SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Progynova® 2 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each memo pack contains 28 tablets each containing estradiol valerate 2.0 mg.

Excipients with known effect
Lactose monohydrate and sucrose
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

White sugar coated tablet for oral administration.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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 is an oestrogen-only product.

One tablet of Progynova 2 mg to be taken daily. It does not matter at what time of day the woman takes her tablet, but once she has selected a particular

time she should keep to it every day. Treatment is continuous, which means that the next pack follows immediately without a break.

For initiation and continuation of treatment of menopausal 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 Progynova 1 mg. If considered necessary, Progynova 2 mg should be used. Once treatment is established the lowest effective dose necessary for relief of symptoms should be used.

For prevention of postmenopausal osteoporosis one tablet of Progynova 2 mg is to be taken daily.

In women with an intact uterus, a progestogen should be added to Progynova for at least 12 - 14 days each month/28 day cycle. Unless there is a previous diagnosis of endometriosis, it is not recommended to add a progestogen in hysterectomised women.

- How to start Progynova 2 mg

If the woman has an intact uterus and is still menstruating, a combination regimen with Progynova and a progestogen, commencing with the oestrogen phase, should begin on the first day of bleeding. If the menstrual periods are very infrequent or if amenorrhoea is established, she may start at any time provided, if appropriate, pregnancy has been excluded (see section 4.6).

In women transferring from a continuous combined HRT product, treatment with Progynova may be started on any day.

In women transferring from cyclic or continuous sequential HRT regimens, the woman should complete the cycle and then change to Progynova without a break in therapy.

- Missed or lost tablets

If the woman forgets to take a tablet at the usual time, she may take it within the following 12 hours. If the woman is more than 12 hours late the forgotten tablet should not be taken and the remaining tablets taken at the usual time on the right days. A missed dose may lead to breakthrough bleeding or spotting.

Paediatric population

Progynova is not indicated for use in children and adolescents.
<u>Geriatric patients</u>

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

<u>Patients with hepatic impairment</u>

Progynova has not been specifically studied in patients with hepatic impairment. Progynova 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 has not been specifically studied in renally impaired patients.

Method of administration

The tablets can be taken with or without food. The tablets should be swallowed whole with a glass of water or milk. The tablets should be taken at the same time each day.

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)
- 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 liver function tests have failed to return to normal
- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1
- 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 risk 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, 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.

<u>Reasons for immediate withdrawal of therapy:</u>
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.

<u>Endometrial hyperplasia and carcinoma</u>

- 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.

- For oral doses of estradiol > 2mg, conjugated equine oestrogens > 0.625 mg and patches > 50 micrograms/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- to 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).

- Generally recognised risk factors for VTE include use of oestrogens, older age, major surgery, prolonged immobilisation, obesity (BMI > 30kg/m^2), pregnancy/post-partum 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.

- Patients with known thromboembolic states have an increased risk of VTE. HRT may add to this risk. HRT is therefore contraindicated in these patients (see Section 4.3).

- 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.

- Those women already on anti-coagulant 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 and dasabuvir with and without ribavirin, 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 or sofosbuvir/velpatasvir/voxilaprevir, 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, ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin 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 following combination drug regimens ombitasvir/paritaprevir/ritonavir and

dasabuvir with or without ribaviringlecaprevir/pibrentasvir or sofosbuvir/velpatasvir/voxilaprevir. 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 hypertriglyceridaemia 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.

- 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.

- Progynova is not suitable as a contraceptive. If appropriate, contraception should be practised with non-hormonal methods.

- Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrose-isomaltase insufficiency should not take this medicine.

- Patients with rare hereditary problems of galactose intolerance, the Lapp lactasedeficiency or glucose-galactose malabsorption should not take this medicine.

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

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

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, carbamazepine) 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).

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

Direct acting antiviral agents (DAAs) and ethinylestradiol-containing medicinal products such as CHCs

During clinical trials with the HCV combination drug regimen ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin, 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. Additionally, also in patients treated with glecaprevir/pibrentasvir or sofosbuvir/velpatasvir/voxilaprevir, ALT elevations were observed in women using ethinylestradiol-containing medications such as CHCs.

Direct acting antiviral agents (DAAs) and medicinal products containing oestrogens other than ethinylestradiol, such as estradiol

Women using medicinal products containing oestrogens other than ethinylestradiol, such as estradiol, and ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin 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 following combination drug regimens: ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin, glecaprevir/pibrentasvir or sofosbuvir/velpatasvir/voxilaprevir. (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 is not indicated during pregnancy. If pregnancy occurs during medication with Progynova 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.

- Breast-feeding

Progynova is not indicated during breast-feeding.

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.

4.8 Undesirable effects

The following undesirable effects have been reported in users of Progynova and other oral HRT preparations.

Neoplasms benign, malignant and unspecified
Breast cancer*, Endometrial cancer*

Immune system disorders
Hypersensitivity reaction, Exacerbation of hereditary angioedema.

Metabolism and nutrition disorder
Porphyria aggravated, Increased or decreased weight, Increased appetite, Carbohydrate tolerance decreased

Psychiatric disorders
Anxiety/depressive symptoms, Decreased or increased libido

Nervous system disorders
Migraine, Headache, Dizziness, Fatigue, Chorea, Stroke*

Eye disorders
Visual disturbances, Intolerance to contact lenses

Cardiac disorders
Palpitations, Myocardial infarction*

Vascular disorders
Hypertension, Thrombophlebitis, Venous Thromboembolism*

Respiratory, thoracic and mediastinal disorders
Epistaxis

Gastrointestinal disorders
Dyspepsia, Abdominal pain, Vomiting, Nausea, Bloating, Flatulence

Hepatobiliary disorders
Gall bladder disease including Cholestasis

Skin and subcutaneous tissue disorders
Rashes, various Skin disorders (including Pruritus, Eczema, Urticaria, Acne, Hirsutism, Hair loss, Erythema nodosum, Erythema multiforme, Rash hemorrhagic, Chloasma (see section 4.4)

Musculoskeletal and connective tissue disorders
Muscle cramps, Leg pain

Renal and urinary disorders
Cystitis-like symptom

Reproductive system and breast disorders
Increased size of uterine fibroids, Vaginal candidosis, Uterine cervical erosions, Changes in vaginal bleeding pattern and abnormal bleeding or flow, Breakthrough bleeding, Spotting (bleeding irregularities usually subside during continued treatment), Dysmenorrhoea, Changes in vaginal secretion, Premenstrual-like syndrome, Breast secretion, Breast tenderness, enlargement or pain.

General disorders and administration site conditions
Oedema

** Please see further information below.*

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)[a]	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
a 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)*	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
*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 of use

Age range (years)	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) [a]
CEE + MPA oestrogen & progestogen [b]			
50 - 79	17	1.2 (1.0 – 1.5)	+4 (0 - 9)
a WHI study in women with no uterus, which did not show an increased in risk of breast cancer. **b** 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 an 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 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 of 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 [a]			
50 - 59	7	1.2 (0.6 – 2.4)	1 (-3 - 10)
Oral combined oestrogen & progestogen [b]			
50 - 59	4	2.3 (1.2 – 4.3)	5 (1 - 13)
a 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-progestogen 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[a] over 5 years of use

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

a 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

Overdose may cause nausea and vomiting and withdrawal bleeding may occur in some women. There are no specific antidotes and treatment should be symptomatic.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Sex hormones and modulators of the genital system, natural and semisynthetic oestrogens, plain, ATC code: G03CA03

- **Estradiol/estradiol valerate:**

Progynova contains estradiol valerate, (the valeric-acid ester of the endogenous female oestrogen, estradiol.

The active ingredient estradiol valerate, a prodrug of the synthetic 17ß-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. Oestrogens prevent bone loss following menopause or ovariectomy.

Ovulation is not inhibited during the use of Progynova, and the endogenous production of hormones is hardly affected.

Clinical trial information

Relief of oestrogen-deficiency symptoms and bleeding patterns

- During the climacteric, the reduction and finally loss of ovarian estradiol secretion can result in instability of thermoregulation, causing hot flushes associated with sleep disturbance and excessive sweating, and urogenital atrophy with symptoms of vaginal dryness, dyspareunia and urinary incontinence. Less specific but often mentioned as part of the climacteric syndrome are symptoms like anginal complaints, palpitations, irritability, nervousness, lack of energy and concentration abilities, forgetfulness, loss of libido and joint and muscle pain. HRT alleviates many of these symptoms of estradiol deficiency in the menopausal woman.
- Relief of menopausal symptoms was achieved during the first few weeks of treatment.
- The addition of a progestogen to an oestrogen replacement regimen like Progynova for at least 10 days per cycle is recommended in women with an intact uterus. It reduces the risk of endometrial hyperplasia and the attendant risk of adenocarcinoma in these women. The addition of a progestogen to an oestrogen replacement regimen has not been shown to interfere with the efficacy of oestrogen for its approved indications.

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. 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.

Observational studies and the WHI trial on conjugated equine oestrogens (CEE) plus medroxyprogesterone acetate (MPA) suggest a reduction of colon cancer morbidity in postmenopausal women taking HRT. In the WHI trial on

CEE mono-therapy a risk reduction was not observed. It is unknown whether these findings also extend to other HRT products.

- **Progestogen:**

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.

5.2 Pharmacokinetic properties

Absorption
After oral administration estradiol valerate is quickly and completely absorbed.

Distribution
Already after 0.5 - 3 hours peak plasma levels of estradiol, the active drug substance, are measured. As a rule, after 6 - 8 hours a second maximum appears, possibly indicating an entero-hepatic circulation of estradiol.

In plasma, estradiol is mainly found in its protein-bound form. About 37% are bound to SHBG and 61% to albumin. Cumulation of estradiol after daily repetitive intake of Progynova does not need to be expected.

The absolute bioavailability of estradiol amounts to 3 - 5% of the oral dose of estradiol valerate.

Biotransformation
Esterases in plasma and the liver quickly decompose estradiol valerate into estradiol and valeric acid. Further decomposition of valeric acid through β-oxidation leads to C_2-units and results in CO_2 and water as end products. Estradiol itself undergoes several hydroxylating steps. Its metabolites as well as the unchanged substance are finally conjugated. Intermediate products of metabolism are estrone and estriol, which exhibit a weak oestrogenic activity of their own, although this activity is not so pronounced as with estradiol. The plasma concentration of conjugated estrone is about 25 to 30 fold higher than the concentration of unconjugated estrone. In a study using radioactive labelled estradiol valerate about 20% of radioactive substances in the plasma could be characterised as unconjugated steroids, 17% as glucuronized steroids and 33% as steroid sulphates. About 30% of all substances could not be extracted from the aqueous phase and, therefore, probably represent metabolites of high polarity.

Elimination
Estradiol and its metabolites are mainly excreted by the kidneys (relation of urine:faeces = 9:1). Within 5 days about 78 - 96% of the administered dose are excreted with an excretion half-life of about 27 hours.

5.3 Preclinical safety data

There are no preclinical safety data which could be of relevance to the prescriber and which are not already included in other relevant sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Maize Starch
Povidone 25
Talc
Magnesium Stearate [E572]
Sucrose
Povidone 90
Macrogol 6000
Calcium Carbonate [E170]
Glycol montanate
Purified Water

6.2 Incompatibilities

None known.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

None.

6.5 Nature and contents of container

Container consists of aluminium foil and PVC blister strips packed in a cardboard carton

Presentation: Carton containing memo-packs of either 1 x 28 tablets or 3 x 28 tablets.

6.6 Special precautions for disposal

None.

7 MARKETING AUTHORISATION HOLDER

Bayer plc
400 South Oak Way
Reading, RG2 6AD

8 MARKETING AUTHORISATION NUMBER(S)

PL 00010/0557

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

1 May 2008

10 DATE OF REVISION OF THE TEXT

07/04/2026