SCHEDULING STATUS: S4

PROPRIETARY NAME (AND DOSAGE FORM)

FEMOSTON® - CONTI Tablets

COMPOSITION

Each film-coated tablet contains oestradiol hemihydrate equivalent to 1 mg oestradiol, and 5 mg of dydrogesterone.

List of excipients:

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

Film-Coating (salmon-coloured colouring agent): Titanium dioxide (E171), iron oxide yellow (E172), iron oxide red (E172), hypromellose, Macrogol 400.

Contains sugar (Lactose monohydrate)

PHARMACOLOGICAL CLASSIFICATION

A. 21.8.2 Progesterones with or without oestrogens.

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

Oestradiol

The active component oestradiol is chemically and biologically identical to the natural human sex hormone oestradiol.

Oestradiol is the primary oestrogen and the most active of the ovarian hormones. Oestrogens affect the release of gonadotrophins by the pituitary gland, contributing to the occurrence of the ovarian cycle. Oestrogens cause cyclical changes in the uterus, cervix and vagina and ensure the retention of tone and elasticity in the urogenital tract. Oestradiol plays an important part in maintaining bone mass, and has a preventive effect on the incidence of osteoporotic fractures. Oral administration of oestrogens has a beneficial effect on the metabolism of lipids and lipoproteins.

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. Dydrogesterone has no androgenic side-effects. In the context of continuous combined hormone replacement therapy (HRT), dydrogesterone produces an atrophic endometrium thereby providing protection against oestrogen-induced increased risk of endometrial hyperplasia and/or carcinoma.

The beneficial effects of oestradiol on bone, lipoprotein, glucose and insulin metabolism are maintained in the presence of dydrogesterone.

Pharmacokinetic properties

Oestradiol

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

Oestrogens are secreted in the milk of breast feeding 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 humans, 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 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 oestrogenic and androgenic effects of dydrogesterone.

After oral administration of dydrogesterone, plasma concentrations of DHD are substantially higher as compared to the parent medicine. 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, as progesterone is. Analysis of endogenous progesterone production based on pregnanediol excretion therefore remains possible.

No clinically relevant interactions occur between oestradiol and dydrogesterone.

INDICATIONS

1. Femoston-conti is indicated as hormone replacement therapy (HRT) for the relief of menopausal symptoms in women with a uterus. Femoston-conti should normally be used only in women more than 12 months post-menopause.
2. Reduction of the risk of osteoporosis in post-menopausal women with an intact uterus.

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

CONTRAINDICATIONS

Hypersensitivity to one of the components of Femoston tablets.

Diagnosed or suspected cancer of the breast, endometrium carcinoma or other hormone-sensitive tumours.

Known or suspected progestogen dependent neoplasms, e.g. meningioma.

Acute or chronic liver disease, and a history of liver disease where liver function tests have failed to return to normal.

Rotor syndrome or Dubin-Johnson syndrome.

Porphyria.

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

Active or recent thrombo-embolic disorders (e.g. angina, myocardial infarction).

Known, or suspected pregnancy.

Vaginal bleeding, of which the cause has not been diagnosed.

Severe renal disease.

Untreated endometrial hyperplasia.

Cerebrovascular accident.

Severe cardiac disease.

WARNINGS

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take Femoston Conti. (see SPECIAL PRECAUTIONS)

INTERACTIONS

No interaction studies have been performed with Femoston-conti.

The metabolism of oestrogens in Femoston-conti may be increased by concomitant use of substances known to induce drug-metabolising enzymes, specifically P450 enzymes, such as anticonvulsants (e.g. phenobarbital, carbamazepine, phenytoin) and anti-infectives (e.g. rifampicin, rifabutin, nevirapine, efavirenz).

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 oestrogens and progestogens in Femoston-conti.

Changes in oestrogen serum concentrations may affect the results of certain endocrine or liver function tests.

Clinically an increase in metabolism of oestrogens and progestogens may lead to decrease in effect and changes in the uterine bleeding profile.

Femoston Conti can be taken with or without food.

PREGNANCY AND LACTATION

Known, or suspected pregnancy is a contraindication. If pregnancy occurs during medication with Femoston Conti treatment should be stopped immediately – see CONTRAINDICATIONS.

Lactation: Femoston Conti is contraindicated during lactation.

DOSAGE AND DIRECTIONS FOR USE

Adults: The dosage is one tablet per day. Femoston Conti should be taken continuously without a break between packs.

Starting Femoston Conti:

Women experiencing a natural menopause should commence treatment with Femoston Conti 12 months after their last natural menstrual bleed. For surgically induced menopause, treatment may start immediately. Femoston Conti is intended to prevent stimulation of the endometrium in postmenopausal women, usually resulting in amenorrhoea.

Before therapy commences it is recommended that the patient is fully informed of all likely benefits and potential risks. She should have a full physical and gynaecological examination with special emphasis on blood pressure, breasts, abdomen and pelvic organs and an endometrial assessment carried out if indicated. Follow-up examinations are recommended every 6-12 months.

Reduction of risk of osteoporosis:

Risk reduction appears to be effective for as long as treatment continues, however data on oestrogen therapy beyond 10 years are limited. A careful reappraisal of the risk-benefit ratio should be undertaken before treating for longer than 5 – 10 years. For long term use, see also SPECIAL PRECAUTIONS.

Changing from sequential HRT:

Patients changing from sequential HRT preparations to Femoston Conti should do so at the end of the oestrogen plus progestogen phase of the sequential therapy, without a tablet-free interval.

Femoston-conti should normally be used only in women more than 12 months post-menopause. If the menopausal status is not known (e.g. because of previous use of sequential HRT or oral combination contraceptives) the endogenous oestrogen may still be high. This could result in unpredictable bleeding patterns, especially in the first few cycles.

Children: Femoston Conti should not be used in children below age 18 due to insufficient data on safety and efficacy.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS

Side-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		

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**
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

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**
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	

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**
Skin and subcutaneous tissue disorders		Allergic skin reactions, rash, urticaria, pruritus		Chloasma or melasma, which may persist when Femoston Conti 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	

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**
Congenital and familial/genetic disorders				Aggravation of porphyria
General disorders and administration site reactions	Asthenia	Peripheral oedema		
Investigations	Increase/ decrease in weight			

Breast cancer:

According to evidence from 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 with increasing duration of HRT use in current or recent HRT users.

For *oestrogen-only* HRT, estimates of relative risk (RR) from a reanalysis of original data from 51 epidemiological studies (in which > 80 % of HRT use was oestrogen-only HRT) and from the epidemiological Million Women Study (MWS) are similar at 1,35 (95 % CI: 1,21-1,49) and 1,30 (95 % CI: 1,21-1,40), respectively.

For *oestrogen plus 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 (conjugated equine oestrogens (CEE) + methyl progesterone acetate (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 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 *oestrogen-progestogen combined* HRT (conjugated equine oestrogens (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 (conjugated equine oestrogens (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).

Endometrial cancer:

In women with an intact uterus, the risk of endometrial hyperplasia and endometrial cancer increases with increasing duration of use of unopposed oestrogens. 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 on the duration of treatment and oestrogen dose, the reported increase in endometrial cancer risk 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.

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

- 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.
- Arterial thromboembolism.
- Increase in size of progestogen dependent neoplasms (e.g. meningioma).

Special precautions:

For the treatment of postmenopausal symptoms, Femoston-conti 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 Femoston Conti should only be continued as long as the benefit outweighs the risk.

Medical examination/follow-up:

Before initiating or re-instituting Femoston Conti, a complete personal or family medical history should be taken. Physical (including pelvic and breast) examination should be guided by this and by the contraindications and warnings for use.

During treatment, periodic check-ups are recommended of a frequency and nature adapted to the individual woman. Women should be advised what changes in their breasts should be reported to their doctor or nurse. Investigations, including mammography, should be carried out in accordance with currently accepted screening practices, modified to the clinical needs of the individual.

Conditions which need supervision:

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

- Leiomyoma (uterine fibroids) or endometriosis
- A history of, or risk factors for, thromboembolic disorders (see below)
- Risk factors for oestrogen dependent tumours, e.g. first degree heredity for breast cancer
- Hypertension
- Liver disorders (e.g. liver adenoma)

- Diabetes mellitus with or without vascular involvement
- Cholelithiasis
- Migraine or (severe) headache
- Systemic lupus erythematosus.
- A history of endometrial hyperplasia (see below)
- Epilepsy
- Asthma
- Otosclerosis

Reasons for immediate withdrawal of therapy:

Therapy should be discontinued in 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
- Pregnancy

Endometrial hyperplasia:

The risk of endometrial hyperplasia and carcinoma is increased when oestrogens are administered alone for prolonged periods. The addition of a progestogen for at least 12 days per cycle in non-hysterectomised women greatly reduces this risk.

Bleeding patterns:

Break-through bleeding and spotting may occur during the first months of treatment. If break-through bleeding or spotting appears after some time on therapy, or continues after treatment has

been discontinued, the reason should be investigated, which may include endometrial biopsy to exclude endometrial malignancy**.**

Breast cancer:

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 diagnosed in women taking oestrogens, oestrogen-progestogen combinations or tibolone for HRT for several years.

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 oestrogens (conjugated equine oestrogens (CEE)) or estradiol (E2) was greater when a progestogen was added, either sequentially or continuously, and regardless of type of progestogen. There was no evidence of a difference in risk between the different routes of administration.

In the WHI study, the continuous combined conjugated equine oestrogen and medroxyprogesterone acetate (conjugated equine oestrogens (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 oestrogen-progestogen combined treatment, increases the density of mammographic images which may adversely affect the radiological 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 randomised 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 1000 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 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 occurrence of such an event is more likely in the first year of HRT than later.

- Generally recognised 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 immobilisation, 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 immobilisation 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. painful swelling of a leg, sudden pain in the chest, dyspnoea).

Coronary artery disease (CAD):

There is no evidence from randomised controlled trials of cardiovascular benefit with continuous combined conjugated oestrogens and MPA. Two large clinical trials (WHI and HERS i.e. Heart and Oestrogen/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 randomised clinical trial (WHI-trial) found, as a secondary outcome, an increased risk of ischaemic stroke in healthy women during treatment with continuous combined conjugated oestrogens 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 oestrogens and MPA for 5 years, the number of additional cases 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.

Ovarian cancer:

Long-term (at least 5-10 years) use of oestrogen-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 oestrogen-only products.

Other conditions:

- Oestrogens may cause fluid retention, and therefore patients with cardiac or renal dysfunction should be carefully observed. Patients with terminal renal insufficiency should be closely observed, since it is expected that the level of circulating active ingredients in Femoston Conti is increased.
- Women with pre-existing hypertriglyceridemia should be followed closely during oestrogen replacement or hormone replacement therapy, since rare cases of large increases of plasma triglycerides leading to pancreatitis have been reported with oestrogen therapy in this condition.
- Oestrogens increase thyroid binding globulin (TBG), leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 levels (by column or by radio-immunoassay) or T3 levels (by radio-immunoassay). T3 resin uptake is decreased, reflecting the elevated TBG. Free T4 and free T3 concentrations are unaltered. Other binding proteins may be elevated in serum, i.e. corticoid binding globulin (CBG), sex-hormone-binding globulin (SHBG) leading to increased circulating corticosteroids and sex steroids, respectively. Free or biological active hormone concentrations are unchanged. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-I-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 conjugated equine oestrogens (CEE) and MPA after the age of 65. It is unknown whether the findings apply to younger post-menopausal women or other HRT products.
- Probable dementia.

Only when indications are not restricted to postmenopausal women:

- This oestrogen-progestogen combination treatment (Femoston Conti) is not a contraceptive. Patients in the peri-menopausal phase should be advised to take non hormonal contraceptive precautions.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take Femoston Conti. (see WARNINGS)

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

No case of overdose has been reported for Femoston conti.

Adults and children: Both oestradiol and dydrogesterone are substances with low toxicity. Theoretically, symptoms such as nausea, vomiting, sleepiness and dizziness could occur in cases of overdosing. If overdosage is discovered within two or three hours and is so large that treatment seems desirable, gastric lavage can safely be used. There is no specific antidote and further treatment should be symptomatic.

IDENTIFICATION

A round, biconvex, salmon film-coated tablet with inscription ‘379’ on one side.

PRESENTATION

28 or 84 tablets in PVC/Aluminium blister strips.

STORAGE INSTRUCTIONS

Store below 25°C, keeping blister strips in outer carton.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

36/21.8.2/0330

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Abbott Laboratories S.A. (Pty) Ltd

Abbott Place, 219 Golf Club Terrace

Abbott Laboratories S.A. (Pty) Ltd
Femoston-Conti
Estradiol 1,0 mg & Dydrogesterone 5,0 mg per Tablet

Constantia Kloof,

1709

South Africa

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