SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Progynova® TS 50 micrograms/24 hours Transdermal Patch

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 12.5 cm^2 patch contains 3.8 mg estradiol (formed from 3.9 mg estradiol hemihydrate), releasing a nominal 50 micrograms of estradiol per 24 hours.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Transdermal patch.

Oval transdermal patch with a translucent homogenous matrix on a transparent carrier film.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- Hormone replacement therapy for estrogen deficiency symptoms in postmenopausal women more than 1 year postmenopause.
- Prevention of osteoporosis in postmenopausal women at high risk of future fractures who are intolerant of, or contraindicated for, other medicinal products approved for the prevention of osteoporosis. (See also Section 4.4)

4.2 Posology and method of administration

Posology

Progynova TS 50 is an oestrogen-only patch applied to the skin once weekly.

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. Treatment to control menopausal symptoms should be initiated with the lowest Progynova TS patch dose. If considered necessary, a higher dosed patch should be used. Once treatment is established the lowest effective dose patch necessary for relief of symptoms should be used.

For prevention of postmenopausal osteoporosis Progynova TS 50 is recommended. Women receiving Progynova TS 100 for postmenopausal symptoms can continue at this dose.

In women with an intact uterus, a progestogen should be added to Progynova TS 50 for at least 12-14 days each month. Unless there is a previous diagnosis of endometriosis, it is not recommended to add a progestogen in hysterectomised women.

For continuous use:

The patches should be applied once weekly on a continuous basis, each used patch being removed after 7 days and a fresh patch applied to a different site.

For cyclical use:

The patches may also be prescribed on a cyclical basis. Where this is the preferred option, the patches should be applied weekly for 3 consecutive weeks followed by a 7 day interval, without a patch being applied, before the next course.

How to start Progynova TS 50

Women who do not take oestrogens or women who change from a continuous combined HRT product may start treatment at any time.

Patients changing from a continuous sequential HRT regimen should begin the day following completion of the prior regimen.

Patients changing from a cyclic HRT regimen should begin the day after the treatment-free period.

Missed or lost patch

In the event that a patch falls off before 7 days are up, it may be reapplied. If necessary, a new patch should be applied for the remainder of the 7-day dosing interval.

If the patient forgets to replace a patch, this should be done as soon as possible after she remembers it. The next patch has to be used after the normal 7-day interval.

After several days without replacement of a new patch there is an increased likelihood of breakthrough bleeding and spotting.

Method of administration

Following removal of the protective liner the adhesive side of Progynova TS patches should be placed on a clean, dry area of the skin of the trunk or buttocks. Progynova TS patches should not be applied to the breasts. The sites of application should be rotated, with an interval of at least one week between applications to a particular site. The area selected should not be oily, damaged or irritated. The waistline should be avoided since tight clothing may rub the patch off. The patch should be applied immediately after opening the pouch and removing the protective liner. The patch should be pressed firmly in place with the palm of the hand for about 10 seconds, making sure there is good contact, especially around the edges. The patch should be

changed once weekly. If the patch is applied correctly, the patient can bath or shower as usual. The patch might, however, become detached from the skin in very hot bath water or in the sauna.

Additional information on special populations

Paediatric population
Progynova TS is not indicated for use in children and adolescents.

Geriatric patients
There are no data suggesting a need for dosage adjustment in elderly patients.

Patients with hepatic impairment
Progynova TS has not been specifically studied in patients with hepatic impairment. Progynova TS is contraindicated in women with severe hepatic disease (see section 4.3). For women with impaired liver function, close supervision is needed and in case of deterioration of markers of liver function, use of HRT should be stopped (see section 4.4).

Patients with renal impairment
Progynova TS has not been specifically studied in renally impaired patients.

4.3 Contraindications

- Known, past or suspected breast cancer
- Known or suspected estrogen dependent malignant tumours, e.g. endometrial cancer
- 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 history of liver disease as long as liver function tests have failed to return to normal
- Porphyria
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

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 reinstituting HRT, a complete personal and 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 Progynova TS 50, 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
- Hereditary angioedema

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 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 estrogen 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 prevent the excess risk associated with oestrogen-only HRT.

- For oral doses of estradiol >2 mg, conjugated equine oestrogens >0.625 mg and patches >50 μg/day the endometrial safety of added progestogens has not been demonstrated.

- 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

The overall evidence shows an increased risk of breast cancer in women taking combined oestrogen-progestogen or 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 a meta-analysis of prospective 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 (1-4) 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 lower than that found in users of oestrogen-progestogen combinations (see section 4.8).

Results from a large meta-analysis showed that after stopping treatment, the excess risk will decrease with time and the time needed to return to baseline depends on the duration of prior HRT use. When HRT was taken for more than 5 years, the risk may persist for 10 years or more.

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.

Epidemiological evidence from a large meta-analysis suggests a slightly increased risk in women taking oestrogen-only or combined oestrogen-progestogen HRT, which becomes apparent within 5 years of use and diminishes over time after stopping.

Some other studies including the WHI trial suggest that the use of combined HRTs may be associated with 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).

Hepatitis C

During clinical trials with the hepatitis C virus (HCV) combination regimen ombitasvir/paritaprevir/ritonavir with and without dasabuvir, ALT elevations greater than 5 times the upper limit of normal (ULN) were significantly more frequent in women using ethinylestradiol-containing medicinal products such as CHCs (combined hormonal contraceptives). Additionally, also in patients treated with glecaprevir/pibrentasvir, ALT elevations were observed in women using ethinylestradiol-containing medications such as CHCs. Women using medicinal products containing oestrogens other than ethinylestradiol, such as estradiol, had a rate of ALT elevation similar to those not receiving any oestrogens; however, due to the limited number of women taking these other oestrogens, caution is warranted for co-administration with the combination drug regimen ombitasvir/paritaprevir/ritonavir with or without dasabuvir and also the regimen glecaprevir/pibrentasvir. See section 4.5.

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.

- Exogenous estrogens may induce or exacerbate symptoms of hereditary and acquired angioedema.

- 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.

- 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.

4.5 Interaction with other medicinal products and other forms of interaction

Note: The prescribing information of concomitant medication should be consulted to identify potential interactions.

Effects of other medicinal products on Progynova TS

Substances increasing the clearance of sex hormones (diminished efficacy by enzyme-induction), e.g.:

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. barbiturates, phenytoin, primidone, carbamazepin) and anti-infectives (e.g. rifampicin, rifabutin, nevirapine, efavirenz) and possibly also felbamate, griseofulvin, oxcarbazepine, topiramate and products containing the herbal remedy St. John's Wort (hypericum perforatum).

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.
Enzyme induction can already be observed after a few days of treatment. Maximal enzyme induction is generally seen within a few weeks. After cessation of drug therapy enzyme induction may be sustained for about 4 weeks.

Substances with variable effects on the clearance of sex hormones:
When co-administered with sex hormones, many combinations of HIV protease inhibitors and non-nucleoside reverse transcriptase inhibitors, including combinations with HCV inhibitors, can increase or decrease plasma concentrations of oestrogen. The net effect of these changes may be clinically relevant in some cases.

Therefore, the prescribing information of concomitant HIV/HCV medications should be consulted to identify potential interactions and any related recommendations.

Substances decreasing the clearance of sex hormones (enzyme inhibitors):
Strong and moderate CYP3A4 inhibitors such as azole antifungals (e.g. fluconazole, itraconazole, ketoconazole, voriconazole), verapamil, macrolides (e.g. clarithromycin, erythromycin), diltiazem and grapefruit juice can increase plasma concentrations of the oestrogen.

Effect of HRT with oestrogens on other medicinal products

Hormone contraceptives containing oestrogens have been shown to significantly decrease plasma concentrations of lamotrigine when co-administered due to induction of lamotrigine glucuronidation. This may reduce seizure control. Although the potential interaction between hormone replacement therapy and lamotrigine has not been studied, it is expected that a similar interaction exists, which may lead to a reduction in seizure control among women taking both medicinal products together.

Other interactions

During clinical trials with the HCV combination drug regimen ombitasvir/paritaprevir/ritonavir with and without dasabuvir, ALT elevations greater than 5 times the upper limit of normal (ULN) were significantly more frequent in women using ethinylestradiol-containing medicinal products such as CHCs. Women using medicinal products containing oestrogens other than ethinylestradiol, such as estradiol, had a rate of ALT elevation similar to those not receiving any oestrogens; however, due to the limited number of women taking these other oestrogens, caution is warranted for co-administration with the combination drug regimen ombitasvir/paritaprevir/ritonavir with or without dasabuvir and also the regimen with glecaprevir/pibrentasvir (see section 4.4).

Laboratory tests

The use of sex steroids may influence the results of certain laboratory tests, including biochemical parameters of liver, thyroid, adrenal and renal function, plasma levels of (carrier) proteins, e.g. corticosteroid binding globulin and lipid/lipoprotein fractions, parameters of carbohydrate metabolism, and parameters of coagulation and fibrinolysis. Changes generally remain within the normal laboratory range. For more information see section 4.4 “Other conditions”.

4.6 Fertility, 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 estrogens indicate no teratogenic or foetotoxic effects.

Breastfeeding

Progynova TS is not indicated during lactation.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. No effects on ability to drive and use machines have been observed in users of Progynova TS.

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].	
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 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.

The increased risk in users of oestrogen-only therapy is 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).

Absolute risk estimations based on results of the largest randomised placebo-controlled trial (WHI-study) and the largest meta-analysis of prospective epidemiological studies are presented.

Largest meta-analysis of prospective epidemiological studies – Estimated additional risk of breast cancer after 5 years' use in women with BMI 27 (kg/m^2)

Age at start HRT (years)	Incidence per 1000 never-users of HRT over a 5 year period (50-54 years)[*1]	Risk ratio	Additional cases per 1000 HRT users after 5 years
		Oestrogen only HRT	
50	13.3	1.2	2.7
		Combined oestrogen-progestogen	
50	13.3	1.6	8.0

[*1] Taken from baseline incidence rates in England in 2015 in women with BMI 27 (kg/m^2).
Note: since the background incidence of breast cancer differs by EU country, the number of additional cases of breast cancer will also change proportionately.

Estimated additional risk of breast cancer after 10 years' use in women with BMI 27 (kg/m^2)

Age at start HRT (years)	Incidence per 1000 never-users of HRT over a 10 year period (50-59 years)[*2]	Risk ratio	Additional cases per 1000 HRT users after 10 years
		Oestrogen only HRT	
50	26.6	1.3	7.1
		Combined oestrogen-progestogen	
50	26.6	1.8	20.8

[*2]Taken from baseline incidence rates in England in 2015 in women with BMI 27 (kg/m^2)

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	Incidence per 1000	Risk ratio & 95%	Additional cases per 1000 HRT users

range (years)	women in placebo arm over 5 years	CI	over 5 years (95% CI)
		CEE oestrogen only	
50-79	21	0.8 (0.7-1.0)	-4 (-6 - 0)[*3]
		CEE + MPA oestrogen & progestogens[§]	
50-79	17	1.2 (1.0-1.5)	+4 (0 - 9)
[*3] WHI study in women with no uterus, which did not show an increase of breast cancer. [§] 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

Use of oestrogen-only or combined oestrogen-progestogen HRT has been associated with a slightly increased risk of having ovarian cancer diagnosed (see Section 4.4).

A meta-analysis from 52 epidemiological studies reported an increased risk of ovarian cancer in women currently using HRT compared to women who have never used HRT (RR 1.43, 95% CI 1.31-1.56). For women aged 50 to 54 years taking 5 years of HRT, this results in about 1 extra case per 2000 users. In women aged 50 to 54 who are not taking HRT, about 2 women in 2000 will be diagnosed with ovarian cancer over a 5-year period.

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 HT (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 & 95% CI	Additional cases per 1000 HRT users
Oral oestrogen-only[*4]			
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)
[*4] Study in women with no uterus.			

Risk of coronary artery disease

The risk of coronary artery disease is slightly increased in users of combined oestrogen/progestagen HRT over the age of 60 (see section 4.4).

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[*5] over 5 years' use

Age range (years)	Incidence per 1000 women in placebo arm over 5 years	Risk ratio & 95% CI	Additional cases per 1000 HRT users
50-59	8	1.3 (1.1 – 1.6)	3 (1 – 5)
[*5] No differentiation was made between ischaemic and haemorrhagic stroke.			

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

- Gall bladder disease.
- Skin and subcutaneous disorders: chloasma, erythema multiforme, erythema nodosum, vascular purpura.
- Probable dementia over the age of 65 (see section 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Natural and semisynthetic oestrogens, plain.

ATC code: G03CA03

Mechanism of action and pharmacodynamic effects

Progynova TS contains synthetic 17ß-estradiol, which is chemically and biologically identical to endogenous human estradiol. It substitutes for the loss of oestrogen production in menopausal women, and alleviates menopausal symptoms. Oestrogens prevent bone loss following menopause or ovariectomy.

Clinical efficacy and safety

- Relief of oestrogen-deficiency symptoms

  - Relief of menopausal symptoms was achieved during the first few weeks of treatment.

- Prevention of osteoporosis

  - Oestrogen deficiency at menopause is associated with an increasing bone turnover and decline in bone mass. The effect of oestrogens on the bone mineral density is dose-dependent. However, in clinical trials, the efficacy of Progynova TS 100 was not significantly better than the efficacy of Progynova TS 50 for the prevention of postmenopausal osteoporosis. Protection appears to be effective for as long as treatment is continued. After discontinuation of HRT, bone mass is lost at a rate similar to that in untreated women.

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

  - Two clinical trial studies in osteoporosis prevention have been conducted with Progynova TS, one in the US and one in Europe.

    Progynova TS 50

  - After two years of treatment, the increase in lumbar spine bone mineral density (BMD) was 6.91% (95% confidence interval (CI) 4.90-8.91) and 4.09% (95%-CI 2.01-6.17) in the European and US study, respectively. In the US study, responder rates were also evaluated. The percentage of women who maintained or gained BMD in the lumbar spine zone during treatment was 94%.

  - Progynova TS 50 also had an effect on femoral neck BMD. The increase after 2 years at the femoral neck was 5.73% (95%-CI 4.25-7.21) and 1.61% (95%-CI 0.09-3.13) in the European and US study, respectively. In the US study, responder rates were also evaluated. The percentage of women who maintained or gained BMD at the femoral neck during treatment was 78%.

    Progynova TS 100

  - After two years of treatment, the increase in lumbar spine (BMD) was 8.43% (95% CI 6.93-9.93) and 4.70% (95%-CI 2.98-6.42) in the European and US study, respectively. In the US study, responder rates

were also evaluated. The percentage of women who maintained or gained BMD in the lumbar spine zone during treatment was 90%.

- Progynova TS 100 also had an effect on femoral neck BMD. The increase after two years at the femoral neck was 5.63% (95%-CI 3.87-7.38) and 1.53% (95%-CI 0.66-3.72) in the European and US study, respectively. In the US study, responder rates were also evaluated. The percentage of women who maintained or gained BMD at the femoral neck during treatment was 68%.

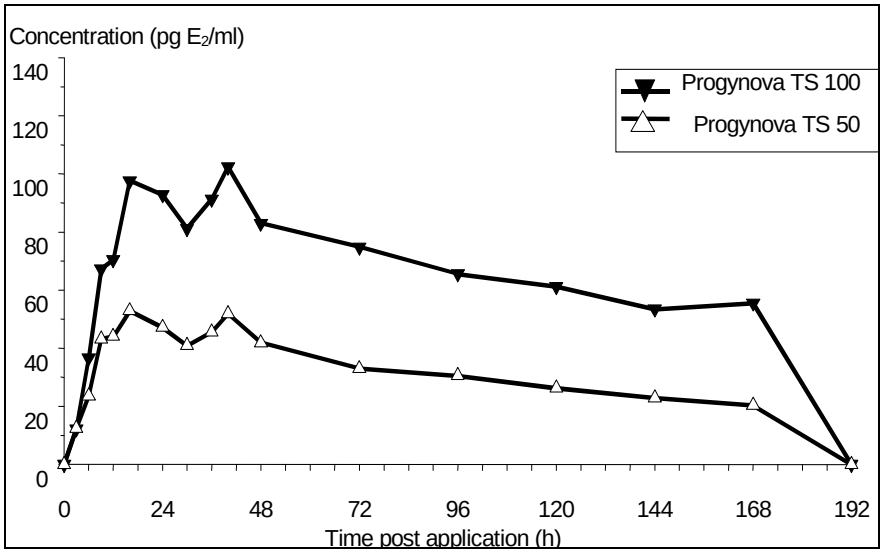
5.2 Pharmacokinetic properties

Absorption

After dermal application of Progynova TS, estradiol is continuously released and transported across intact skin leading to sustained circulating levels of estradiol during a 7-day treatment period as shown in Figure 1. The systemic availability of estradiol after transdermal administration is about 20 times higher than that after oral administration. This difference is due to the absence of first pass metabolism when estradiol is given by the transdermal route. The major pharmacokinetic parameters of estradiol are summarised in the following table:

Transdermal Delivery System	Daily Delivery Rate, mg/day	Application Site	AUC(0-tlast) ngxh/mL / nmolxh/L	Cmax pg/mL / pmol/L	Cavg pg/mL / pmol/L	tmax h	Cmin pg/mL / pmol/L
Progynova TS 50	0.050	Abdomen	5.44 / 20	55 / 202	35 / 129	26	30 / 110
Progynova TS 100	0.100	Abdomen	11.5 / 42	110 / 404	70 / 257	31	56 / 206

Figure 1: Mean baseline uncorrected serum 17 β-estradiol concentrations vs. time profile following application of Progynova TS 50 and Progynova TS 100



Distribution

The distribution of exogenous estrogens is similar to that of endogenous estrogens. The apparent volume of distribution of estradiol after single intravenous administration is about 1 l/kg. Estrogens circulate in the blood largely bound to serum proteins. About 61% of estradiol is bound non-specifically to serum albumin and about 37% specifically to sex hormone binding globulin (SHBG).

Biotransformation

After transdermal administration, the biotransformation of estradiol leads to concentrations of estrone and of the respective conjugates within the range as seen during the early follicular phase in the reproductive life period, indicated by an estradiol/estrone serum level ratio of approximately 1. Unphysiologically high estrone levels as a result of the intensive "first pass" metabolism during oral estradiol hormone replacement therapy, reflected in estradiol/estrone ratios as low as 0.1, are avoided.

The biotransformation of the transdermally administered estradiol is the same as that of the endogenous hormone: Estradiol is mainly metabolized in the liver but also extrahepatically e.g. in gut, kidney, skeletal muscles and target organs. These processes involve the formation of estrone, estriol, catecholestrogens and sulfate and glucuronide conjugates of these compounds, which are less estrogenic or even nonestrogenic.

Elimination

The total serum clearance of estradiol following single intravenous administration shows high variability in the range of 10-30 ml/min/kg. Estradiol and its metabolites are excreted in the bile and undergo a so-called enterohepatic circulation. Ultimately estradiol and its metabolites are mainly excreted as sulfates and glucuronides with the urine.

Steady-state conditions

Accumulation of estradiol and estrone was not observed following multiple 1-week patch applications. Accordingly, steady-state serum levels of estradiol and estrone correspond to those observed after a single application.

5.3 Preclinical safety data

The toxicity profile of estradiol is well known. There are no preclinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

In primary dermal irritation studies, application of Progynova TS patches resulted in mild irritation related to mechanical trauma at removal. Progynova TS patches had no dermal sensitising potential.

Studies on the components (adhesive matrix, backing and release liner) did not indicate any risk related to the use of the Progynova TS patch.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Isooctyl acrylate/acrylamide/vinyl acetate copolymer
Ethyl oleate
Isopropyl myristate
Glycerol monolaurate
Polyester release liner
Polyethylene backing film

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store below 30ºC.

Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Each patch is sealed in a multilaminate pouch containing a desiccant. The desiccant consists of sodium alumino silicate;

Pack of 4 or 12 patches.

(Not all pack sizes may be marketed).

6.6 Special precautions for disposal

After use the patch still contains substantial quantities of estradiol, which may have harmful effects if reaching the aquatic environment. Therefore, the used patch should be discarded carefully. Any used or unused patches should be folded in half, adhesive side together, and disposed off in the solid waste disposal system. Used patches should not be flushed down the toilet nor placed in liquid waste disposal systems.

7 MARKETING AUTHORISATION HOLDER

Bayer plc
400 South Oak Way
Reading
RG2 6AD

8 MARKETING AUTHORISATION NUMBER(S)

PL 00010/0560

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

06/09/2005

10 DATE OF REVISION OF THE TEXT

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