

Public Assessment Report
Decentralised Procedure

**Femoston-conti 0.5mg/2.5mg, Film-coated
Tablets**

Estradiol hemihydrate/Dydrogesterone

UK/H/0369/02/DC

UK licence no: PL 00512/0397

Applicant: Solvay Healthcare Ltd

LAY SUMMARY

On 28th May 2010, the MHRA granted Solvay Healthcare Ltd a Marketing Authorisation (licence) for the medicinal product Femoston-conti 0.5mg/2.5mg Film-coated Tablets. This medicine is only available on prescription from your doctor.

Femoston-conti 0.5mg/2.5mg is a continuous combined Hormone Replacement Therapy (HRT) which is taken each day without interruption. This product is suitable for postmenopausal women who have not had their periods for more than a year.

Femoston-conti 0.5mg/2.5mg contains the active ingredients estradiol and dydrogesterone. The body's natural oestrogen is also called estradiol. Estradiol replaces the body's natural oestrogen, thereby controlling menopausal symptoms. Women who still have a womb should normally take some form of progesterone (a progestogen), because oestrogen alone can cause problems due to a build up of the womb lining and can also cause cancer of the womb lining. Taking dydrogesterone helps to prevent a build up of the womb lining and cancer of the womb lining.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Femoston-conti 0.5mg/2.5mg Film-coated Tablets outweigh the risks, hence, a Marketing Authorisation has been granted.

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Module 1

Product Name	Femoston-conti 0.5/2.5 Film-coated Tablets
Type of Application	Article 8.3 Known active substance
Active Substance	Estradiol hemihydrate & Dydrogesterone
Form	Film-coated Tablets
Strength	0.5/2.5mg
MA Holder	Solvay Healthcare Ltd., Mansbridge road, West End, Southampton, SO18 3JD, United Kingdom
RMS	UK
CMS	AT, BE, CZ, DE, EE, EL, FI, FR, HU, IE, IT, LT, LU, LV, MT, NL, PL, PT, RO and SK
Procedure Number	UK/H/0369/02/DC
Timetable	Day 210 – 2 nd May 2010

Module 2

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Femoston-conti 0.5mg/2.5mg, film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 0.5 mg estradiol (as hemihydrate) and 2.5 mg dydrogesterone.

Excipient(s): Lactose

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

A round, biconvex, yellow film-coated tablet with the inscription 379 on one side and S on the other Side

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Hormone replacement therapy (HRT) for oestrogen deficiency symptoms in postmenopausal women.

Femoston-conti 0.5mg/2.5mg should be used only in women more than 12 months postmenopause.

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

4.2 Posology and method of administration

There is no relevant use of Femoston-conti 0.5mg/2.5mg in the children and adolescents.

Femoston-conti 0.5mg/2.5mg is a continuous combined HRT for oral use.

The dosage is one tablet per day. Femoston-conti 0.5mg/2.5mg should be taken continuously without a break between packs.

Femoston-conti 0.5mg/2.5mg can be taken with or without food.

Starting Femoston-conti 0.5mg/2.5mg:

Women experiencing a natural menopause should commence treatment with Femoston-conti 0.5mg/2.5mg not earlier than at least 12 months after their last natural menstrual bleed. For surgically induced menopause, treatment may start immediately.

In women who are not taking hormone replacement therapy or women, who switch from a continuous combined hormone replacement therapy, treatment may be started on any convenient day. In women transferring from a cyclic or continuous sequential HRT regimen, treatment should begin the day following completion of the prior regimen.

If a dose has been forgotten, it should be taken as soon as possible. When more than 12 hours have elapsed, it is recommended to continue with the next dose without taking the forgotten tablet. The likelihood of breakthrough bleeding or spotting may be increased.

For initiation and continuation of treatment of postmenopausal symptoms, the lowest effective dose for the shortest duration (see also section 4.4) should be used.

4.3 Contraindications

- Known hypersensitivity to the active substances or to any of the excipients.
- Known, past or suspected breast cancer
- Known or suspected oestrogen-dependent malignant tumours (e.g. endometrial cancer)
- Known or suspected progestogen dependent neoplasms
- Undiagnosed genital bleeding
- Untreated endometrial hyperplasia
- Previous or current venous thromboembolism (deep venous thrombosis, pulmonary embolism)
- Known thrombophilic disorders (e.g. protein C, protein S, or antithrombin deficiency, see section 4.4)
- 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

4.4 Special warnings and 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.

Evidence regarding the risks associated with HRT in the treatment of premature menopause is limited. Due to the low level of absolute risk in younger women, however, the balance of benefits and risks for these women may be more favourable than in older women:

Medical examination/follow-up

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 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 (see 'Breast cancer' below).. Investigations, including appropriate imaging tools, e.g. 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, in particular:

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

Reasons for immediate withdrawal of therapy:

Therapy should be discontinued in case a contra-indication 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 and carcinoma

- In women with an intact uterus the risk of endometrial hyperplasia and carcinoma is increased when oestrogens are administered alone for prolonged periods. The reported increase in endometrial cancer risk among oestrogen-only users varies from 2- to 12- fold greater compared with non-users, depending on the duration of treatment and oestrogen dose (see section 4.8). After stopping treatment risk may remain elevated for at least 10 years.
- The addition of a progestogen cyclically for at least 12 days per month/28 day cycle or continuous combined oestrogen-progestogen therapy in non-hysterectomised women prevents the excess risk associated with oestrogen-only HRT.
- Breakthrough bleeding and spotting may occur during the first months of treatment. If breakthrough bleeding or spotting appears after some time on therapy, or continues after treatment has been discontinued, the reason should be investigated, which may include endometrial biopsy to exclude endometrial malignancy.

Breast cancer

The overall evidence suggests an increased risk of breast cancer in women taking combined oestrogen-progestogen and possibly also oestrogen-only HRT, that is dependent on the duration of taking HRT.

Combined oestrogen-progestogen therapy

- The randomised placebo-controlled trial the (Women's Health Initiative study (WHI), and epidemiological studies are consistent in finding an increased risk of breast cancer in women taking combined oestrogen-progestogen for HRT that becomes apparent after about 3 years (see Section 4.8).

Oestrogen-only therapy

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

The excess risk becomes apparent within a few years of use but returns to baseline within a few (at most five) years after stopping treatment.

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

Ovarian cancer

Ovarian cancer is much rarer than breast cancer. Long-term (at least 5-10 years) use of oestrogen-only HRT products has been associated with a slightly increased risk of ovarian cancer (see Section 4.8). Some studies, including the WHI trial suggest that the long-term use of combined HRT may confer a similar, or slightly smaller, risk (see Section 4.8).

Venous thromboembolism

- HRT is associated with a 1.3-3 fold risk of developing venous thromboembolism (VTE), i.e. deep vein thrombosis or pulmonary embolism. The occurrence of such an event is more likely in the first year of HRT than later (see Section 4.8).
- Patients with known thrombophilic states have an increased risk of VTE and HRT may add to this risk. HRT is therefore contraindicated in these patients (see Section 4.3).
- Generally recognised risk factors for VTE include, use of oestrogens, older age, major surgery, prolonged immobilisation, obesity (BMI > 30 kg/m²), pregnancy/postpartum period, systemic lupus erythematosus (SLE), and cancer. There is no consensus about the possible role of varicose veins in VTE.

As in all postoperative patients, prophylactic measures need be considered to prevent VTE following surgery. If prolonged immobilisation is to follow elective surgery temporarily stopping HRT 4 to 6 weeks earlier is recommended. Treatment should not be restarted until the woman is completely mobilised.

- In women with no personal history of VTE but with a first degree relative with a history of thrombosis at young age, screening may be offered after careful counselling regarding its limitations (only a proportion of thrombophilic defects are identified by screening).

If a thrombophilic defect is identified which segregates with thrombosis in family members or if the defect is 'severe' (e.g., antithrombin, protein S, or protein C deficiencies or a combination of defects) HRT is contraindicated.

- Women already on chronic anticoagulant treatment require careful consideration of the benefit-risk of use of HRT.

If VTE develops after initiating therapy, the drug should be discontinued. Patients should be told to contact their 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 protection against myocardial infarction in women with or without existing CAD who received combined oestrogen-progestogen or oestrogen-only HRT.

Combined oestrogen-progestogen therapy

The relative risk of CAD during use of combined oestrogen+progestogen HRT is slightly increased. As the baseline absolute risk of CAD is strongly dependent on age, the number of extra cases of CAD due to oestrogen+progestogen use is very low in healthy women close to menopause, but will rise with more advanced age.

Oestrogen-only

Randomised controlled data found no increased risk of CAD in hysterectomised women using oestrogen-only therapy

Ischaemic Stroke

- Combined oestrogen-progestogen and oestrogen-only therapy are associated with an up to 1.5-fold increase in risk of ischaemic stroke. The relative risk does not change with age or time since menopause. However, as the baseline risk of stroke is strongly age-dependent, the overall risk of stroke in women who use HRT will increase with age (see Section 4.8).

Other conditions

- Oestrogens may cause fluid retention, and therefore patients with cardiac or renal dysfunction should be carefully observed.
- 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).
- HRT use does not improve cognitive function. There is some evidence of increased risk of probable dementia in women who start using continuous combined or oestrogen-only HRT after the age of 65.
- Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.
- This oestrogen-progestogen combination treatment is not contraceptive. Patients in the perimenopausal phase should be advised to take non-hormonal contraceptive precautions.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

- 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, 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.

Femoston-conti 0.5mg/2.5mg can be administered irrespective of food intake.

4.6 Pregnancy and lactation

Pregnancy

Femoston-conti 0.5mg/2.5mg is not indicated during pregnancy. If pregnancy occurs during medication with Femoston-conti 0.5mg/2.5mg treatment should be withdrawn immediately.

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

Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

Lactation

Femoston-conti 0.5mg/2.5mg is not indicated during lactation.

4.7 Effects on ability to drive and use machines

Femoston-conti 0.5mg/2.5mg has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Undesirable effects reported in clinical trials and in post marketing experience of all dosage forms are the following:

MedDRA system organ class	Common ≥1/100 to <1/10	Uncommon ≥1/1,000 to <1/100	Rare ≥1/10,000 to <1/1,000	Very rare <1/10,000 incl. not known (cannot be estimated from the available data)
Infections and infestations		Cystitis- like syndrome, vaginal candidiasis		
Neoplasms benign, malignant and unspecified		Increase in size of leiomyoma		
Blood and the lymphatic system disorders				Haemolytic anaemia
Immune system disorders				Hypersensitivity
Psychiatric disorders		Depression, influence on libido, nervousness		
Nervous system disorders	Migraine, headache	Dizziness		Chorea
Eye disorders			Steepening of corneal curvature, contact lenses intolerance	
Cardiac disorders				Myocardial infarction
Vascular disorders		Peripheral vascular disease, varicose vein, venous thromboembolism*		Stroke
Gastrointestinal disorders	Nausea, abdominal pain, flatulence	Dyspepsia		Vomiting
Hepatobiliary disorders		Gall bladder disease	Hepatic function abnormal sometimes with jaundice asthenia or malaise, and abdominal pain.	

MedDRA system organ class	Common ≥1/100 to <1/10	Uncommon ≥1/1,000 to <1/100	Rare ≥1/10,000 to <1/1,000	Very rare <1/10,000 incl. not known (cannot be estimated from the available data)
Skin and subcutaneous tissue disorders		Allergic skin reactions(e.g. rash, urticaria, pruritus)		Angioedema, erythema multiforme, erythema nodosum, vascular purpura, chloasma or melasma, which may persist when drug is discontinued.
Musculoskeletal and connective tissue disorders	Leg cramps	Back pain		
Reproductive system and breast disorders	Breast pain/tenderness, metrorrhagia and postmenopausal spotting pelvic pain	Uterine cervical erosion, cervical discharge, dysmenorrhoea, menorrhagia,	Breast enlargement, premenstrual syndrome	
Congenital and familial/genetic disorders				Porphyria aggravated
General disorders and administration site reactions	Asthenia	Oedema peripheral		
Investigations	Weight abnormal			

* see below for further information

Breast cancer risk

- An up to 2-fold increased risk of having breast cancer diagnosed is reported in women taking combined oestrogen-progestogen therapy for more than 5 years.
- Any increased risk in users of oestrogen-only therapy is substantially lower than that seen in users of oestrogen-progestogen combinations.
- The level of risk is dependent on the duration of use (see section 4.4).
- Results of the largest randomised placebo-controlled trial (WHI-study) and largest epidemiological study (MWS) are presented:

Million Women study– Estimated additional risk of breast cancer after 5 years' use

Age range (years)	Additional cases per 1000 never-users of HRT over a 5 year period ¹	Risk ratio & 95%CI#	Additional cases per 1000 HRT users over 5 years (95%CI)
Oestrogen only HRT			
50-65	9-12	1.2	1-2 (0-3)

Taken from baseline incidence rates in developed countries

		Combined oestrogen-progestogen	
50-65	9-12	1.7	6 (5-7)
#Overall risk ratio. The risk ratio is not constant but will increase with increasing duration on use Note: Since the background incidence of breast cancer differs by EU country, the number of additional cases of breast cancer will also change proportionately.			

US WHI studies - additional risk of breast cancer after 5 years' use

Age range (yrs)	Incidence per 1000 women in placebo arm over 5 years	Risk ratio & 95%CI	Additional cases per 1000 HRT users over 5 years (95%CI)
CEE oestrogen-only			
50-79	21	0.8 (0.7 – 1.0)	-4 (-6 – 0) ²
CEE+MPA oestrogen & progestogen [‡]			
50-79	14	1.2 (1.0 – 1.5)	+4 (0 – 9)

[‡]When the analysis was restricted to women who had not used HRT prior to the study there was no increased risk apparent during the first 5 years of treatment: after 5 years the risk was higher than in non-users.

Endometrial cancer risk

Postmenopausal women with a uterus

The endometrial cancer risk is about 5 in every 1000 women with a uterus not using HRT.

In women with a uterus, use of oestrogen-only HRT is not recommended because it increases the risk of endometrial cancer (see Section 4.4).

Depending on the duration of oestrogen-only use and oestrogen dose, the increase in risk of endometrial cancer in epidemiology studies varied from between 5 and 55 extra cases diagnosed in every 1000 women between the ages of 50 and 65.

Adding a progestogen to oestrogen-only therapy for at least 12 days per cycle can prevent this increased risk. In the Million Women Study the use of five years of combined (sequential or continuous) HRT did not increase risk of endometrial cancer (RR of 1.0 (0.8-1.2))

Ovarian cancer

Long-term use of oestrogen-only and combined oestrogen-progestogen HRT has been associated with a slightly increased risk of ovarian cancer. In the Million Women Study 5 years of HRT resulted in 1 extra case per 2500 users.

Risk of venous thromboembolism

HRT is associated with a 1.3-3-fold increased relative risk of developing venous thromboembolism (VTE), i.e. deep vein thrombosis or pulmonary embolism. The occurrence of such an event is more likely in the first year of using HRT (see Section 4.4). Results of the WHI studies are presented:

WHI Studies - Additional risk of VTE over 5 years' use

Age range (years)	Incidence per 1000 women in placebo arm over 5 years	Risk ratio and 95%CI	Additional cases per 1000 HRT users
Oral oestrogen-only ³			
50-59	7	1.2 (0.6-2.4)	1 (-3 – 10)
Oral combined oestrogen-progestogen			
50-59	4	2.3 (1.2 – 4.3)	5 (1 - 13)

Risk of coronary artery disease

The risk of coronary artery disease is slightly increased in users of combined oestrogen-progestogen HRT over the age of 60 (see Section 4.4).

WHI study in women with no uterus, which did not show an increase in risk of breast cancer

Study in women with no uterus

Risk of ischaemic stroke

The use of oestrogen-only and oestrogen + progestogen therapy is associated with an up to 1.5 fold increased relative risk of ischaemic stroke. The risk of haemorrhagic stroke is not increased during use of HRT.

This relative risk is not dependent on age or on duration of use, but as the baseline risk is strongly age-dependent, the overall risk of stroke in women who use HRT will increase with age (see Section 4.4).

WHI studies combined - Additional risk of ischaemic stroke over 5 years' use

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

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

Neoplasms benign, malignant and unspecified:

- Oestrogen-dependent neoplasms both benign and malignant, e.g. endometrial cancer, ovarian cancer
- Increase in size of progestagen-dependent neoplasms (e.g. meningioma), (see section 4.3).

Immune system disorders:

- Systemic lupus erythematosus

Nervous system disorders:

- Probable dementia - exacerbation of epilepsy

Vascular disorders:

- Arterial thromboembolism

4.9 Overdose

No case of overdose has been reported for Femoston-conti 0.5mg/2.5mg.

Both estradiol and dydrogesterone are substances with low toxicity. Theoretically, symptoms such as nausea, vomiting, somnolence 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.

5 PHARMACOLOGICAL PROPERTIES**5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Genito urinary system and sex hormones, progestogens and oestrogens, fixed combinations, ATC code: G03FA14.

Estradiol

The active ingredient, synthetic 17 β -estradiol, is chemically and biologically identical to endogenous human estradiol. It substitutes for the loss of oestrogen production in menopausal women, and alleviates menopausal symptoms.

Dydrogesterone

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.

Clinical trial information

With Femoston 0.5mg/2.5 mg the reduction of moderate to severe hot flushes was statistically significant versus placebo from week 4 onward. The number of moderate to severe hot flushes decreased further until end of treatment period in week 13.

In two studies amenorrhoea (no bleeding or spotting) was seen in 91% and in 88% of the women respectively during months 10-12 of treatment. Irregular bleeding and or spotting appeared in 10% and 21% of the women during the first 3 months of treatment and in 9% and in 12% during months 10-12 of treatment.

no differentiation was made between ischaemic and haemorrhagic stroke.

5.2 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. These metabolites can contribute to the oestrogen activity, either directly or after conversion to estradiol. The multiple dose pharmacokinetics of E2 and E1 was linear. For E1S AUC_{0-τ} at steady state was estimated to be 79% of the AUC after single dose. Steady state concentrations were reached for E2 and the metabolites E1 and E1S within 11 days of dosing. The following table depicts the respective C_{max}, C_{min} and steady state values of estradiol and its metabolites:

	E2 pg/ml	E1 pg/ml	E1S ng/ml
C _{max}	28.3	160	6.35
C _{min}	12.4	70.6	1.52
C _{av} (*)	18.1	106	3.07

*: calculated as AUC(0-tau)/24

The AUC and C_{max} ratios of estrone to estradiol are around 6 at steady state. The metabolite ratios E1/E2 and E1S/E2 showed no marked differences between single and multiple dosing. The T_{max} values of E2, E1 and E1S were 2, 4 and 3.5 hours respectively. The mean terminal half lives of baseline corrected estradiol, estrone and estrone sulphate are 16, 15 and 15 hours respectively. 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 characterised 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. The following table depicts the respective C_{max}, C_{min} and steady state values of dydrogesterone and its metabolite DHD:

	D ng/ml	DHD ng/ml
C _{max}	0.695	17.6
C _{min}	0.0251	1.10
C _{av} (*)	0.109	3.40

*: calculated as AUC(0-tau)/24

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.

5.3 Preclinical safety data

Supraphysiologically high doses (and prolonged application) of estradiol have been associated with the induction of tumours in oestrogen-dependent target organs in all rodent species tested. Furthermore, inherent to its hormonal activity, estradiol displays untoward embryotoxic effects and feminisation of male fetuses was occasionally observed. The changes observed with dydrogesterone in animal toxicity studies are associated with the effects of progesterone-like compounds. Genotoxicity studies with dydrogesterone showed negative results in vitro and in vivo. Doses of dydrogesterone administered to rats and mice sufficient to produce hormone mediated changes gave no evidence of carcinogenesis.

Embryo-foetal developmental toxicity studies in rabbits showed adverse effects (reduced foetal weight and slightly increased incidence of minor skeletal abnormalities) at the highest dose tested. Such findings were attributed to maternal toxicity and not considered an indication of a teratogenic effect. A pre- and postnatal developmental study in rats with dydrogesterone showed an elongated gestational period and potential of increasing the incidence of hypospadias associated with infertility in male pups at high dosage.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:

Lactose monohydrate

Hypromellose

Maize starch

Colloidal anhydrous silica

Magnesium stearate

Film-coating:

Macrogol 3350

Polyvinyl alcohol

Talc

Titanium dioxide (E171)

Iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

48 months.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/Aluminium blister strips in a printed carton.

Packs of 28, 84, 280 and 14 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

Solvay Healthcare Ltd

Mansbridge Road

West End

Southampton SO18 3JD

8 MARKETING AUTHORISATION NUMBER(S)

PL 00512/0397

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

28/05/2010

10 DATE OF REVISION OF THE TEXT

28/05/2010





Module 3

PACKAGE LEAFLET: INFORMATION FOR THE USER

Femoston-Conti 0.5 mg /2.5 mg, film-coated tablets

Active substances: estradiol/dydrogesterone

Read all of this leaflet carefully before you start taking this medicine.

-  Keep this leaflet. You may need to read it again.
-  If you have any further questions, ask your doctor or pharmacist.
-  This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
-  If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What Femoston-Conti 0.5mg/2.5mg is and what it is used for
2. Before you take Femoston-Conti 0.5mg/2.5mg
3. How to take Femoston-Conti 0.5mg/2.5mg
4. Possible side effects
5. How to store Femoston-Conti 0.5mg/2.5mg
6. Further information

1. WHAT FEMOSTON-CONTI 0.5MG/2.5MG IS AND WHAT IT IS USED FOR

Femoston-Conti 0.5mg/2.5mg is a continuous combined Hormone Replacement Therapy or HRT which is taken each day without interruption. Femoston-Conti 0.5mg/2.5mg is suitable for postmenopausal women who have not had their periods since more than a year.

Femoston-Conti 0.5mg/2.5mg contains estradiol and dydrogesterone. Your body's natural oestrogen is also called estradiol. Estradiol replaces your body's natural oestrogen, thereby controlling your menopausal symptoms. Women who still have a womb should normally take some form of progesterone (a progestogen), because oestrogen alone can cause problems due to a build up of the womb lining and cancer of the womb lining. Taking dydrogesterone helps to prevent a build up of the womb lining and cancer of the womb lining.

Femoston-Conti 0.5mg/2.5mg is used to

- treat symptoms of oestrogen deficiency like hot flushes, night sweats and vaginal dryness in postmenopausal women. Femoston-Conti 0.5 mg/2.5 mg should be used only in postmenopausal women more than 12 months after menopause. The experience in treating women older than 65 years is limited.

2. BEFORE YOU TAKE FEMOSTON-CONTI 0.5MG/2.5MG

DO NOT take Femoston-Conti 0.5mg/2.5mg if you:

- ☐ are allergic (hypersensitive) to estradiol, dydrogesterone or to any of the other ingredients of Femoston-Conti 0.5mg/2.5mg.
- ☐ have, have had or your doctor thinks you might have breast cancer
- ☐ have, or your doctor thinks you might have a malignant tumour that is related to the levels of oestrogens in the blood (such as cancer of the lining of the womb (*endometrial cancer*)).
- ☐ have, or your doctor thinks you might have progesterone dependent tumours (*neoplasms*)
- ☐ have undiagnosed vaginal bleeding.
- ☐ have untreated overgrowth of the lining of the womb (*endometrial hyperplasia*).
- ☐ have or have had blood clots in the veins or lungs (*venous thromboembolism*)
- ☐ have a clotting disorder (*thrombophilic disorder, such as protein C, protein S, or antithrombin deficiency*)
- ☐ have or have recently had a disease caused by blood clots in the arteries, such as angina pectoris or a heart attack.
- ☐ have or have had liver disease that has not recovered completely.
- ☐ have a rare blood pigment disorder (*porphyria*).

Stop taking Femoston-Conti 0.5mg/2.5mg and see a doctor as soon as possible if you notice any of the following conditions or symptoms:

- If you develop any of the conditions mentioned in the 'Do not take' section
- if you develop yellowing of the skin (*jaundice*).
- if you develop liver problems.
- if your blood pressure increases considerably.
- if you develop migraine-like headaches.
- if you become pregnant.

When to take special care with Femoston-Conti 0.5mg/2.5mg

HRT should only be initiated for symptoms that adversely affect your quality of life. As well as benefits, HRT has some risks which need to be considered when deciding whether to take it, or whether to carry on taking it. A careful appraisal of the risks and benefits should be undertaken at least annually and HRT should only be continued as long as the benefits outweigh the risks.

Before starting or restarting HRT, your doctor will ask about your own and your family's medical history. A physical examination will also be performed which may include examination of your breasts and pelvis.

Screening tests including appropriate imaging tools, e.g. mammography (an X-ray of the breasts), should be performed according to current medical recommendations. Your doctor will inform you how often these tests should be performed

Periodic check-ups are recommended at least once a year while you are on HRT. Your doctor will tell you how often these check-ups should take place. More frequent check-ups may be required if you suffer or have suffered from any of the conditions listed below or if any of these conditions have been aggravated during pregnancy or previous HRT, since these may return or be aggravated under HRT:

- ☐ growths in the womb (*fibroids*)
- ☐ lining of the womb growing outside the womb (*endometriosis*)
- ☐ risk factors for blood clots in the veins or lungs (*thromboembolic disorders*)
- ☐ an increased risk of developing tumours related to the levels of oestrogens in the blood (such as having a close relative with breast cancer)
- ☐ high blood pressure
- ☐ liver problems
- ☐ diabetes
- ☐ gallstones (*cholelithiasis*)
- ☐ migraine or severe headache
- ☐ systemic lupus erythematosus (a disease of the immune system that affects many organs of the body)
- ☐ a history of an overgrowth of the lining of the womb (*endometrial hyperplasia*)
- ☐ epilepsy
- ☐ asthma
- ☐ disease affecting the eardrum and hearing (*otosclerosis*)

Please also tell your doctor if you have or have had any of the following medical conditions since he will have to monitor you more closely:

- heart disease
- kidney impairment
- a high level of fat in the blood (*hypertriglyceridemia*)

Effects on your risk of developing cancer

Overgrowth of the lining of the womb (*endometrial hyperplasia*) and cancer of the womb lining (*endometrial cancer*)

In women with an intact womb taking oestrogen-only HRT for a longer time the risk of overgrowth of the lining of the womb (*endometrial hyperplasia*) and cancer of the womb lining (*endometrial cancer*) is increased.

Taking a progestogen as well as the oestrogen, such as Femoston-Conti, helps to lower the extra risk.

Breakthrough bleeding or spotting may occur during the first few months of HRT. But if it continues for more than a few months, appears after you have been on HRT for a while or carries on after you have stopped HRT,

- **make an appointment to see your doctor.**

Your doctor will investigate the cause which may include a biopsy of the womb lining in order to find out whether you have cancer of the womb lining.

Compare

Looking at women who still have a womb and who are not taking HRT on average 5 in 1000 will be diagnosed with endometrial cancer.

For women who take oestrogen-only HRT the number of extra cases will be between 5 and 55 in 1000 users between the ages of 50 and 65 depending on the dose and for how long it is taken.

The addition of a progestogen to oestrogen-only HRT substantially reduces the risk of endometrial cancer.

Breast cancer

Evidence suggests that taking combined oestrogen-progestogen and possibly also oestrogen-only HRT increases the risk of breast cancer. This depends on how long you take HRT, and the extra risk is visible after about 3 years. However, it returns to normal within a few (at most five) years after stopping.

Therefore, you should **regularly check your breasts (self-examination)** and tell your doctor about any changes. Your doctor will tell you what signs to look out for.

Compare

Looking at women aged 50 to 65 who are not taking HRT on average, 9 – 12 in 1000 will be diagnosed with breast cancer over a 5 year period.

For women aged 50 – 65 who are taking oestrogen plus progestogen HRT over 5 years the number of extra cases will be 6 in 1000 users. Looking at women aged 50 to 79 who are not taking HRT on average, 14 in 1000 will be diagnosed with breast cancer over a 5 year period.

For women aged 50 – 79 who are taking oestrogen plus progestogen HRT over 5 years the number of extra cases will be 4 in 1000 users.

Ovarian cancer

Ovarian cancer is much rarer than breast cancer. Long-term (at least 5-10 years) use of oestrogen-only HRT products is thought to carry a slightly increased risk of ovarian cancer. Some studies suggest that the long-term use of combined HRTs may carry a similar, or slightly smaller, risk. For women who are taking HRT over 5 years there will be one extra case per 2500 users.

Effects on your heart and circulation

Blood clots in the veins or lungs (venous thromboembolism or VTE)

HRT increases the risk of VTE 1.3-3 fold, especially during the first year of taking it.

You are generally more likely to get a blood clot if one or more of the following applies to you:

- use of oestrogens
- older age
- major surgery (if surgery is planned, tell your doctor well in advance that you are on HRT, since treatment might have to be stopped as a precaution. Your doctor will tell you when to start again)
- being bed-ridden for a longer period through surgery, injury or illness
- being very overweight
- pregnancy/period after birth
- an autoimmune collagen disease, which may affect many organ systems (*systemic lupus erythematosus* (SLE))
- cancer
- any of your close family have had blood clots at young age

Compare

Looking at women in their 50s who are not taking HRT on average, over a 5-year period, 4 in 1000 would be expected to get a blood clot.

For women in their 50s who are taking HRT over 5 years, the number of extra cases will be 5 in 1000 users.

If you get painful swelling in your leg, sudden chest pain or have difficulty breathing:

- **see a doctor as soon as possible**
- **do not take any more HRT** until your doctor says you can.

These may be signs of a blood clot

If you have any blood clotting problem that needs treatment with a medicine to prevent clots (an *anticoagulant*) your doctor needs to pay special attention to the benefit-risk of using HRT.

Heart disease (Coronary artery disease (CAD))

There is no evidence that HRT will help to prevent heart disease.

Women taking oestrogen-progestogen HRT are slightly more likely to get heart disease than those not taking any HRT. As the risk of CAD strongly depends on age, the number of extra cases of CAD due to oestrogen+progestogen use is very low in healthy women close to menopause, but will rise with more advanced age.

If you get a pain in your chest that spreads to your arm or neck:

- **see a doctor as soon as possible**

- **do not take any more HRT** until your doctor says you can.
This pain could be a sign of heart disease.

Stroke

Combined oestrogen-progestogen and oestrogen-only HRT increase the risk of stroke up to 1.5-fold. The risk of users compared to non-users does not change with age or time since menopause. However, as the risk of stroke is strongly age-dependent, the overall risk of stroke in women who use HRT will increase with age.

Compare

Looking at women in their 50s who are not taking HRT on average, over a 5-year period, 8 in 1000 would be expected to have a stroke.

For women in their 50s who are taking HRT over 5 years, the number of extra cases will be 3 in 1000 users.

If you get a severe **unexplained headache or migraine** (which can include disturbed vision):

- **see a doctor as soon as possible**
- **do not take any more HRT** until your doctor says you can.

This may be an early warning sign of a stroke.

HRT will not improve thought processes. There are hints of an increased risk of probable dementia in women who start using HRT after the age of 65.

Femoston-Conti 0.5mg/2.5mg is not intended to be used by women who still have child bearing potential. In case of doubt, use a non hormonal contraceptive. Consult your doctor.


Changes can occur in the levels of certain proteins and hormones in the blood. The action of the hormones in the body is not affected. You should tell your doctor that you are taking HRT if you are to have a blood test.

Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines. This includes medicines, herbal remedies, health foods or supplements that you have obtained without a prescription.

You must tell your doctor and take special care if you are taking any of the following medicines:

- ☞ anticonvulsants (such as phenobarbital, carbamazepine, phenytoin),
- ☞ anti-infectives (such as rifampicin, rifabutin, nevirapine, efavirenz),
- ☞ ritonavir, nelfinavir (treatments for HIV infection [AIDS])

 herbal preparations 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).

These medicines can stop Femoston-Conti 0.5mg/2.5mg working properly, which can give rise to bleeding or spotting.

Taking Femoston-Conti 0.5mg/2.5mg with food and drink

Femoston-Conti 0.5mg/2.5mg can be taken with or without food.

Children

Femoston-Conti 0.5mg/2.5mg is intended for postmenopausal women only.

Pregnancy and breast-feeding

Femoston-Conti 0.5mg/2.5mg is intended for postmenopausal women only.

Do not take Femoston-Conti 0.5mg/2.5mg if you are pregnant. If you are not sure if you are pregnant you should carry out a pregnancy test. If you are pregnant or think you are pregnant, you should stop taking Femoston-Conti 0.5mg/2.5mg and tell your doctor.

Do not take Femoston-Conti 0.5mg/2.5mg if you are breast-feeding.

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

Driving and using machines

The effect of Femoston-Conti 0.5mg/2.5mg on driving or using machinery has not been studied. An effect is unlikely.

Important information about some of the ingredients of Femoston-Conti 0.5mg/2.5mg tablets

Femoston-Conti 0.5mg/2.5mg tablets contain lactose (milk sugar). If you have been informed that you have intolerance to certain sugars, tell your doctor before taking this medicine. This includes some rare hereditary disorders that affect how the body uses lactose.

3. HOW TO TAKE FEMOSTON-CONTI 0.5MG/2.5MG

Always take Femoston-Conti 0.5mg/2.5mg exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

How to take Femoston-Conti 0.5mg/2.5mg

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 your ovaries have been removed or are switching from a continuous combined preparation you can start taking Femoston on any convenient day.

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

Take one tablet every day, without a break between packs. The blisters are marked with the days of the week to make it easier for you to remember when to take your tablets.

Swallow the tablet with water. Femoston-Conti 0.5mg/2.5mg can be taken with or without food.

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

Your doctor will aim to give you the lowest dose for the shortest time to treat your symptoms but he may increase the dose, if necessary.

Femoston-Conti 0.5mg/2.5mg:

Take one yellow coloured tablet daily for a 28 day cycle

If you take more Femoston-Conti 0.5mg/2.5mg than you should

If you or somebody else takes too many Femoston-Conti 0.5mg/2.5mg tablets, they are unlikely to come to any harm. Nausea (feeling sick), vomiting, sleepiness and dizziness may occur. No treatment is necessary, but if you are worried contact your doctor for advice.

If you forget to take Femoston-Conti 0.5mg/2.5mg

Take the missed tablet as soon as you remember. If it is more than 12 hours after you should have taken the tablet, take the next dose at the regular time without taking the forgotten tablet. Do not take a double dose. Bleeding or spotting may occur if you miss a dose.

If you stop taking Femoston-Conti 0.5mg/2.5mg

Do not stop taking Femoston-Conti 0.5mg/2.5mg without first talking to your doctor.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Femoston-Conti 0.5mg/2.5mg can cause side effects, although not everybody gets them. Evaluation of the side effects is based on the following frequencies:

Very common:	In more than 1 in 10 patients treated
Common:	In less than 1 in 10, but more than 1 in 100 patients treated
Uncommon:	In less than 1 in 100, but more than 1 in 1,000 patients treated
Rare:	In less than 1 in 1,000, but more than 1 in 10,000 patients treated
Very rare:	In less than 1 in 10,000 patients treated, not known (cannot be estimated from the available data)

Common:

- migraine; headache
- feeling sick (*nausea*); abdominal pain; wind (*flatulence*)
- leg cramps
- breast pain or tenderness; irregular periods (*metrorrhagia*) and postmenopausal spotting; pelvic pain
- feeling weak (*asthenia*)
- weight changes

Uncommon:

- bladder inflammation (cystitis)-like syndrome; vaginal thrush (a vaginal infection due to a fungus called *Candida albicans*)
- increased size of growths in the womb (increased fibroids)
- depression; change in sex drive; nervousness
- dizziness
- narrowing of blood vessels in the legs or arms restricting blood flow (peripheral vascular disease); varicose veins; blood clots in the legs or lungs (venous thromboembolism)
- dyspepsia
- gallbladder disease
- allergic skin reactions (such as rash, severe itching (*pruritus*) or hives (*urticaria*))
- back pain
- erosion of the neck of the womb (uterine cervical erosion); discharge from the neck of the womb (cervical discharge); painful menstruation (*dysmenorrhoea*); heavy periods (*menorrhagia*)
- fluid collection under the skin usually observed as swelling of the ankles (peripheral oedema)

Rare:

- change in the surface of the eye (steepening of corneal curvature); intolerance to contact lenses
- liver disorders, which may include yellowing of the skin (jaundice), feeling weak (asthenia), general malaise, and abdominal pain
- swelling of the breasts; pre-menstrual syndrome (PMS)

Very rare:

- not enough red blood cells (haemolytic anaemia)
- hypersensitivity reactions
- involuntary muscle twitches (chorea)
- heart attack (myocardial infarction)
- stroke (see “Effects on your heart or circulation” for more information)
- vomiting
- swelling of the skin around the face and throat. This 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).
- worsening of porphyria (a rare blood pigment disease).

There is a slightly increased risk of developing the following diseases in women on HRT:

- breast cancer (see “Effects on your risk of developing cancer” for more information).
- overgrowth or cancer of the lining of the womb (endometrial hyperplasia or cancer) (see “Effects on your risk of developing cancer” for more information).
- blood clots in the legs or lungs (*venous thromboembolism*) (see “Effects on your heart or circulation” for more information)
- coronary artery disease (see “Effects on your heart or circulation” for more information)

Other side effects reported with the use of HRT:

- tumours that may be affected by the levels of oestrogens, such as endometrial cancer, ovarian cancer (see “Effects on your risk of developing cancer” for more information).
- increased size of tumours that may be affected by the levels of progestogens (such as meningioma)
- systemic lupus erythematosus (a disease where the immune system malfunctions and affects the body's own organs and tissues)
- probable dementia
- worsening of epilepsy
- arterial thromboembolism

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

5. HOW TO STORE FEMOSTON-CONTI 0.5MG/2.5MG

This medicinal product does not require any special storage conditions.

Keep out of the reach and sight of children.

Do not use Femoston- Conti 0.5 mg/2.5 mg after the expiry date which is stated on the blister and the carton after {exp date}. The expiry date refers to the last day of that month

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Femoston-Conti 0.5mg/2.5mg contains

➤ The active substances are estradiol as estradiol hemihydrate and dydrogesterone.

One film-coated tablet contains 0.5 mg estradiol as estradiol hemihydrate and 2.5 mg dydrogesterone

➤ The other ingredients are:

Core:

- lactose monohydrate,
- hypromellose,
- maize starch,
- colloidal anhydrous silica,
- magnesium stearate

Film-coating:

- macrogol 3350
- polyvinyl alcohol
- talc
- titanium dioxide (E171)
- yellow iron oxide (E172)

What Femoston-Conti 0.5mg/2.5mg looks like and the contents of the pack

This medicinal product is a film-coated tablet. The tablet is round, biconvex, yellow with the inscription 379 on one side and S on the other side

PVC/Aluminium blister strips in a printed carton.
Packs of 28, 84, 280 and 14 film-coated tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and

Manufacturer

Solvay Biologicals B.V.
Veerweg 12
8121 AA Olst
The Netherlands

This medicinal product is authorised in the Member States of the EEA under the following names:

This leaflet was last approved in ...

Module 4

Labelling

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**BLISTER****1. NAME OF THE MEDICINAL PRODUCT**

Femoston-Conti 0.5 mg/2.5 mg film-coated tablets

Estradiol and dydrogesterone

2. NAME OF THE MARKETING AUTHORISATION HOLDER

To be completed nationally

3. EXPIRY DATE

Exp date: {MM/YYYY}

4. BATCH NUMBER

Batch: {number}

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING**OUTER CARTON****1. NAME OF THE MEDICINAL PRODUCT**

Femoston-Conti 0.5 mg/2.5 mg film-coated tablets

Estradiol and dydrogesterone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 0.5mg estradiol (as hemihydrate) and 2.5mg dydrogesterone.

3. LIST OF EXCIPIENTS

Also contains lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

28 film-coated tablets

84 film-coated tablets

280 (10 x 28) film-coated tablets

Sample: 14 tablets film-coated

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use.

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY**8. EXPIRY DATE**

exp date: {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

This medicinal product does not require any special storage conditions.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

To be completed nationally

12. MARKETING AUTHORISATION NUMBER(S)

To be completed nationally

13. BATCH NUMBER

Batch: {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

To be completed nationally.

15. INSTRUCTIONS ON USE**16. INFORMATION IN BRAILLE**

To be completed nationally

Module 5

Scientific discussion during the initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Reference Member State (RMS) considers that the application for Femoston-conti 0.5mg/2.5mg Film coated Tablets as hormone replacement therapy (HRT) due to estrogen deficiency symptoms in postmenopausal women, could be approved.

This application has been submitted via a decentralised procedure according to Article 8(3) of Directive 2001/83/EC. It is an application for new, lower strength tablets containing estradiol 0.5mg and dydrogesterone 2.5mg.

Estradiol

The active ingredient, estradiol, is chemically and biologically identical to 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.

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 estrogen-primed 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 reduces the estrogen-induced risk of endometrial hyperplasia in non-hysterectomised women.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place at all sites responsible for the manufacture and assembly of this product.

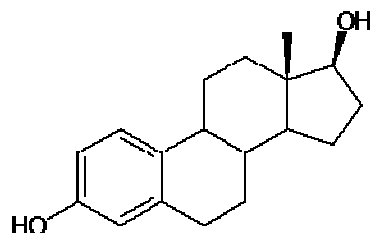
The RMS and Concerned Member States considered that the applications could be approved with the end of procedure (Day 210) on 2nd May 2010. The Marketing Authorisation was granted in the UK on 28th May 2010.

ABOUT THE PRODUCT

Name of the product in the Reference Member State	Femoston-conti 0.5mg/2.5mg Film-coated Tablets
Name(s) of the active substance(s) (INN)	Estradiol hemihydrate & Dydrogesterone
Pharmacotherapeutic classification (ATC code)	G03FA14 Genito urinary system and sex hormones, progestogens and oestrogens, fixed combinations
Pharmaceutical form and strength(s)	Film-coated Tablets, 0.5/2.5mg
Reference number(s) for the Decentralised Procedure	UK/H/0369/02/DC
Reference Member State	United Kingdom
Concerned Member States	AT, BE, CZ, DE, EE, EL, FI, FR, HU, IE, IT, LT, LU, LV, MT, NL, PL, PT, RO and SK
Marketing Authorisation Number(s)	PL 00512/0397
Name and address of the authorisation holder	Solvay Healthcare Ltd., Mansbridge road, West End, Southampton, SO18 3JD, United Kingdom

SCIENTIFIC OVERVIEW AND DISCUSSION**II. QUALITY ASPECTS****DRUG SUBSTANCE****INN: estradiol hemihydrate**Chemical Name: (17 β)-estra-1,3,5(10)-triene-3,17-diol

Structure:

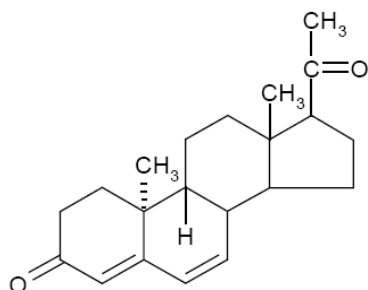
Molecular Formula: C₁₈H₂₄O₂

Molecular Weight: 272.38

All aspects of the manufacture and control of the estradiol drug substance are covered by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability.

INN: DydrogesteroneChemical name: (9 β ,10 α)-pregna,-4,6,diene-3,20-dione

Structure

Molecular formula: C₂₁H₂₈O₂

Molecular mass: 312.5

Appearance: White to almost white crystalline powder

Synthesis of the drug substance from the designated starting material has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant certificates of analysis.

An appropriate specification is provided for the drug substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Certificate of Analysis for all working standards have been provided.

Batch analysis data are provided and comply with the proposed specification.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging used to store the drug substance. Confirmation has been provided that the primary packaging complies with current guidelines concerning materials in contact with food.

Appropriate stability data have been generated, supporting a suitable retest period when the drug substance is stored in the packaging proposed.

DRUG PRODUCT

Other ingredients

Other ingredients consist of the pharmaceutical excipients lactose monohydrate, hypromellose, maize starch, colloidal anhydrous silica, magnesium stearate, macrogol 3350, polyvinyl alcohol, talc, titanium dioxide (E171) and iron oxide yellow (E172).

All excipients comply with their respective European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for all excipients.

The supplier of lactose monohydrate states that the material is derived from milk from healthy animals under the same conditions as milk collected for human consumption. Confirmation has been provided that the magnesium stearate used in the tablets is of vegetable origin.

Pharmaceutical Development

The objective of the development programme was to develop tablets containing estradiol 0.5 mg and dydrogesterone 2.5 mg.

A suitable product development section has been provided.

Manufacture

Satisfactory batch formulae have been provided for the manufacture of product, together with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished product specification

The finished product specification is satisfactory. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for any working standards used.

Container-Closure System

The finished product is packed in PVC/Aluminium blister strips in a printed carton in pack sizes of 14, 28, 84 and 280 Film-coated Tablets.

Specifications and Certificates of Analysis for all packaging materials have been provided. These are satisfactory. All primary packaging complies with EU legislation regarding contact with food.

Stability

Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing.

Based on the results, a shelf-life of 48 months has been set. This is acceptable.

SPC, PIL, Labels

The SPC, PIL and labels are pharmaceutically acceptable.

A package leaflet has been submitted to the MHRA together with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

The marketing authorisation holder has stated that they do not intend to market all pack sizes for all product licences at the present time. However, they have committed to submitting mock-ups for any pack sizes to the regulatory authorities for approval before marketing.

Pharmacovigilance System and Risk Management Plan

The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Risk Management Plan

A suitable justification has been provided for not submitting a risk management plan for this product.

Marketing Authorisation Application form (MAA)

The MAA forms are pharmaceutically satisfactory.

Expert report

The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion

It is recommended that Marketing Authorisation is granted for this application.

III. PRE-CLINICAL ASPECTS

As the pharmacodynamic, pharmacokinetic and toxicological properties of estradiol and dydrogesterone are well-known, no further studies are required and none have been provided.

The applicant's non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the products' pharmacology and toxicology.

A suitable justification has been provided for non-submission of an environmental risk assessment.

There are no objections to the approval of this product from a preclinical viewpoint.

IV. CLINICAL ASPECTS**Pharmacodynamics**

Pharmacodynamic properties of estradiol and dydrogesterone have been well established during the initial authorisation of the Femoston-conti 1mg/5mg Tablets. No new pharmacodynamic studies have been conducted for this application and this is acceptable.

Pharmacokinetics

To support the application of the new lower strength, the pharmacokinetic characteristics of estradiol (E2), estrone (E1), estrone sulphate (E1S), dydrogesterone (DYD) and dihydrodydrogesterone (DHD) following administration of E0.5mg/DYD2.5mg, were investigated in healthy non-hysterectomized, postmenopausal women.

This was an open-label, single and multiple-dose study, where all subjects received a single dose of low dose estradiol/dydrogesterone tablet on day 1 and once daily from day 4 up to day 17. Serial blood samples for the determination of E2, E1, E1S, DYD and DHD were taken on days 1 and 17 (until 72 hours after dosing).

Treatment consisted of a single dose administration on day 1, a wash-out period of three days, and once daily administration from Day 4 until Day 17.

Table 10 Summary of Analysis for the Main Pharmacokinetic Parameters for Baseline Corrected E2, E1 and E1S (Pharmacokinetic Sample)

Analyte	Analysis	Ratio	Estimate	90%CI
baseline corrected E2	Accumulation	$AUC_{0-\tau \text{ Day 17}} \text{ VS } AUC_{0-\tau \text{ Day 1}}$	1.66	[1.46, 1.88]
		$C_{\max \text{ Day 17}} \text{ VS } C_{\max \text{ Day 1}}$	1.62	[1.39, 1.89]
	Linearity	$AUC_{0-\tau \text{ Day 17}} \text{ VS } AUC_{\text{Day 1}}$	1.05	[0.90, 1.22]
baseline corrected E1	Accumulation	$AUC_{0-\tau \text{ Day 17}} \text{ VS } AUC_{0-\tau \text{ Day 1}}$	1.52	[1.33, 1.74]
		$C_{\max \text{ Day 17}} \text{ VS } C_{\max \text{ Day 1}}$	1.45	[1.28, 1.64]
	Linearity	$AUC_{0-\tau \text{ Day 17}} \text{ VS } AUC_{\text{Day 1}}$	0.98	[0.88, 1.10]
baseline corrected E1S	Accumulation	$AUC_{0-\tau \text{ Day 17}} \text{ VS } AUC_{0-\tau \text{ Day 1}}$	1.10	[1.02, 1.19]
		$C_{\max \text{ Day 17}} \text{ VS } C_{\max \text{ Day 1}}$	1.06	[0.97, 1.17]
	Linearity	$AUC_{0-\tau \text{ Day 17}} \text{ VS } AUC_{\text{Day 1}}$	0.79	[0.73, 0.87]

It was a well conducted phase I study to investigate the Pharmacokinetics (PK) of E0.5mg/DYD2.5mg after single and multiple dose administration. Study design was appropriate. PK parameters obtained were similar to those reported for the higher strength E1mg/DYD5mg tablets.

Clinical Efficacy

A study was carried out to demonstrate efficacy of continuous combined E0.5mg/DYD2.5mg versus placebo in the treatment of vasomotor symptoms after a treatment period of 3 months and to compare the bleeding pattern of low strength E0.5mg/DYD2.5mg and currently approved high strength E1mg/DYD5mg products over a 1 year period.

This study was a phase III, randomized, placebo-controlled, double-blind, parallel group multicentre study to demonstrate efficacy in continuous combined 0.5 mg estradiol and 2.5 mg dydrogesterone in the treatment of vasomotor symptoms in postmenopausal women in comparison to placebo over 3 months, and to investigate the bleeding pattern over a double-blind treatment period of 1 year compared with continuous combined 1 mg estradiol and 5 mg dydrogesterone.

The efficacy study was conducted according to the EMEA guideline on the investigation of HRT products. The difference in the change of moderate to severe hot flushes per day from baseline to Week 13 between E0.5 mg/DYD2.5 mg treatment and placebo was statistically significant [1.1898 (95% CI: 0.5238; 1.8557)].

During the treatment period of 52 weeks bleeding was mainly mild and most of the subjects had no bleeding at all. Mean number of bleeding/spotting days in E 0.5mg/D 2.5mg group was slightly lower than in E 1mg/D 5mg group.

The continuous combined regimen containing E0.5mg/DYD2.5mg was generally well tolerated, with most AEs (> 90%) being mild to moderate. The overall incidence of AEs was comparable in all the treatment groups. No new adverse events were reported in the study, adverse events reported were similar to those described for the E1mg/DYD5mg.

Clinical Safety

The safety evaluation was based on the Points to Consider on Hormone Replacement Therapy and the Guideline on Clinical Investigations of Medicinal Products for Hormone Replacement Therapy of Estrogen Deficiency Symptoms in Postmenopausal Women (EMA/CHMP/021/97 Rev. 1).

This study was a phase III, one-year, open label, uncontrolled, multi-center study to investigate endometrial safety of a low dose continuous combined hormone replacement regimen E0.5mg/D2.5mg in postmenopausal women.

Inclusion and exclusion criteria were appropriate and in line with recommendations and investigation of endometrial biopsy data was performed according to the EMA guideline on the investigation of HRT products.

Full safety assessment was performed in this study. No new safety signals were raised. The active ingredients of E0.5mg/DYD2.5mg have been in clinical usage for many years and all of the adverse events reported in this study have also been reported for the higher strength E1mg/DYD5mg tablets.

Expert Reports

A clinical overall summary, written by an appropriately qualified physician, has been provided and it is satisfactory.

Module 1 – Administrative information

MAA forms

The MAA form is medically satisfactory.

SPC, PIL, Labels

The SPC, PIL and label are medically acceptable. The SPCs are consistent with that for the originator product.

Conclusion

It is recommended that Marketing Authorisation is granted for this application.

V. OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT QUALITY

The important quality characteristics of Femoston-conti 0.5mg/2.5mg Film-coated Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

The pharmacodynamic, pharmacokinetic and toxicological properties of estradiol and dydrogesterone are well known. Therefore, no further studies are required and the applicant provides none. An overview based on a literature review is, thus, appropriate.

EFFICACY

No new or unexpected safety concerns arise from this application.

The SPC and PIL are satisfactory and consistent with that of the reference product.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The risk benefit is, therefore, considered to be positive.

Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome