Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Prempak-C 0.625mg Coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Conjugated estrogens tablet: 28 maroon tablets each containing 0.625mg of conjugated estrogens.
Norgestrel tablet: 12 light brown tablets each containing 0.15mg of norgesterel.

Excipients with known effect:

0.625mg conjugated estrogens tablet
Each tablet contains lactose monohydrate 91.8 mg, sucrose 126.0 mg and sunset yellow (E110).

0.15mg norgestrel tablet
Each tablet contains lactose monohydrate 33 mg, sucrose 21.4 mg.
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Coated tablet.

Conjugated estrogen tablets:
Oval maroon sugar coated tablets marked with “0.625” in white ink.

Norgesterel tablets:
Round light brown sugar coated tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

- Hormone Replacement Therapy (HRT) for estrogen deficiency symptoms in postmenopausal women.
- Prevention of osteoporosis in postmenopausal women at high risk of future fractures who are intolerant of, or contraindicated for, other medicinal products approved for the prevention of osteoporosis, (see also section 4.4).

4.2 Posology and method of administration

Posology

Adults:

Prempak-C is taken orally in a continuous sequential 28-day regimen of conjugated estrogen tablets, with 12 days of Norgestrel tablets taken with the estrogen tablets on days 17 to 28 of the woman’s cycle with no breaks 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 vasomotor symptoms, atrophic vaginitis, kraurosis vulvae, atrophic urethritis:
0.625-1.25 mg 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.

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 norgestrel is administered to reduce the risk of endometrial hyperplasia and endometrial carcinoma, patients without a uterus do not require Prempak-C 0.625mg.

Commencing treatment advice:

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. Withdrawal bleeding usually occurs within three to seven days after the last norgestrel tablet. In women transferring from another sequential hormone replacement therapy regimen, treatment should begin the day following completion of the prior regimen.

Breakthrough bleeding may occasionally occur in the first few weeks after initiating treatment and will usually settle. It can also be the result of poor compliance, or concurrent antibiotic use. It may, however, indicate endometrial pathology and therefore any doubt as to the cause of breakthrough bleeding is an indication for endometrial evaluation including endometrial biopsy.

Forgotten tablet:

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

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

Elderly

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

Paediatric population

Not recommended.

Method of administration

For oral use only.

4.3 Contraindications

1. Hypersensitivity to conjugated estrogen or to norgestrel 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 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 a history of liver disease as long as 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 Prempak-C, 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
- A history of endometrial hyperplasia (see below)
- Epilepsy
- Asthma
- Otosclerosis

Reasons for immediate withdrawal of therapy

Therapy should be discontinued in case a contra-indication is discovered and in the following situations:
- Jaundice or deterioration in liver function

- Significant increase in blood pressure
- New onset of migraine-type headache
- Pregnancy

Endometrial hyperplasia and carcinoma

- In women with an intact uterus the risk of endometrial hyperplasia and carcinoma is increased when estrogens are administered alone for prolonged periods. The reported increase in endometrial cancer risk among estrogen-only users varies from 2-to 12-fold greater compared with non-users, depending on the duration of treatment and estrogen dose (see section 4.8). After stopping treatment risk may remain elevated for at least 10 years.

- The addition of a progestogen cyclically for at least 12 days per month/28 day cycle or continuous combined estrogen-progestogen therapy in non-hysterectomised women prevents the excess risk associated with estrogen-only HRT.

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

Breast cancer

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

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

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

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

Ovarian cancer

Ovarian cancer is much rarer than breast cancer.

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

- 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 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 (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, prophylactic measures need be considered to prevent VTE following surgery. If prolonged immobilisation is to follow elective surgery temporarily stopping HRT 4 to 6 weeks earlier is recommended. Treatment should not be restarted until the woman is completely mobilised.

- In women with no personal history of VTE but with a first degree relative with a history of thrombosis at young age, screening may be offered after careful counselling regarding its limitations (only a proportion of thrombophilic defects are identified by screening). If a thrombophilic defect is identified which segregates with thrombosis in family members or if the defect is 'severe' (e.g., antithrombin, protein S, or protein C deficiencies or a combination of defects) HRT is contraindicated.

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

- If VTE develops after initiating therapy, the drug should be discontinued. Patients should be told to contact their doctors immediately when they are aware of a potential thromboembolic symptom (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 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.

Ischaemic Stroke

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

Other Conditions

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

- Women with pre-existing hypertriglyceridemia should be followed closely during estrogen replacement or hormone replacement therapy, since rare cases of large increases of plasma triglycerides leading to pancreatitis have been reported with estrogen therapy in this condition.

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

Estrogens increase thyroid binding globulin (TBG), leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 levels (by column or by radio-immunoassay) or T3 levels (by radio-immunoassay). T3 resin uptake is decreased, reflecting the elevated TBG. Free T4 and free T3 concentrations are 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 unchanged. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-I-antitrypsin, ceruloplasmin).

- 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.
- A two- to four-fold increase in the risk of gall bladder 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.
- Estrogens should be used with caution in patients with disease that can predispose to severe hypocalcaemia.

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

This medicine also contains E110 (sunset yellow) which may cause allergic reactions.

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.

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.

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 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

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 following adverse reactions have been reported with Prempak-C or are undesirable effects associated with estrogens.

System Organ Class	Frequency Of Occurrence Of Adverse Reactions				
	Very common (≥1/10)	**Common (≥1/100 to <1/10)**	**Uncommon (≥1/1,000 to <1/100)**	**Rare (≥1/10,000 to <1/1,000)**	**Very rare (<1/10,000)**
Infections and infestations		Vaginitis	Vaginal candidiasis		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				Breast cancer, ovarian cancer, fibrocystic breast changes; Growth potentiation of benign meningioma	Endometrial cancer; Enlargement of hepatic haemangiomas
Immune system disorders				Urticaria, angioedema; Anaphylactic/ anaphylactoid reactions	
Metabolism and nutrition disorders				Glucose intolerance	Exacerbation of porphyria; Hypocalcaemia (in patients with disease that can predispose to severe hypocalcaemia)
Psychiatric disorders		Depression	Changes in libido; Mood disturbances; Dementia	Irritability	
Nervous system disorders			Anxiety; Dizziness; Headache (including migraine)	Exacerbation of epilepsy; Stroke	Exacerbation of chorea
Eye disorders			Intolerance of contact lenses		Retinal vascular thrombosis
Cardiac disorders				Myocardial infarction	
Vascular disorders			Venous thrombosis; pulmonary embolism	Superficial thrombophlebitis	

Respiratory, thoracic and mediastinal disorders				Exacerbation of asthma	
Gastrointestinal disorders			Nausea; bloating; Abdominal pain	Vomiting; Pancreatitis; Ischaemic colitis	
Hepatobiliary disorders			Gall bladder disease		Cholestatic jaundice
Skin and subcutaneous tissue disorders			Acne; alopecia; Pruritus	Chloasma/melasma; Hirsutism; Rash	Erythema multiforme; Erythema nodosum
Musculoskeletal and connective tissue disorders		Arthralgias; Leg cramps			
Reproductive system and breast disorders	Breast pain	Breakthrough bleeding/ dys-menorrhoea; spotting, breast tenderness, enlargement, discharge	Changes in menstrual flow; Change in cervical ectropion and secretion	Galactorrhoea; Increased size of uterine leiomyomata	Endometrial hyperplasia
General disorders and administration site Conditions			Oedema		
Investigations		Changes in weight (increase or decrease); Increased triglycerides			Increase in blood pressure

Breast cancer risk

- An up to 2-fold increased risk of having breast cancer diagnosed is reported in women taking combined estrogen-progestogen therapy for more than 5 years.
- Any increased risk in users of estrogen-only therapy is substantially lower than that seen in users of estrogen-progestogen combinations.
- The level of risk is dependent on the duration of use (see section 4.4).
- Results of the largest randomised placebo-controlled trial (WHI-study) and largest epidemiological study (MWS) are presented.

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

Age range (years)	Additional cases per 1000 never-users of HRT over a 5 year period*	Risk ratio & 95%CI#	Additional cases per 1000 HRT users over 5 years (95% CI)
		Estrogen only HRT	
50-65	9-12	1.2	1-2 (0-3)
		Combined estrogen-progestogen	
50-65	9-12	1.7	6 (5-7)

#Overall risk ratio. The risk ratio is not constant but will increase with increasing duration on use
Note: Since the background incidence of breast cancer differs by EU country, the number of additional cases of breast cancer will also change proportionately.

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

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

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

Endometrial cancer risk

Postmenopausal women with a uterus
The endometrial cancer risk is about 5 in every 1000 women with a uterus not using HRT.

In women with a uterus, use of estrogen-only HRT is not recommended because it increases the risk of endometrial cancer (see section 4.4).
Depending on the duration of estrogen-only use and estrogen dose, the increase in risk of endometrial cancer in epidemiology studies varied from between 5 and 55 extra cases diagnosed in every 1000 women between the ages of 50 and 65.

Adding a progestogen to estrogen-only therapy for at least 12 days per cycle can prevent this increased risk. In the Million Women Study the use of five years of combined (sequential or continuous) HRT did not increase risk of endometrial cancer (RR of 1.0 (0.8-1.2)).

Ovarian cancer

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* 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 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 (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 authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

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

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 and 17α/β-estradiol. These substitute for the loss of estrogen production in menopausal women, and alleviate menopausal symptoms. Estrogens prevent bone loss following menopause or ovariectomy.

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

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

Prevention of osteoporosis
Estrogen deficiency at menopause is associated with an increasing bone turnover and decline in bone mass. The effect of estrogens on the bone mineral density is dose-dependent. Protection appears to be effective for as long as treatment is continued. After discontinuation of HRT, bone mass is lost at a rate similar to that in untreated women.

Evidence from the WHI trial and meta-analysed trials shows that current use of HRT, alone or in combination with a progestogen – given to predominantly healthy women – reduces the risk of hip, vertebral, and other osteoporotic fractures. HRT may also prevent fractures in women with low bone density and/or established osteoporosis, but the evidence for that is limited.

After 2 years of treatment with conjugated estrogens 0.625mg tablets, the increase in lumbar spine bone mineral density (BMD) was 2.46 ± 0.37 % (adjusted mean ± SE).

Total hip was measured by femoral neck and femoral trochanter.

After 2 years of treatment with conjugated estrogens 0.625mg tablets, the increase in femoral neck bone mineral density (BMD) was 1.82 ± 0.45 % (adjusted mean ± SE).

After 2 years of treatment with conjugated estrogens 0.625mg tablets, the increase in femoral trochanter bone mineral density (BMD) was 3.82 ± 0.58 % (adjusted mean ± SE).

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. The conjugated estrogens tablet releases conjugated estrogens slowly over several hours.

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.

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 exist as sulfate conjugates, especially estrone sulfate, which serves as a circulating reservoir for the formation of more active estrogens.

Elimination

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

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
Carnauba wax
Microcrystalline cellulose
Glyceryl mono-oleate
Lactose monohydrate
Magnesium stearate
Methylcellulose
Polyethylene glycol
Shellac solution
Sucrose
Sodium benzoate
Povidone
Titanium dioxide (E171)
Opalux maroon colour AS-3910†

Printing Ink (Opacode S-8-28905) ††

†Opalux maroon colour contains:
Sucrose
Erythrosine (E127)
Titanium dioxide (E171)
Sunset yellow (E110)
Indigo carmine (E132)
Polyvinylpyrrolidone
Sodium benzoate

†† Printing Ink (Opacode S-28905) contains:
Titanium dioxide (E171)
Shellac (E904)

Norgestrel tablets:

Bleached wax
Calcium carbonate
Carnauba wax
Lactose monohydrate
Magnesium stearate
Polyethylene glycol
Povidone
Starch
Sucrose
Talc
Titanium dioxide (E171)
Colour – iron oxide (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 calendar pack per carton.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

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

8 MARKETING AUTHORISATION NUMBER

PA0822/097/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 16 November 1988

Date of last renewal: 16 November 2008

10 DATE OF REVISION OF THE TEXT

May 2017