenital and familial/genetic disorders				Aggravation of porphyria
General disorders and administration site reaction	Asthenia	Peripheral oedema		
Investigations	Increase/decrease in weight			

*See below for further information

Breast cancer

According to the evidence from a large number of epidemiological studies and one randomized placebo-controlled trial, the women's Health Initiative (WHI), the overall risk of breast cancer increases with increasing duration of HRT use in current or recent HRT users.

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

For *estrogen plus progestagen* combined HRT, several epidemiological studies have reported

an overall higher risk for breast cancer than with estrogens alone.

The MWS reported that, compared to never users, the use of various types of estrogen-progestagen combined HRT was associated with a higher risk of breast cancer (RR = 2.00, 95% CI 1.88-2.12) than use of estrogens 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 estrogen-progestagen 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 estrogen-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 estrogen plus progestagen* 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 *estrogen-progestagen 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 estrogen + progestagen 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 Special warnings and special precautions for use).

<u>Other adverse reactions have been reported in association with estrogen/progestagen treatment:</u>

- Oestrogen dependent neoplasms both benign and malignant, e.g. endometrial cancer , ovarian cancer.
- Venous thromboembolism, i.e. deep leg or pelvic venous thrombosis and pulmonary embolism, is more frequent among hormone replacement therapy users than among non-users. For further information, see section 4.3 Contraindications and 4.4 Special warnings and Precautions for use.
- Arterial thromboembolism, for further information see sections Contraindications and Special warnings and precautions for use.
- Increase in size of progestogen dependent neoplasms (e.g. meningioma), (see section Contraindications).
- Probable dementia (see section Special warnings and special precautions for use).

<u>**Endometrial cancer</u> In women with an intact uterus, the risk of endometrial hyperplasia and endometrial cancer increases with increasing duration of use of unopposed estrogens. According to data from epidemiological studies, the best estimate of the risk is that for women

not using HRT, about 5 in every 1000 are expected to have endometrial cancer diagnosed between the ages of 50 and 65. Depending in the duration of treatment and estrogen dose, the reported increase in endometrial cancer risk among unopposed estrogen users varies from 2- to 12- fold greater compared with non-users. Adding a progestagen to estrogen-only therapy greatly reduces this increased risk.

Overdose
No case of overdose has been reported for Femoston conti 1/5.
Both estradiol and dydrogesterone are substances with low toxicity. Theoretically, symptoms such as nausea, vomiting, sleepiness and dizziness could occur in cases of overdosing. It is unlikely that any specific symptomatic treatment will be necessary. Aforementioned information is applicable for overdosing by children also.

Pharmaceutical particulars
Tablet core: Lactose monohydrate, hypromellose, maize starch, colloidal anhydrous silica, magnesium stearate

Film coating: Salmon-colored tablet (1 mg estradiol and 5 mg dydrogesterone): Opadry OY-8734 (titanium dioxide (EI71), iron oxide yellow (EI72), iron oxide red (EI72), hypromellose, Macrogol 400).

Incompatibilites

Not applicable

Storage
Store below 30°C. Shelf life 3 years.

Packaging
Box of 1 blister @ 28 tablet. Reg No.: DKI1181601417A1

ON MEDICAL PRESCRIPTION ONLY
HARUS DENGAN RESEP DOKTER

Manufactured by Abbott Biologicals, B.V., The Netherlands
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