Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Premarin 0.3 mg Prolonged-release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 0.3 mg conjugated oestrogens.

Excipients with known effect:
Each tablet contains lactose monohydrate 61.7 mg and sucrose 45.0 mg

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release tablet
Green, oval, biconvex, coated tablets branded with “0.3” in white ink.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Premarin is indicated for hormone replacement therapy (HRT) for oestrogen deficiency symptoms in menopausal women 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 section 4.4).

4.2 Posology and method of administration

Premarin is an oestrogen only HRTfor oral use.

Posology

Adults

Premarin 0.625-1.25 mg daily is the usual starting dose for women without a uterus. Continuous administration is recommended.

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. Patients should be re-evaluated periodically to determine if treatment for symptoms is still necessary.

Vasomotor symptoms:

0.625-1.25 mg daily depending on the response of the individual.

Atrophic vaginitis, kraurosis vulvae, atrophic urethritis:

0.625-1.25 mg daily depending on the response of the individual.

Prophylaxis of postmenopausal osteoporosis:

When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis and non-oestrogen medications should be carefully considered.

The minimum effective dose is 0.625 mg for most patients.

Concomitant progestogen use for women with a uterus:

Unless there is a previous diagnosis of endometriosis, it is not recommended to add a progestogen in hysterectomised women (see section 4.4).

Commencing treatment advice:

For most postmenopausal women, therapy may be commenced at any convenient time.

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

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

Forgotten tablet:

If a tablet is forgotten, it should be taken as soon as the patient remembers. Therapy should then be continued as before. If more than one tablet has been forgotten, only the most recent tablet should be taken.

Missed pills may cause breakthrough bleeding in women with a uterus.

Elderly

There are no special dosage requirements for elderly patients, but as with all medicines, the lowest effective dose should be used.

Paediatric population

Premarin is not recommended for use in children.

Safety and effectiveness in paediatric patients have not been established. Oestrogen treatment of prepubertal girls induces premature breast development and vaginal cornification, and may induce uterine bleeding.
Since large and repeated doses of oestrogen over an extended time period have been shown to accelerate epiphyseal closure, hormonal therapy should not be started before epiphyseal closure has occurred in order not to compromise final growth.

Method of administration

For oral use only.

Tablets should be taken whole; do not divide, crush, chew, or dissolve tablets in mouth.

4.3 Contraindications

1. Hypersensitivity to conjugated oestrogen or to any of the excipients listed in section 6.1.

2. Known, suspected or history of breast cancer.

3. Known or suspected oestrogen-dependent malignant tumours (e.g. endometrial cancer).

4. Undiagnosed genital bleeding.

5. Untreated endometrial hyperplasia.

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

7. Known thrombophilic disorders (e.g. protein C, protein S, or antithrombin deficiency, see section 4.4).

8. Active or recent arterial thromboembolic disease (e.g. angina, myocardial infarction).

9. Acute liver disease or a history of liver disease where the liver function tests have failed to return to normal.

10. 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 the 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 women. 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 Premarin, in particular:

- Leiomyoma (uterine fibroids) or endometriosis
- Risk factors for thromboembolic disorders (see below)
- Risk factors for oestrogen dependent tumours (e.g. first degree heredity for breast cancer)

- Hypertension

- Liver disorders (e.g. liver adenoma)
- Diabetes mellitus with or without vascular involvement
- Cholelithiasis
- Migraine or (severe) headaches
- Systemic lupus erythematosus (SLE)
- A history of endometrial hyperplasia (see below)
- Epilepsy
- Asthma

- Otosclerosis Reasons for immediate withdrawal of therapy

Therapy should be discontinued in case a contraindication is discovered and in the following situations:

- Jaundice or deterioration in liver function
- Significant increase in blood pressure
- New onset of migraine-type headache
- Pregnancy

Endometrial hyperplasia and carcinoma

- In women with an intact uterus the risk of endometrial hyperplasia and carcinoma is increased when oestrogens are administered alone for prolonged periods. The reported increase in endometrial cancer risk among oestrogen-only users varies from 2-to 12-fold greater compared with non-users, depending on the duration of treatment and oestrogen dose (see section 4.8). After stopping treatment risk may remain elevated for at least 10 years.
- The addition of a progestogen cyclically for at least 12 days per month/28 day cycle or continuous combined oestrogen-progestogen therapy in non-hysterectomised women prevents the excess risk associated with oestrogen-only HRT.

- For oral doses of estradiol >2 mg, conjugated equine oestrogens >0.625 mg and patches >50 mg/day the endometrial safety of added progestogen 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, especially 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.

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

- Hormone replacement therapy (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 use 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 (Body Mass Index >30 kg/m^2) 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 thrombophillic 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 doctor immediately when they are aware of potential thromboembolic symptoms (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 oestrogens-progesterone or oestrogen-only HRT.

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).
In the WHI oestrogen-alone substudy, a statistically significant increased risk of stroke was reported in women 50 to 79 years of age receiving daily CE (0.625 mg) compared to women receiving placebo (45 versus 33 per 10,000 women-years). The increase in risk was demonstrated in year one and persisted.
Subgroup analyses of women 50 to 59 years of age suggest no increased risk of stroke for those women receiving CE (0.625 mg) versus those receiving placebo (18 versus 21 per 10,000 women-years).

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 Premarin is increased.

- The use of oestrogens may influence the laboratory results of certain endocrine tests and liver enzymes.

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 usually unaltered. Patients dependent on thyroid hormone replacement therapy may require increased doses in order to maintain their free thyroid hormone levels in an acceptable range.
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 usually unchanged. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-I-antitrypsin, ceruloplasmin).

- A two- to four-fold increase in the risk of gallbladder disease requiring surgery in women receiving HRT has been reported.

- A worsening of glucose tolerance may occur in patients taking oestrogens and therefore diabetic patients should be carefully observed while receiving hormone replacement therapy.

- Oestrogens should be used with caution in patients with disease that can predispose to severe hypocalcaemia.

- 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.

- 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.

- Laboratory monitoring

Oestrogen administration should be guided by clinical response rather than by hormone levels (e.g., estradiol, FSH).

- This product contains lactose monohydrate and sucrose. Patients with rare hereditary problems of galactose intolerance, fructose intolerance, the Lapp lactase deficiency, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

4.5 Interaction with other medicinal products 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 3A4 (CYP3A4) enzymes. Therefore, inducers or inhibitors of CYP3A4 may affect oestrogen drug metabolism. Inducers of CYP3A4, such as St. John's wort (Hypericum perforatum) preparations, phenobarbital, phenytoin, carbamazepine, rifampicin, rifabutin, nevirapine, efavirenz and dexamethasone, may reduce plasma concentrations of oestrogens, possibly resulting in a decrease in therapeutic effects and/or changes in the uterine bleeding profile. Inhibitors of CYP3A4, such as cimetidine, erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir, nelfinavir and grapefruit juice, may increase plasma concentrations of oestrogens and may result in side effects.

Interference with Laboratory and Other Diagnostic Tests

Laboratory test interactions

Increased platelet count decreased levels of antithrombin III, and increased plasminogen antigen and activity.

Oestrogens increase thyroid-binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T_4 levels by column or by radioimmunoassay or T_3 levels by radioimmunoassay. T_3 resin uptake is decreased, reflecting the elevated TBG. Free T_4 and free T_3 concentrations are unaltered.

Other binding proteins may be elevated in serum, i.e., corticosteroid binding globulin (CBG), sex hormone-binding globulin (SHBG) leading to increased circulating corticosteroid and sex steroids, respectively. Free or biologically active hormone concentrations may be decreased.

Increased plasma HDL and HDL_2 cholesterol subfraction concentrations, reduced LDL cholesterol concentrations, increased triglyceride levels.

Impaired glucose tolerance.

The response to metyrapone may be reduced.

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.

4.6 Fertility, pregnancy and lactation

Pregnancy

Premarin is not indicated for use during pregnancy.

If pregnancy occurs during medication with Premarin, 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

Premarin is not indicated during lactation.

4.7 Effects on ability to drive and use machines

No studies on the effect of ability to drive or use machines have been performed.

4.8 Undesirable effects

See also section 4.4

Adverse drug reactions (ADRs)

The adverse reactions listed in the table are based on post-marketing spontaneous reporting rates, clinical trials and class-effects.

System Organ Class	Common (>1/100, < 1/10)	Uncommon (>1/1,000, <1/100)	Rare (>1/10,000, <1/1,000)	Very Rare (<1/10,000), isolated reports
Infections and infestations		Vaginitis, including vaginal candidiasis		
Neoplasms benign and malignant (including cysts and polyps)			Breast cancer; Fibrocystic breast changes; Ovarian cancer; Growth potentiation of benign meningioma	Endometrial cancer; Enlargement of hepatic haemangiomas
Immune system			Anaphylactic/	

disorders			anaphylactoid reactions, including urticaria and angioedema	
Metabolism and nutrition disorders			Glucose intolerance	Exacerbation of porphyria; Hypocalcaemia (in patients with disease that can predispose to severe hypocalcaemia)
Psychiatric disorders	Depression	Changes in libido; Mood disturbances; Dementia	Irritability	
Nervous system disorders		Dizziness; Headache; Migraine; Anxiety	Stroke; Exacerbation of epilepsy;	Exacerbation of chorea
Eye disorders		Intolerance to contact lenses		Retinal vascular thrombosis
Cardiac disorders			Myocardial infarction	
Vascular disorders		Venous thrombosis	Pulmonary embolism; Superficial thrombophlebitis	
Respiratory, thoracic and mediastinal disorders			Exacerbation of asthma	
Gastrointestinal disorders		Nausea; Bloating; Abdominal pain	Vomiting; Pancreatitis; Ischaemic colitis	
Hepatobiliary disorders		Gallbladder disease		Cholestatic jaundice
Skin and subcutaneous tissue disorders	**Alopecia**	Chloasma/melasma; Hirsutism; Pruritus; Rash		Erythema multiforme; Erythema nodosum
Musculoskeletal, connective tissue and bone disorders	**Arthralgias; Leg cramps**			
Reproductive system & breast disorders	Breakthrough bleeding/spotting; Breast pain, Tenderness, Enlargement, Discharge	Change in menstrual flow; Change in cervical ectropion and secretion	Dysmenorrhoea; Galactorrhoea; Increased size of uterine leiomyomata	Endometrial hyperplasia
General disorders and administration site conditions		Oedema		
Investigations	Changes in weight (increase or decrease); Increased triglycerides			Increase in blood pressure

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)*	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
*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' use

Age range (yrs)	Incidence per 1000 women in placebo arm over 5 years	Risk ratio & 95%CI	Additional cases per 1000 HRT users over 5 years (95%CI)
		CEE oestrogen-only	
50-79	21	0.8 (0.7 – 1.0)	-4 (-6 – 0)*
		CEE+MPA oestrogen & progestogen‡	
50-79	17	1.2 (1.0 – 1.5)	+4 (0 – 9)

*WHI study in women with no uterus, which did not show an increase in risk 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 and 95%CI	Additional cases per 1000 HRT users
Oral oestrogen-only*			
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)

**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* over 5 years' use

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

**no differentiation was made between ischaemic and haemorrhagic stroke.*

Other adverse reactions reported in association with oestrogen/progestogen treatment including Premarin:

- Oestrogen-dependent neoplasms benign and malignant, e.g. endometrial hyperplasia, 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 (see sections 4.3 and 4.4).
- Retinal vascular thrombosis.
- Myocardial infarction and stroke.
- Increases in blood pressure.
- Cholestatic jaundice.
- Enlargement of hepatic haemangiomas.
- Skin and subcutaneous disorders: erythema multiforme, erythema nodosum; vascular purpura.
- Probable dementia over the age of 65 (see section 4.4).
- Exacerbation of chorea.
- Exacerbation of porphyria.
- Exacerbation of hypocalcaemia. Reporting of suspected adverse reactionsReporting 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 HPRA Pharmacovigilance. Website: www.hpra.ie.

4.9 Overdose

Numerous reports of ingestion of large doses of oestrogen-containing oral contraceptives by young children indicate that acute serious ill effects do not occur. Overdosage of oestrogens may cause nausea and vomiting, and withdrawal bleeding may occur in females. There is no specific antidote and further treatment should be symptomatic.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Progestogens and oestrogens.

ATC Code: G03C A57

Conjugated Oestrogens

The active ingredients are primarily the sulfate esters of estrone, equilin sulfate and 17a/b-estradiol. These substitute for the loss of oestrogen production in menopausal women, and alleviate menopausal symptoms. Oestrogens prevent bone loss following menopause or ovariectomy.

Mechanism of action

Endogenous oestrogens are largely responsible for the development and maintenance of the female reproductive system and secondary sexual characteristics. Although circulating oestrogens exist in a dynamic equilibrium of metabolic interconversions, estradiol is the principal intracellular human oestrogen and is substantially more potent than its metabolites, estrone and estriol, at the receptor level.

The primary source of oestrogen in normally cycling adult women is the ovarian follicle, which secretes 70 to 500 mcg of estradiol daily, depending on the phase of the menstrual cycle. After menopause, most endogenous oestrogen is produced by conversion of androstenedione, which is secreted by the adrenal cortex, to estrone in the peripheral tissues. Thus, estrone and the sulfate-conjugated form, estrone sulfate, are the most abundant circulating oestrogens in postmenopausal women.

Oestrogens act through binding to nuclear receptors in oestrogen-responsive tissues. To date, two oestrogen receptors have been identified. These vary in proportion from tissue to tissue. Circulating oestrogens modulate the pituitary secretion of the gonadotropins, luteinizing hormone (LH) and follicle stimulating hormone (FSH), through a negative feedback mechanism. Oestrogens act to reduce the elevated levels of these gonadotropins seen in postmenopausal women.

Clinical efficacy and safety

Effects on oestrogen-deficiency (vasomotor) symptoms

In the first year of the Health and Osteoporosis, Progestin and Oestrogen (HOPE) Study, a total of 2,805 postmenopausal women (average age 53.3 ± 4.9 years) were randomly assigned to one of eight treatment groups, receiving either placebo or conjugated oestrogens, with or without medroxyprogesterone acetate. Efficacy for vasomotor symptoms was assessed during the first 12 weeks of treatment in a subset of symptomatic women (n = 241) who had at least seven moderate-to-severe hot flushes daily, or at least 50 moderate-to-severe hot flushes during the week before randomization. With conjugated oestrogen (0.3 mg, 0.45 mg, and 0.625 mg tablets), the decrease of both the frequency and severity of moderate-to-severe vasomotor symptoms was shown to be statistically improved compared with placebo at weeks 4 and 12.

Table 1 shows the observed mean number of hot flushes in the CE 0.3 mg, 0.45 mg, and 0.625 mg and placebo treatment groups over the initial 12-week period.

TABLE 1. SUMMARY TABULATION OF THE NUMBER OF HOT FLUSHES PER DAY– MEAN VALUES AND COMPARISONS BETWEEN THE CE TREATMENT GROUPS AND THE PLACEBO GROUP: PATIENTS WITH AT LEAST 7 MODERATE TO SEVERE FLUSHES PER DAY OR AT LEAST 50 PER WEEK AT BASELINE, EFFICACY EVALUABLE (EE) POPULATION				
Treatment (No. of Patients)	**---------- No. of Hot Flushes/Day ----------**			
Time Period (week)	**Baseline Mean ± SD**	**Observed Mean ± SD**	**Mean Change ± SE[a]**	**p-Values vs. Placebo[a]**
0.625 mg CE				
4 (n=27)	12.29 ± 3.89	1.95 ± 2.77	-10.34 ± 0.90	<0.001
12 (n=26)	12.03 ± 3.73	0.45 ± 0.95	-11.58 ± 0.88	<0.001
0.45 mg CE				
4 (n=32)	12.25 ± 5.04	5.04 ± 5.31	-7.21 ± 0.83	<0.001
12 (n=30)	12.49 ± 5.11	2.33 ± 3.39	-10.16 ± 0.82	<0.001
0.3 mg CE				
4 (n=30)	13.77 ± 4.78	4.65 ± 3.71	-9.12 ± 0.85	<0.001
12 (n=29)	13.83 ± 4.86	2.20 ± 2.73	-11.63 ± 0.83	<0.001
Placebo				

4 (n=28)	11.69 ± 3.87	7.89 ± 5.28	-3.80 ± 0.88	-
12 (n=25)	11.61 ± 3.79	5.27 ± 4.97	-6.34 ± 0.89	-
[a.] Standard errors based on assumption of equal variances.				

Prevention of osteoporosis

At present there is no established screening programme for determining women at risk of developing osteoporotic fracture. Epidemiological studies suggest a number of individual risk factors which contribute to the development of postmenopausal osteoporosis. These include: early menopause; family history of osteoporosis; thin, small frame; cigarette use; recent prolonged systemic corticosteroid use.

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 help prevent fractures in women with low bone density and/or established osteoporosis, but the evidence for that is limited.

Effect on bone mineral density

Health and Osteoporosis, Progestin and Oestrogen (HOPE) Study

The HOPE study was a double-blind, randomized, placebo/active-drug-controlled, multicenter study of healthy postmenopausal women with an intact uterus. Subjects (mean age 53.3 ± 4.9 years) were 2.3 ± 0.9 years on average since menopause and took one 600 mg tablet of elemental calcium (Caltrate™) daily. Subjects were not given Vitamin D supplements. They were treated with conjugated oestrogen 0.625 mg, 0.45 mg, 0.3 mg, or placebo. Prevention of bone loss was assessed by measurement of bone mineral density (BMD), primarily at the anteroposterior lumbar spine (L2 to L4). Secondarily, BMD measurements of the total body, femoral neck, and trochanter were also analyzed. Serum osteocalcin, urinary calcium, and N telopeptide were used as bone turnover markers (BTM) at cycles 6, 13, 19, and 26.

Intent-to-treat subjects

All active treatment groups showed significant differences from placebo in each of the four BMD endpoints at cycles 6, 13, 19, and 26. The percent changes from baseline to final evaluation are shown in Table 2.

TABLE 2. PERCENT CHANGE IN BONE MINERAL DENSITY: COMPARISON BETWEEN CE AND PLACEBO GROUPS IN THE INTENT-TO-TREAT POPULATION, LOCF.				
Region Evaluated Treatment Group[a]	**No. of Subjects**	**Baseline (g/cm^2) Mean ± SD**	**Change from Baseline (%) Adjusted Mean ± SE**	**p-Value vs Placebo**
L_2 to L_4 BMD				
0.625	83	1.17 ± 0.15	2.32 ± 0.35	<0.001
0.45	91	1.13 ± 0.15	2.08 ± 0.34	<0.001
0.3	87	1.14 ± 0.15	1.24 ± 0.34	<0.001
Placebo	85	1.14 ± 0.14	-2.46 ± 0.35	
Total body BMD				
0.625	84	1.15 ± 0.08	0.66 ± 0.17	<0.001
0.45	91	1.14 ± 0.08	0.71 ± 0.16	<0.001
0.3	87	1.14 ± 0.07	0.37 ± 0.16	<0.001

Placebo	85	1.13 ± 0.08	-1.52 ± 0.16	
Femoral neck BMD				
0.625	84	0.91 ± 0.14	1.74 ± 0.43	<0.001
0.45	91	0.89 ± 0.13	1.95 ± 0.41	<0.001
0.3	87	0.86 ± 0.11	0.57 ± 0.42	<0.001
Placebo	85	0.88 ± 0.14	-1.81 ± 0.43	
Femoral trochanter BMD				
0.625	84	0.78 ± 0.13	3.78 ± 0.57	<0.001
0.45	91	0.76 ± 0.12	3.46 ± 0.54	<0.001
0.3	87	0.75 ± 0.10	3.19 ± 0.55	0.003
Placebo	85	0.75 ± 0.12	0.93 ± 0.56	
[a.] Identified by dosage (mg) of CE or placebo. BMD = Bone mineral density; L_2 to L_4 = anteroposterior lumbar spine; LOCF = Last observation carried forward; SD = Standard deviation; SE = Standard error.				

The bone turnover markers serum osteocalcin and urinary N-telopeptide significantly decreased ($p < 0.001$) in all active-treatment groups at cycles 6, 13, 19, and 26 compared with the placebo group. Larger mean decreases from baseline were seen with the active groups than with the placebo group. Significant differences from placebo were seen less frequently in urine calcium.

WHI Oestrogen-Alone Substudy

Timing of the initiation of oestrogen therapy relative to the start of menopause may affect the overall risk benefit profile. The WHI oestrogen-alone substudy stratified by age showed in women 50-59 years of age, a non-significant trend towards reduced risk for CHD and overall mortality compared with placebo in women who initiated hormone therapy closer to menopause than those initiating therapy more distant from menopause.

Table 3 describes the primary results of the Oestrogen-alone substudy stratified by age at baseline.

TABLE 3. WOMEN'S HEALTH INITIATIVE OESTROGEN-ALONE SUBSTUDY RESULTS STRATIFIED BY AGE AT BASELINE						
	AGE					
Endpoint	**50-59 years**		**60-69 years**		**70-79 years**	
	CE (N=1637)	**Placebo (N=1673)**	**CE (N=2387)**	**Placebo (N=2465)**	**CE (N=1286)**	**Placebo (N=1291)**
CHD[a,b]						
Number of cases	21	34	96	106	84	77
Absolute risk (N) [c]	17	27	58	62	98	88
Hazard ratio (95% CI)	0.63 (0.36-1.09)		0.94 (0.71-1.24)		1.13 (0.82-1.54)	
Stroke[b]						
Number of cases	18	21	84	54	66	52
Absolute risk (N)[c]	15	17	51	31	76	59
Hazard ratio (95% CI)	0.89 (0.47-1.69)		1.62 (1.15-2.27)		1.21 (0.84-1.75)	
DVT[b]						

Number of cases	16	10	39	29	30	20
Absolute risk (N)[c]	13	8	23	17	34	22
Hazard ratio[d] (95% CI)	1.64 (0.74-3.60)		3.02 (1.51-6.06)		4.54 (2.22-9.31)	
VTE[b] [16]						
Number of cases	20	15	54	43	37	28
Absolute risk (N)[c]	16	12	32	25	42	31
Hazard ratio [d] (95% CI)	1.37 (0.70-2.68)		2.82 (1.59-5.01)		3.77 (2.07-6.89)	
Pulmonary Embolism [b]						
Number of cases	12	8	28	17	12	14
Absolute risk (N)[c]	10	6	17	10	14	16
Hazard ratio[d] (95% CI)	1.54 (0.63-3.77)		2.80 (1.28-6.16)		2.36 (0.96-5.80)	
Invasive Breast Cancer						
Number of cases	25	35	42	60	27	29
Absolute risk (N)[c]	21	29	26	36	32	34
Hazard ratio (95% CI)	0.72 (0.43-1.21)		0.72 (0.49-1.07)		0.94 (0.56-1.60)	
Colorectal Cancer						
Number of cases	8	14	26	31	27	13
Absolute risk (N)[c]	7	12	16	19	32	15
Hazard ratio (95% CI)	0.59 (0.25-1.41)		0.88 (0.52-1.48)		2.09 (1.08-4.04)	
Hip Fracture[b]						
Number of cases	5	1	9	20	32	52
Absolute risk (N)[c]	4	1	5	12	37	58
Hazard ratio (95% CI)	5.02 (0.59-43.02)		0.47 (0.22-1.04)		0.64 (0.41-0.99)	
Total Fractures[b]						
Number of cases	153	173	220	348	167	240
Absolute risk (N)[c]	126	139	132	201	191	269
Hazard ratio (95% CI)	0.90 (0.72-1.12)		0.63 (0.53-0.75)		0.70 (0.57-0.85)	
Overall Mortality[b]						
Number of cases	34	48	129	131	134	113
Absolute risk (N)[c]	28	38	77	75	153	127
Hazard ratio (95% CI)	0.71 (0.46-1.11)		1.02 (0.80-1.30)		1.20 (0.93-1.55)	

[a.] CHD defined as myocardial infarction or coronary death
[b.] Based on adjudicated data over a mean duration of therapy of 7.1 years
[c.] Absolute risk is per 10,000 person-years.
[d.] VTE hazard ratios compared with women aged 50-59 taking placebo

5.2 Pharmacokinetic properties

Absorption
Conjugated oestrogens are soluble in water and are well absorbed from the gastrointestinal tract after release from the drug formulation. The conjugated oestrogens tablet releases conjugated oestrogens slowly over several hours. Maximum plasma

concentrations are achieved approximately 6-10 hours following administration. The oestrogens are generally eliminated in near-parallel fashion, with half-lives ranging from 10-20 hours, when corrected for endogenous concentrations as needed.

The pharmacokinetic profile of unconjugated and conjugated oestrogens following a dose of 1 x 0.625 mg is provided in Table 1.

Table 1 – Pharmacokinetic parameters for Premarin

Pharmacokinetic profile of unconjugated oestrogens following a dose of 1 x 0.625 mg

	Premarin 0.625 mg			
PK Parameter Arithmetic Mean (%CV)	C_{max} (pg/mL)	t_{max} (h)	$t_{1/2}$ (h)	AUC (pg.h/mL)*
estrone	87 (33)	9.6 (33)	50.7 (35)	5557 (59)
baseline-adjusted estrone	64 (42)	9.6 (33)	20.2 (40)	1723 (52)
equilin	31 (38)	7.9 (32)	12.9 (112)	602 (54)

Pharmacokinetic profile for conjugated oestrogens following a dose of 1 x 0.625 mg

	Premarin 0.625 mg			
PK Parameter Arithmetic Mean (%CV)	C_{max} (ng/mL)	t_{max} (h)	$t_{1/2}$ (h)	AUC (pg.h/mL)*
total estrone	2.7 (43)	6.9 (25)	26.7 (33)	75 (52)
baseline-adjusted total estrone	2.5 (45)	6.9 (25)	14.8 (35)	46 (48)
total equilin	1.8 (56)	5.6 (45)	11.4 (31)	27 (56)

Distribution
The distribution of exogenous oestrogens is similar to that of endogenous oestrogens. Oestrogens are widely distributed in the body and are generally found in higher concentration in the sex hormone target organs. Oestrogens circulate in the blood largely bound to sex hormone binding globulin (SHBG) and albumin.

Biotransformation
Exogenous oestrogens are metabolised in the same manner as endogenous oestrogens. Circulating oestrogens exist in a dynamic equilibrium of metabolic interconversions. These transformations take place mainly in the liver. Estradiol is converted reversibly to estrone, and both can be converted to estriol, which is the major urinary metabolite. Oestrogens also undergo enterohepatic recirculation via sulfate and glucuronide conjugation in the liver, biliary secretion of conjugates into the intestine, and hydrolysis in the gut followed by reabsorption. In postmenopausal women a significant proportion of the circulating oestrogens exists as sulfate conjugates, especially estrone sulfate, which serves as a circulating reservoir for the formation of more active oestrogens.

Elimination
Estradiol, estrone and estriol are excreted in the urine, along with glucuronide and sulfate conjugates.

Special Populations
No pharmacokinetic studies were conducted in special populations, including patients with renal or hepatic impairment.

5.3 Preclinical safety data

Long-term continuous administration of natural and synthetic oestrogens in certain animal species increases the frequency of carcinomas of the breast, cervix, vagina and liver.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Compressed Tablet Cores:
Lactose monohydrate (spray dried)
Microcrystalline cellulose
Hypromellose 2208, K100M (100,000 cps)
Magnesium stearate

Tablet Coating:
Filler Coat
Sucrose
Microcrystalline cellulose
Hydroxypropyl cellulose
Hypromellose, 2910, E6 (6 cps)
Hypromellose, 2910, E15 (15 cps)
Polyethylene glycol 400

Colour Coat
Opadry® Green 15B21511#

Polishing
Hypromellose, 2910, E6 (6 cps)
Carnauba wax

Brand
Opacode® WB NS-78-18011, White Ink##

The colorant Opadry® Green 15B21511 contains: HPMC 2910/ Hypromellose, 3 cP, HPMC 2910/ Hypromellose 2910, 6 cP, Quinoline Yellow Aluminium Lake (E104), Macrogol/ PEG 400, FD&C Blue #2/ Indigo Carmine Aluminium Lake (E132), Titanium Dioxide and Polysorbate 80

The white branding ink Opacode® WB NS-78-18011 contains: Titanium Dioxide, Propylene Glycol and Hypromellose 2910, 3 cPs.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Blister pack consisting of a PVC/Aclar®/PVC and a hard tempered aluminium foil lid containing 28 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Pfizer Healthcare Ireland Unlimited Company

The Watermarque Building
Ringsend Road
Dublin 4
D04 K7N3
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0822/095/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25th July 1988
Date of last renewal: 25th July 2008

10 DATE OF REVISION OF THE TEXT

December 2024