SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Premique Low Dose 0.3mg/1.5mg modified-release tablets
Conjugated oestrogens/medroxyprogesterone acetate Pfizer 0.3mg/1.5mg modified-release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Conjugated oestrogens[†] 0.3 mg and medroxyprogesterone acetate (MPA) 1.5 mg.

[†]Conjugated oestrogens contain the sodium sulfate conjugates of estrone, equilin, 17α-dihydroequilin, 17α-estradiol, 17β-dihydroequilin, 17α-dihydroequilenin, 17β-dihydroequilenin, equilenin, 17β-estradiol and Δ8,9-dehydro-estrone.

Excipients with known effect
Contains 61.7mg of lactose monohydrate and 40.69mg of sucrose.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Modified-release tablet.
Cream oval biconvex sugar coated tablet marked “PREMPRO 0.3/1.5” in black ink.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Hormone replacement therapy for oestrogen deficiency symptoms in postmenopausal women with an intact uterus.

4.2 Posology and method of administration

Posology

Adults:

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

In women who are not taking hormone replacement therapy or women who switch from another 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.

For treatment of postmenopausal symptoms: Take one tablet per day.

Breakthrough bleeding and spotting may occur in the early stages of this medicine therapy. If breakthrough bleeding persists and endometrial abnormality has been ruled out, a higher dose of treatment or cyclic therapy should be considered as an alternative.

The lowest dose and regimen that will control symptoms should be chosen.

Maintenance/Continuation/Extended treatment

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.

The benefits of the lower risk of endometrial hyperplasia and endometrial cancer due to adding a progestogen should be weighed against the increased risk of breast cancer (see sections 4.4 and 4.8).

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, the patient should not take double the usual dose to make up for missed tablets.

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

This medicine is taken orally.

4.3 Contraindications

1. Hypersensitivity to the active substances or to any of the excipients of this medicine tablets listed in section 6.1.

2. Known, past or suspected 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 (e.g. 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 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 this medicine, in particular:

- Leiomyoma (uterine fibroids) or endometriosis
- Risk factors for thromboembolic disorders (see below)
- Risk factors for oestrogen dependent tumours (e.g. 1st degree heredity for breast cancer)
- Hypertension
- Liver disorders (e.g. liver adenoma)
- Diabetes mellitus with or without vascular involvement

- Cholelithiasis
- Migraine or (severe) 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 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 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. Unless there is a previous diagnosis of endometriosis it is not recommended to add a progestogen in hysterectomised women.

The reduction in risk to the endometrium should be weighed against the increase in the risk of breast cancer of added progestogen (see 'Breast cancer' below and section 4.8).

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 oestrogen-progestogen or oestrogen-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 oestrogen-progestogen combinations 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 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).

Meningioma

Meningiomas have been reported following long term administration of progestogens, including medroxyprogesterone acetate. Medroxyprogesterone should be discontinued if a meningioma is diagnosed. Caution is advised when recommending medroxyprogesterone to patients with a history of meningioma.

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 than later (see section 4.8).

Patients with a history of VTE or known thrombophilic states have an increased risk of VTE. HRT may add to this risk. HRT is therefore contraindicated in these patients (see section 4.3). Personal or strong family history of thromboembolism or recurrent spontaneous abortion should be investigated in order to exclude a thrombophilic predisposition.

Generally recognised risk factors for VTE include, use of oestrogens, older age, major surgery, prolonged immobilisation, obesity (BMI > 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 scrupulous attention should be given to prophylactic measures to prevent VTE following surgery. Where prolonged immobilisation is liable to follow elective surgery, particularly abdominal or orthopaedic surgery to the lower limbs, consideration should be given to temporarily stopping HRT 4-6 weeks earlier, if this is possible. 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 anticoagulant treatment require careful consideration of the benefit-risk of use of HRT.

If venous thromboembolism develops after initiating therapy the drug should be discontinued. Patients should be told to contact their doctors 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 MPA.

The relative risk of CAD during use of combined oestrogen+progestogen HRT is slightly increased. As the baseline absolute risk of CAD is strongly dependent on age, the number of extra cases of CAD due to oestrogen+progestogen use is very low in healthy women close to menopause, but will rise with more advanced age.

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).

Other conditions

- Oestrogens/progestogens 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 this medicine is increased.
- 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.

    - The use of oestrogen 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. 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).

  Some patients dependent on thyroid hormone replacement therapy may require increased doses in order to maintain their free thyroid hormone levels in an acceptable range. Therefore, patients should have their thyroid function monitored more frequently when commencing concurrent treatment in order to maintain their free thyroid hormone levels in an acceptable range.

- 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.

- There is an increase in the risk of gallbladder disease in women receiving HRT (see conditions that need supervision).

- A worsening of glucose tolerance may occur in some patients on oestrogen/progestogen therapy and therefore diabetic patients should be carefully observed while receiving hormone replacement therapy.

- 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.

- Oestrogens should be used with caution in individuals with severe hypocalcaemia.

4.5 Interaction with other medicinal products and other forms of interaction

The metabolism of oestrogens 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.

Herbal preparations containing St John's wort (*Hypericum perforatum*) may induce the metabolism of oestrogens and progestogens.

Clinically, an increased metabolism of oestrogens 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.

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
This medicine is not indicated during pregnancy. If pregnancy occurs during medication with this medicine 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 oestrogens and progestogens indicate no teratogenic or foetotoxic effect.

Breast-feeding
This medicine is not indicated during lactation.

4.7 Effects on ability to drive and use machines

This medicine should not affect the ability to drive or use machinery.

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 rate), 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 and polyps)				Fibrocystic breast changes, Ovarian cancer	Enlargement of hepatic hemangiomas
Immune system disorders				Anaphylactic/ anaphylactoid reactions, including urticaria and angioedema	
Metabolism and nutrition disorders				Glucose intolerance	Exacerbation of porphyria; Hypocalcemia
Psychiatric disorders		Depression	Changes in libido; Mood disturbances	Irritability	
Nervous system			Dizziness;	Stroke;	Exacerbation of

disorders			Headache; Migraine; Anxiety	Exacerbation of epilepsy	chorea
Eye disorders			Intolerance to contact lenses		Retinal vascular thrombosis
Cardiac disorders				Myocardial infarction	
Vascular disorders			Pulmonary embolism	Superficial thrombophlebitis	
Respiratory, thoracic and mediastinal disorders				Exacerbation of asthma	
Gastrointestinal disorders			Nausea; Bloating; Abdominal pain	Vomiting; Pancreatitis	
Hepatobiliary disorders			Gallbladder disease	None	Cholestatic jaundice
Skin and subcutaneous tissue disorders			Alopecia; Acne; Pruritus	Chloasma/ melasma; Hirsutism; Pruritus; Rash	
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	
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	Incidenceper 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 this medicine:

- 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. For further information, see section 4.3 and 4.4.
- Myocardial infarction
- Stroke
- Skin and subcutaneous disorders: erythema multiforme, erythema nodosum, vascular purpura
- Probable dementia (see section 4.4)
- Exacerbation of otosclerosis

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

4.9 Overdose

Symptoms of overdosage of oestrogen-containing products in adults and children may include nausea, vomiting, breast tenderness, dizziness, abdominal pain, drowsiness/fatigue 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, fixed combinations, ATC Code: GO3F A12 (Medroxyprogesterone & oestrogen).

Conjugated Oestrogens

The active ingredients are primarily the sulfate esters of estrone, equilin sulfates, 17α-estradiol and 17β-estradiol. These substitute for the loss of oestrogen production in menopausal women, and alleviate menopausal symptoms.

Progestogen:

As oestrogens promote the growth of the endometrium, unopposed oestrogens increase the risk of endometrial hyperplasia and cancer. The addition of a progestogen reduces but does not eliminate the oestrogen-induced risk of endometrial hyperplasia in non-hysterectomised women.

Relief of oestrogen-deficiency symptoms

In a 1-year clinical trial (n=2,808), vasomotor symptoms were assessed for efficacy during the first 12 weeks of treatment in a subset of symptomatic women (n=241) who had at least 7 moderate or severe hot flushes daily or 50 moderate to severe hot flushes during the week before randomisation. Premique 0.625mg/2.5mg (conjugated oestrogens/medroxyprogesterone acetate) was shown to be statistically better than placebo at weeks 4, 8 and 12 for relief of both frequency and severity of moderate to severe vasomotor symptoms.

In two clinical trials, the incidence of amenorrhoea (no bleeding or spotting) increased over time in women treated with Premique 0.625 mg/2.5 mg. Amenorrhoea was seen in 68% of women at cycle 6 and 77% of women at cycle 12. Breakthrough bleeding and/or spotting appeared in 48% during the first 3 months, and in 24% of women during months 10-12 of treatment.

5.2 Pharmacokinetic properties

Absorption
This medicine contains a formulation of medroxyprogesterone acetate (MPA) that is immediately released and conjugated oestrogens that are slowly released over several hours.

Following single dose administration of this medicine under fasting conditions, the time taken to reach the peak plasma concentration (Tmax) was 6 – 9 hours and the peak plasma concentration (Cmax±SD) was 149±52 pg/ml and 83± 32pg/ml for the unconjugated oestrogens, estrone and equilin, respectively. Peak plasma concentration (Cmax±SD) of 724±475 pg/ml was reached at 2 hours (Tmax) for MPA.

When single doses of this medicine were administered with a high-fat meal, there was a two-fold increase in MPA Cmax (1830±1050 pg/ml) and AUC was increased by approximately 30%. Food had little or no significant effect on the exposure of unconjugated and conjugated oestrogens. These changes to MPA Cmax and AUC after a high fat meal are not considered to be clinically meaningful as the pharmacokinetics of MPA are highly variable and safety of a wide range of MPA doses up to 10mg have been demonstrated.

This medicine can be administered with or without food.

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 concentrations in the sex hormone target organs. Oestrogens circulate in the blood largely bound to sex hormone binding globulin (SHBG) and albumin. MPA is approximately 90% bound to plasma proteins but does not bind to SHBG.

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. 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 extracted as glucuronide conjugates with only minor amounts secreted as sulfates.

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.

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 oestrogen, MPA binds to fewer glucocorticosteriod 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 core:	Lactose Monohydrate Microcrystalline Cellulose Hypromellose 2208, K100M Magnesium Stearate Purified Water
Tablet coating:	Sucrose

	Microcrystalline Cellulose Hydroxypropyl Cellulose Hypromellose, 2910, E6 Hypromellose, 2910, E15 Polyethylene Glycol 400 Purified Water Eudragit NE 30 D (30% solids) (Ethyl Acrylate and Methacrylate Copolymer Dispersion) Spectrablend light Yellow [a] Purified Water
	Hypromellose 2910 E6 Carnauba Wax Purified Water
Printing on tablet:	Opacode® WB NS-78-17821, Black Ink (Purified Water, Iron Oxide Black (E172), Isopropyl Alcohol, Propylene Glycol, Hypromellose 2910)

[a]Contains: Hypromellose 2910, Titanium Dioxide (E171) and Yellow Iron Oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 25□C. Keep blister in the outer carton to protect from light.

6.5 Nature and contents of container

Blister pack, consisting of a polyvinyl chloride (PVC)/Aclar® film and aluminum foil with heat seal coating containing 28 tablets. Each carton contains 28 tablets (1 blister pack) or 84 tablets (3 blister packs).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Pfizer Limited
Ramsgate Road
Sandwich
Kent
CT13 9NJ
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 00057/1288

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

31/10/2025

10 DATE OF REVISION OF THE TEXT

31/10/2025