SCHEDULING STATUS: S2

1. NAME OF THE MEDICINE

PREMARIN® CREAM 0,625 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gram of PREMARIN cream contains 0,625 mg conjugated oestrogens in a non-liquefying base.

PREMARIN (conjugated oestrogens) is a mixture of oestrogens, obtained exclusively from natural sources, occurring as the sodium salts of water-soluble oestrogen 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.

Excipients with known effect

Each gram of PREMARIN cream contains 1 % m/m benzyl alcohol.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Vaginal cream.

PREMARIN cream is a white cream containing 0,625 mg conjugated estrogens per gram, in a non-liquefying base.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PREMARIN cream 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

4.2 Posology and method of administration

Posology

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

For treatment of atrophic vaginitis

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

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

Usual dosage

0,5 to 2 gram(s) daily, intravaginally, depending on the severity of the condition.

Special populations

Elderly use

The oestrogen-alone sub study 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 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 when compared with placebo (see section 5.1).

Paediatric population

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 is not indicated in children.

Method of administration

For intravaginal use.

4.3 Contraindications

PREMARIN cream is contraindicated in patients with:

- known or suspected 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
- active or chronic liver dysfunction or disease
- 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

Systemic absorption may occur with the use of PREMARIN cream. Warnings and precautions associated with oral PREMARIN treatment should be taken into account.

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 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 cream should be discontinued immediately.

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.

Venous thromboembolism (VTE)

In the estrogen-alone sub study 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, PREMARIN cream should be discontinued immediately (see section 5.1).

If feasible, PREMARIN cream 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 cream 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 cream 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 the 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 postmenopausal estrogen therapy 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.

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.

Dementia

A sub study 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. 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 has been reported.

Visual abnormalities

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

Hypercalcaemia

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

The following special precautions are relevant to PREMARIN cream and/or treatment with estrogens:

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 cream 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.

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 cream 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.

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 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 cream 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 monitoring

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

Uterine bleeding

Certain patients may develop abnormal uterine bleeding.

Latex condoms

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

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

Breastfeeding

PREMARIN cream should not be used during lactation. Estrogen administration to nursing women have 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 cream 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. However, the adverse effects of PREMARIN cream include dizziness, which could affect the ability to drive or use machines (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

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

Tabulated summary of adverse reactions

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

System organ class	**Adverse reaction**
Infections and infestations	Vaginitis, including vaginal candidiasis; cystitis-like syndrome
Neoplasms benign malignant and unspecified (including cysts and polyps)	Breast cancer; ovarian cancer; fibrocystic breast changes; endometrial cancer; enlargement of hepatic haemangiomas; growth potentiation of benign meningioma
Immune system disorders	Anaphylactic/anaphylactoid reactions, including urticaria and angioedema; hypersensitivity
Endocrine disorders	Precocious puberty
Metabolism and	Glucose intolerance; hypocalcaemia (in

nutrition disorders	patients with disease that can predispose to severe hypocalcaemia)
Psychiatric disorders	Changes in libido; mood disturbances; depression; irritability; dementia
Nervous system disorders	Dizziness; headache; migraine; nervousness; cerebrovascular accident/stroke; exacerbation of chorea
Eye disorders	Intolerance to contact lenses; retinal vascular thrombosis
Cardiac disorders	Myocardial infarction
Vascular disorders	Pulmonary embolism; venous thromboembolism, venous thrombosis
Gastrointestinal disorders	Nausea; bloating; abdominal pain; vomiting; pancreatitis; ischaemic colitis
Hepato-biliary disorders	Gallbladder disease; cholestatic jaundice
Skin and subcutaneous tissue disorders	Alopecia; chloasma/melasma; hirsutism; pruritus; rash; erythema multiforme; erythema nodosum
Musculoskeletal, connective tissue and bone disorders	Arthralgias; leg cramps
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; leucorrhoea; gynaecomastia in males;

	increased size of uterine leiomyomata; endometrial hyperplasia
General disorders and administration site conditions	Oedema
Investigations	Changes in weight (increase or decrease); increased triglycerides; 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

Currently, 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 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 estrogen-alone sub study 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 sub study 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 sub study 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 CE vs. placebo (95 % nCI[b])	Placebo n=5 429	CE n=5 310
		Absolute risk per 10 000 women-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)	57 43 16	54 40 16
All strokes[c]	1,33 (1,05 – 1,68)	33	45
Ischaemic stroke[c]	1,55 (1,19 – 2,01)	25	38
Deep vein thrombosis[c,d]	1,47 (1,06 – 2,06)	15	23
Pulmonary embolism[c]	1,37 (0,90 – 2,07)	10	14
Invasive breast cancer[c]	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[c,d]	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[e,f]	1,08 (0,88 – 1,32)	50	53
Overall mortality[c,d]	1,04 (0,88 – 1,22)	75	79
Global Index[g]	1,02 (0,92 – 1,13)	201	206

[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.

Women’s Health Initiative Memory Study

In the estrogen-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 estrogens (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 sub 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 oestrogens are soluble in water and are well-absorbed through the skin, mucous membranes, and from the gastrointestinal tract. The vaginal delivery of oestrogens circumvents first-pass metabolism.

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

Benzyl alcohol (preservative)

Cetyl alcohol

Cetyl esters wax

Glycerin

Glyceryl monostearate

Methyl stearate

Mineral oil heavy

Propylene glycol monostearate

Sodium lauryl sulfate

White wax

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

18 months.

6.4 Special precautions for storage

Store in a cool dry place at or below 25 ºC.

For external use only.

6.5 Nature and contents of container

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

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. REFERENCE NUMBER

G3019 (Act 101/1965)

9. DATE OF FIRST AUTHORISATION

Not applicable (Old medicine)

10. DATE OF REVISION OF THE TEXT

28 October 2022

BOTSWANA: S2

Reg. No.: B931995

ZIMBABWE: PP

Reg. No.: 86/17.03/2030