PROFESSIONAL INFORMATION

SCHEDULING STATUS S4

1. NAME OF THE MEDICINE

Femoston Conti 0.5 mg/2.5 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains estradiol hemihydrate equivalent to 0.5 mg estradiol and 2.5 mg dydrogesterone.

Excipient with known effect: lactose monohydrate 117.4

For the full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Round, biconvex marked on one side with ‘379’ (diameter 7mm).

Yellow tablets.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Hormone replacement therapy (HRT) for oestrogen deficiency symptoms in menopausal women at least 12 months since last menses.

Experience with treatment of women older than 65 years is limited.

4.2. Posology and method of administration

Femoston Conti 0.5 mg/2.5 mg is a continuous combined hormone replacement therapy (HRT) for oral use. The oestrogen and the progestogen are given every day without interruption.

For each cycle of 28 days one tablet is taken each day.
The treatment cycles of Femoston Conti 0,5 mg/2,5 mg therefore follow one another without a break.

For the treatment of oestrogen deficiency in postmenopausal women as an initial and maintenance dose the lowest effective dose should be used consistently and the duration of treatment period should be kept as short as possible (see also section 4.4).

Continuous combined treatment may be started with Femoston Conti 0.5 mg/2.5 mg, depending on the time that has elapsed since the menopause and the severity of the symptoms. Women who have reached the menopause naturally may not start Femoston Conti 0.5 mg/2.5 mg until at least 12 months after their last natural period. Women who have reached the menopause following

surgery can start treatment immediately.

Depending on the clinical response the dose can be adjusted accordingly.

Women switching from cyclical or continuous sequential hormone replacement therapy should complete the 28 day cycle first and then start with Femoston Conti 0.5 mg/2.5 mg.

In women switching from continuous combined hormone replacement therapy, the treatment can be started on any convenient time.

If a tablet is missed, the tablet should be taken as soon as possible. If more than 12 hours have elapsed, it is recommended to continue with the next tablet without taking the forgotten tablet. The chance of breakthrough bleeding or spotting may be increased.

Femoston Conti 0.5 mg/2.5 mg can be taken both with and without food.

Paediatric patients

There are no relevant indications for the use of Femoston Conti 0.5 mg/2.5 mg in paediatric patients.

4.3. Contra-indications

- Presence or suspicion of breast cancer; history of breast cancer;
- Presence or suspicion of oestrogen-sensitive tumours (e.g. endometrial cancer);
- Vaginal bleeding of which the cause has not been determined;

- Untreated endometrial hyperplasia;
- History of active venous thromboembolism (deep vein thrombosis, pulmonary embolism);
- Presence of a thrombophilic condition (e.g. protein C, protein S or antithrombin deficiency, see section 4.4);
- Active or recent arterial thromboembolic disease (angina pectoris, myocardial infarction);
- Acute liver disease or history of liver disease as long as the liver function values have not returned to normal;
- Porphyry.
- Known hypersensitivity to one of the active ingredients or to one of the excipients listed in section 6.1.

4.4. Special warnings and precautions for use

For the treatment of symptoms of oestrogen-deficiency in postmenopausal women, treatment with Femoston Conti 0.5 mg/2.5 mg should only be initiated if these symptoms adversely affect the quality of life. A careful appraisal of the advantages and disadvantages of HRT should be carried out regularly, at least annually, and the treatment should only be continued if the advantages outweigh the disadvantages.

Evidence relating to the risks associated with HRT in the treatment of premature menopause is limited, but because of the low absolute risk in young women the balance of advantages and disadvantages for these women are more positive than for older women.

Medical examination / follow up

Before starting Femoston Conti 0.5 mg/2.5 mg or if its use is to be reinstated the use after an interruption, a full medical history (including family history) should be taken. Physical examination (including gynaecological and breast examination) should be carried out guided by the history, contra-indications and warnings. During the treatment period regular check-ups are recommended of a frequency and nature adapted to the individual woman. Women should be advised what changes in their breasts should be reported to their doctor or nurse immediately (see the section "Breast cancer" below).

Regular examination of the breasts, including imaging techniques such as mammography, should be carried out accordance with the current guidelines for healthy women, taking into account the medical needs of each individual woman.

Conditions which need supervision

If one of the following conditions is present, was present in the past and/or has been aggravated during pregnancy or previous hormone treatment, the patient should be closely supervised. It should be taken into account that these conditions may recur or be aggravated during the treatment with Femoston Conti 0.5 mg/2.5 mg, in particular in case of:

- Leiomyoma (uterine fibroma) or endometriosis
- Risk factors for thromboembolic disorders (see below)
- Risk factors for oestrogen-sensitive tumours (breast cancer in first degree family member)
- Hypertension

- Liver disease (e.g. liver adenoma)
- Diabetes Mellitus with or without vascular symptoms
- Cholelithiasis
- Migraine or (severe) headache
- Systemic Lupus Erythematosus
- A history of endometrial hyperplasia (see below)
- Epilepsy
- Asthma
- Otosclerosis
- Meningioma

Reasons for immediate discontinuance of treatment

Femoston Conti 0.5 mg/2.5 mg should be discontinued immediately where a contra-indication is discovered and in the following situations:

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

Endometrial hyperplasia and carcinoma

In women whose uterus has not been removed the risk of endometrial hyperplasia and endometrial cancer is increased if over a prolonged period oestrogen-only HRT is taken. After stopping the treatment the risk remains high for at least 10 years.

The cyclical combination of an oestrogen preparation with a progestogen for at least 12 days per month/per 28-day cycle or continuous combined oestrogen-progestogen treatment in women with a uterus protects against the increased risk associated with oestrogen preparations.

Breakthrough bleeding and spotting may occur during the first months of the treatment. If breakthrough bleeding or spotting appears after some time on therapy or continues after treatment has been discontinued, further investigation is indicated. This may mean that an endometrial biopsy must be taken to exclude malignancy.

Breast cancer

Femoston Conti 0.5 mg/2.5 mg can increase the risk of breast cancer. The increased risk is apparent after around 3 years (see section 4.8). Treatment with Femoston Conti 0.5 mg/2.5 mg can increase the density of the mammography images, which may adversely effect on the radiological detection of breast cancer.

Ovarian cancer

Femoston Conti 0.5 mg/2.5 mg may increase the risk of ovarian cancer (see section 4.8).

Venous thromboembolism

Femoston Conti 0.5 mg/2.5 mg is associated with a risk of developing venous thromboembolism (VTE), i.e. deep vein thrombosis or pulmonary embolism. This is greater during the first year of treatment than afterwards (see section 4.8).

Patients with a known thrombophilic status have an increased risk of VTE and Femoston Conti 0.5 mg/2.5 mg may increase the risk further. Femoston Conti 0.5 mg/2.5 mg is therefore contra-indicated in these patients (see section 4.3).

General risk factors for the occurrence of VTE are: the use of oestrogens, greater age, major surgical intervention, prolonged immobilisation, obesity (Body Mass Index > 30 kg/m^2), pregnancy/ postpartum period, systemic lupus erythematosus (SLE) and carcinoma.

There is no consensus about the possible role of varicosis in VTE. Precautions should be taken after surgery to prevent VTE. Where prolonged immobilisation is anticipated after elective surgery, consideration should be given to stopping Femoston Conti 0.5 mg/2.5 mg 4 to 6 weeks before the operation and only restarting it when the woman is completely mobilised again.

Women without a history of VTE, but with a first-degree family member with a history of thrombosis at a young age, should be offered screening after careful information relating to the limitations of

such screening (only a proportion of thrombophilic conditions are identified in screening). If a congenital thrombophilic condition is identified, which is accompanied in a family with thrombosis or if the condition is serious (e.g. antithrombin, protein S or protein C deficiencies or a combination of conditions). Femoston Conti 0.5 mg/2.5 mg is contra-indicated see section 4.3).

In women already treated chronically with anticoagulation therapy, careful consideration should be given to the advantages and disadvantages of the treatment.

If VTE develops after initiating therapy, the administration of medication should be discontinued immediately. Patients must be informed that they should contact their doctor immediately if potential thromboembolic symptoms occur (for example: painful swelling of a leg, sudden pain in the chest, shortness of breath).

Coronary artery disease (CAD)

Femoston Conti 0.5 mg/2.5 mg has no protective effect against myocardial infarction in women with or without existing coronary artery disease. Femoston Conti 0.5 mg/2.5 mg may increase the risk of coronary artery disease. The risk increases with age.

Ischaemic Stroke

Femoston Conti 0.5 mg/2.5 mg is associated with a higher risk of an ischaemic stroke. The relative risk does not change with age or with the time after the menopause. However, because

the absolute risk of a CVA in the initial situation is strongly dependent on age, the overall risk of a CVA in women using Femoston Conti 0.5 mg/2.5 mg will increase with age (see section 4.8).

Other conditions

Oestrogens may cause fluid retention. For this reason, patients with a reduced cardiac or renal function must be carefully observed.

Women with a pre-existing hypertriglyceridaemia should be closely followed during treatment with Femoston Conti 0.5 mg/2.5 mg because of the high risk for pancreatitis.

Oestrogens cause an increase in the thyroid binding globulin (TBG), which leads to increased total circulating thyroid hormone, measured as the protein bound iodine (PBI), T4 levels (column or RIA) or T3 levels (RIA). The T3-resin uptake is decreased as a result of the increased TBG levels. The free T3 and T4 concentrations remain unchanged. Other binding proteins may also be elevated in the serum, such as corticoid binding globulin (CBG) and the sex-hormone binding globulin (SHBG), leading to increased blood levels of corticosteroids and sex hormones. Free or biologically active hormone concentrations remain unchanged. Other plasma proteins may be increased (angiotensin-renin substrate, alpha-1-antitrypsin, ceruloplasmin).

Femoston Conti 0.5 mg/2.5 mg does not improve cognitive functions. There is no evidence of increased risk of possible dementia in women who start using treatment of combined preparations or oestrogen preparations after the age of 65 years.

Patients with rare hereditary conditions, such as galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Femoston Conti 0.5 mg/2.5 mg is not a contraceptive product.

4.5. Interactions with other medicinal products and other forms of interaction

No interaction studies have been carried out.

The efficacy of oestrogens and progestogens may be disrupted:

The metabolism of oestrogens (and progestogens) may be increased by concomitant use of substances known to induce enzymes which are involved in the metabolism of medicinal products. This applies particularly for P450 enzymes, such as anti-epileptics (phenobarbital, phenytoin, carbamazepine) and antibacterials /antivirals (for example rifampicin, rifabutin, nevirapine, efavirenz).

Ritonavir and nelfinavir, although known as strong inhibitors, do in fact have an inducing

effect when used concomitantly with steroid hormones. Herbal preparations containing St. John's wort (*Hypericum perforatum*) may also increase the metabolism of oestrogens (and progestogens).

Clinically an increased metabolism of oestrogens and progestogens may lead to a reduced efficacy of Femoston Conti 0.5 mg/2.5 mg and to changes in the bleeding pattern.

4.6. Fertility, pregnancy and lactation

Pregnancy

Femoston Conti 0.5 mg/2.5 mg is not indicated during pregnancy. If pregnancy occurs during the

treatment with Femoston Conti 0.5 mg/2.5 mg, the treatment should be stopped immediately.

There are no adequate data available on the use of estradiol/dydrogesterone during pregnancy.

The results of most epidemiological studies to date that are relevant for the assessment of effects of inadvertent foetal exposure to combined oestrogens and progestogens indicate no teratogenic risk or toxic effect for the foetus.

Lactation

Femoston Conti 0.5 mg/2.5 mg is not indicated in women who are breastfeeding.

Fertility

Femoston Conti 0.5 mg/2.5 mg is not indicated in women of child-bearing age.

4.7. Influence on the ability to drive or to operate machinery

Femoston Conti 0.5 mg/2.5 mg has no or negligible effect on the ability to drive and/or to operate machinery.

4.8. Undesirable effects

The most commonly reported undesirable effects in patients that were treated in clinical trials with estradiol/dydrogesterone are headache, abdominal pain, breast pain/tenderness and back pain.

The following undesirable effects have been observed during clinical trials (n=4929) with the

frequencies indicated below. *Undesirable effects from spontaneous reports that were not observed in clinical trials have been added to the frequency “rare”.

Organ system	**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**
Infections and parasitic infestations		Vaginal candidiasis	Cystitis-like syndrome	
Neoplasms, benign, malignant and unspecified			Increase in size of myoma	
Blood and lymphatic system disorders				Haemolytic anaemia*
Immune system disorders			Hypersensitivity	
Psychiatric disorders		Depression; Nervousness	Change in libido	
Central nervous system disorders	Headache	Migraine; Dizziness		Meningioma
Eye disorders				Steepening of the cornea*; Intolerance to contact lenses*

Organ system	**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**
Cardiac disorders				Myocardial infarction
Vascular disorders			Venous thrombo-embolism*; Hypertension; Peripheral vascular disease; Varicosis;	Stroke*
Gastrointestinal disorders	Abdominal pain	Nausea; Vomiting; Flatulence	Dyspepsia	
Hepatobiliary disorders			Abnormal liver function (sometimes combined with jaundice, asthenia or malaise and	

Organ system	**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**
			abdominal pain); Gall bladder disorders	
Skin and subcutaneous tissue disorders		Allergic skin reactions (e.g. rash, urticaria, pruritus)		Angioedema, Erythema nodosum*; Vascular purpura; Chloasma or melasma which may persist when the treatment is discontinued*;
Musculoskeletal and connective tissue disorders	Back pain			Leg cramps*

Organ system	**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**
Reproductive system and breast disorders	Breast pain/ tenderness;	Menstruation disorders (including postmenopausal spotting; metrorrhagia; oligo/ amenorrhoea, irregular menstruation, dysmenorrhoea); Pelvic pain Cervical secretion	Breast enlargement; Premenstrual syndrome (PMS)	
General disorders and administration site reactions		Asthenic disorders (asthenia, fatigue, malaise);		

Organ system	**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**
		Peripheral oedema		
Investigations		Increase in weight	Decrease in weight	

Risk of breast cancer

An up to 2 times higher risk of the diagnosis of breast cancer is reported in women who have used combined oestrogen-progestogen HRT for more than 5 years.

For users of oestrogen monotherapy the increased risk is substantially lower than for users of combined oestrogen -progestogen therapy.

The level of the risk depends on the duration of use (see section 4.4).

Risk of endometrial cancer

Postmenopausal women with a uterus:

The risk of endometrial cancer is around 5 in every 1,000 women with a uterus not using HRT.

In women with a uterus the use of oestrogen monotherapy is not recommended, because this increases the risk of endometrial cancer (see section 4.4).

Depending on the duration of use of oestrogen monotherapy and the oestrogen dose used, the increase in the risk of endometrial cancer in epidemiologic studies varied between 5 and 55 extra cases diagnosed per 1,000 women aged between 50-65 years.

The addition of a progestogen to the oestrogen monotherapy for at least 12 days per cycle may prevent this increased risk. In the Million Women Study the risk of endometrial cancer did not increase for 5 years of combined (sequential or continuous) HRT (RR of 1.0 (0.8-1.2)).

Ovarian cancer

Use of oestrogen-only or combined oestrogen-progestogen HRT has been associated with a slightly increased risk of having ovarian cancer diagnosed (see section 4.4).

A meta-analysis from 52 epidemiological studies reported an increased risk of ovarian cancer in women currently using HRT compared to women who have never used HRT (RR 1.43, 95% CI 1.31-1.56). For women aged 50 to 54 years taking 5 years of HRT, this results in about 1 extra case per 2,000 users. In women aged 50 to 54 who are not taking HRT, about 2 women in 2,000 will be diagnosed with ovarian cancer over a 5-year period.

Risk of venous thromboembolism

HRT is associated with a 1.3 to 3 times higher relative risk of developing venous thromboembolism (VTE), i.e. deep vein thrombosis or pulmonary embolism. The chance of this is greater during the first year of HRT treatment (see section 4.4). The results of the WHI are set

out below:

WHI Studies – extra risk of VTE during 5 years use

Age group (years)	Incidence per 1,000 women in the placebo group over a period of 5 years	Risk ratio and 95% CI	Extra cases per 1,000 HRT users over a period of 5 years (95% CI)
Oral estrogen mono HRT*			
50-59	7	1.2 (0.6-2.4)	1 (-3 – 10)
Oral combined estrogen-progestogen HRT			
50-59	4	2.3 (1.2 – 4.3)	5 (1 - 13)

* Study in women with no uterus

Risk of coronary artery disease

The risk of coronary artery disease is slightly increased in users aged over 60 years for combined oestrogen-progestogen HRT (see section 4.4).

Risk of an ischemic stroke

The use of oestrogen monotherapy and combined oestrogen-progestogen HRT is associated with up to a 1.5 times higher relative risk of an ischemic stroke. The risk of a haemorrhagic stroke is not increased during use of HRT.

This relative risk does not depend on the age or the duration of use, but because the risk in the initial situation is strongly dependent on age, the risk of a stroke in users of HRT generally increases with the increase in age (see section 4.4).

Combined WHI studies – extra risk of an ischemic stroke* during 5 years use

Age group (years)	Incidence per 1,000 women in the placebo group over a period of 5 years	Risk ratio and 95% CI	Extra cases per 1,000 HRT users over a period of 5 years (95% CI)
50-59	8	1.3 (1.1-1.6)	3 (1-5)

*No distinction is made between ischemic and haemorrhagic stroke

Other reported undesirable effects associated with oestrogen/progestogen treatment:

Neoplasms, benign, malignant and unspecified:

Benign and malignant oestrogen-dependent neoplasms, for example endometrial cancer and ovarian cancer. Increase in size of meningioma.

Immune system disorders:

Systemic Lupus Erythematosus (SLE).

Nutritional and metabolic disorders:

Hypertriglyceridaemia.

Central nervous system disorders:

Possible dementia, chorea, aggravation of epilepsy.

Vascular disorders:

Arterial thromboembolism.

Gastrointestinal disorders:

Pancreatitis (in women with pre-existing hypertriglyceridaemia).

Skin and sub-cutaneous disorders:

Erythema multiforme

Renal and urinary tract disorders:

Urine incontinence

Reproductive system and breast disorders:

Fibrocystic breast disorder, uterine cervical erosion.

Congenital, familial and genetic disorders

Aggravation of porphyria.

Investigations:

Increased level of total thyroid hormone.

Report of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. 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 such as nausea, vomiting, breast tenderness, dizziness, abdominal pain, drowsiness/fatigue and withdrawal bleeding may occur in case of overdosing. It is unlikely that any specific or symptomatic treatment will be necessary.

The aforementioned information also applies for overdosing in children.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic category: urogenital system and sex hormones, progestogens and oestrogens, fixed combinations.

ATC code: G03FA14.

Estradiol

The active ingredient, synthetic 17β-estradiol is chemically and biologically identical to the natural human female sex hormone estradiol. It substitutes for the loss of own oestrogen production in postmenopausal women and alleviates menopausal symptoms.

Dydrogesterone

Dydrogesterone is an orally active progestogen that has an activity comparable with parenterally administered progesterone.

As oestrogens promote the growth of the endometrium, if no progestogen is used, they will lead to an increased risk of endometrial hyperplasia and carcinoma. The addition of a progestogen largely reduces the oestrogen-induced risk in women with a uterus.

Information from clinical studies

Alleviation of oestrogen-deficiency complaints and the bleeding patterns:

Alleviation of menopausal symptoms was achieved in the first few weeks of therapy.

A significant reduction in moderate to severe hot flushes compared with placebo was achieved with estradiol 0.5 mg/ dydroprogesterone 2.5 mg from week 4. The number of moderate to severe to flushes decreased further until the end of the treatment period in week 13.

In two studies amenorrhoea (no bleeding or spotting) occurred in respectively 91 % and 88 % of the women in the 10^{th} to the 12^{th} month of treatment. Irregular bleeding and/or spotting occurred in 10 % and 21 % of the women during the first 3 months of the treatment and for 9 % and 12 % in the 10^{th} to the 12^{th} month of treatment.

5.2. Pharmacokinetic properties

Estradiol

Absorption:

Absorption of estradiol depends on the particle size: micronized estradiol is readily absorbed from the gastrointestinal tract.

The following table gives the average steady state pharmacokinetic parameters of estradiol (E2), estrone (E1) and estrone sulphate (E1S) for each dose of micronized estradiol. Data are presented as averages (SD).

Estradiol 0.5 mg				
Parameters	E2	E1	Parameters	E1S
C_{max} (pg/ml)	34.8 (30.4)	182 (110)	C_{max} (ng/ml)	6.98 (3.32)
C_{min} (pg/ml)	-	-	-	-
C_{av} (pg/ml)	21.5 (16.0)	-	-	-
AUC_{0-T} (pg.h/ml)	516 (383)	2959 (2135)	AUC_{0-T} (ng.h/ml)	82.0 (42.6)

Distribution:

Oestrogens may occur bound or unbound. Approx. 98-99 % of the estradiol dose binds to plasma proteins, with approx. 30-52 % to albumin and approx. 46-69 % to sex-hormone binding globulin (SHBG).

Biotransformation:

Following oral administration estradiol is metabolised on a large scale. The main unconjugated and conjugated metabolites are estrone and estrone sulphate. These metabolites may contribute to oestrogen activity, either directly, or after conversion into estradiol. Estrone sulphate may undergo enterohepatic circulation.

Elimination:

Glucuronides are the main components of estrone and estradiol in the urine. The elimination half-life is between 10 and 16 hours. Oestrogens are secreted in the breast milk.

Dose and time dependencies:

Following daily oral administration of Femoston estradiol concentrations reach a steady state after around 5 days.

Generally steady state concentrations appear to be reached within 8 to 11 days of dosing.

Dydrogesterone

Absorption:

Following oral administration dydrogesterone is quickly absorbed with a T_{max} between 0.5 and 2.5 hours. The absolute biological availability of dydrogesterone (20 mg oral dose versus 7.8 mg intravenous infusion) is 28 %.

The following table gives the steady state pharmacokinetic parameters of dydrogesterone (D) and dihydrodydrogesterone (DHD). Data are presented as averages (SD).

Dydrogesterone 2.5 mg		
Parameters	D	DHD
C_{max} (ng/ml)	0.759 (0.313)	18.9 (7.22)

C_{min} (ng/ml)	0.0309 (0.0209)	-
C_{av} (ng/ml)	0.117 (0.0455)	-
$AUC_{0-\tau}$ (ng·h/ml)	2.81 (1.09)	90.4 (44.1)

Distribution:

Following intravenous administration of dydrogesterone the steady-state distribution volume is around 1400 L. More than 90 % of dydrogesterone and DHD is bound to plasma proteins.

Biotransformation:

Following oral administration dydrogesterone is quickly metabolized to DHD. The levels of the main active metabolite 20α-dihydrodydrogesterone (DHD) show a peak around 1.5 hours after administering the dose. The plasma levels of DHD are substantially higher than those of the related medicinal product. The AUC and C_{max} ratios of DHD and dydrogesterone are of the order of magnitude of respectively 40 and 25. The mean terminal half-life of dydrogesterone and DHD varies from respectively 5 to 7 and 14 to 17 hours. A common feature of all metabolites described is the retention of the 4,6-diene-3-one configuration of the original molecule and the absence of 17α-hydroxylation. This explains the absence of oestrogen and androgenic effects of dydrogesterone.

Elimination:

Following oral administration of labelled dydrogesterone on average 63 % of the dose is excreted

in the urine. The total plasma clearing is 6.4 L/minute. Excretion is complete within 72 hours.

DHD is predominantly present in the urine as the conjugated glucuronic acid.

Dose and time dependencies:

The pharmacokinetics of single and multiples doses are linear in the oral dosage range of 2.5 to 10 mg. Comparison of the kinetics of single and multiple doses shows that the pharmacokinetics of dydrogesterone and DHD do not change as a result of repeated doses.

Steady state was reached after 3 days treatment.

5.3. Preclinical safety data

There are no relevant preclinical data for the prescriber that are in addition to the data already stated in other sections of the Professional Information.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Composition of the tablet core

Lactose monohydrate

Hypromellose

Maize starch

Colloidal (anhydrate) silica

Magnesium stearate

Composition of the film coating

Macrogol 3350, Polyvinyl alcohol, Talc, Titanium dioxide (E171), Yellow iron oxide (E172)

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

3 years.

6.4. Special precautions for storage

Store at or below 30°C

6.5. Nature and contents of container

Calendar packs of 28, 84 (3 x 28) or 280 (10 x 28) tablets in PVC-Aluminium blister strips in a printed carton.

Not all pack sizes listed are marketed.

6.6. Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local

requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Abbott Laboratories S.A. (Pty) Ltd

Abbott Place

219 Golf Club Terrace

Constantia Kloof, 1709

Republic of South Africa

8. REGISTRATION NUMBER

47/21.8.2/0947

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

03 August 2021

10. DATE OF REVISION OF THE TEXT

Not applicable