Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Cathate 0.625mg Coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Cathate tablets contain 0.625 mg Conjugated Estrogens.

Excipients with known effect:
Each tablet contains Lactose Monohydrate 91.8mg and sucrose 124 mg.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Coated Tablet.

A white, oval, coated tablet printed “0.625” in black.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Cathate is indicated for hormone replacement therapy (HRT) 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.

(See also section 4.4)

4.2 Posology and method of administration

Cathate Tablets are an estrogen only HRT for oral use.

Posology:

Adults
Cathate 0.625-1.25mg daily is the usual starting dose for women without a uterus. Continuous administration is recommended.

For initiation and continuation of treatment of postmenopausal symptoms, the lowest effective dose for the shortest duration (see also section 4.4) should be used. Patients should be re-evaluated periodically to determine if treatment for symptoms is still necessary.

Vasomotor symptoms:

0.625-1.25mg daily depending on the response of the individual.

Atrophic vaginitis, kraurosis vulvae, atrophic urethritis:

0.625-1.25mg daily depending on the response of the individual.

Prophylaxis of postmenopausal osteoporosis:

When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis and non-estrogen medications should be carefully considered.

The minimum effective dose is 0.625mg for most patients (see section 5.1).

Concomitant progestogen use for women with a uterus:

Unless there is a previous diagnosis of endometriosis, it is not recommended to add a progestogen in hysterectomised women (see section 4.4)

Commencing treatment advice:
For most postmenopausal women, therapy may be commenced at any convenient time.

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

Before therapy commences it is recommended that the patient is fully informed of all the likely benefits and potential risks. She should have a complete physical and gynaecological examination with special emphasis on blood pressure, breasts, abdomen and pelvic organs and an endometrial assessment carried out if appropriate. Follow-up examinations are recommended every 6-12 months.

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 older people, but as with all medicine the lowest effective dose should be used.

Paediatric population:

Cathate is not recommended for use in children.

Safety and effectiveness in pediatric patients have not been established. Estrogen treatment of prepubertal girls induces premature breast development and vaginal cornification, and may induce uterine bleeding.
Since large and repeated doses of estrogen over an extended time period have been shown to accelerate epiphyseal closure, hormonal therapy should not be started before epiphyseal closure has occurred in order not to compromise final growth.

Method of administration

For Oral administration
Tablets should be taken whole; do not divide, crush, chew, or dissolve tablets in mouth.

4.3 Contraindications

1. Known, suspected or history of breast cancer.

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

3. Undiagnosed abnormal genital bleeding.
4. Untreated endometrial hyperplasia.
5. Previous or current venous thromboembolism (deep venous thrombosis, pulmonary embolism).
6. Known thrombophilic disorders (e.g. protein C, protein S, or antithrombin deficiency, see section 4.4).
7. Active or recent arterial thromboembolic disease (e.g. angina, myocardial infarction).
8. Acute liver disease or history of liver disease where the liver function tests have failed to return to normal.
9. Known hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
10. Porphyria.

4.4 Special warnings and precautions for use

- For the treatment of postmenopausal symptoms, HRT should only be initiated for symptoms that adversely affect the quality of life. In all cases, a careful appraisal of the risks and benefits should be undertaken at least annually and HRT should only be continued as long as the benefit outweighs the risk.

- Evidence regarding the risks associated with HRT in the treatment of premature menopause is limited. Due to the low level of absolute risk in younger women, however, the balance of benefits and risks for these women may be more favourable than in older women.

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 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 Cathate, in particular:

- Leiomyoma (uterine fibroids) or endometriosis
- Risk factors for thromboembolic disorders (see below)
- Risk factors for estrogen dependent tumours (e.g. first degree heredity for breast cancer)
- Hypertension
- Liver disorders (e.g. liver adenoma)
- Diabetes mellitus with or without vascular involvement
- Cholelithiasis
- Migraine or (severe) headaches
- Systemic lupus erythematosus (SLE)
- A history of endometrial hyperplasia (see below)
- Epilepsy
- Asthma
- Otosclerosis

3. Reasons for immediate withdrawal of therapy

Therapy should be discontinued in case a contraindication is discovered and in the following situations:

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

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 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.

- For oral doses of estradiol >2 mg, conjugated equine estrogens >0.625 mg and patches >50 μg/day the endometrial safety of added progestogen has not been demonstrated.

- 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.

- Unopposed estrogen stimulation may lead to pre-malignant or malignant transformation in the residual foci of endometriosis. Therefore, the addition of progestogens to estrogen replacement therapy should be considered in women who have undergone hysterectomy because of endometriosis, if they are known to have residual endometriosis.

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.

The WHI trial found no increase in the risk of breast cancer in hysterectomised women using estrogen-only HRT. Observational studies have mostly reported a small increase in risk of having breast cancer diagnosed that is substantially lower than that found in users of estrogen-progestogen combinations (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.

6. Ovarian Cancer

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

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 use than later (see Section 4.8).

- Patients with known thrombophilic states have an increased risk of VTE and HRT may add to this risk. HRT is therefore contraindicated in these patients (see section 4.3).

- Generally recognised risk factors for VTE include use of estrogens, older age, major surgery, prolonged immobilisation, obesity (Body Mass Index >30 kg/m^2), pregnancy/postpartum period, systemic lupus erythematosus (SLE) and cancer. There is no consensus about the possible role of varicose veins in VTE.

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

- In women with no personal history of VTE but with a first degree relative with a history of thrombosis at young age, screening may be offered after careful counselling regarding its limitations (only a proportion of thrombophillic defects are identified by screening).

  If a thrombophilic defect is identified which segregates with thrombosis in family members or if the defect is 'severe' (e.g, antithrombin, protein S, or protein C deficiencies or a combination of defects) HRT is contraindicated.

- Women already on chronic anticoagulant treatment require careful consideration of the benefit-risk of use of HRT.
- If VTE develops after initiating therapy, the drug should be discontinued. Patients should be told to contact their 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

There is no evidence from randomised controlled trials of protection against protection against myocardial infarction in women with or without existing CAD who received combined estrogens-progesterone or estrogen-only HRT.

Randomised controlled data found no increased risk of CAD in hysterectomised women using estrogen-only therapy.

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).

In the WHI estrogen-alone substudy, a statistically significant increased risk of stroke was reported in women 50 to 79 years of age receiving daily CE (0.625 mg) compared to women receiving placebo (45 versus 33 per 10,000 women-years). The increase in risk was demonstrated in year one and persisted.
Subgroup analyses of women 50 to 59 years of age suggest no increased risk of stroke for those women receiving CE (0.625 mg) versus those receiving placebo (18 versus 21 per 10,000 women-years).

Other Conditions

10. Estrogens 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 Cathate is increased.

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. 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 biological active hormone concentrations are usually unchanged. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-I-antitrypsin, ceruloplasmin).

12. A two- to four-fold increase in the risk of gallbladder disease requiring surgery in women receiving HRT has been reported.

13. A worsening of glucose tolerance may occur in patients taking estrogens and therefore diabetic patients should be carefully observed while receiving hormone replacement therapy.

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 patients with disease that can predispose to severe hypocalcaemia.

16. 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.

17. Laboratory monitoring
Estrogen administration should be guided by clinical response rather than by hormone levels (e.g, estradiol, FSH).

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

4.5 Interaction with other medicinal products and other forms of interaction

The metabolism of estrogens may be increased by concomitant use of substances known to induce drug-metabolising enzymes, specifically cytochrome P450 3A4 enzymes. Therefore, inducers or inhibitors of CYP3A4 may affect estrogen drug metabolism. Inducers of CYP3A4, such as St. John's Wort (Hypericum perforatum) preparations, phenobarbital, phenytoin, carbamazepine, rifampicin, rifabutin, nevirapine, efavirenz and dexamethasone , may reduce plasma concentrations of estrogens, possibly resulting in a decrease in therapeutic effects and/or changes in the uterine bleeding profile. Inhibitors of CYP3A4, such as cimetidine, erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir, nelfinavir and grapefruit juice, may increase plasma concentrations of estrogens and may result in side effects.

Interference with Laboratory and Other Diagnostic Tests

Laboratory test interactions
Increased platelet count decreased levels of antithrombin III, and increased plasminogen antigen and activity. Estrogens increase thyroid-binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T_4 levels by column or by radioimmunoassay or T_3 levels by radioimmunoassay. T_3 resin uptake is decreased, reflecting the elevated TBG. Free T_4 and free T_3 concentrations are unaltered.

Other binding proteins may be elevated in serum, ie, corticosteroid binding globulin (CBG), sex hormone-binding globulin (SHBG) leading to increased circulating corticosteroid and sex steroids, respectively. Free or biologically active hormone concentrations may be decreased.

Increased plasma HDL and HDL_2 cholesterol subfraction concentrations, reduced LDL cholesterol concentrations,

increased triglyceride levels.

Impaired glucose tolerance.

The response to metyrapone may be reduced.

4.6 Fertility, pregnancy and lactation

Pregnancy:

Cathate is not indicated for use during pregnancy.

If pregnancy occurs during medication with Cathate, treatment should be withdrawn immediately. The results of most epidemiological studies to relevant to inadvertent foetal exposure to estrogens indicate no teratogenic or foetotoxic effects.

Breast-feeding:

Cathate 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 rates, clinical trials and class-effects.

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, including vaginal candidiasis		
Neoplasms benign and malignant (including cysts and polyps)	-	-	Breast cancer; Fibrocystic breast changes Ovarian cancer; Growth potentiation of benign meningioma	Endometrial cancer; Enlargement of hepatic haemangiomas
Immune system disorders			Anaphylactic/ anaphylactoid reactions, including urticaria and angioedema	
Metabolism and nutrition disorders			Glucose intolerance	Exacerbation of porphyria; Hypocalcaemia (in patients with disease that can predispose to severe

				hypocalcaemia)
Psychiatric disorders	Depression	Changes in libido; Mood disturbances; dementia	Irritability	
Nervous system disorders		Dizziness; Headache; Migraine; Anxiety	Stroke; Exacerbation of epilepsy;	Exacerbation of chorea
Eye disorders		Intolerance to contact lenses		Retinal vascular thrombosis
Cardiac disorders			Myocardial infarction	
Vascular disorders		Venous thrombosis	Pulmonary embolism; Superficial thrombophlebitis	
Respiratory, thoracic and mediastinal disorders			Exacerbation of asthma	
Gastrointestinal disorders		Nausea; Bloating; Abdominal pain	Vomiting; Pancreatitis; Ischaemic colitis	
Hepatobiliary disorders	-	Gallbladder disease	-	Cholestatic jaundice
Skin and subcutaneous tissue disorders	Alopecia	Chloasma/melasma; Hirsutism; Pruritus; Rash		Erythema multiforme; erythema nodosum
Musculoskeletal, connective tissue and bone disorders	Arthralgias; Leg cramps	None		
Reproductive system & breast disorders	Breakthrough bleeding/spotting; breast pain, tenderness, enlargement, discharge	Change in menstrual flow; Change in cervical ectropion and secretion	Dysmenorrhoea; Galactorrhoea; Increased size of uterine leiomyomata	Endometrial hyperplasia
General disorders and administration site conditions		Oedema		
Investigations	Changes in weight (increase or decrease); Increased triglycerides	-	-	Increase in blood pressure

Breast cancer risk

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

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

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

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

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

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

Endometrial cancer risk

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

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

Ovarian cancer

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

Risk of venous thromboembolism

HRT is associated with a 1.3-3-fold increased relative risk of developing venous thromboembolism (VTE), i.e. deep vein thrombosis or pulmonary embolism. The occurrence of such an event is more likely in the first year of using HT (see section 4.4). Results of the WHI studies are presented:

WHI Studies - Additional risk of VTE over 5 years' use

Age range (years)	Incidence per 1000 women in placebo arm over 5 years	Risk ratio and 95%CI	Additional cases per 1000 HRT users
Oral estrogen-only*			
50-59	7	1.2 (0.6-2.4)	1 (-3 – 10)
Oral combined estrogen-progestogen			
50-59	4	2.3 (1.2 – 4.3)	5 (1 - 13)

**Study in women with no uterus*

Risk of coronary artery disease

The risk of coronary artery disease is slightly increased in users of combined estrogen-progestogen HRT over the age of 60 (see section 4.4).

Risk of ischaemic stroke

The use of estrogen-only and estrogen + progestogen therapy is associated with an up to 1.5 fold increased relative risk of ischaemic stroke. The risk of haemorrhagic stroke is not increased during use of HRT.
This relative risk is not dependent on age or on duration of use, but as the baseline risk is strongly age-dependent, the overall risk of stroke in women who use HRT will increase with age, see section 4.4.

WHI studies combined - Additional risk of ischaemic stroke* over 5 years' use

Age range (years)	Incidence per 1000 women in placebo arm over 5 years	Risk ratio and 95%CI	Additional cases per 1000 HRT users over 5 years
50-59	8	1.3 (1.1 1.6)	3 (1-5)

**no differentiation was made between ischaemic and haemorrhagic stroke.*

Other adverse reactions reported in association with estrogen/progestogen treatment including Cathate:

- 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 .
- Retinal vascular thrombosis.
- Myocardial infarction and stroke.
- Increases in blood pressure.
- Cholestatic jaundice.
- Enlargement of hepatic heamangiomas.
- Skin and subcutaneous disorders: erythema multiforme, erythema nodosum; vascular purpura.
- Probable dementia (see section 4.4).
- Exacerbation of chorea.
- Exacerbation of porphyria.
- Exacerbation of hypocalcaemia.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, 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 containing oral contraceptives by young children indicate that acute serious ill effects do not occur. 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

ATC Code: G03C A57

Conjugated Estrogens

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

Mechanism of Action
Endogenous estrogens are largely responsible for the development and maintenance of the female reproductive system and secondary sexual characteristics. Although circulating estrogens exist in a dynamic equilibrium of metabolic interconversions, estradiol is the principal intracellular human estrogen and is substantially more potent than its metabolites, estrone and estriol, at the receptor level.
The primary source of estrogen in normally cycling adult women is the ovarian follicle, which secretes 70 to 500 mcg of estradiol daily, depending on the phase of the menstrual cycle. After menopause, most endogenous estrogen is produced by conversion of androstenedione, which is secreted by the adrenal cortex, to estrone in the peripheral tissues. Thus, estrone and the sulfate−conjugated form, estrone sulfate, are the most abundant circulating estrogens in postmenopausal women.
Estrogens act through binding to nuclear receptors in estrogen-responsive tissues. To date, two estrogen receptors have been identified. These vary in proportion from tissue to tissue. Circulating estrogens modulate the pituitary secretion of the gonadotropins, luteinizing hormone (LH) and follicle stimulating hormone (FSH), through a negative feedback mechanism. Estrogens act to reduce the elevated levels of these gonadotropins seen in postmenopausal women.

Effects on estrogen-deficiency (vasomotor) 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 0.625 mg 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.

Table 1 shows the observed mean number of hot flushes in the CE 0.3 mg, 0.45 mg, and 0.625 mg and placebo treatment groups over the initial 12-week period.

TABLE 1. SUMMARY TABULATION OF THE NUMBER OF HOT FLUSHES PER DAY– MEAN VALUES AND COMPARISONS BETWEEN THE CE TREATMENT GROUPS AND THE PLACEBO GROUP: PATIENTS WITH AT LEAST 7 MODERATE TO SEVERE FLUSHES PER DAY OR AT LEAST 50 PER WEEK AT BASELINE, EFFICACY EVALUABLE (EE) POPULATION

Treatment (No. of Patients)	---------- **No. of Hot Flushes/Day** ----------			
Time Period (week)	**Baseline Mean ± SD**	**Observed Mean ± SD**	**Mean Change ± SE[a]**	**p-Values vs. Placebo[a]**
0.625 mg CE				

4 (n=27)	12.29 ± 3.89	1.95 ± 2.77	-10.34 ± 0.90	<0.001
12 (n=26)	12.03 ± 3.73	0.45 ± 0.95	-11.58 ± 0.88	<0.001
0.45 mg CE				
4 (n=32)	12.25 ± 5.04	5.04 ± 5.31	-7.21 ± 0.83	<0.001
12 (n=30)	12.49 ± 5.11	2.33 ± 3.39	-10.16 ± 0.82	<0.001
0.3 mg CE				
4 (n=30)	13.77 ± 4.78	4.65 ± 3.71	-9.12 ± 0.85	<0.001
12 (n=29)	13.83 ± 4.86	2.20 ± 2.73	-11.63 ± 0.83	<0.001
Placebo				
4 (n=28)	11.69 ± 3.87	7.89 ± 5.28	-3.80 ± 0.88	-
12 (n=25)	11.61 ± 3.79	5.27 ± 4.97	-6.34 ± 0.89	-

[a.] Standard errors based on assumption of equal variances.

Prevention of osteoporosis

At present there is no established screening programme for determining women at risk of developing osteoporotic fracture. 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 prevent fractures in women with low bone density and/or established osteoporosis, but the evidence for that is limited.

Effect on bone mineral density

Health and Osteoporosis, Progestin and Estrogen (HOPE) Study
The HOPE study was a double-blind, randomized, placebo/active-drug-controlled, multicenter study of healthy postmenopausal women with an intact uterus. Subjects (mean age 53.3 ± 4.9 years) were 2.3 ± 0.9 years on average since menopause and took one 600 mg tablet of elemental calcium (Caltrate™) daily. Subjects were not given Vitamin D supplements. They were treated with conjugated estrogen 0.625 mg, 0.45 mg, 0.3 mg, or placebo. Prevention of bone loss was assessed by measurement of bone mineral density (BMD), primarily at the anteroposterior lumbar spine (L2 to L4). Secondarily, BMD measurements of the total body, femoral neck, and trochanter were also analyzed. Serum osteocalcin, urinary calcium, and N telopeptide were used as bone turnover markers (BTM) at cycles 6, 13, 19, and 26.

Intent-to-treat subjects
All active treatment groups showed significant differences from placebo in each of the four BMD endpoints at cycles 6, 13, 19, and 26. The percent changes from baseline to final evaluation are shown in Table 2.

TABLE 2. PERCENT CHANGE IN BONE MINERAL DENSITY: COMPARISON BETWEEN CE AND

PLACEBO GROUPS IN THE INTENT-TO-TREAT POPULATION, LOCF.				
Region Evaluated Treatment Group[a]	**No. of Subjects**	**Baseline (g/cm^2) Mean ± SD**	**Change from Baseline (%) Adjusted Mean ± SE**	**p-Value vs Placebo**
L_2 to L_4 BMD				
0.625	83	1.17 ± 0.15	2.32 ± 0.35	<0.001
0.45	91	1.13 ± 0.15	2.08 ± 0.34	<0.001
0.3	87	1.14 ± 0.15	1.24 ± 0.34	<0.001
Placebo	85	1.14 ± 0.14	-2.46 ± 0.35	
Total body BMD				
0.625	84	1.15 ± 0.08	0.66 ± 0.17	<0.001
0.45	91	1.14 ± 0.08	0.71 ± 0.16	<0.001
0.3	87	1.14 ± 0.07	0.37 ± 0.16	<0.001
Placebo	85	1.13 ± 0.08	-1.52 ± 0.16	
Femoral neck BMD				
0.625	84	0.91 ± 0.14	1.74 ± 0.43	<0.001
0.45	91	0.89 ± 0.13	1.95 ± 0.41	<0.001
0.3	87	0.86 ± 0.11	0.57 ± 0.42	<0.001
Placebo	85	0.88 ± 0.14	-1.81 ± 0.43	
Femoral trochanter BMD				
0.625	84	0.78 ± 0.13	3.78 ± 0.57	<0.001
0.45	91	0.76 ± 0.12	3.46 ± 0.54	<0.001
0.3	87	0.75 ± 0.10	3.19 ± 0.55	0.003
Placebo	85	0.75 ± 0.12	0.93 ± 0.56	

[a.] Identified by dosage (mg) of CE or placebo.
BMD = Bone mineral density; L_2 to L_4 = anteroposterior lumbar spine; LOCF = Last observation carried forward; SD = Standard deviation; SE = Standard error.

The bone turnover markers serum osteocalcin and urinary N-telopeptide significantly decreased ($p < 0.001$) in all active-treatment groups at cycles 6, 13, 19, and 26 compared with the placebo group. Larger mean decreases from baseline were seen with the active groups than with the placebo group. Significant differences from placebo were seen less frequently in urine calcium.

WHI Estrogen-Alone Substudy

Timing of the initiation of estrogen therapy relative to the start of menopause may affect the overall risk benefit profile. The WHI estrogen-alone substudy stratified by age showed in women 50-59 years of age, a non-significant trend towards reduced risk for CHD and overall mortality compared with placebo in women who initiated hormone therapy closer to menopause than those initiating therapy more distant from menopause.

Table 3 describes the primary results of the Estrogen-alone substudy stratified by age at baseline.

TABLE 3. WOMEN'S HEALTH INITIATIVE ESTROGEN-ALONE SUBSTUDY RESULTS STRATIFIED BY AGE AT BASELINE						
	AGE					
Endpoint	**50-59 years**		**60-69 years**		**70-79 years**	
	CE (N=1637)	**Placebo (N=1673)**	**CE (N=2387)**	**Placebo (N=2465)**	**CE (N=1286)**	**Placebo (N=1291)**
CHD[a,b]						
Number of cases	21	34	96	106	84	77

Absolute risk (N) [c]	17	27	58	62	98	88
Hazard ratio (95% CI)	0.63 (0.36-1.09)		0.94 (0.71-1.24)		1.13 (0.82-1.54)	
Stroke[b]						
Number of cases	18	21	84	54	66	52
Absolute risk (N)[c]	15	17	51	31	76	59
Hazard ratio (95% CI)	0.89 (0.47-1.69)		1.62 (1.15-2.27)		1.21 (0.84-1.75)	
DVT[b]						
Number of cases	16	10	39	29	30	20
Absolute risk (N)[c]	13	8	23	17	34	22
Hazard ratio[d] (95% CI)	1.64 (0.74-3.60)		3.02 (1.51-6.06)		4.54 (2.22-9.31)	
VTE [b] [16]						
Number of cases	20	15	54	43	37	28
Absolute risk (N)[c]	16	12	32	25	42	31
Hazard ratio [d] (95% CI)	1.37 (0.70-2.68)		2.82 (1.59-5.01)		3.77 (2.07-6.89)	
Pulmonary Embolism [b]						
Number of cases	12	8	28	17	12	14
Absolute risk (N)[c]	10	6	17	10	14	16
Hazard ratio[d] (95% CI)	1.54 (0.63-3.77)		2.80 (1.28-6.16)		2.36 (0.96-5.80)	
Invasive Breast Cancer						
Number of cases	25	35	42	60	27	29
Absolute risk (N)[c]	21	29	26	36	32	34
Hazard ratio (95% CI)	0.72 (0.43-1.21)		0.72 (0.49-1.07)		0.94 (0.56-1.60)	
Colorectal Cancer						
Number of cases	8	14	26	31	27	13
Absolute risk (N)[c]	7	12	16	19	32	15
Hazard ratio (95% CI)	0.59 (0.25-1.41)		0.88 (0.52-1.48)		2.09 (1.08-4.04)	
Hip Fracture[b]						
Number of cases	5	1	9	20	32	52
Absolute risk (N)[c]	4	1	5	12	37	58
Hazard ratio (95% CI)	5.02 (0.59-43.02)		0.47 (0.22-1.04)		0.64 (0.41-0.99)	
Total Fractures[b]						
Number of cases	153	173	220	348	167	240
Absolute risk (N)[c]	126	139	132	201	191	269
Hazard ratio (95% CI)	0.90 (0.72-1.12)		0.63 (0.53-0.75)		0.70 (0.57-0.85)	

Overall Mortality[b]						
Number of cases	34	48	129	131	134	113
Absolute risk (N)[c]	28	38	77	75	153	127
Hazard ratio (95% CI)	0.71 (0.46-1.11)		1.02 (0.80-1.30)		1.20 (0.93-1.55)	

[a.] CHD defined as myocardial infarction or coronary death

[b.] Based on adjudicated data over a mean duration of therapy of 7.1 years

[c.] Absolute risk is per 10,000 person-years.

[d.] VTE hazard ratios compared with women aged 50-59 taking placebo

5.2 Pharmacokinetic properties

Absorption

Conjugated estrogens are soluble in water and are well absorbed from the gastrointestinal tract after release from the drug formulation. The conjugated estrogens tablet releases conjugated estrogens slowly over several hours. Maximum plasma concentrations are achieved approximately 6-10 hours following administration. The estrogens are generally eliminated in near-parallel fashion, with half-lives ranging from 10-20 hours, when corrected for endogenous concentrations as needed.

The pharmacokinetic profile of unconjugated and conjugated estrogens following a dose of 2 x 0.625mg is provided in Table 1.

Table 1 – Pharmacokinetic parameters for Premarin

Pharmacokinetic profile for unconjugated estrogens following a 2 x 0.625mg

_	Premarin 0.625mg			
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)

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

_	Premarin 0.625mg			
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)

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 sulphate and glucuronide conjugation in the liver, biliary secretion of conjugates into the intestine, and hydrolysis in the gut followed by reabsorption. In postmenopausal women a significant proportion of the circulating estrogens exists as sulphate conjugates, especially estrone sulphate, which serves as a circulating reservoir for the formation of more active estrogens.

Elimination

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

Special Populations
No pharmacokinetic studies were conducted in special populations, including patients with renal or hepatic impairment.

5.3 Preclinical safety data

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet Core:

Lactose monohydrate
Methylcellulose
Magnesium stearate

Coating:

Sucrose
Glycerol Mono-oleate (60% Acylglycerol)
Polyethylene glycol 20000
Carnauba wax
Calcium sulphate
Shellac solution
Microcrystalline cellulose
Stearic acid
Titanium dioxide (E171)
Edible printing ink (containing iron oxide black (E172), shellac, ethanol, n-butylalcohol, propylene glycol and ethyl acetate)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Three years.

6.4 Special precautions for storage

Do not store above 25°C. Store in the original container to protect from moisture.

6.5 Nature and contents of container

Polyvinylchloride (PVC)/Aluminium foil blisters and polypropylene Securitainers.
Blister strips of 21 or 28 tablets and Securitainers of 100 tablets.

Not all pack sizes may be marketed.

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

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