Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Premique Cycle 5 Separate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Premique Cycle 5 Separate is available as two separate tablets.

Premarin tablets contain 0.625 mg conjugated estrogens*.

MPA tablets contain 5 mg medroxyprogesterone acetate.

*Conjugated estrogens contains sodium estrone, sodium equilin sulphate, 17α-dihydroequilin, 17α-estradiol, equilenin, 17α-dihydroequilenin, 17β-dihydroequilenin, 17β-estradiol and 8, 9-dehydro-estrone.

Excipients with known effect: Each 0.625 mg conjugated estrogen tablet contains 91.8 mg lactose monohydrate, sucrose and sunset yellow (E110).

Each 5 mg medroxyprogesterone acetate tablet contains 87.5 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Coated tablet and tablet.

Premarin tablets are maroon, biconvex, sugar-coated tablets. MPA tablets are white, round tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Premique Cycle 5 Separate is indicated for hormone replacement therapy (HRT) for estrogen-deficiency symptoms in menopausal and postmenopausal women with an intact uterus.

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

Premique Cycle 5 Separate is taken orally in a continuous sequential 28-day regimen of conjugated estrogen tablets and with 14 days of MPA tablets taken with the estrogen tablet on days 15-28 with no break between packs.

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.

For treatment of moderate to severe vasomotor symptoms, atrophic vaginitis and atrophic urethritis associated with estrogen deficiency: Conjugated estrogens 0.625mg taken daily and MPA 5mg taken daily on days 15 to 28.

For prevention of osteoporosis associated with estrogen deficiency: Conjugated estrogens 0.625mg taken daily and MPA 5mg taken daily on days 15 to 28. For prevention of osteoporosis long-term treatment is necessary.

Breakthrough bleeding and spotting may occur in the early stages of Premique Cycle 5 Separate therapy. To reduce the likelihood of breakthrough bleeding/spotting occurring and to achieve amenorrhoea, a starting dose of 5mg is appropriate. If breakthrough bleeding persists and endometrial abnormality has been ruled out, cyclic therapy should be considered as an alternative.

During the peri-menopausal period, women generally would benefit from a sequential regimen of 0.625mg Premarin with 5.0mg or 10mg MPA (Premique Cycle). This regimen will result in regular withdrawal bleeding. Later in the menopause a regimen producing amenorrhoea may be preferred, in which case a continuous combined regimen is recommended. (Premique). The continuous combined regimen is frequently associated with the development of an atrophic endometrium.

When Premarin/MPA is given in a sequential regimen, MPA 5 or 10 mg is administered from days 15 to 28 and is usually associated with a withdrawal bleed.

Concomitant progestogen use:
Unless there is a previous diagnosis of endometriosis, it is not recommended to add a progestogen in hysterectomised women *(see 4.4-Special warnings and special precautions for use).* Since MPA is administered to reduce the risk of endometrial hyperplasia and endometrial carcinoma, patients without a uterus do not require Premique Cycle 5 Separate.

Commencing treatment advice:
For most postmenopausal women, therapy may be commenced at any convenient time although if the patient is still menstruating commencement on the first day of bleeding is recommended. 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 likely benefits and potential risks.

Method of administration

Premique Cycle 5 Separate is available for oral use as Premarin tablets and MPA tablets.

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.

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

Children
Not recommended.

4.3 Contraindications

1. Known, past or suspected breast cancer.
2. Known or suspected estrogen-dependent malignant tumours (e.g. endometrial cancer).
3. Undiagnosed genital bleeding.
4. Untreated endometrial hyperplasia.
5. Previous or current venous thromboembolism (deep vein thrombosis, pulmonary embolism).
6. Known thrombophilic disorders (e.g. protein C, protein S or antithrombin deficiency, see section 4.4).
7. Active or recent arterial thromboembolic disease (e.g. angina, myocardial infarction).
8. Acute liver disease or history of liver disease where the liver function tests have failed to return to normal.

9. Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
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 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 Premique Cycle 5 Separate, in particular:

- Leiomyoma (uterine fibroids) or endometriosis
- Risk factors for thromboembolic disorders (see below)
- Risk factors for estrogen 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 contra-indication is discovered and in the following situations:

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

Endometrial hyperplasia and carcinoma
In women with an intact uterus the risk of endometrial hyperplasia and carcinoma is increased when estrogens are administered alone for prolonged periods. The reported increase in endometrial cancer risk among estrogen-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 per cycle or continuous combined estrogen-progestogen therapy in non-hysterectomised women prevents the excess risk associated with estrogen-only HRT.

Break through bleeding and spotting may occur during the first months of treatment. If breakthrough bleeding or spotting appears after some time on therapy, or continues after treatment has been discontinued, the reason should be investigated, which may include endometrial biopsy to exclude endometrial malignancy.

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

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

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

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

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

Venous thromboembolism
Hormone replacement therapy (HRT) is associated with a1.3-3 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 estrogens, older age, major surgery, prolonged immobilisation, obesity (Body Mass Index >30kg/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 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 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 protection against myocardial infarction in women with or without existing CAD who received combined conjugated estrogens progesterone or estrogen-only HRT.

The relative risk of CAD during use of combined estrogen+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 estrogen+progestogen use is very low in healthy women close to menopause, but will rise with more advanced age.

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

Other conditions
Estrogens 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 estrogen 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.
The use of estrogens may influence the laboratory results of certain endocrine tests and liver enzymes.

Estrogens 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.
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 biologically 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 some patients on estrogen/progestogen therapy and therefore diabetic patients should be carefully observed while receiving hormone replacement therapy.

Patients with rare hereditary problems of galactose or fructose intolerance, the Lapp lactase deficiency, sucrase-isomaltase insufficiency or glucose-galactose malabsorption should not take this medicine, as the excipients in the tablet include lactose monohydrate and sucrose.

Estrogens should be used with caution in individuals with severe hypocalcaemia.

Women with pre-existing hypertriglyceridemia should be followed closely during estrogen replacement or hormone replacement therapy, since rare cases of large increases of plasma triglycerides leading to pancreatitis have been reported with estrogen 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 estrogen-only HRT after the age of 65. It is unknown whether the findings apply to younger postmenopausal women or other HRT products.

4.5 Interaction with other medicinal products and other forms of interaction

Data from a drug-drug interaction study involving conjugated estrogens and medroxyprogesterone acetate indicated that the pharmacokinetic disposition of both drugs was not altered when the drugs were co-administered. Other clinical drug-drug interaction studies have not been conducted with conjugated estrogens.

The metabolism of estrogens and progestogens may be increased by concomitant use of substances known to induce drug-metabolising enzymes, specifically cytochrome P450 enzymes, such as anticonvulsants (e.g. phenobarbital, phenytoin, carbamazepine) and anti-infectives (e.g. rifampicin, rifabutin, nevirapine, efavirenz).

Ritonavir and nelfinavir, although known as strong inhibitors, by contrast exhibit inducing properties when used concomitantly with steroid hormones.

Hot flushes and vaginal bleeding have been reported in patients taking HRT and St. John's wort. Herbal preparations containing St. John's wort (*Hypericum perforatum*) may inducethe metabolism of estrogens.

CYP3A4 inhibitors such as cimetidine, erythromycin and ketoconazole may increase plasma concentrations of 17β-estradiol and may result in side effects.

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

The response to metyrapone may be reduced.

Aminogluthimide administered concomitantly with MPA may significantly depress the bioavailability of MPA.

4.6 Fertility, pregnancy and lactation

Pregnancy
Premique Cycle 5 Separate is not indicated during pregnancy. If pregnancy occurs during medication with Premique Cycle 5 Separate, treatment should be withdrawn immediately. Clinically, data on a limited number of exposed pregnancies indicate no adverse effects of MPA on the foetus. The results of most epidemiological studies to date relevant to inadvertent foetal exposure to combinations of estrogens and progestogens indicate no teratogenic or foetotoxic effect

Lactation
Premique Cycle 5 Separate is not indicated during lactation.

4.7 Effects on ability to drive and use machines

Not applicable.

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. Breast pain is a very common adverse event reported in ≥ 10% of patients.

System Organ Class	**Very Common ADRs (>1/10)**	**Common ADRs (>1/100, < 1/10)**	**Uncommon ADRs (>1/1000, <1/100)**	**Rare ADRs (>1/10000, <1/1000)**	**Very Rare ADRs (<1/10000), isolated reports**
Infections and infestations		Vaginitis,	Vaginal candidiasis		
Neoplasms benign and malignant (including cysts				Breast cancer; Fibrocystic breast changes Ovarian cancer,	Endometrial cancer; Enlargement of hepatic

and polyps)				Growth potentiation of benign meningioma	hemangiomas
Immune system disorders				Anaphylactic/ 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; Acne; Pruritus	Chloasma/melasma; Hirsutism; Pruritus; Rash	Erythema multiforme; Erythema nodosum
Musculoskeletal, connective tissue and bone disorders		Arthralgias; Leg cramps			

Reproductive system & breast disorders	Breast pain	Breakthrough bleeding/spotting Dysmenorrhea, Breast tenderness, enlargement, discharge	Change in menstrual flow; Change in cervical ectropion and secretion	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 estrogen-progestogen therapy for more than 5 years.
- Any increased risk in users of estrogen-only therapy is substantially lower than that seen in users of estrogen-progestogen combinations.
- The level of risk is dependent on the duration of use (see section 4.4).
- Results of the largest randomised placebo-controlled trial (WHI-study) and largest epidemiological study (MWS) are presented.

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

Age range (years)	Additional cases per 1000 never-users of HRT over a 5 year period*	Risk ratio & 95%CI#	Additional cases per 1000 HRT users over 5 years (95%CI)
		Estrogen only HRT	
50-65	9-12	1.2	1-2 (0-3)
		Combined estrogen-progestogen	
50-65	9-12	1.7	6 (5-7)
#Overall risk ratio. The risk ratio is not constant but will increase with increasing duration on use Note: Since the background incidence of breast cancer differs by EU country, the number of additional cases of breast cancer will also change proportionately.			

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

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

‡When the analysis was restricted to women who had not used HRT prior to the study there was no increased risk apparent during the first 5 years of treatment: after 5 years the risk was higher than in non-users.
*Taken from baseline incidence rates in developed countries.
**WHI study in women with no uterus, which did not show an increase in risk of breast cancer.

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 estrogen-only HRT is not recommended because it increases the risk of endometrial cancer (see section 4.4).
Depending on the duration of estrogen-only use and estrogen 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 estrogen-only therapy for at least 12 days per cycle can prevent this increased risk. In the Million Women Study the use of five years of combined (sequential or continuous) HRT did not increase risk of endometrial cancer (RR of 1.0 (0.8-1.2)).

Ovarian cancer

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

Risk of venous thromboembolism

HRT is associated with a 1.3-3-fold increased relative risk of developing venous thromboembolism (VTE), i.e. deep vein thrombosis or pulmonary embolism. The occurrence of such an event is more likely in the first year of using 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 estrogen-only*			
50-59	7	1.2 (0.6-2.4)	1 (-3 – 10)
Oral combined estrogen-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 estrogen-progestogen HRT over the age of 60 (see section 4.4).

Risk of ischaemic stroke

- The use of estrogen-only and estrogen + 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 estrogen/progestogen treatment including Premique:

- Estrogen-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. For further information, *see sections 4.3 Contraindications and 4.4 Special warnings and precautions for use.*
- Cholestatic jaundice
- Enlargement of hepatic haemangiomas
- Skin and subcutaneous disorders: vascular purpura
- Probable dementia over the age of 65 *(see section 4.4)*
- Exacerbation of hypocalcaemia

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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

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

There are no reported cases of medroxyprogesterone acetate overdose.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: GO3F A12

Conjugated Estrogens
The active ingredients are primarily the sulphate esters of estrone, equilin sulphates and 17α/β-estradiol. These substitute for the loss of estrogen production in menopausal women, and alleviate menopausal symptoms. Estrogens prevent bone loss following menopause or ovariectomy.

Progestogen:
As estrogens promote the growth of the endometrium, unopposed estrogens increase the risk of endometrial hyperplasia and cancer. The addition of a progestogen greatly reduces the estrogen-induced risk of endometrial hyperplasia in non-hysterectomised women.

Relief of estrogen-deficiency symptoms
In the first year of the Health and Osteoporosis, Progestin and Estrogen (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 estrogens, 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 randomisation. With conjugated estrogens 0.625mg tablets, the relief 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.

Prevention of osteoporosis
Estrogen deficiency at menopause is associated with an increasing bone turnover and decline in bone mass. The effect of estrogens 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.

5.2 Pharmacokinetic properties

Absorption

Conjugated estrogens are soluble in water and are well absorbed from the gastrointestinal tract after release from the drug formulation.

The following pharmacokinetic parameters were obtained from a single dose study using 2 x 0.625 mg CE/5 mg MPA Combination Tablets (n = 51)

PK Parameter	**----**	**C_{max}** (pg/mL)	**t_{max}** (h)	**$t_{1/2}$** (h)	**AUC** (pg•h/mL)
Arithmetic Mean (%CV)					
Unconjugated Oestrogens					
Estrone	----	124 (43)	10 (35)	62.2 (137)	6303 (40)
BA* -Estrone	----	104 (49)	10 (35)	26.0 (100)	3136 (51)
Equilin	----	54 (43)	8.9 (34)	15.5 (53)	1179 (56)
PK Parameter	**----**	**C_{max}** (ng/mL)	**t_{max}** (h)	**$t_{1/2}$** (h)	**AUC** (ng•h/mL)
Arithmetic Mean (%CV)					
Conjugated Oestrogens					
Total Estrone	----	6.3 (48)	9.1 (29)	23.6 (36)	151 (42)
BA* -Total Estrone	----	6.2 (48)	9.1 (29)	20.6 (35)	139 (40)
Total Equilin	----	4.2 (52)	7.0 (36)	17.2 (131)	72 (50)
PK Parameter	**----**	**C_{max}** (ng/mL)	**t_{max}** (h)	**$t_{1/2}$** (h)	**AUC** (ng•h/mL)
Arithmetic Mean (%CV)					
Medroxyprogesterone Acetate					
MPA	----	4.8 (31)	2.4 (50)	46.3 (39)	102 (28)

BA* = Baseline adjusted

C_{max} = peak plasma concentration

t_{max} = time peak concentration occurs

$t_{1/2}$ = apparent terminal-phase disposition half-life ($0.693/\lambda_z$)

AUC = total area under the concentration-time curve

Distribution

The distribution of exogenous estrogens is similar to that of endogenous estrogens. Estrogens are widely distributed in the body and are generally found in higher concentration in the sex hormone target organs. Estrogens circulate in the blood largely bound to sex hormone binding globulin (SHBG) and albumin. MPA is approximately 90 percent bound to plasma proteins, but does not bind to SHBG.

Metabolism

Exogenous estrogens are metabolised in the same manner as endogenous estrogens. Circulating estrogens 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. Estrogens also undergo enterohepatic recirculation via sulphate 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 estrogens exists as sulphate conjugates, especially estrone sulphate, which serves as a circulating reservoir for the formation of more active estrogens. Metabolism and elimination of MPA occur primarily in the liver via hydroxylation, with subsequent conjugation and elimination in the urine.

Excretion

Estradiol, estrone, and estriol are excreted in the urine, along with glucuronide and sulphate conjugates. Most metabolites of MPA are excreted as glucuronide conjugates, with only minor amounts excreted as sulphates.

5.3 Preclinical safety data

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

In a two-year oral study in which female rats were exposed to MPA dosages of up to 5000µg/kg/day in their diets (50 times higher - based on AUC values - than the level observed in women taking 10mg of MPA), a dose-related increase in pancreatic islet cell tumours (adenomas and carcinomas) occurred. Pancreatic tumour incidence was increased at 1000 and 5000µg/kg/day, but not at 200µg/kg/day.

The cortisol activity of MPA at these high doses is thought to increase serum glucose in rats which reactively stimulates the beta cells of the pancreatic islets to produce insulin. This repeated stimulation is thought to cause the tumours in rats. Similar lesions are not likely to occur in humans since the endocrine system of rats is more sensitive to hormones than that of women. When MPA is combined with estrogen, MPA binds to fewer glucocorticosteroid receptors and thus has less effect on plasma glucose. In humans, the diabetogenic response to MPA at therapeutic doses is slight. Moreover, an extensive literature search revealed no evidence that MPA causes pancreatic tumours in humans.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Constituents in the conjugated estrogen tablets are:

Tablet Core:
Lactose monohydrate
Magnesium stearate
Methylcelluose

Sugar coating:
Calcium sulphate anhydrous
Carnauba wax
Microcrystalline cellulose

Glycerol mono-oleate
Macrogol 20000
Pharmaceutical glaze (shellac solution)
Sucrose
Titanium Dioxide (E171)
Opalux Maroon AS 3910 (contains sucrose, povidone, sodium benzoate (E211) and colours titanium dioxide (E171), sunset yellow (E110) indigo carmine blue (E132), and erythrosine aluminium lake (E127)).

Constituents in MPA tablets are:
Lactose monohydrate
Magnesium stearate
Methylcellulose
Microcrystalline Cellulose

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package.

6.5 Nature and contents of container

Polyvinylchloride (PVC)/Aluminium foil blister pack containing 28 conjugated estrogen tablets and 14 MPA tablets in a cardboard carton.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Pfizer Healthcare Ireland
9 Riverwalk
National Digital Park
Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0822/096/005

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 30 April 1996

Date of last renewal: 30 April 2006

10 DATE OF REVISION OF THE TEXT

March 2015