SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Prempak-C® 1.25 mg/0.15 mg Coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Prempak-C 1.25mg consists of 28 tablets containing 1.25mg conjugated estrogens , and 12 tablets containing 0.15mg norgestrel.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Coated tablets.

Yellow oval biconvex sugar coated tablet marked with “1.25” in black ink.
Round light brown sugar coated tablets containing norgestrel 0.15mg.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- Hormone replacement therapy for estrogen deficiency symptoms in menopausal and postmenopausal women
- Prevention of osteoporosis in postmenopausal women at high risk of future fractures who are intolerant of, or contraindicated for, other medicinal products approved for the prevention of osteoporosis.

4.2 Posology and method of administration

Posology

Adults:

Prempak-C is available for oral use in a sequential regimen for treatment of women with a uterus. The recommended starting dose is 0.625 mg-1.25 mg conjugated estrogens daily. One norgestrel tablet should be taken daily from

day 17 to day 28 of estrogen therapy. Continuous estrogen administration is recommended. For maintenance, the lowest effective dose should be used.

For treatment of postmenopausal symptoms:

0.625-1.25mg conjugated estrogens daily depending on the response of the individual. One norgestrel tablet should be taken daily from day 17 to day 28 of estrogen therapy.

Prophylaxis of osteoporosis:

The minimum effective dose is 0.625 mg daily for most patients. One norgestrel tablet should be taken daily from day 17 to day 28 of estrogen therapy (see section 5.1).

For most postmenopausal women therapy may be commenced at any convenient time although if the patient is still menstruating, commencement on first day of bleeding is recommended. In women transferring from another sequential hormone replacement therapy regimen, treatment should begin the day following completion of the prior regimen. Withdrawal bleeding usually occurs within three to seven days after the last norgestrel tablet.

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 the forgotten tablet.

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 the active substances or to any of the excipients listed in section 6.1

2. Known, past or suspected cancer of the breast

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

4. Undiagnosed abnormal 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.

1. Medical examination/Follow up

Before initiating or reinstituting HRT, a complete personal and family medical history should be taken. Physical (including pelvic and breast) examination should be guided by this and by the contraindications and warnings for use. During treatment, periodic check-ups are recommended of a frequency and nature adapted to the individual women. Women should be advised what changes in their breasts should be reported to their doctor or nurse (see 'Breast Cancer' below). Investigations, including appropriate imaging tools, e.g. mammography, should be carried out in accordance with currently accepted screening practices, modified to the clinical needs of the individual.

2. Conditions that 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 Prempak-C, in particular:

- Leiomyoma (uterine fibroids) or endometriosis
- A family history of, or other 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

3. Reasons for immediate withdrawal of therapy

Therapy should be discontinued if 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

4. 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 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. 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.

5. 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.

A randomised placebo-controlled trial, the Women's Health Initiative study (WHI), and epidemiological studies, including the Million Women Study (MWS), have reported an increased risk of breast cancer in women taking estrogen-progestogen combinations for HRT that becomes apparent after 3 years (see section 4.8).

For all HRT, an excess risk becomes apparent within a few years of use and increases with the duration of intake 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.

6. 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).

7. 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. Women

already on chronic anticoagulant treatment require careful consideration of the benefit-risk of use of HRT.

Generally recognised risk factors for VTE include a personal or family history, use of estrogens, older age, major surgery, prolonged immobilisation, obesity (BMI > 30 kg/m2), 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 to be considered 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. 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.

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).

8. 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 estrogen-progestogen 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.

9. 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

10. Estrogens/progestogens may cause fluid retention and therefore patients with cardiac or renal dysfunction should be carefully observed.

11. The use of estrogen 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.

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.

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

13. 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.

    This product contains lactose 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.

14. 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.

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

16. HRT does not improve cognitive function. There is some evidence from the WHI trial of increased risk of probable dementia in women who start using continuous combined or estrogen-only HRT after the age of 65.

17. Exogenous estrogens may induce or exacerbate symptoms of angioedema, particularly in women with hereditary angioedema.

4.5 Interaction with other medicinal products and other forms of interaction

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.

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

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.

4.6 Fertility, Pregnancy and lactation

Pregnancy:

Prempak-C is not indicated during pregnancy. If pregnancy occurs during medication with Prempak-C 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.

Breast-feeding:

Prempak-C is not indicated during lactation.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

See also section 4.4.

Adverse drug reactions (ADRs)

The adverse reactions listed in the table are based on post-marketing spontaneous (reporting rate), clinical trials and class-effects. Breast pain is a very common adverse event reported in ≥ 10% of patients.

System Organ Class	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, Hypocalcaemia
Psychiatric disorders	Depression	Changes in libido; Mood disturbances,	Irritability	
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		Pulmonary embolism, Deep vein thrombosis	Superficial thrombophlebitis	
Respiratory, thoracic and mediastinal disorders			Exacerbation of asthma	
Gastrointestinal disorders		Nausea, Bloating, Abdominal pain	Vomiting, Pancreatitis	
Hepatobiliary disorders		Gallbladder disease		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	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

- 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

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 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 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*5 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)

Other adverse reactions reported in association with estrogen/progestogen treatment including Prempak-C:

- 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 and 4.4.
- Myocardial infarction.
- Skin and subcutaneous disorders: erythema multiforme, erythema nodosum, vascular purpura.
- Probable dementia over the age of 65 (see section 4.4).
- Exacerbation of otosclerosis.

Reporting of side effects
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 estrogen-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 estrogens, fixed combinations; ATC Code: **G03F A10**

Conjugated Estrogens

The active ingredients are primarily the sulfate esters of estrone, equilin sulfates, 17α-estradiol and 17β-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 reduces but does not eliminate the estrogen-induced risk of endometrial hyperplasia in non-hysterectomised women.

The following data are from studies done with a different progestogen to that in Prempak-C. However, since the effect is due to the conjugated estrogens, these results can be extrapolated to other conjugated estrogen plus progestogen combination products.

Relief of estrogen-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 0.625 mg/2.5 mg (conjugated estrogens/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.

Prevention of osteoporosis

Epidemiological studies suggest a number of individual risk factors which contribute to the development of postmenopausal osteoporosis. These include: early menopause; family history of osteoporosis; thin, small frame; cigarette use; recent prolonged systemic corticosteroid use.

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

After 3 years of treatment with Premique 0.625 mg/2.5 mg, the increase in lumbar spine bone mineral density (BMD) was 4.87% ± 0.66. The percentage of women who maintained (less than 1% BMD loss per year) or gained BMD in lumbar zone during treatment was 92%.

Premique 0.625 mg/2.5 mg also had an effect on hip BMD. The increase after 3 years was 1.94% ± 0.44 at total hip. The percentage of women who maintained (less than 1% BMD loss per year) or gained BMD in hip zone during treatment was 88%.

5.2 Pharmacokinetic properties

Conjugated Estrogens

Absorption

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

(conjugated estrogens only) release conjugated estrogens slowly over several hours. The pharmacodynamic profile of unconjugated and conjugated estrogens following a dose of 2 x 0.625 mg is provided in Table 1.

Distribution

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

Biotransformation

Exogenous estrogens are metabolised in the same manner as endogenous estrogens. Circulating estrogens exist in 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 following reabsorption. In post-menopausal 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.

Elimination

Estriol, estrone and estradiol are excreted in the urine along with glucuronide and sulfate conjugates.

Table 1 – Pharmacokinetic parameters for Premarin

Pharmacokinetic profile for unconjugated estrogens following a dose of 2 x 0.625.mg

Drug PK Parameter Arithmetic Mean (%CV)	C_{max} (pg/mL)	t_{max} (h)	$t_{1/2}$ (h)	AUC (pg.h/mL)*
estrone	139 (37)	8.8 (20)	28.0 (13)	5016 (34)
baseline-adjusted estrone	120 (42)	8.8 (20)	17.4 (37)	2956 (39)
equilin	66 (42)	7.9 (19)	13.6 (52)	1210 (37)

* $t_{1/2}$ = terminal-phase disposition half-life (0.693/γ)

Pharmacokinetic profile for conjugated estrogens following a dose of 2 x 0.625 mg

Drug PK Parameter Arithmetic Mean (%CV)	C_{max} (ng/mL)	t_{max} (h)	$t_{1/2}$ (h)	AUC (pg.h/mL)*
total estrone	7.3 (41)	7.3 (51)	15.0 (25)	134 (42)
baseline-adjusted total estrone	7.1 (41)	7.3 (25)	13.6 (27)	122 (39)
total equilin	5.0 (42)	6.2 (26)	10.1 (27)	65 (45)

* $t_{1/2}$ = terminal-phase disposition half-life (0.693/γ)

Norgestrel

Norgestrel is a racemic mixture consisting of a levo-rotatory isomer, which is biologically inactive, and the biologically active dextro-rotatory isomer, commonly known as levonorgestrel.

The biologically active isomer, levonorgestrel, is rapidly and almost completely absorbed after administration by mouth, and undergoes little first pass hepatic metabolism. It is highly bound to plasma proteins; 42 to 68% to sex hormone binding globulin and 30 to 56% to albumin. Levonorgestrel and norgestrel are metabolised in the liver to sulfate and glucuronide conjugates, which are excreted in the urine and to a lesser extent in the faeces.

The pharmacokinetic profile of levonorgestrel following an oral dose of 150 micrograms and repeat dosing performed until a steady state was achieved is provided in Table 1.

The proportion of levonorgestrel bound to sex hormone binding globulin is higher when it is given with an estrogen. This indicates that the pharmacokinetic parameters for each active substance will differ when used in combination.

Table 1 – Pharmacokinetic parameters for Levonorgestrel following a dose of 150 microgram and repeat dosing until steady state achieved

PK Parameter Mean value (SD provided in square brackets)	C_{max} (µg/L)	t_{max} (h)	$t_{1/2DIST}$ (h)	$t_{1/2\beta}$ (h)	Vd (L)	CL (ml/min/kg)	AUC (µg/L·h)
Single Dose (150µg)	4.3 [1.3]	1.2 [0.5]	0.6 [0.2]	13.9 [3.2]	108 [37]	1.5 [0.6]	30.9 [11.9]
Repeat dose (to steady state)	2.7 [0.3]	1.0 [0.3]	0.5 [0.2]	17.4 [3.6]	226 [61]	2.5 [0.4]	25.0 [5.9]

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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Conjugated estrogen tablets:

Calcium sulfate anhydrous
Carnauba wax
Microcrystalline cellulose
Glyceryl mono-oleates
Lactose monohydrate
Magnesium stearate
Methylcellulose
Macrogol 20000
Shellac solution (Pharmaceutical glaze)
Sucrose
Titanium dioxide (E171)
Stearic acid

Colours

Sunset yellow (E110)
Quinoline yellow aluminium lake (E104)
Edible ink (Opacode S-8-27741) containing;
Iron oxide black (E172)
Shellac
Purified water
Ethanol
n-Butyl alcohol
Propylene glycol
Ammonium solution
Ethyl acetate

Norgestrel tablets:

Bleached wax
Calcium carbonate
Carnauba wax
Lactose hydrous
Magnesium stearate
Macrogol,
Polyvinyl pyrrolidone
Starch
Sucrose
Talc
Titanium dioxide (E171)
Colour E172.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Three years.

6.4 Special precautions for storage

Do not store above 25°C

6.5 Nature and contents of container

Polyvinylchloride (PVC)/Aluminium foil blisters containing 28 conjugated estrogen and 12 norgestrel tablets. One carton pack contains 3 blisters.

6.6 Special precautions for disposal

Not applicable.

7 MARKETING AUTHORISATION HOLDER

Pfizer Limited
Ramsgate Road
Sandwich
Kent
CT13 9NJ
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 00057/1292

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

11/08/2011

10 DATE OF REVISION OF THE TEXT

19/08/2016