PSUR WORK-SHARING PROCEDURE UK/PSUR/0039/001

ESTRADIOL (transdermal)

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4.3 Contraindications

- Known, past or suspected breast cancer
- Known or suspected oestrogen dependent malignant tumours, e.g. endometrial cancer
- Undiagnosed genital bleeding
- Untreated endometrial hyperplasia
- Previous idiopathic or current venous thromboembolism (deep venous thrombosis, pulmonary embolism)
- Active or recent arterial thromboembolic disease (e.g. angina, myocardial infarction)
- Acute liver disease, or history of liver disease as long as liver function tests have failed to return to normal
- Porphyria
- Known hypersensitivity to the active substance or any of the excipients

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.

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

- Before initiating or reinstituting HRT, a complete personal and family medical history should be taken. Physical (including pelvic and breasts) 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.

<u>Conditions which need supervision</u>

- If any of the following conditions are present, have occurred previously, and/or have been aggravated during pregnancy or previous hormone treatment, the patient should be closely supervised. It should be taken into account that these conditions may recur or be aggravated during treatment with Progynova TS 50, 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. 1 st 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
- Hereditary angioedema

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

- The risk of endometrial hyperplasia and carcinoma is increased when oestrogens are administered alone for prolonged periods (see section 4.8). The addition of a progestogen for at least 12 days per cycle in non-hysterectomised women greatly reduces this risk.
- For Progynova TS 100 (100 µg/day) the endometrial safety of added progestogens has not been studied.
- 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.
- Unopposed oestrogen stimulation may lead to premalignant or malignant transformation in the residual foci of endometriosis. Therefore, the addition of progestogens to oestrogen replacement therapy should be considered in women who have undergone hysterectomy because of endometriosis, if they are known to have residual endometriosis.

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 in women taking oestrogens, oestrogen-progestogen combinations or tibolone for HRT for several years (see Section 4.8).

- 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 (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 (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 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 (BMI > 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 postoperative 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 4 to 6 weeks earlier, if possible. Treatment should not be restarted until the woman is completely mobilised.

- 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 cardiovascular benefit with continuous combined conjugated oestrogens and medroxyprogesterone acetate (MPA). Two large clinical trials (WHI and HERS, i.e. Heart and Estrogen/progestin Replacement Study) showed a possible increased risk of cardiovascular morbidity in the first year of use and no overall benefit. For other HRT products there are only limited data from randomised controlled trials examining effects in cardiovascular morbidity and 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 women 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 Progynova TS 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).

- Chloasma may occasionally occur, especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should minimise exposure to the sun or ultraviolet radiation whilst taking HRT.

- There is no conclusive evidence for improvement of cognitive function. There is some evidence from the WHI trial of increased risk of probable dementia in women who start using continuous combined CEE and MPA after the age of 65. It is unknown whether the findings apply to younger postmenopausal women or other HRT products.

4.5 Interaction with other medicaments and other forms of interaction

The metabolism of oestrogens may be increased by concomitant use of substances known to induce drug-metabolising enzymes, specifically cytochrome P450 enzymes, such as anticonvulsants (e.g. phenobarbital, phenytoin, carbamezapin) 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.
At transdermal administration, the first-pass effect in the liver is avoided and, thus, transdermally applied oestrogens might be less affected than oral hormones by enzyme inducers.

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

4.6 Pregnancy and lactation

- **Pregnancy**

Progynova TS is not indicated during pregnancy. If pregnancy occurs during medication with Progynova TS treatment should be withdrawn immediately.

The results of most epidemiological studies to date relevant to inadvertent foetal exposure to oestrogens indicate no teratogenic or foetotoxic effects.

- **Lactation**

Progynova TS is not indicated during lactation.

4.7 Effects on ability to drive and use machines

None known.

4.8 Undesirable effects

During the first few months of treatment, breakthrough bleeding, spotting and breast tenderness or enlargement can occur. These are usually temporary and normally disappear after continued treatment. The table below lists adverse drug reactions recorded in clinical studies as well as adverse drug reactions reported post-marketing. Adverse drug reactions were recorded in 3 phase III clinical studies (n = 611 women at risk) and were included in the table when considered at least possibly related to treatment with 50 µg/day estradiol or 100 µg/day estradiol, respectively, following transdermal application.

The experience of adverse drug reactions is overall expected in 76% of the patients. Adverse drug reactions appearing in > 10% of patients in clinical trials were application site reactions and breast pain.

Organ system	**Adverse events reported in clinical trials**		**Adverse events reported post marketing**
	Common (≥ 1/100, < 1/10)	**Uncommon (≥ 1/1000, < 1/100)**	
BODY AS A WHOLE	Pain.	Fatigue, abnormal laboratory test[1], asthenia[1], fever[1], flu syndrome[1], malaise[1].	

Organ system	Adverse events reported in clinical trials		Adverse events reported post marketing
	Common (≥ 1/100, < 1/10)	**Uncommon (≥ 1/1000, < 1/100)**	
CARDIOVASCULAR SYSTEM	-	Migraine, palpitations, superficial phlebitis[1], hypertension[1].	Cerebral ischaemic events.
DIGESTIVE SYSTEM	Flatulence, nausea.	Increased appetite, constipation, dyspepsia[1], diarrhoea[1], rectal disorder[1].	Abdominal pain, bloating (abdominal distension), cholestatic jaundice
IMMUNE SYSTEM DISORDERS			Exacerbation of hereditary angioedema
METABOLIC and NUTRITIONAL DISORDER	Oedema, weight gain.	Hypercholesteremia[1]	
HAEMATOLOGICAL and LYMPHATIC SYSTEM	-	Purpura[1].	
MUSCULOSKELETAL SYSTEM	-	Joint disorder, muscle cramps.	
RESPIRATORY SYSTEM	-	Dyspnoea[1], rhinitis[1].	
NERVOUS SYSTEM	Depression, dizziness, nervousness, lethargy, headache, increased sweating, hot flushes.	Anxiety, insomnia, apathy, emotional lability, impaired concentration, paraesthesia, libido changed, euphoria[1], tremor[1], agitation[1].	
SKIN and APPENDAGES	Application site pruritus, rash.	Acne, alopecia, dry skin, benign breast neoplasm, breast enlargement, breast tenderness, nail disorder[1], skin nodule[1], hirsutism[1]	Contact dermatitis, eczema, breast pain
UROGENITAL SYSTEM	Menstrual disorder, vaginal discharge, disorder of vulva/vagina.	Increased urinary frequency/urgency, benign endometrial neoplasm, endometrial hyperplasia, urinary incontinence[1], cystitis[1], urine discoloration[1], haematuria[1], uterine disorder[1].	Uterine fibroids
SPECIAL SENSES		Abnormal vision[1], dry eye[1]	

[1] have been reported in single cases. Given the small study population (n=611) it cannot be determined based on these results if the events are uncommon or rare.

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 (CEE + MPA) in all users compared with placebo.
The absolute risks calculated from the MWS and the WHI trial 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 progestogen* combined HRT,
        - between 5 and 7 (best estimate = 6) for 5 years' use
        - between 18 and 20 (best estimate = 19) for 10 years' use.

The WHI trial estimated that after 5.6 years of follow-up of women between the ages of 50 and 79 years, an *additional* 8 cases of invasive breast cancer would be due to *oestrogen-progestogen combined* HRT (CEE + MPA) per 10,000 women years. According to calculations from the trial data, it is estimated that:

- For 1000 women in the placebo group,

    - about 16 cases of invasive breast cancer would be diagnosed in 5 years.

- For 1000 women who used *oestrogen + progestogen combined* HRT (CEE + MPA), the number of *additional* cases would be

    - between 0 and 9 (best estimate = 4) for 5 years' use.

The number of additional cases of breast cancer in women who use HRT is broadly similar for women who start HRT irrespective of age at start of use (between the ages of 45-65) see section 4.4).

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 benign and malignant, e.g. endometrial cancer.

- Venous thromboembolism, i.e. deep leg or pelvic venous thrombosis and pulmonary embolism, is more frequent among hormone replacement therapy users than among non-users. For further information, see section 4.3 Contraindications and 4.4 Special warnings and precautions for use.

- Myocardial infarction and stroke (see also section 4.4).

- Gall bladder disease.

- Skin and subcutaneous disorders: chloasma, erythema multiforme, erythema nodosum, vascular purpura.

- Probable dementia (see section 4.4)

4.9 Overdose

Overdosage is unlikely with this type of application. Nausea, vomiting and withdrawal bleeding may occur in some women. There is no specific antidote and treatment should be symptomatic. The patch(es) should be removed.