SCHEDULING STATUS:

S 4

PROPRIETARY NAME AND DOSAGE FORM:

PREMARIN® 0,3 (Tablet)

PREMARIN® 0,625 (Tablet)

PREMARIN® 1,25 (Tablet)

COMPOSITION:

Each **PREMARIN** 0,3 tablet contains 0,3 mg Conjugated Oestrogens.

Each **PREMARIN** 0,625 tablet contains 0,625 mg Conjugated Oestrogens.

Each **PREMARIN** 1,25 tablet contains 1,25 mg Conjugated Oestrogens.

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:

Oestrogens are important in the development and maintenance of the female reproductive system and secondary sex characteristics.

Oestrogens contribute to the maintenance of tone and elasticity of urogenital structures. Oestrogens participate in the maintenance of normal bone structure. Oestrogens are also involved in psychological and emotional aspects of feminine behaviour.

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

Conjugated oestrogens are soluble in water and are well absorbed from the gastrointestinal tract. 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.

Oestrogen decreases loss of bone mass in postmenopausal women. Oestrogen acts by decreasing bone resorption. The effect on bone mass conservation is sustained only as long as conjugated oestrogen therapy is continued.

Pharmacodynamic properties:

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 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. 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 0,61, 95 % nCI 0,41-0,91), (RR 0,62, 95 % nCI 0,42-0,93), and (RR 0,70, 95 % nCI 0,63-0,79), 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[a]

Event	**Relative Risk ERT vs. placebo (95 % nCI*[a])**	**ERT n = 5 310**	**Placebo n = 5 429**
		Absolute Risk per 10 000 Person-years	
CHD events[b]	0,95 (0,79 –1,16)	53	56

RELATIVE AND ABSOLUTE RISK SEEN IN THE OESTROGEN-ALONE SUBSTUDY OF WHI[a]			
Event	**Relative Risk ERT vs. placebo (95 % nCI*[a])**	**ERT n = 5 310**	**Placebo n = 5 429**
		Absolute Risk per 10 000 Person-years	
Non-fatal MI[b]	0,91 (0,73-1,14)	40	43
CHD death[b]	1,01 (0,71-1,43)	16	16
Stroke[c]	1,37 (1,09 – 1,73)	45	33
Deep vein thrombosis[b]	1,47 (1,06 – 2,06)	23	15
Pulmonary embolism[b]	1,37(0,90 – 2,07)	14	10
Invasive breast cancer[b]	0,80 (0,62 – 1,04)	28	34
Colorectal cancer[c]	1,08 (0,75-1,55)	17	16
Hip fracture [c]	0,61 (0,41-0,91)	11	17
Vertebral fractures [c]	0,62 (0,42 – 0,93)	11	17
Total fractures[c]	0,70 (0,63 – 0,79)	139	195
Death due to other causes [c d]	1,08 (0,88-1,32)	53	50
Overall mortality[c]	1,04 (0,88-1,22)	81	78

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

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

* Final adjudicated results for CHD events from the oestrogen-alone substudy, after an average follow-up of 7,1 years, reported no overall difference for primary CHD events (non-fatal MI, silent MI and CHD death) in women receiving CEE alone compared with placebo.

The oestrogen-plus-progestin substudy was also stopped early., According to the predefined stopping rule, after an average follow-up of 5,2 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 oestrogen-plus-progestin substudy 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 oestrogen-plus-progestin substudy, an increase in CHD risk was associated with combined hormonal therapy (RR 1,24, 95 % nCI 1,00 – 1,54). 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 substudy also reported a statistically significant increased RR of overall stroke (RR 1,31, 95 % nCI 1,02 – 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). Oestrogen 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 oestrogen plus progestin use.

Oestrogen plus progestin use was associated with a statistically significant decreased risk of invasive colorectal cancer (RR 0,56, 95 % nCI 0,38 – 0,81) 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 oestrogen-plus progestin substudy 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 0,98, 95 % nCI 0,82 –1,18).These confidence intervals are unadjusted for multiple looks and multiple comparisons.

RELATIVE AND ABSOLUTE RISK REPORTED FROM THE OESTROGEN-PLUS-PROGESTIN SUBSTUDY OF WHI AT AN AVERAGE OF 5,6 YEARS [a]			
Event	**Relative Risk ERT vs placebo (95 % nCI)**	**HRT n = 8 506**	**Placebo n = 8 102**
		Absolute Risk per 10 000 Person-years	
CHD events	1,24 (1,00-1,54)	39	33
Non-fatal MI	1,28 (1,00-1,63)	31	25
CHD death	1,10 (0,70-1,75)	8	8
All Strokes	1,31 (1,02-1,68)	31	24
Ischaemic stroke	1,44 (1,09-1,90)	26	18
Deep vein thrombosis	1,95 (1,43-2,67)	26	13
Pulmonary embolism	2,13 (1,45-3,11)	18	8
Invasive breast cancer [ac]	1,24 (1,01-1,54)	41	33
Invasive colorectal cancer	0,56 (0,38-0,81)	9	16
Endometrial cancer	0,81 (0,48-1,36)	6	7
Cervical cancer	1,44 (0,47-4,42)	2	1
Hip fracture	0,67 (0,47-0,96)	11	16
Vertebral fractures	0,65 (0,46-0,92)	11	17
Lower arm/wrist fractures	0,71 (0,59-0,85)	44	62
Total fractures	0,76 (0,69-0,83)	152	199

[a] Results are based on centrally adjudicated data. Mortality data was not part of the adjudicated data; however, data at 5,2 years of follow-up showed no difference between the groups in terms of all-cause mortality (RR 0,98, 95 % nCI 0,82 – 1,18).

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

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

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 randomized to CEE plus MPA (0,625 mg/2,5 mg daily) or placebo. In a second population of WHIMS 2 947 hysterectomized women, aged 65 – 79 years, were randomized to CEE (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 oestrogen-plus-progestin group compared to placebo. In the oestrogen-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 WARNINGS AND SPECIAL PRECAUTIONS).

INDICATIONS:

PREMARIN (Conjugated Oestrogens USP) is indicated for oestrogen replacement therapy of oestrogen-deficient states, whether naturally occurring (climacteric, menopause) or artificially induced. PREMARIN is also indicated in the treatment of pathological states of reproductive endocrine imbalance.

1. 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 products should be considered.
- Senile atrophic vaginitis.

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

Prevention of osteoporosis: When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis and for whom non-oestrogen medications are not considered to be appropriate.

Management of osteoporosis*:* When prescribing solely for the management of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis and for whom non-oestrogen medications are not considered to be appropriate.

3. 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.

Oestrogen Replacement Therapy (ERT) and Hormone Replacement Treatment (HRT) should not be initiated or continued to prevent cardiovascular disease or dementia (See WARNINGS AND SPECIAL PRECAUTIONS).

The benefits and risks of HRT must always be carefully weighed, including consideration of emergence of risks as therapy continues (See WARNINGS AND SPECIAL PRECAUTIONS).

Oestrogens 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 oestrogens and oestrogen/ progestin combinations.

CONTRAINDICATIONS:

1. Known or suspected pregnancy (see PREGNANCY AND LACTATION).
2. Known, suspected or past cancer of the breast (except in appropriately selected patients being treated for metastatic disease).
3. Known or suspected oestrogen-dependent neoplasia (e.g., endometrial cancer, endometrial hyperplasia).
4. Undiagnosed abnormal genital bleeding.
5. Active or past history of confirmed venous thromboembolism (deep venous thrombosis, pulmonary embolism).
6. Active or recent arterial thromboembolic disease (e.g., stroke, myocardial infarction).
7. PREMARIN Tablets should not be used in patients hypersensitive to its ingredients.
8. Endometriosis.
9. Endometrial carcinoma
10. Acute or chronic liver disease or history of liver disease where the liver function test have failed to return to normal. Rotor syndrome or Dubin-Johnson syndrome.

WARNINGS AND SPECIAL PRECAUTIONS:

1. General:

Oestrogen Replacement Therapy (ERT) and Hormone Replacement Therapy (HRT) have been associated with increased risks of certain cancers and cardiovascular diseases. The use of

unopposed oestrogens in women with an intact uterus is associated with an increased risk of endometrial cancer.

Oestrogen Replacement Therapy (ERT) or Hormone Replacement Treatment (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.

Oestrogens 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 oestrogens and oestrogen/ progestin combinations.

2. Cardiovascular risk:

ERT has been associated with an increased risk of stroke and deep venous thrombosis (DVT).

Hormone Replacement Therapy (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 oestrogen-alone substudy of the WHI (see PHARMACOLOGICAL ACTION), 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.

In the oestrogen-plus-progestin substudy of the WHI, a statistically significant increased risk of stroke was reported in women receiving the oestrogen/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 oestrogen-alone substudy 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 oestrogen alone compared to placebo.

In the oestrogen-plus-progestin substudy of WHI, no statistically significant increase of coronary heart disease (CHD) events was reported in women receiving the oestrogen/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 equine oestrogen plus medroxyprogesterone acetate demonstrate no cardiovascular benefit. During an average follow-up of 4,1 years, treatment with oral conjugated equine oestrogen plus medroxyprogesterone acetate did not reduce the overall rate of CHD events in postmenopausal women with established coronary heart disease. There were more CHD events in the hormone-treated group than in the placebo group in year one, but not during the subsequent years.

Large doses of oestrogen (5 mg conjugated oestrogens 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

In the oestrogen-alone substudy of WHI, the risk of VTE (deep venous thrombosis [DVT] and PE) was reported to be increased for women taking conjugated equine oestrogens (30 vs. 22 per 10 000 person-years), although only the increased risk of DVT reached statistical significance (23 vs. 15 per 10 000 person-years). The increase in VTE risk was observed during the first two years.

In the oestrogen-plus-progestin substudy of WHI (see PHARMACOLOGICAL ACTION) a statistically significant 2-fold greater rate of VTE, was reported in women receiving the estrogen/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, 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

In some studies, use of ERT and HRT has been associated with an increased risk of breast cancer.

In the oestrogen-alone substudy of WHI, after an average of 7,1 years of follow-up, CEE (0,625 mg per day) was not associated with an increased risk of invasive breast cancer (RR 0,80, 95 % nCI 0,62 – 1,04).

In the oestrogen–plus-progestin substudy, after a mean follow-up of 5,6 years, the WHI, substudy reported in increased risk of invasive breast cancer (RR 1,24, 95 % nCI 1,01 – 1,54) invasive breast cancers were larger and diagnosed at a more advanced stage in the active therapy group compared to those in the placebo group. The absolute risk was 41 vs. 33 cases per 10 000 person-years, for oestrogen plus progestin compared with placebo, respectively. Metastatic disease was rare with no apparent difference between groups. Other prognostic factors such as histologic subtype, grade and hormone receptor status did not differ between groups.

Epidemiologic studies (not necessarily including PREMARIN tablets) have reported an increased risk of breast cancer in women taking oestrogens or oestrogen/ progestin combinations for HRT for several years. The excess risk increases with duration of use and seems to return to baseline in the course of about five years after stopping treatment. These studies also suggest that the risk of breast cancer is greater and becomes apparent earlier with oestrogen/ progestin combination therapy as compared to the use of oestrogens alone.

Studies evaluating various HRT formulations did not show significant variation in the relative risk of breast cancer among formulations regardless of the oestrogen/ progestin components, doses, regimens, or route of administration.

According to data from epidemiologic studies, about 32 women in every 1000 women who never used HRT are expected to have breast cancer diagnosed between the ages of 50 and 65 years. Among 1 000 current or recent users of oestrogen-only preparations, it is estimated that 5 and 10 years of use beginning at age 50 result in 1,5 (95 % confidence interval (CI), 0-3) and 5 (95 % CI, 3-7), respectively, additional breast cancers diagnosed by age 65 years. The corresponding numbers for those using oestrogen/ progestin combinations are 6 (95 % CI, 5-7) and 19 (95 % CI, 18-20) respectively.

Use of oestrogen alone and oestrogen plus progestin has been reported to result in an increase in abnormal mammograms requiring further evaluation.

All women should receive yearly breast examinations by a health care provider and perform monthly breast self-examinations. In addition, mammography examinations should be scheduled based on patient age, risk factors, and prior mammogram results.

Endometrial cancer

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

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. Most studies show no significant increased risk associated with use of oestrogens 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.

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

Adding a progestin to ERT has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer (see SIDE EFFECTS).

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

Clinical surveillance of all women taking oestrogen/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 vaginal bleeding.

Ovarian cancer

In some epidemiologic studies, use of oestrogen-only products, in particular for ten or more years, has been associated with an increased risk of ovarian cancer. Other epidemiologic studies have not found these associations**.** The analysis of the WHI data suggested that oestrogen plus progestin therapy may increase the risk of ovarian cancer.

4. Dementia:

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 randomized to CEE plus MPA (0,625 mg/2,5 mg daily) or placebo. In a second population of WHIMS 2 947 hysterectomized women, aged 65 – 79 years, were randomized to CEE (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 oestrogen-plus-progestin compared to placebo. In the oestrogen-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 (see SIDE EFFECTS)

5. Effects during Pregnancy:

PREMARIN should not be used during pregnancy (see CONTRAINDICATIONS and WARNINGS AND SPECIAL PRECAUTIONS).

6. Gallbladder Disease:

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

7. 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.

8. 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.

9. 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 contra-indications 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.

10. Fluid retention:

Because oestrogens/progestins 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 oestrogens are prescribed.

11 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. Women with pre-existing hypertriglyceridaemia should be followed closely during oestrogen replacement or hormone replacement therapy.

12: Impaired liver function:

Oestrogens/progestins may be poorly metabolised in patients with impaired liver function.

13: Past 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, medication should be discontinued.

14. 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 oestrogen administration or daily with oestrogen in a continuous regimen, have reported a lowered incidence of endometrial hyperplasia than would be induced by oestrogen treatment alone. Endometrial hyperplasia may be a precursor to endometrial cancer.

In a subset of WHI (see PHARMACOLOGICAL ACTION) no increased risk of endometrial cancer after an average of 5,2 years of treatment with the oestrogen/progestin combination compared to placebo was observed.

There are, however, possible risks that may be associated with the use of progestins in oestrogen replacement regimens compared to oestrogen-alone regimens. These include (a) an increased risk

of breast cancer (see WARNINGS AND SPECIAL PRECAUTIONS); (b) adverse effects on lipoprotein metabolism, (e.g. lowering HDL, raising LDL); and (c) impairment of glucose tolerance.

15. 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 generalised effect of ERT on blood pressure was not seen. Blood pressure should be monitored at regular intervals with oestrogen use.

16: Exacerbation of other conditions:

Oestrogen replacement/hormone 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 replacement 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.

17. Hypocalcaemia:

Oestrogens should be used with caution in individuals with severe hypocalcaemia.

18. 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 below).

19. Laboratory monitoring:

Oestrogen administration should generally be guided by clinical response at the lowest dose, rather than laboratory monitoring, for relief of symptoms for those indications in which symptoms are observable.

20. Uterine bleeding:

Certain patients may develop abnormal uterine bleeding (see WARNINGS AND SPECIAL PRECAUTIONS).

Paediatric use:

Although oestrogen replacement therapy 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.

Oestrogen 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.

Geriatric use:

Of the total number of subjects in the oestrogen-alone substudy of the Women's Health Initiative (WHI) study, 46 % (n=4943) were 65 years and over, while 7,1 % (n=767) were 75 years and over. There was a higher relative risk (CEE vs. placebo) of stroke in women less than 75 years of age compared to women 75 years and over.

Of the total number of subjects in the conjugated equine oestrogens in combination with medroxyprogesterone acetate substudy of the (WHI) study, 44 % (n= 7320) were 65-74 years of

age, while 6,6 % (n= 1095) were 75 and over (see PHARMACOLOGICAL ACTION). There was a higher relative risk of non-fatal stroke and invasive breast cancer in women 75 and over compared to younger subjects. In women greater than 75, the increased risk of non-fatal stroke and invasive breast cancer observed in the oestrogen-plus-progestin combination group compared to the placebo group was 75 vs 24 per 10 000 person-years and 52 vs. 12 per 10 000 person-years, respectively.

In WHIMS, 2 947 hysterectomized women, aged 65 – 79 years, were randomized to CEE (0,625 mg daily) or placebo; 81 % (n=2 383) were 65 to 74 while 19 % (n=564) were 75 and over. Approximately 50 % of the women had no prior ERT use. After an average follow-up of 5,2 years, the absolute risk of developing probable dementia with oestrogen alone was 37 cases per 10 000 person-years compared to 25 cases per 10 000 person-years with placebo (RR 1,49, 95 % CI 0,83 – 2,66).(see WARNINGS AND SPECIAL PRECAUTIONS) .

The second population of WHIMS including 4 532 women 65 years of age and older, was followed for an average of four years, 82 % (n= 3729) were 65 to 74 while 18 % (n=803) were 75 and over. Most women (80 %) had no prior HRT use. After an average follow-up of 4 years, the absolute risk of developing probable dementia with oestrogen plus progestin was 45 cases per 10 000 person-years compared to 22 cases per 10 000 person-years with placebo (RR 2,05, 95 % CI 1,21-3,48) (see WARNINGS AND SPECIAL PRECAUTIONS)

Alzheimer's disease was the most common classification of probable dementia in both the treatment groups and placebo groups. Seventy nine percent of the cases of probable dementia occurred in women that were older than 70 for the CEE group, and 82 percent of the cases of probable dementia occurred in women that were older than 70 in the CEE plus MPA group. (see WARNINGS AND SPECIAL PRECAUTIONS).

When data from the two populations were pooled, the absolute risk of developing probable dementia with either ERT or HRT was 41 cases per 10 000 person-years compared to 23 cases per 10 000 person-years with placebo (RR 1,76, 95 % CI 1,19 – 2,60). .

INTERACTIONS:

Data from a drug-drug interaction study involving conjugated equine oestrogens and medroxyprogesterone acetate indicate that the pharmacokinetic disposition of both drugs are 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 17ß-oestradiol, one of the components of conjugated equine oestrogens, is metabolised partially by Cytochrome P450 3A4 (CYP3A4). Therefore, strong CYP3A4 inducers such as phenobarbital, phenytoin, carbamazepine, rifampicin and dexamethasone may reduce plasma concentrations of 17ß-oestradiol. This may lead to a decreased effect and/or changes in the uterine bleeding profile. CYP3A4 inhibitors such as cimetidine, erythromycin and ketoconazole may increase plasma concentrations of 17ß-oestradiol 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 should not be used during pregnancy (see CONTRAINDICATIONS).

PREMARIN should not be used during lactation.

DOSAGE AND DIRECTIONS FOR USE:

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.

The lowest effective dose should be administered.

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

Usual dosage ranges:

1. Climacteric Symptoms

For treatment of moderate to severe vasomotor symptoms and atrophic vaginitis associated with the menopause, the lowest dose that will control symptoms should be chosen.

Vasomotor Symptoms: 0,3 mg to 1,25 mg daily.

Atrophic Vaginitis: 0,3 mg to 1,25 mg daily depending upon the tissue responses of the individual patient.

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

2. Osteoporosis Prevention and Management:

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 drug followed by 5 days off the drug) as is medically appropriate on an individualized basis.

3. Hypoestrogenism due to:

a. 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.

b. Female castration or primary ovarian failure :1,25 mg daily, cyclically.

Adjust dosage upward or downward according to severity of symptoms and response of the patient. For maintenance, adjust dosage to lowest level that will provide effective control.

4. Advanced androgen-dependent carcinoma:

a. 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.

b. Palliation of Mammary Carcinoma:

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

SIDE EFFECTS:

The following adverse effects may occur:

Adverse reactions are listed in CIOMS frequency categories:

Very Common	≥ 10 %
Common	≥ 1 % and < 10 %
Uncommon	≥ 0,1 % and < 1 %
Rare	≥ 0,01 % and < 0,1 %
Very rare	< 0,01 %

System Organ Class	***Adverse Reaction***
Reproductive system and breast disorders:	
Common	Breakthrough bleeding/spotting; breast pain, tenderness; enlargement; discharge
Uncommon	Change in menstrual flow; change in cervical ectropion and secretion
Rare	Dysmenorrhoea; galactorrhoea, increased size of uterine eiomyomata
Very rare	Endometrial hyperplasia

Gastro-intestinal disorders:

Uncommon	Nausea; bloating; abdominal pain/cramps
Rare	Vomiting; pancreatitis

Nervous system disorders:

Uncommon	Dizziness; headache; migraine; nervousness
Rare	Cerebrovascular accident/ stroke; exacerbation of epilepsy
Very rare	Exacerbation of chorea

Musculoskeletal, connective tissue and bone disorders:

Common	Arthralgias; leg cramps

Psychiatric disorders:

Uncommon	Changes in libido; mood disturbances; depression; dementia
Rare	Irritability

Vascular disorders:

Uncommon	Venous thrombosis
Rare	Pulmonary embolism; venous thromboembolism
	Superficial thrombophlebitis

General disorders and administration site conditions:

Uncommon	Oedema

Skin and subcutaneous tissue disorders:

Common	Alopecia
Uncommon	Chloasma/melasma; hirsutism; pruritus; rash

Very rare	Erythema multiforme; erythema nodosum

Hepato-biliary disorder:

Uncommon	Gallbladder disease
Very rare	Cholestatic jaundice

Infections and infestations:

Uncommon	Vaginitis, including vaginal candidiasis

Neoplasms benign and malignant (including cysts and polyps):

Rare	Breast cancer; ovarian cancer, fibrocystic breast changes
Very rare	Endometrial cancer, enlargement of hepatic hemangiomas

Immune system disorders:

Rare	Anaphylactic/anaphylactoid reactions, including urticaria and angioedema

Metabolism and nutrition disorders:

Rare	Glucose intolerance
Very rare	Exacerbation of porphyria; hypocalcaemia

Eye disorders:

Uncommon	Intolerance to contact lenses
Very rare	Retinal vascular thrombosis

Cardiac disorders:

Rare	Myocardial infarction

Respiratory, thoracic and mediastinal disorders:

Rare	Exacerbation of asthma

Investigations:

Common	Changes in weight (increase or decrease); increased triglycerides
Very rare	Increases in blood pressure

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 Side effects

Treatment is symptomatic and supportive.

IDENTIFICATION:

PREMARIN (Conjugated Oestrogens) tablets are sugar coated.

PREMARIN Tablets 0,3 are oval, green and biconvex, coated tablet branded “0,3” in white ink.

PREMARIN Tablets 0,625 are oval, maroon and biconvex, coated tablet branded “0,625” in white ink.

PREMARIN Tablets 1,25 are oval, yellow and biconvex, coated tablet branded “1,25”in black ink.

PRESENTATION:

PREMARIN 0,3: Securitainers with 20 and 100 tablets. Blister packs of 28's.

PREMARIN 0,625: Securitainers with 10, 20, 100 and 500 tablets. Blister packs of 28's

PREMARIN 1,25: Securitainers with 20, 100 and 500 tablets. Blister packs of 28's.

STORAGE INSTRUCTIONS:

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

Keep out of reach of children.

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

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

Pfizer Laboratories (Pty) Ltd

85 Bute Lane

Sandton 2196

SOUTH AFRICA

DATE OF PUBLICATION OF THIS PACKAGE INSERT:

14 June 1993

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