SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

PREMARIN® 0,3 tablets

PREMARIN® 0,625 tablets

PREMARIN® 1,25 tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each PREMARIN 0,3 tablet contains 0,3 mg conjugated estrogens.

Each PREMARIN 0,625 tablet contains 0,625 mg conjugated estrogens.

Each PREMARIN 1,25 tablet contains 1,25 mg conjugated estrogens.

PREMARIN (conjugated estrogens) is a mixture of estrogens, obtained exclusively from natural sources, occurring as the sodium salts of water-soluble estrogen sulfates 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 sulfate esters.

Contains sugar (lactose monohydrate and sucrose).

Excipients with known effect

Each PREMARIN 0,3 mg tablet contains 61,7 mg lactose monohydrate and 45,0 mg sucrose.

Each PREMARIN 0,625 mg tablet contains 54,1 mg lactose monohydrate and 45,0 mg sucrose.

Each PREMARIN 1,25 mg tablet contains 120,3 mg lactose monohydrate and 115,0 mg sucrose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Sugar coated tablets.

PREMARIN 0,3: Oval, green and biconvex, coated tablet branded “0,3” in white ink.

PREMARIN 0,625: Oval, maroon and biconvex, coated tablet branded “0,625” in white ink.

PREMARIN 1,25: Oval, yellow and biconvex, coated tablet branded “1,25” in black ink.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PREMARIN is indicated for estrogen replacement therapy of estrogen-deficient states, whether naturally occurring (climacteric, menopause) or artificially induced.

PREMARIN is also indicated in the treatment of pathological states of reproductive endocrine imbalance.

Climacteric and menopausal symptoms

- Moderate to severe vasomotor symptoms associated with the menopause.
- Atrophic vaginitis and urethritis. When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal medicines should be considered.
- Senile atrophic vaginitis.

PREMARIN contributes to prevent or retard the development of osteoporosis induced by estrogen-deficiency states and in these cases PREMARIN should be used in conjunction with other pertinent measures.

Prevention and management of osteoporosis

Prevention and management of postmenopausal osteoporosis.

Other endocrine indications

- Female castration and primary ovarian failure
- Amenorrhoea

- Female hypogenitalism or hypogonadism
- Palliation of selected cases of inoperable prostatic cancer, and of mammary carcinoma in women who are postmenopausal for a minimum of 5 years

Estrogen Replacement Therapy (ERT) and Hormone Replacement Treatment (HRT) should not be initiated or continued to prevent cardiovascular disease or dementia (see section 4.4).

The benefits and risks of HRT must always be carefully weighed, including consideration of emergence of risks as therapy continues (see section 4.4).

4.2 Posology and method of administration

Estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman. In the absence of comparable data, the risks of HRT should be assumed to be similar for all estrogens and estrogen plus progestin combinations.

Administration of PREMARIN may be continuous (i.e. without a break in therapy) or cyclic (e.g. three weeks on and one week off).

Continuous daily administration of PREMARIN is generally recommended.

For women with an intact uterus, it is recommended that a progestogen should be administered (see section 4.4) and for continuous PREMARIN administration in women with an intact uterus, a progestogen should be added for 10 - 14 consecutive days each month.

Posology

Usual dosage ranges

Vasomotor symptoms and atrophic vaginitis

0,3 mg to 1,25 mg daily.

Patients should be re-evaluated periodically to determine if treatment for symptoms is still necessary.

Prevention and management of osteoporosis

0,625 mg to 1,25 mg daily depending upon the response of the individual patient.

PREMARIN therapy may be given continuously with no interruption in therapy, or in cyclical regimens (regimens such as 25 days on the medicine followed by 5 days off the medicine) as is medically appropriate on an individualised basis.

Hypoestrogenism due to:

Female hypogonadism

1,25 mg to 7,5 mg daily, administered cyclically (e.g., three weeks on and one week off). Doses are adjusted depending on the severity of symptoms and responsiveness of the endometrium. The dosage may be gradually titrated upward at 6 to 12 month intervals as needed to achieve appropriate bone age advancement and eventual epiphyseal closure.

Available data suggest that chronic dosing with 0,625 mg is sufficient to induce artificial cyclic menses with sequential progestin treatment and to maintain bone mineral density after skeletal maturity is achieved. For maintenance adjust dosages to the lowest effective dose.

Female castration or primary ovarian failure

1,25 mg daily, cyclically.

Advanced androgen-dependent carcinoma

Palliation of prostatic carcinoma

1,25 mg to 2,5 mg PREMARIN three times daily. The effectiveness of therapy can be judged by phosphatase determinations, as well as by symptomatic improvement of the patient.

Palliation of mammary carcinoma

Suggested dosage - up to 10 mg PREMARIN three times daily for a period of at least three months.

Special populations

Elderly use

The estrogen-alone sub study of the Women's Health Initiative (WHI) reported an increased risk of stroke compared with placebo in postmenopausal women 60 to 79 years of age (see section 5.1).

A sub study of the Women's Health Initiative Memory Study (WHIMS), an ancillary study of WHI conducted in women aged 65 to 79, reported an increased risk of developing probable dementia and mild cognitive impairment when compared with placebo (see section 5.1).

Paediatric population

Although ERT has been used for the induction of puberty in adolescents with some forms of pubertal delay, safety and effectiveness in paediatric patients have not otherwise been established.

Estrogen treatment of prepubertal girls also induces premature breast development and vaginal cornification and may induce vaginal bleeding.

Since large and repeated doses of oestrogen 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 use.

4.3 Contraindications

PREMARIN is contraindicated in patients with:

- known hypersensitivity to conjugated estrogens or to any of the excipients of PREMARIN (listed in section 6.1)
- known or suspected pregnancy (see section 4.6)
- undiagnosed abnormal genital bleeding
- personal and family history of known or suspected breast cancer
- history of non-cancerous breast diseases (atypical hyperplasia or lobular carcinoma *in situ*)
- previous treatment using radiation therapy to the chest or breast
- known or suspected estrogen-dependent neoplasia (e.g., endometrial cancer, endometrial hyperplasia)
- active or history of arterial thromboembolic disease (e.g., stroke, myocardial infarction)
- previous proven deep-vein thrombosis (DVT)
- previous pulmonary embolism
- inherited thrombophilia
- known protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders)
- endometriosis
- endometrial carcinoma
- active or chronic liver dysfunction or disease
- Rotor syndrome or Dubin-Johnson syndrome
- known inherited genetic mutations: BRCA1 and BRCA2 genes
- early menstrual periods (before the age of 12 years)
- previous exposure to diethylstilbestrol (DES)

4.4 Special warnings and precautions for use

General

ERT and HRT have been associated with increased risks of certain cancers and cardiovascular diseases. The use of unopposed estrogens in women with an intact uterus is associated with an increased risk of endometrial cancer.

ERT or HRT should not be initiated or continued to prevent cardiovascular disease or dementia.

The benefits and risks of ERT and HRT must always be carefully weighed, including consideration of emergence of risks as therapy continues.

Physical examination

Before initiating or reinstating ERT/HRT, a complete personal and family medical history should be taken, together with a thorough general and gynaecological examination guided by the contraindications and warnings for use. Before starting treatment, pregnancy should be excluded. During treatment, periodic check-ups are recommended of a frequency and nature adapted to the individual woman. A careful appraisal of the risks and benefits should be undertaken over time in women treated with ERT/HRT therapy.

Cardiovascular risk

ERT has been reported to increase the risk of stroke and deep venous thrombosis (DVT).

HRT has been associated with an increased risk of myocardial infarction (MI), as well as stroke, venous thrombosis and pulmonary embolism (PE).

Patients who have risk factors for thrombotic disorders should be kept under careful observation.

Stroke

In the estrogen-alone sub study of the Women's Health Initiative (WHI) (see section 5.1), a statistically significant increased risk of stroke was reported in women receiving estrogen 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 a stroke occur or be suspected, PREMARIN should be discontinued immediately.

In the estrogen plus progestin sub study of the WHI, a statistically significant increased risk of stroke was reported in women receiving the estrogen plus progestin combination compared to women receiving placebo (31 vs. 24 per 10 000 person-years). The increase in risk was demonstrated after the first year and persisted.

Coronary heart disease

In the estrogen alone sub study of WHI, 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 estrogen alone compared to placebo.

In the estrogen plus progestin sub study of WHI, no statistically significant increase of CHD events was reported in women receiving the estrogen plus progestin combination compared to women receiving placebo (39 vs. 33 per 10 000 person-years). An increase in relative risk was demonstrated in year one, and a trend toward decreasing relative risk was reported in year 2 through 5.

In postmenopausal women with documented heart disease (n=2 763, average age 66,7 years) a controlled clinical trial of secondary prevention of cardiovascular disease (Heart and Estrogen/Progestin Replacement Study; HERS) treatment with oral conjugated estrogen plus medroxyprogesterone acetate demonstrated no cardiovascular benefit. During an average follow-up of 4,1 years, treatment with oral conjugated estrogen plus medroxyprogesterone acetate did not reduce the overall rate of CHD events in postmenopausal women with established CHD. There were more CHD events in the hormone-treated group than in the placebo group in year one, but not during the subsequent years.

Palliative therapy in men

Large doses of estrogen (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast, have been shown in a large prospective clinical trial in men to increase the risks of nonfatal myocardial infarction, pulmonary embolism, and thrombophlebitis.

Venous thromboembolism (VTE)

In the estrogen alone sub study of 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 venous thromboembolism (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, PREMARIN should be discontinued immediately (see section 5.1).

In the estrogen plus progestin sub study of WHI (see section 5.1) a statistically significant 2-fold greater rate of VTE, was reported in women receiving the estrogen plus progestin combination, compared to women receiving placebo (35 vs. 17 per 10 000 person-years). Statistically significant increases in risk for both DVT (26 vs. 13 per 10 000 person-years) and PE (18 vs. 8 per 10 000 person-years) were also demonstrated. The increase in VTE risk was observed during the first year and persisted.

If feasible, PREMARIN should be discontinued at least 4 to 6 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilisation.

Malignant neoplasms

Breast cancer

PREMARIN contains estrogen which, on prolonged use, may increase the risk of developing breast cancer. A meta-analysis of prospective epidemiological studies from 1992 to 2018 reported a significant increase in the risk of developing breast cancer in 55 575 women 40 – 59 years of age who used menopausal hormone therapy (MHT). The risk increased steadily with duration of use and was slightly greater for estrogen plus progestogen than estrogen only preparations, and the risk persisted for more than 10 years after stopping the treatment. The relative risk (RR) to develop breast cancer for estrogen plus progestogen preparations was 1,60 at 1 – 4 years and RR=2,08 at 5 – 14 years, while that for estrogen only preparations were 1,17 at 1 – 4 years and 1,33 at 5 – 14 years. There was no risk to develop breast cancer in women who started MHT at 60 years of age.

All women on PREMARIN should receive yearly breast examinations by a health care provider and perform monthly breast self-examinations. Mammography evaluations should be done based on patient age, risk factors, and prior mammogram results.

Endometrial cancer

The use of unopposed estrogens in women with an intact uterus has been associated with an increased risk of endometrial cancer.

The reported endometrial cancer risk among unopposed estrogen users is about 2- to 12-fold greater than in non-users and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with use of estrogens for less than 1 year. 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 ERT has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer.

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

There is no evidence that the use of natural estrogens results in a different endometrial risk profile than synthetic estrogens of equivalent estrogen dose.

In a subset of WHI (see section 5.1), no increased risk of endometrial cancer after an average of 5,6 years of treatment with the estrogen plus progestin combination compared to placebo was observed.

Ovarian cancer

In some epidemiologic studies, the use of estrogen only medicines has been associated with an increased risk of ovarian cancer over multiple years of use. Other epidemiologic studies have not found these associations. The analysis of the WHI data suggested that estrogen plus progestin therapy may increase the risk of ovarian cancer.

Dementia

In the Women's Health Initiative Memory Study (WHIMS), an ancillary study of WHI, one population of 4532 women aged 65 to 79 years was randomised to CE plus MPA (0,625 mg/2,5 mg daily) or placebo. In a second population of WHIMS 2947 hysterectomised women, aged 65 – 79 years, were randomised to CE (0,625 mg

daily) or placebo. After an average follow-up of four years, a relative risk of 2,05 (95 % CI 1,21 – 3,48) for probable dementia was reported in the estrogen plus progestin compared to placebo. In the estrogen alone group, after an average follow-up of 5,2 years, a relative risk of 1,49 (95 % CI 0,83 – 2,66) for probable dementia was reported compared to placebo. When data from the two populations was pooled as planned in the WHIMS protocol, the reported overall relative risk for probable dementia was 1,76 (95 % CI 1,19 - 2,60).

Since this study was conducted in women aged 65 – 79 years, it is unknown whether these findings apply to younger postmenopausal women.

Gallbladder disease

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

Visual abnormalities

Retinal vascular thrombosis has been reported in patients receiving estrogens. Discontinue PREMARIN 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, PREMARIN should be withdrawn.

Hypercalcaemia

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

Angioedema

Exogenous estrogens may exacerbate symptoms of angioedema in women with hereditary angioedema.

Fluid retention

Because estrogens 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 is prescribed.

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 estrogen therapy in this population. Women with pre-existing hypertriglyceridaemia should be followed closely during ERT or HRT.

Hepatic impairment

Estrogens may be poorly metabolised in patients with impaired liver function.

Past history of cholestatic jaundice

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

Addition of a progestin when a woman has not had a hysterectomy

Studies of the addition of a progestin for 10 or more days of a cycle of estrogen administration or daily with estrogen in a continuous regimen, have reported a lowered incidence of endometrial hyperplasia than would be induced by estrogen treatment alone. Endometrial hyperplasia may be a precursor to endometrial cancer.

In a subset of WHI (see section 5.1) no increased risk of endometrial cancer after an average of 5,2 years of treatment with the estrogen plus progestin combination compared to placebo was observed.

There are, however, possible risks that may be associated with the use of progestins in ERT regimens compared to estrogen-alone regimens. These include an increased risk of breast cancer; adverse effects on lipoprotein metabolism, (e.g., lowering HDL, raising LDL); and impairment of glucose tolerance (see section 4.5).

Elevated blood pressure

In a small number of case reports, substantial increases in blood pressure during ERT have been attributed to idiosyncratic reactions to estrogens. In a large, randomised, placebo-controlled clinical trial a generalised effect of ERT on blood pressure was not seen. Blood pressure should be monitored at regular intervals with estrogen use.

Exacerbation of other conditions

ERT/HRT may cause an exacerbation of asthma, epilepsy, migraine, diabetes mellitus, porphyria, systemic lupus erythematosus and hepatic haemangiomas, and should be used with caution in women with these conditions.

Depression

Depressed mood and depression are well-known undesirable effects of hormonal contraceptive use and preparations containing estrogen and/or progesterone/progestogen (see section 4.8). Depression can be serious and is a well-known risk factor for suicidal behaviour and suicide. Women should be advised to contact their medical practitioner in case of mood changes and depressive symptoms, including shortly after initiating the treatment.

Exacerbation of endometriosis

Endometriosis may be exacerbated with administration of ERT. Addition of a progestin should be considered in women who have undergone hysterectomy, but are known to have residual endometriosis, since malignant transformation after ERT has been reported.

Hypocalcaemia

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

Hypothyroidism

Estrogen administration leads to increased thyroid-binding globulin (TBG) levels. Patients dependent on thyroid hormone replacement therapy may require increased doses of their thyroid replacement therapy. These women should have their thyroid function monitored in order to maintain their free thyroid hormone levels in an acceptable range (see section 4.5, *Laboratory test interactions*).

Laboratory monitoring

PREMARIN administration should be guided by clinical response at the lowest dose, rather than by hormone levels (e.g. estradiol, FSH).

Uterine bleeding

Certain patients may develop abnormal uterine bleeding.

Excipients with known effect

PREMARIN contains lactose and sucrose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency, fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

4.5 Interaction with other medicines and other forms of interaction

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

In vitro and *in vivo* studies have shown that estrogens, are metabolised partially by cytochrome P450 3A4 (CYP3A4). Therefore, inducers or inhibitors of CYP3A4 may affect estrogen medicine metabolism. Inducers of CYP3A4, such as St. John's Wort preparations (*Hypericum perforatum*), phenobarbital, phenytoin, carbamazepine, rifampicin and dexamethasone may reduce plasma concentrations of estrogens, 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 estrogens and may result in side effects.

Laboratory test interactions

- Increased platelet count, decreased levels of antithrombin III, and increased plasminogen antigen and activity.
- 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.
- Other binding proteins may be elevated in serum, i.e. corticosteroid binding globulin (CBG), sex-hormone binding globulin (SHBG), leading to increased circulating corticosteroid and sex steroids respectively. Free hormone concentrations may be decreased. Other plasma proteins may be increased (angiotensin/renin substrate, alpha-1-antitrypsin, ceruloplasmin).
- Increased plasma high-density lipoprotein (HDL) and HDL_2 cholesterol subfraction concentrations, reduced low-density lipoprotein (LDL) cholesterol concentrations, increased triglyceride levels (see section 4.4).
- Impaired glucose tolerance.
- The response to metyrapone may be reduced.

4.6 Fertility, pregnancy and lactation

Pregnancy

PREMARIN should not be used during pregnancy (see section 4.3).

Breastfeeding

PREMARIN should not be used during lactation. Estrogen administration to nursing women has been shown to decrease the quantity and quality of the breast milk. Detectable amounts of estrogens have been identified in the breast milk of mothers receiving estrogen-alone therapy. Caution should be exercised when PREMARIN is administered to a nursing woman.

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

Tabulated summary of adverse reactions

The following adverse effects may occur:

Adverse reactions are listed in CIOMS frequency categories: 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), unknown (cannot be estimated from the available data).

System organ class	Frequency	Adverse reaction
Infections and infestations	Uncommon	Vaginitis, including vaginal candidiasis
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Rare	Breast cancer; ovarian cancer; fibrocystic breast changes; growth potentiation of benign meningioma
	Very rare	Endometrial cancer; enlargement of hepatic haemangiomas
Immune system disorders	Uncommon	Hypersensitivity
	Rare	Anaphylactic/ anaphylactoid reactions, including urticaria and angioedema
Metabolism and nutrition disorders	Rare	Glucose intolerance
	Very rare	Exacerbation of porphyria; hypocalcaemia (in patients with disease that can predispose to severe hypocalcaemia)
Psychiatric disorders	Uncommon	Changes in libido; mood disturbances; depression; dementia
	Rare	Irritability

Nervous system disorders	Uncommon	Dizziness; headache; migraine; nervousness
	Rare	Cerebrovascular accident/stroke; exacerbation of epilepsy
	Very rare	Exacerbation of chorea
Eye disorders	Uncommon	Intolerance to contact lenses
	Very rare	Retinal vascular thrombosis
Cardiac disorders	Rare	Myocardial infarction
Vascular disorders	Uncommon	Venous thrombosis; pulmonary embolism
	Rare	Venous thromboembolism; superficial thrombophlebitis
Respiratory, thoracic and mediastinal disorders	Rare	Exacerbation of asthma
Gastrointestinal disorders	Uncommon	Nausea; bloating; abdominal pain/cramps
	Rare	Vomiting; pancreatitis; ischaemic colitis
Hepato-biliary disorders	Uncommon	Gallbladder disease
	Very rare	Cholestatic jaundice
Skin and subcutaneous tissue disorders	Common	Alopecia
	Uncommon	Chloasma/melasma; hirsutism; pruritus; rash
	Rare	Erythema multiforme; erythema nodosum
Musculoskeletal and connective tissue disorders	Common	Arthralgia; leg cramps
Reproductive system and breast disorders	Common	Abnormal uterine bleeding; breast pain, tenderness, enlargement, discharge; leucorrhoea
	Uncommon	Change in menstrual flow; change in cervical ectropion and secretion

	Rare	Dysmenorrhoea/pelvic pain; galactorrhoea; increased size of uterine leiomyomata
	Very rare	Endometrial hyperplasia
	Unknown	Gynaecomastia in males
General disorders and administration site conditions	Uncommon	Oedema
Investigations	Common	Changes in weight (increase or decrease); increased triglycerides
	Very rare	Increases in blood pressure

Post-marketing reported side effects

Severe depression with a higher risk of suicidal thoughts/behaviour and suicide.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Symptoms of overdosage of estrogen-containing medicines 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 section 4.8).

Treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 21.8.1 Estrogens

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.

Pharmacodynamics

There are no pharmacodynamic data known for conjugated estrogens alone.

Clinical efficacy and safety

Women's Health Initiative Studies (WHI)

The Women's Health Initiative (WHI) enrolled approximately 27 000 predominantly healthy postmenopausal women in two sub studies to assess the risks and benefits of conjugated estrogens (CE) (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 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 estrogen-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 estrogen 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 estrogen alone compared with placebo. Results of the estrogen-alone sub study which included 10 739 women (average age of 63 years, range 50 to 79; 75,3 % White, 15,1 % Black, 6,1 % Hispanic, 3,6 % Other); after an average follow-up of 7,1 years are presented in the table below.

In the estrogen-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] 0,78 - 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. Estrogen 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 estrogen 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 estrogen-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 estrogen-alone substudy of WHI[a]			
Event	Relative risk ERT vs. placebo (95 % nCI[b])	ERT n=5310	Placebo n=5429
		Absolute risk per 10 000 person-years	
CHD events[c] Non-fatal MI[c] CHD death[c]	0,95 (0,78 – 1,16) 0,91 (0,73 - 1,14) 1,01 (0,71 - 1,43)	54 40 16	57 43 16
All strokes[c]	1,33 (1,05 – 1,68)	45	33
Ischaemic stroke[c]	1,55 (1,19 – 2,01)	38	25
Deep vein thrombosis[c,d]	1,47 (1,06 – 2,06)	23	15
Pulmonary embolism[c]	1,37 (0,90 – 2,07)	14	10
Invasive breast cancer[c]	0,80 (0,62 – 1,04)	28	34
Colorectal cancer[c]	1,08 (0,75 - 1,55)	17	16
Hip fracture[c]	0,65 (0,45 – 0,94)	12	19
Vertebral fractures[c,d]	0,64 (0,44 – 0,93)	11	18
Lower arm/wrist fractures[c,d]	0,58 (0,47 – 0,72)	35	59
Total fractures[c,d]	0,71 (0,64 – 0,80)	144	197
Death due to other causes[e,f]	1,08 (0,88 - 1,32)	53	50

Overall mortality[c,d]	1,04 (0,88 - 1,22)	79	75
Global Index[g]	1,02 (0,92 – 1.13)	206	201

[a] Adapted from numerous WHI publications

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

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

[d] Not included in global index.

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

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

[g] 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.

The estrogen-plus-progestin sub study was also stopped early. According to the predefined stopping rule, after an average follow-up of 5,6 years of treatment, the increased risk of breast cancer and cardiovascular events, at that time, exceeded the specified benefits (such as the reduction of colorectal cancer and hip fracture). Results of the estrogen-plus-progestin sub study of WHI which included 16 608 women (average age of 63 years; range 50 to 79; 83,9 % White, 6,8 % Black, 5,4 % Hispanic, 3,9 % Other) for an average follow-up of 5,6 years are presented in the table below. These results reflect centrally adjudicated data after an average follow-up of 5,6 years.

In the WHI estrogen-plus-progestin substudy, an increase in CHD risk was associated with combined hormonal therapy (RR 1,23, 95 % nCI 0,99 – 1,53). This was most apparent in the first year of the study (RR 1,81, 95 % nCI 1,09 – 3,01). The RR of invasive breast cancer (RR 1, 24, 95 % nCI 1,01 – 1,54) was increased in women on combined hormone therapy. The sub study also reported a statistically significant increased RR of overall stroke (RR 1,31, 95 % nCI 1,03 – 1,68), ischaemic stroke (RR 1,44, 95 % nCI 1,09 – 1,90), DVT (RR 1,95, 95 % nCI 1,43 – 2,67), and PE (RR 2,13, 95 % nCI 1,45 – 3,11). Estrogen plus progestin was found to increase bone mineral density vs. placebo (3,7 % vs. 0,14 %, P<0,001) after three years. A statistically significant reduced RR of hip (RR 0,67, 95 % nCI 0,47 – 0,96), vertebral

(RR 0,65, 95 % nCI 0,46 – 0,92), lower arm/wrist (RR 0,71, 95 % nCI 0,59 – 0,85), and total fractures (RR 0,76, 95 % nCI 0,69 – 0,83) was associated with estrogen plus progestin use.

Estrogen plus progestin use was associated with a statistically significant decreased risk of invasive colorectal cancer (RR 0,61, 95 % nCI 0,42 – 0,87) although when colorectal cancers were diagnosed in combined hormone users, they were more advanced. Additional analyses showed no statistically significant differences in relative risk of endometrial (RR 0,81, 95 % nCI 0,48 – 1,36) or cervical (RR 1,44, 95 % nCI 0,47 – 4,42) cancers in patients on combined hormone replacement vs. placebo. After an average of 5,2 years of follow-up, the estrogen-plus progestin sub study did not report a statistically significant effect on death due to other causes (RR 0,92, 95 % nCI 0,74 – 1,14), and there was no effect on overall mortality risk (RR 1,00, 95 % nCI 0,83 – 1,19).These confidence intervals are unadjusted for multiple looks and multiple comparisons.

Relative and absolute risk reported from the estrogen-plus-progestin substudy of WHI at an average of 5,6 years[a,b]			
Event	Relative risk ERT vs placebo (95 % nCI[c])	HRT n = 8506	Placebo n = 8102
		Absolute risk per 10 000 person-years	
CHD events Non-fatal MI CHD death	1,23 (0,99 – 1,53) 1,28 (1,00 - 1,63) 1,10 (0,70 - 1,75)	41 31 8	34 25 8
All strokes Ischaemic stroke	1,31 (1,03 - 1,68) 1,44 (1,09 - 1,90)	33 26	25 18

Deep vein thrombosis[d]	1,95 (1,43 - 2,67)	26	13
Pulmonary embolism	2,13 (1,45 - 3,11)	18	8
Invasive breast cancer[c]	1,24 (1,01 - 1,54)	41	33
Colorectal cancer	0,61 (0,42 – 0,87)	10	16
Endometrial cancer[d]	0,81 (0,48 - 1,36)	6	7
Cervical cancer[d]	1,44 (0,47 - 4,42)	2	1
Hip fracture	0,67 (0,47 - 0,96)	11	16
Vertebral fractures[d]	0,65 (0,46 - 0,92)	11	17
Lower arm/wrist fractures[d]	0,71 (0,59 - 0,85)	44	62
Total fractures[d]	0,76 (0,69 - 0,83)	152	199
Overall mortality[f]	1,00 (0,83 – 1,19)	52	52
Global index[g]	1,13 (1,02 – 1,25)	184	165

[a] Adapted from numerous WHI publications

[b] Results are based on centrally adjudicated data.

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

[d] Not included in global index.

[e] Includes metastatic and non-metastatic breast cancer with the exception of *in situ* breast cancer.

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

[g] 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 Women's Health Initiative Memory Study (WHIMS), an ancillary study of WHI, one population of 4 532 women aged 65 to 79 years was randomised to CE plus MPA (0,625 mg/2,5 mg daily) or placebo. In a second population of WHIMS 2 947 hysterectomised women, aged 65 – 79 years, were randomised to CE (0,625 mg daily) or placebo. After an average follow-up of four years, a relative risk of 2,05 (95 % CI 1,21 – 3,48) for probable dementia was reported in the estrogen-plus-progestin group compared to placebo. In the estrogen-alone group, after an average follow-up of 5,2 years, a relative risk of 1,49 (95 % CI 0,83 – 2,66) for probable dementia was reported compared to placebo. When the data from the two populations was pooled as planned in the WHIMS protocol, the reported overall relative risk for probable dementia was 1,76 (95 % CI 1,19 – 2,60). Since this study was conducted in women aged 65 – 79 years, it is unknown whether these findings apply to younger postmenopausal women (see section 4.4).

5.2 Pharmacokinetic properties

Absorption

Conjugated estrogens are soluble in water and are well-absorbed from the gastrointestinal tract. The CE 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 exists 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.

Special populations

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Hypromellose

Lactose monohydrate

Magnesium stearate

Microcrystalline cellulose

Tablet coating

Hydroxypropyl cellulose

Hypromellose

Microcrystalline cellulose

Opadry green 15B21511, (0,3 mg)

Opadry maroon 03B16083 (0,625 mg)

Opadry yellow 15B32143 (1,25 mg)

Polyethylene glycol

Sucrose

Polish

Carnauba wax

Hypromellose

Printing ink

Opacode WB NS-78-18011, white ink (0,3 mg and 0,625 mg)

Opacode NS-78-17821, black ink (1,25 mg)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store in a cool, dry place at or below 25 °C.

6.5 Nature and contents of container

PREMARIN 0,3: Blister packs (clear or opaque PVC/Aclar/PVC/Al) of 28’s.

PREMARIN 0,625: Blister packs (clear or opaque PVC/Aclar/PVC/Al) of 28’s.

PREMARIN 1,25: Blister packs (clear or opaque PVC/Aclar/PVC/Al) of 28’s.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Pfizer Laboratories (Pty) Ltd

85 Bute Lane

Sandton 2196

South Africa

Tel: +27(0)11 320 6000 / 0860 734 937 (Toll-free South Africa)

8. REGISTRATION NUMBERS

PREMARIN 0,3: G/21.8.1/3016

PREMARIN 0,625: G/21.8.1/3015

PREMARIN 1,25: G/21.8.1/3014

9. DATE OF FIRST AUTHORISATION

PREMARIN 0,3: 16 October 1995

PREMARIN 0,625: 23 March 1995

PREMARIN 1,25: 09 November 1995

10. DATE OF REVISION OF THE TEXT

24 October 2022

NAMIBIA: S2

PREMARIN 0,3 mg – Reg. No.: 04/21.8.1/1125

PREMARIN 0,625 mg – Reg. No.: 04/21.8.1/1126

PREMARIN 1,25 mg – Reg. No.: 04/21.8.1/1127

BOTSWANA: S2

PREMARIN 0,3 mg – Reg. No.: B9319970

PREMARIN 0,625 mg – Reg. No.: B9319975

PREMARIN 1,25 mg – Reg. No.: B9319980

ZIMBABWE: PP

PREMARIN 0,3 mg – Reg. No.: 83/17.3/1750

PREMARIN 0,625 mg – Reg. No.: 83/17.3/1751

PREMARIN 1,25 mg – Reg. No.: 83/17.3/1752

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