SCHEDULING STATUS:

S2

PROPRIETARY NAME AND DOSAGE FORM:

PREMARIN® CREAM 0,625 mg

COMPOSITION:

Each gram of PREMARIN Cream contains 0,625 mg Conjugated Oestrogens USP in a non-liquefying base containing cetyl esters wax, cetyl alcohol, white wax, glyceryl monostearate, propylene glycol monostearate, methyl stearate, sodium lauryl sulphate, glycerin, mineral oil and 1 % benzyl alcohol as the preservative.

PREMARIN (Conjugated Oestrogens USP) is a mixture of oestrogens, obtained exclusively from natural sources, occurring as the sodium salts of water-soluble oestrogen sulphates blended to represent the average composition of material derived from pregnant mares' urine. It contains estrone, equilin, and 17α-dihydroequilin, together with smaller amounts of 17α-estradiol, equilenin, and 17α-dihydroequilenin as salts of their sulphate esters.

PHARMACOLOGICAL CLASSIFICATION:

A 21.8.1 Oestrogens.

PHARMACOLOGICAL ACTION:

The pharmacologic effects of conjugated oestrogens are similar to those of endogenous oestrogens.

In responsive tissues (female urogenital organs, breasts, hypothalamus, pituitary) oestrogens enter the cell and are transported into the nucleus. As a result of oestrogenic activity, specific RNA and protein synthesis occurs.

Oestrogens have many effects on lipid metabolism, the most important being the increase in high-density lipoprotein (HDL) levels and a decrease in low-density lipoprotein (LDL) values which results in a beneficial ratio of HDL to LDL. Metabolism and inactivation occur primarily in the liver.

Some oestrogens are excreted in the bile; however, they are reabsorbed from the intestine and returned to the liver through the portal venous system. Water-soluble oestrogen conjugates are strongly acidic and are ionized in body fluids, which favours excretion through the kidneys since tubular reabsorption is minimal.

Topical conjugated equine oestrogen provides local oestrogenic activity.

Women's Health Initiative Studies (WHI)

The Women's Health Initiative (WHI) enrolled approximately 27 000 predominantly healthy postmenopausal women in two substudies to assess the risks and benefits of conjugated equine oestrogens (CEE) [0,625 mg daily] alone or in combination with medroxyprogesterone acetate (MPA) [0,625 mg/2,5 mg daily] compared to placebo. The primary endpoint was the incidence of coronary heart disease (CHD), i.e. non-fatal myocardial infarction (MI), silent MI and coronary death. The primary safety endpoint was incidence of invasive breast cancer. The study did not evaluate the effects of hormone replacement therapy on menopausal symptoms.

The oestrogen-alone substudy was stopped early because an increased risk of stroke was observed and it was deemed that no further information would be obtained regarding the risks and benefits of oestrogen alone in predetermined primary endpoints.

No overall effect on coronary heart disease (CHD) events (defined as non-fatal MI, silent MI, or death due to CHD) was reported in women receiving oestrogen alone compared with placebo. Results of the oestrogen-alone substudy which included 10 739 women (average age of 63 years, range 50 to 79; 75,3 % White, 15,1 % Black, 6,1 % Hispanic, 3,3 % Other); after an average follow-up of 6,8 years are presented in the table below.

In the oestrogen-alone substudy of WHI, there was no significant overall effect on the relative risk (RR) of CHD (RR 0,95, 95 % nominal confidence interval [nCI]
0,79 -1,16); a slightly elevated RR of CHD was reported in the early follow-up period and diminished over time. There was no significant effect on the RR of invasive breast cancer (RR 0,80, 95 % nCI 0,62- 1,04) or colorectal cancer (RR 1,08, 95 % nCI 0,75-1,55) reported. Oestrogen use was associated with a statistically significant increased risk of stroke (RR 1,37, 95 % nCI 1,09- 1,73) and deep vein thrombosis (DVT) (RR 1,47, 95 % nCI 1,06- 2,06). The RR of PE (RR 1,37, 95 % nCI 0,90-2,07) was not significantly increased. A statistically significant reduced risk of hip, vertebral and total fractures was reported with oestrogen use (RR 0,65, 95 % nCI 0,45 – 0,94), (RR 0,64, 95 % nCI 0,44-0,93), and (RR 0,71, 95 % nCI 0,64 - 0,80), respectively. The oestrogen-alone substudy did not report a statistically significant effect on death due to other causes (RR 1,08, 95 % nCI 0,88-1,32). There was no effect on overall mortality risk (RR 1,04, 95 % nCI 0,88-1,22). These confidence intervals are unadjusted for multiple looks and multiple comparisons.

RELATIVE AND ABSOLUTE RISK SEEN IN THE OESTROGEN-ALONE SUBSTUDY OF WHI			
Event	Relative Risk CEE vs. Placebo (95 % nCI[a])	Placebo n = 5 429	CEE n = 5 310
		Absolute Risk per 10 000 Women-years	
CHD events[b]	0,95 (0,78 – 1,16)	57	54
Non-fatal MI[b]	0,91 (0,73 – 1,14)	43	40

RELATIVE AND ABSOLUTE RISK SEEN IN THE OESTROGEN-ALONE SUBSTUDY OF WHI			
Event	Relative Risk CEE vs. Placebo (95 % nCI[a])	Placebo n = 5 429	CEE n = 5 310
		Absolute Risk per 10 000 Women-years	
CHD death[b]	1,01 (0,71 – 1,43)	16	16
All Stroke[c]	1,33 (1,05 – 1,68)	33	45
Ischaemic[b]	1,55 (1,19 – 2,01)	25	38
Deep vein thrombosis[b,d]	1,47 (1,06 – 2,06)	15	23
Pulmonary embolism[b]	1,37(0,90 – 2,07)	10	14
Invasive breast cancer[b]	0,80 (0,62 – 1,04)	34	28
Colorectal cancer[c]	1,08 (0,75 – 1,55)	16	17
Hip fracture [c]	0,65 (0,45 – 0,94)	19	12
Vertebral fractures [c, d]	0,64 (0,44 – 0,93)	18	11
Lower arm/wrist fractures [b,c]	0,58 (0,47 – 0,72)	59	35
Total fractures[c, d]	0,71 (0,64 – 0,80)	197	144
Death due to other causes [c,e]	1,08 (0,88 – 1,32)	50	53
Overall mortality[c, d]	1,04 (0,88 – 1,22)	75	79
Global Index [c,f]	1,02 (0,92 – 1,13)	201	206

[a] Nominal confidence intervals unadjusted for multiple looks and multiple comparisons.

[b] Results are based on centrally adjudicated data for an average follow-up of 7,1 years.

[c] Not included in global index.

[d] Results are based on an average follow-up of 6,8 years.

[e] All deaths, except from breast or colorectal cancer, definite/probable CHD, PE or cerebrovascular disease.

[f] A subset of the events was combined in a “global index”, defined as the earliest occurrence of CHD events, invasive breast cancer, stroke, pulmonary embolism, colorectal cancer, hip fracture, or death due to other causes.

Women’s Health Initiative Memory Study

In the oestrogen-alone Women’s Health Initiative Memory Study (WHIMS), an ancillary study of WHI, a population of 2 947 predominantly healthy hysterectomised postmenopausal women aged 65-79 years was randomised to conjugated oestrogens (CE) (0,625 mg daily) or placebo. The relative risk of probable dementia for CE alone vs. placebo was 1,49 (95 % CI 0,83-2,66). The absolute risk of probable dementia for CE alone vs. placebo was 37 vs. 25 cases per 10 000 women-years. Probable dementia as defined in this study included Alzheimer’s disease (AD), vascular dementia (VaD) and mixed types (having features of both AD and VaD). The most common classification of probable dementia in both the treatment and placebo groups was AD. Since the substudy was conducted in women aged 65-79 years, it is unknown whether these findings apply to younger postmenopausal women (see WARNINGS and SPECIAL PRECAUTIONS).

INDICATIONS:

PREMARIN Cream 0,625 mg is indicated for the treatment of postmenopausal and senile vulvovaginitis, atrophic vaginitis, pruritus vulvae caused by atrophic changes in the vulval epithelium, dyspareunia associated with an atrophic vaginal epithelium, and for use prior to plastic pelvic surgery in menopausal cases.

CONTRAINDICATIONS:

1) Known or suspected pregnancy (see PREGNANCY AND LACTATION).

2) Undiagnosed abnormal uterine bleeding.

3) Known or suspected oestrogen-dependent neoplasia (e.g.,endometrial cancer, endometrial hyperplasia).

4) Active or history of arterial thromboembolic disease (eg. stroke, myocardial infarction) or venous thromboembolism (such as deep venous thrombosis, pulmonary embolism).

5) Active or chronic liver dysfunction or disease.

6) Known or suspected hypersensitivity to its ingredients.

WARNINGS AND SPECIAL PRECAUTIONS:

1. General:

Systemic absorption may occur with the use of PREMARIN Cream 0,625 mg.
Warnings and precautions associated with oral Premarin (CEE) treatment should be taken into account.

2. Cardiovascular risk:

Estrogen Replacement Therapy **(**ERT**)** has been reported to increase the risk of stroke and deep venous thrombosis (DVT).
Patients who have risk factors for thrombotic disorders should be kept under careful observation.

Stroke

In the oestrogen-alone substudy of the WHI a statistically significant increased risk of stroke was reported in women receiving oestrogen alone compared to women receiving placebo (45 vs. 33 per 10 000 person-years). The increase in risk was observed during year one and persisted. Should

stroke occur or be suspected, oestrogens should be discontinued immediately (see PHARMACOLOGICAL ACTION).

Venous thromboembolism

In the oestrogen-alone substudy of the WHI the increased risk of deep vein thrombosis (DVT), was reported to be statistically significant (23 vs. 15 per 10 000 person-years). The risk of pulmonary embolism (PE) was reported to be increased although it did not reach statistical significance. The increase in VTE (DVT and PE) risk was demonstrated during the first two years (30 vs. 22 per 10 000 person-years). Should a VTE occur or be suspected, oestrogens should be discontinued immediately (see PHARMACOLOGICAL ACTION).

If feasible, oestrogens should be discontinued at least four to six weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization.

3. Malignant neoplasms

Breast cancer

Studies involving the use of oestrogens by postmenopausal women have reported inconsistent results on the risk of breast cancer. The most important randomized clinical trial providing information about this issue is the Women's Initiative (WHI) (see PHARMACOLOGICAL ACTION). In the oestrogen-alone substudy of WHI, after an average of 7,1 years of follow-up, CEE (0,625 mg daily) was not associated with an increased risk of invasive breast cancer.

Some observational studies have reported an increased risk of breast cancer for oestrogen-alone therapy after several years of use. The risk increased with duration of use, and appeared to return to baseline within approximately five years after stopping treatment (only the observational studies

have substantial data on risk after stopping).

The use of oestrogen has been reported to result in an increase in abnormal mammograms requiring further evaluation.

Endometrial cancer

The use of unopposed oestrogens in women with an intact-uterus has been associated with an increased risk of endometrial cancer *(*see WARNINGS AND SPECIAL PRECAUTIONS and PHARMACOLOGICAL ACTION*).*

The reported endometrial cancer risk among unopposed oestrogen users is about 2- to 12-fold greater than in non-users, and appears dependent on duration of treatment and on oestrogen dose. The greatest risk appears associated with prolonged use, with increased risks of 15- to 24-fold for 5 to 10 years or more, and this risk has been shown to persist for at least 8 to 15 years after ERT is discontinued. Adding a progestin to postmenopausal oestrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer (see WARNINGS AND SPECIAL PRECAUTIONS).

Clinical surveillance of all women taking oestrogen or oestrogen-plus-progestin combinations is important. Adequate diagnostic measures, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal uterine bleeding.

Ovarian cancer

In some epidemiologic studies, the use of oestrogen-only products, has been associated with an increased risk of ovarian cancer over multiple years of use. Other epidemiologic studies have not found these associations.

4. Dementia:

A substudy of the Women's Health Initiative Memory Study (WHIMS), an ancillary study of WHI conducted in women aged 65-79, reported an increased risk of developing probable dementia when compared with placebo (see WARNINGS AND SPECIAL PRECAUTIONS and PHARMACOLOGICAL ACTION).

5. Gallbladder Disease:

A 2- to 4- fold increase in the risk of gallbladder disease requiring surgery in women receiving post-ERT has been reported.

6. Visual abnormalities:

Retinal vascular thrombosis has been reported in patients receiving oestrogens.
Discontinue medication pending examination if there is sudden partial or complete loss of vision, or a sudden onset of proptosis, diplopia, or migraine. If examination reveals papilledema or retinal vascular lesions, medication should be withdrawn**.**

7. Hypercalcaemia:

Administration of oestrogens may lead to severe hypercalcaemia in patients with breast cancer and bone metastases. If this occurs, the drug should be stopped and appropriate measures be taken to reduce the serum calcium level.

The following special precautions are relevant to PREMARIN Cream 0,625 mg and/ or treatment with oestrogens.

1. Fluid retention:

Because oestrogens may cause some degree of fluid retention, patients with conditions which might be influenced by this factor, such as cardiac or renal dysfunction, warrant careful observation when Premarin Cream is prescribed.

2. Hypertriglyceridaemia:

Caution should be exercised in patients with pre-existing hypertriglyceridaemia since rare cases of large increases of plasma triglycerides leading to pancreatitis have been reported with oestrogen therapy in this population.

3. History of cholestatic jaundice

For patients with a history of cholestatic jaundice associated with past oestrogen use or with pregnancy, caution should be exercised and in the case of recurrence, PREMARIN Cream should be discontinued.

4. Elevated blood pressure:

In a small number of case reports, substantial increases in blood pressure during oestrogen replacement therapy have been attributed to idiosyncratic reactions to oestrogens. In a large, randomized placebo-controlled clinical trial a generalized effect of ERT on blood pressure was not seen.

5. Exacerbation of other conditions:

Oestrogen replacement therapy may cause an exacerbation of asthma, epilepsy, migraine, diabetes mellitus, porphyria, systemic lupus erythematosus and hepatic hemangiomas and should be used with caution in women with these conditions.

Endometriosis may be exacerbated with administration of oestrogen therapy.

Addition of a progestin should be considered in women who have undergone hysterectomy, but are known to have residual endometriosis, since malignant transformation after oestrogen-only therapy has been reported.

6. Hypocalcaemia:

PREMARIN Cream should be used with caution in individuals with disease that can predispose to severe hypocalcaemia.

7. Hypothyroidism:

Patients dependent on thyroid hormone replacement therapy may require increased doses in order to maintain their free thyroid hormone levels in an acceptable range (see Laboratory test interactions).

8. Laboratory monitoring:

Premarin Cream administration should be guided by clinical response rather than by hormone levels (eg. Estradiol, FSH).

9. Latex condoms:

PREMARIN Cream 0,625 mg has been shown to weaken latex condoms. The potential for PREMARIN Cream 0,625 mg to weaken and contribute to the failure of condoms, diaphragms, or cervical caps made of latex or rubber should be considered.

Paediatric use:

Clinical studies have not been conducted in the paediatric population.
Safety and effectiveness in paediatric patients have not been established.
PREMARIN Cream treatment of prepubertal girls may induce premature breast development and vaginal cornification, and may induce uterine bleeding. Large and repeated doses of PREMARIN Cream over an extended time period have been shown to accelerate epiphyseal closure and should therefore not be started before epiphyseal closure has occurred in order not to compromise final growth.

PREMARIN Cream 0,625 mg is not indicated in children.

Geriatric use:

The oestrogen-alone substudy of the Women's Health Initiative (WHI) reported an increased risk of stroke compared with placebo in postmenopausal women 65 years of age or older (see WARNINGS and SPECIAL PRECAUTIONS and PHARMACOLOGICAL ACTION).

A substudy of the Women's Health Initiative Memory Study (WHIMS), an ancillary study of WHI conducted in women aged 65-79, reported an increased risk of developing probable dementia when compared with placebo (see WARNINGS AND SPECIAL PRECAUTIONS and PHARMACOLOGICAL ACTION).

INTERACTIONS:

Data from an interaction study involving conjugated equine oestrogens and medroxyprogesterone acetate indicate that the pharmacokinetic disposition of both drugs is not altered when the drugs are co-administered. Other clinical drug-drug interaction studies have not been conducted with conjugated equine oestrogens.

In *vitro* and in *vivo* studies have shown that oestrogens are metabolized partially by cytochrome P450 3A4 (CYP3A4). Therefore, inducers or inhibitors of CYP3A4 may affect oestrogen drug metabolism. Inducers of CYP3A4, such as St. John's Wort preparations (*Hypericum perforatum*), phenobarbital, phenytoin, carbamazepine, rifampicin and dexamethasone may reduce plasma concentrations of oestrogens, possibly resulting in a decrease in the therapeutic effects and/or changes in the uterine bleeding profile. Inhibitors of CYP3A4, such as cimetidine, erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir and grapefruit juice, may increase plasma concentrations of oestrogens and may result in side effects.

Laboratory test interactions:

a. Increased 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.

b. The response to metyrapone may be reduced.

c. Other binding proteins may be elevated in serum, i.e. corticosteroid binding globulin (CBG), sex-hormone binding globulin, leading to increased circulating corticosteroid and sex steroids respectively.

d. Other plasma proteins may be increased (angiotensin/renin substrate, alpha-1-antitrypsin, ceruloplasmin).

PREGNANCY AND LACTATION:

PREMARIN Cream 0,625 mg should not be used during pregnancy (see CONTRAINDICATIONS).

Oestrogen administration to nursing mothers has been shown to decrease the quantity of breast milk. Detectable amounts of oestrogens have been identified in the milk of mothers receiving the drug. Caution should be exercised when oestrogens are administered to a nursing woman.

DOSAGE AND DIRECTIONS FOR USE:

Administration should be cyclic (e.g., three weeks on and one week off) and for short use only.

For treatment of atrophic vaginitis.

The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible.

Attempts to discontinue or taper medication should be made at three-to six-month intervals.

Usual dosage:

½ to 2 gram(s) daily, intravaginally, depending on the severity of the condition.

SIDE EFFECTS:

Systemic absorption may occur with the use of PREMARIN vaginal cream. Adverse reactions associated with oral PREMARIN treatment should be taken into account.

The following adverse reactions have been either reported with PREMARIN Cream 0,625 mg or are undesirable effects associated with oestrogens. It is not possible to calculate frequencies for these events based on prescription data for patient exposure because the dose of PREMARIN vaginal cream varies from patient to patient and the product is available worldwide in various sized units.

System Organ Class	***Adverse Reaction***
Reproductive system and breast disorders:	
	Breakthrough bleeding/spotting; dysmenorrhoea/pelvic pain breast pain, tenderness; enlargement; discharge
	Application site reactions of vulvovaginal discomfort including burning, irritation, and genital pruritus; vaginal discharge, leukorrhoea; gynaecomastia in males
	Increased size of uterine leiomyomata
	Endometrial hyperplasia
Gastro-intestinal disorders:	
	Nausea; bloating; abdominal pain
	Vomiting; pancreatitis, ischaemic colitis
Nervous system disorders:	
	Dizziness; headache; migraine; nervousness,
	Cerebrovascular accident/ stroke; exacerbation of Chorea

Musculoskeletal, connective tissue and bone disorders:

Arthralgias; leg cramps

Psychiatric disorders:

Changes in libido; mood disturbances; depression, irritability;

dementia

Vascular disorders:

Pulmonary embolism; venous thromboembolism; venous

thrombosis

General disorders and administration site conditions:

Oedema

Skin and subcutaneous tissue disorders:

Alopecia

Chloasma/melasma; hirsutism; pruritus; rash

Erythema multiforme; erythema nodosum

Hepato-biliary disorder:

Gallbladder disease

Cholestatic jaundice

Infections and infestations:

Vaginitis, including vaginal candidiasis

Cystitis-like syndrome

Neoplasms benign and malignant (including cysts and polyps):

Breast cancer; ovarian cancer, fibrocystic breast changes; endometrial cancer, enlargement of hepatic hemangiomas , growth potentiation of benign meningioma

Immune system disorders:

Anaphylactic/anaphylactoid reactions, including urticaria and angioedema; hypersensitivity

Metabolism and nutrition disorders:

Glucose intolerance, hypocalcaemia (in patients with disease that can predispose to severe hypocalcaemia)

Eye disorders:

Intolerance to contact lenses

Retinal vascular thrombosis

Cardiac disorders:

Myocardial infarction

Investigations:

Changes in weight (increase or decrease)

Increased triglycerides

Increases in blood pressure

Endocrine:

Precocious puberty

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Symptoms of overdosage of oestrogen-containing products in adults and children may include nausea, vomiting, breast tenderness, dizziness, abdominal pain, drowsiness/fatigue; withdrawal bleeding may occur in females. There is no specific antidote and further treatment if necessary should be symptomatic.

See also Side effects.

Treatment is symptomatic and supportive.

IDENTIFICATION:

PREMARIN® Vaginal Cream is a white cream containing 0,625 mg Conjugated Oestrogens USP per gram, in a non-liquefying base.

PRESENTATION:

Each pack contains a 42,5 g tube with one calibrated applicator.

STORAGE INSTRUCTIONS:

Store in a cool dry place below 25 ºC.

Keep out of the reach of children.

For external use only.

REGISTRATION NUMBER:

G3019 (Act 101/1965)

NAME AND BUSINESS ADDRESS OFTHE HOLDER OF THE CERTIFICATE REGISTRATION:

Pfizer Laboratories (Pty) Limited

85 Bute Lane

Sandton 2196

SOUTH AFRICA

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