Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Premique 0.625mg/5mg Coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 0.625mg of conjugated estrogens[†] and 5.0mg of medroxyprogesterone acetate (MPA).

[†]Conjugated estrogens contain sodium estrone sulfate, sodium equilin sulfate, 17α-dihydroequilin, 17α-estradiol, equilenin, 17α-dihydroequilenin, 17β-dihydroequilin, 17 β-dihydroequilenin, 17 β-estradiol and 8,9-dehydro-estrone.

Excipients with known effect
Contains 98.47mg of lactose monohydrate and 212.0mg of sucrose per tablet.

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Coated Tablet
A light blue oval biconvex sugar-coated tablet marked with "0.625/5".

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Premique is indicated for hormone replacement therapy (HRT) for estrogen-deficiency symptoms in 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

Posology

Adults

Premique is taken orally in a continuous combined 28-day regimen of one tablet daily with no break between packs.

For initiation and continuation of treatment of postmenopausal symptoms, the lowest effective dose for the shortest duration (see 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: The usual starting dose is one tablet 0.625mg/5.0mg per day.

For prevention of osteoporosis associated with estrogen deficiency: The usual starting dose is one tablet 0.625mg/5.0mg per day.
For prevention of osteoporosis long-term treatment is necessary.

Breakthrough bleeding and spotting may occur in the early stages of Premique therapy. To reduce the likelihood of breakthrough bleeding/spotting occurring and to achieve amenorrhoea, a starting medroxyprogesterone acetate (MPA) dose of 5mg is appropriate.

During the peri-menopausal period, women generally would benefit from a sequential regimen of conjugated estrogens with MPA (Premique Cycle 10). 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.

Concomitant progestogen use:

Unless there is a previous diagnosis of endometriosis it is not recommended to add a progestogen in hysterectomised women (see section 4.4). Since MPA is administered to reduce the risk of endometrial hyperplasia and endometrial carcinoma, patients without a uterus do not require Premique.

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.

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.

Paediatric population:

Not recommended

Method of administration

For oral use only.

4.3 Contraindications

1. Hypersensitivity to conjugated estrogen or to medroxyprogesterone or to any of the excipients listed in section 6.1.
2. Known, past or suspected breast cancer.
3. Known or suspected estrogen-dependent malignant tumours (e.g. endometrial cancer).
4. Undiagnosed genital bleeding.
5. Untreated endometrial hyperplasia.
6. Previous idiopathic or current venous thromboembolism (deep vein 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 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 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, 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 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 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 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 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. **Breast**

cancer The overall evidence shows an increased risk of breast cancer in women taking combined estrogen-progestogen or 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 a meta-analysis of prospective 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 3 (1-4) years (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 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. Epidemiological evidence from a large meta-analysis suggests a slightly increased risk in women taking estrogen-only or combined estrogen-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 estrogens, 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 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.
- 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 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 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 patients with disease that can predispose to 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 interactions

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. St. John’s wort may induce hepatic microsomal enzymes which theoretically may result in reduced efficacy of HRT.

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 medroxyprogesterone acetate (MPA) may significantly depress the bioavailiablity of MPA.

4.6 Fertility, pregnancy and lactation

Pregnancy

Premique 0.625mg/5mg is not indicated during pregnancy. If pregnancy occurs during medication with Premique 0.625mg/5mg, treatment should be withdrawn immediately.

Clinically, data on a limited number of exposed pregnancies indicate no adverse effects of medroxyprogesterone acetate (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.

Breast-feeding

Premique 0.625mg/5mg 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 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 ^{3} 10% of patients.

System Organ Class	**Very Common ADRs (>1/10)**	**Common ADRs (>1/100, < 1/10)**	**Uncommon ADRs (>1/1,000, <1/100)**	**Rare ADRs (>1/10,000, <1/1,000)**	**Very Rare ADRs (<1/10,000), isolated reports**
Infections and infestations		**Vaginitis,**	Vaginal candidiasis	None	None
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 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	None
Nervous system disorders			Dizziness; Headache; Migraine; Anxiety	Stroke; Exacerbation of epilepsy;	Exacerbation of chorea
Eye disorders			Intolerance to contact lenses	None	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; Pruritis	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.
- The increased risk in users of estrogen-only therapy is 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).
- 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
		Estrogen only HRT	

50	13.3	1.2	2.7
		Combined estrogen-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
		estrogen only HRT	
50	26.6	1.3	7.1
		Combined estrogen-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 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)

*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 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

Use of estrogen-only or combined estrogen-progestogen HRT has been associated with a slightly increased risk having of 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 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 (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 (see section 4.4)
- Exacerbation of chorea
- Exacerbation of porphyria
- 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 Website: www.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 overdosage.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Progestogens and estrogens, fixed combinations.

ATC Code: GO3F A12 (Medroxyprogesterone & estrogen).

Conjugated Estrogens

The active ingredients are primarily the sulfate esters of estrone, equilin sulfates 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.

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.

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.

Biotransformation

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 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 estrogens exists as sulfate conjugates, especially estrone sulfate, 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.

Elimination

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

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 medroxyprogesterone acetate (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 200microgram/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

Tablet Cores:
Lactose monohydrate
Methylcellulose (E461)
Magnesium stearate (E572)

Tablet coating ink and polish excipients:
Macrogol (E405)
Glyceryl mono-oleates
Pharmaceutical glaze
Calcium sulfate anhydrous (E516)
Microcrystalline cellulose

Sucrose
Titanium dioxide (E171)
Povidone (E1201)
Carnauba wax (E903)
Stearic Acid
Calcium phosphate tribasic (E341)
Powdered cellulose
FD&C Blue, No 2 Aluminium Lake HT 5625
Edible Ink (Opacode Black S-8-27741)†
†contains iron oxide black (E172), shellac (E904), purified water, ethanol, N-butyl alcohol, propylene glycol (E1520), ethyl acetate and ammonia solution.

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 original package.

6.5 Nature and contents of container

Polyvinylchloride (PVC)/aluminium foil blister pack of 28 tablets.

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

PA0822/096/003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28 May 1998

Date of last renewal: 28 May 2008

10 DATE OF REVISION OF THE TEXT

October 2020