SCHEDULING STATUS

S3

1 NAME OF THE MEDICINE

DIENOGEST 2 mg PHARMC tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each DIENOGEST 2 mg PHARMC tablet contains 2 mg dienogest (micronised).

Contains sugar: lactose monohydrate 60,93 mg per tablet.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablets.

White, round, biconvex and plain tablet, with a diameter of 5 mm approximately and thickness about 3 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of endometriosis.

Safety and efficacy beyond 24 months have not been established.

4.2 Posology and method of administration

Posology

Tablet-taking from the very first pack should start on day 1 of the woman's natural cycle (i.e., the first day of her menstrual bleeding). The dosage of DIENOGEST 2 mg PHARMC is one tablet

daily without any break, taken preferably at the same time each day with some liquid as needed. Tablets must be taken throughout 28 days without regard for bleeding. When a pack is finished the next one should be started without interruption.

The efficacy of DIENOGEST 2 mg PHARMC may be reduced in the event of missed tablets, vomiting, and/ or diarrhoea (if occurring within 3 to 4 hours after tablet taking). In the event of missed tablet(s), the woman should take one tablet only, as soon as she remembers, and should then continue next day to take tablet at her usual time. A tablet not absorbed due to vomiting or diarrhoea should likewise be replaced by one tablet.

Method of administration:

For oral use.

4.3 Contraindications

DIENOGEST 2 mg PHARMC should not be used in the presence of any condition listed below. Should any of the conditions appear during the use of DIENOGEST 2 mg PHARMC, the use of DIENOGEST 2 mg PHARMC must be discontinued immediately:

- Hypersensitivity to dienogest or to any of the excipients (see section 6.1).
- Known or suspected pregnancy.
- Lactation.
- History of or active venous thromboembolic disorder.
- Arterial and cardiovascular diseases, past or present (e.g., myocardial infarction, cerebrovascular events, ischaemic heart disease).
- Diabetes mellitus with vascular involvement.
- Presence or history of severe hepatic disease as long as liver function values have not returned to normal.
- Presence or history of liver tumours (benign or malignant).
- Known or suspected sex hormone-dependent malignancies.
- Undiagnosed vaginal bleeding.

4.4 Special warnings and precautions for use

As DIENOGEST 2 mg PHARMC is a progestogen-only preparation it can be assumed that the special warnings and precautions for use of progestogen-only preparations are also valid for the use of DIENOGEST 2 mg PHARMC although not all of the warnings and precautions are based on respective findings in the clinical studies with dienogest.

If any of the conditions/risk factors mentioned below is present or deteriorates, an individual risk-benefit analysis should be done before treatment with DIENOGEST 2 mg PHARMC can be started or continued.

Serious uterine bleeding

Uterine bleeding, for example in women with adenomyosis uteri or uterine leiomyomata, may be aggravated with the use of DIENOGEST 2 mg PHARMC. If bleeding is heavy and continuous over time, this may lead to anemia (severe in some cases). In the event of anemia, discontinuation of DIENOGEST 2 mg PHARMC should be considered.

Changes in bleeding pattern

The majority of patients treated with dienogest experience changes in their menstrual bleeding pattern (see section 4.8).

Circulatory disorders

From epidemiological studies there is little evidence for an association between progestogen-only preparations and an increased risk of myocardial infarction or cerebral thromboembolism. Rather, the risk of cardiovascular and cerebral events is related to increasing age, hypertension, and smoking. In women with hypertension the risk of stroke may be slightly enhanced by progestogen-only preparations.

Although not statistically significant, some studies indicate that there may be a slightly increased risk of venous thromboembolism (deep venous thrombosis, pulmonary embolism) associated with the use of progestogen-only preparations. Generally recognized risk factors for venous thromboembolism (VTE) include a positive personal or family history (VTE in a sibling or a parent

at a relatively early age), age, obesity, prolonged immobilization, major surgery or major trauma. In case of long-term immobilisation, it is advisable to discontinue the use of DIENOGEST 2 mg PHARMC (in the case of elective surgery at least four weeks in advance) and not to resume treatment until two weeks after complete remobilisation.

The increased risk of thromboembolism in the puerperium must be considered.

Treatment should be stopped at once if there are symptoms of an arterial or venous thrombotic event or suspicion thereof.

Tumours

A meta-analysis from 54 epidemiological studies reported that there is a slightly increased relative risk (RR = 1,24) of having breast cancer diagnosed in women who are currently using oral contraceptives (OCs), mainly using oestrogen-progestogen preparations. The excess risk gradually disappears during the course of the 10 years after cessation of combined OC (COC) use. Because breast cancer is rare in women under 40 years of age, the excess number of breast cancer diagnoses in current and recent COC users is small in relation to the overall risk of breast cancer. The risk of having breast cancer diagnosed in users of progestogen-only preparations is possibly of similar magnitude to that associated with COC. However, for progestogen-only preparations, the evidence is based on much smaller populations of users and so is less conclusive than that for COCs. These studies do not provide evidence for causation. The observed pattern of increased risk may be due to an earlier diagnosis of breast cancer in OC users, the biological effects of OCs or a combination of both. The breast cancers diagnosed in users of OCs tend to be less advanced clinically than the cancers diagnosed in those who have never used OCs.

In rare cases, benign liver tumours, and even more rarely, malignant liver tumours have been reported in users of hormonal substances such as the one contained in DIENOGEST 2 mg PHARMC. In isolated cases, these tumours have led to life-threatening intra-abdominal haemorrhages. A hepatic tumour should be considered in the differential diagnosis when severe upper abdominal pain, liver enlargement or signs of intra-abdominal haemorrhage occur in women taking DIENOGEST 2 mg PHARMC.

Osteoporosis

Changes in bone mineral density (BMD).

The use of dienogest in adolescents (12 to <18 years) over a treatment period of 12 months was associated with a decrease in bone mineral density (BMD) in the lumbar spine (L2-L4). The mean relative change in BMD from baseline to the end of treatment (EOT) was – 1,2 % with a range between -6 % and 5 % (IC 95 %: -1,70 % and -0,78 %, n=103.

Repeated measurement at 6 months after the EOT in a subgroup with decreased BMD values showed a trend towards recovery. (Mean relative change from baseline: –2,3 % at EOT and –0,6 % at 6 months after EOT with a range between -9 % and 6 % (IC 95 %: -1,20 % and 0,06 % (n=60).

Loss of BMD is of particular concern during adolescence and early adulthood, a critical period of bone accretion. It is unknown if BMD decrease in this population will reduce peak bone mass and increase the risk for fracture in later life.

In patients who are at an increased risk of osteoporosis a careful risk-benefit assessment should be performed before starting DIENOGEST 2 mg PHARMC because endogenous oestrogen levels are moderately decreased during treatment with DIENOGEST 2 mg PHARMC.

Adequate intake of calcium and Vitamin D, whether from the diet or from supplements, is important for bone health in women of all ages.

Other conditions

Patients who have a history of depression should be carefully observed and the DIENOGEST 2 mg PHARMC should be discontinued if the depression recurs to a serious degree.

Dienogest generally does not appear to affect blood pressure in normotensive women. However, if a sustained clinically significant hypertension develops during the use of DIENOGEST 2 mg PHARMC, it is advisable to withdraw DIENOGEST 2 mg PHARMC and treat the hypertension.

Recurrence of cholestatic jaundice and/or pruritus which occurred first during pregnancy or previous use of sex steroids necessitates the discontinuation of DIENOGEST 2 mg PHARMC.

DIENOGEST 2mg PHARMC may have a slight effect on peripheral insulin resistance and glucose tolerance. Diabetic women, especially those with a history of gestational diabetes mellitus, should be carefully observed while taking DIENOGEST 2 mg PHARMC.

Chloasma may occasionally occur, especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should avoid exposure to the sun or ultraviolet radiation whilst taking DIENOGEST 2 mg PHARMC.

Pregnancies that occur among users of progestogen-only preparations used for contraception are more likely to be ectopic than are pregnancies among users of combined oral contraceptives. Therefore, in women with a history of extrauterine pregnancy or an impairment of tube function, the use of DIENOGEST 2 mg PHARMC should be decided on only after carefully weighing the benefits against the risks.
Patients are advised to use non-hormonal methods of contraception (barrier contraception, e.g., condom) to prevent unwanted pregnancies.

Persistent ovarian follicles (often referred to as functional ovarian cysts) may occur during the use of DIENOGEST 2 mg PHARMC. Most of these follicles are asymptomatic, although some may be accompanied by pelvic pain.

Excipient warning

DIENOGEST 2 mg PHARMC contains lactose monohydrate which may have an effect on the glycaemic control of patients with diabetes mellitus. Patients with rare hereditary conditions of galactose intolerance e.g., galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take DIENOGEST 2 mg PHARMC.

4.5 Interaction with other medicines and other forms of interaction

Note: The prescribing information of concomitant medication should be consulted to identify potential interactions.

Effects of other medicines on DIENOGEST 2 mg PHARMC

Individual enzyme-inducers or inhibitors (CYP3A4):

Progestogens including dienogest are metabolised mainly by the cytochrome P450 3A4 system (CYP3A4) located both in the intestinal mucosa and in the liver. Therefore, inducers or inhibitors of CYP3A4 may affect the progestogen metabolism.

An increased clearance of sex hormones due to enzyme induction may reduce the therapeutic effect of DIENOGEST 2 mg PHARMC and may result in undesirable effects e.g., changes in the uterine bleeding profile.

A reduced clearance of sex hormones due to enzyme inhibition may increase the exposure to dienogest and may result in undesirable effects.

Medicines with enzyme-inducing properties:

Interactions can occur with medicines increasing the clearance of sex hormones (diminished efficacy by enzyme-induction), e.g.: phenytoin, barbiturates, primidone, carbamazepine, rifampicin, and possibly also oxcarbazepine, topiramate, felbamate, griseofulvin, and medicines containing St. John's wort (*Hypericum perforatum*).

Enzyme induction can already be observed after a few days of treatment. Maximum enzyme induction is generally seen within a few weeks. After cessation of therapy enzyme induction may be sustained for about 4 weeks.

The effect of the CYP 3A4 inducer rifampicin was studied in healthy postmenopausal women. Co-administration of rifampicin with oestradiol valerate/dienogest tablets led to significant decreases in steady state concentrations and systemic exposures of dienogest and oestradiol. The systemic exposure of dienogest and oestradiol at steady state, measured by AUC(0-24h), were decreased by 83 % and 44 %, respectively.

Medicines with variable effects on the clearance of sex hormones:

When co-administered with sex hormones, many combinations of HIV protease inhibitors and non-nucleoside reverse transcriptase inhibitors, including combinations with HCV inhibitors can

increase or decrease plasma concentrations of the progestin. The net effect of these changes may be clinically relevant in some cases.

Medicines decreasing the clearance of sex hormones (enzyme inhibitors):
Known CYP3A4 inhibitors like azole antifungals (e.g., ketoconazole, itraconazole, fluconazole), cimetidine, verapamil, macrolides (e.g., erythromycin, clarithromycin and roxithromycin), diltiazem, protease inhibitors (e.g., ritonavir, saquinavir, indinavir, nelfinavir), antidepressants (e.g., nefazodone, fluvoxamine, fluoxetine) may increase plasma levels of progestogens and result in undesirable effects.
Dienogest is a substrate of cytochrome P450 (CYP) 3A4. The clinical relevance of potential interactions with enzyme inhibitors remains unknown.
Concomitant administration of strong CYP3A4 inhibitors can increase plasma concentrations of dienogest.
Coadministration with the strong CYP3A4 enzyme inhibitor ketoconazole resulted in a 2,9-fold increase of AUC (0-24h) at steady state for dienogest. Concomitant administration of the moderate inhibitor erythromycin increased the AUC (0-24h) of dienogest at steady state by 1,6-fold.

Effects of DIENOGEST 2 mg PHARMC on other medicines

Based on *in vitro* inhibition studies, a clinically relevant interaction of dienogest with the cytochrome P450 enzyme mediated metabolism of other medication is unlikely.

Interaction with food

A standardised high fat meal did not affect the bioavailability of dienogest 2 mg. Due to the metabolism of dienogest, which is mainly by the cytochrome P450 3A4 system (CYP3A4), patients should avoid grapefruit juice while being treated with DIENOGEST 2 mg PHARMC, as grapefruit juice is an inhibitor of CYP3A4.

Laboratory tests

The use of progestogens may influence the results of certain laboratory tests, including biochemical parameters of liver, thyroid, adrenal and renal function, plasma levels of (carrier) proteins (e.g., corticosteroid binding globulin and lipid/lipoprotein fractions), parameters of carbohydrate metabolism and parameters of coagulation and fibrinolysis. Changes generally remain within the normal laboratory range.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is limited data from the use of dienogest in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity.

DIENOGEST 2 mg PHARMC must not be administered to pregnant women because there is no need to treat endometriosis during pregnancy.

Breastfeeding

Treatment with DIENOGEST 2 mg PHARMC during lactation is not recommended. It is unknown whether dienogest is excreted in human milk. Data in animals have shown excretion of dienogest in rat milk.

Fertility

Based on the available data, ovulation is inhibited in the majority of patients during treatment with dienogest. However, DIENOGEST 2 mg PHARMC is not a contraceptive. If contraception is required a non-hormonal method should be used (see section 4.2).

Based on available data, the menstrual cycle returns to normal within 2 months after cessation of treatment with DIENOGEST 2 mg PHARMC.

4.7 Effects on ability to drive and use machines

No effects on the ability to drive and use machines have been observed in users of medicines containing dienogest.

4.8 Undesirable effects

a. Summary of the safety profile

Undesirable effects are more frequent during the first months after the start of treatment with DIENOGEST 2 mg PHARMC and subside with continued treatment. There may be changes in bleeding pattern, such as spotting, irregular bleeding or amenorrhea. The following undesirable effects have been reported in users of dienogest 2 mg tablets.

The most frequently reported undesirable effects under treatment with dienogest 2 mg are headache (9,0 %), breast discomfort (5,4 %), depressed mood (5,1 %) and acne (5,1 %).

The frequencies of adverse drug reactions (ADRs) by MedDRA system organ classes (MedDRA SOCs) reported with dienogest 2 mg are summarised in the table below. Within each frequency grouping, undesirable effects are presented in order of decreasing frequency.

MedDRA system organ class	**Frequency**	**Adverse reactions**
Blood and lymphatic system disorders	Less frequent	Anaemia
Metabolism and nutrition disorders	Frequent	Increased weight
	Less frequent	Decreased weight, increased appetite
Psychiatric disorders	Frequent	Depressed mood, sleep disorder, nervousness, loss of libido, altered mood
	Less frequent	Anxiety, depression, mood swings
Nervous system	Frequent	Headache, migraine

MedDRA system organ class	**Frequency**	**Adverse reactions**
disorders	Less frequent	Autonomic nervous system imbalance, disturbance in attention
Eye disorders	Less frequent	Dry eyes
Ear and labyrinth disorders	Less frequent	Tinnitus
Cardiac disorders	Less frequent	Unspecific circulatory system disorder palpitations
Vascular disorders	Less frequent	Hypotension
Respiratory, thoracic and mediastinal disorders	Less frequent	Dyspnoea
Gastrointestinal disorders	Frequent	Nausea, abdominal pain, flatulence, abdominal distension vomiting
	Less frequent	Diarrhoea, constipation, abdominal discomfort, gastrointestinal inflammation, gingivitis
Skin and subcutaneous tissue disorders	Frequent	Acne, alopecia
	Less frequent	Dry skin, hyperhidrosis, pruritus, hirsutism, onychoclasis, dandruff, dermatitis, abnormal hair growth, photosensitivity reaction, pigmentation disorder
Musculoskeletal and connective tissue disorders	Frequent	Back pain
	Less frequent	Bone pain, muscle spasms, pain in extremity,

MedDRA system organ class	Frequency	Adverse reactions
		heaviness in extremities
Renal and urinary disorders	Less frequent	Urinary tract infection
Reproductive system and breast disorders	Frequent	Breast discomfort, ovarian cyst, hot flushes, uterine / vaginal bleeding including spotting
	Less frequent	Vaginal candidiasis, vulvovaginal dryness, genital discharge, pelvic pain, atrophic vulvovaginitis, breast mass, fibrocystic breast disease, breast induration
General disorders and ~~A~~administrative site conditions	Frequent	Asthenic conditions irritability
	Less frequent	Oedema

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 & Quality Problem Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Acute toxicity studies performed with dienogest did not indicate a risk of acute adverse effects in case of inadvertent intake of a multiple of the daily therapeutic dose. There is no specific antidote.

A daily intake of 20 - 30 mg dienogest (10 to 15 times higher dose than in DIENOGEST 2 mg PHARMC) over 24 weeks of use was very well tolerated.

Treatment is symptomatic and supportive.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: progestogens; ATC code: G03DB08

Pharmacological classification: A 21.8.2 Progesterones with or without oestrogens.

Dienogest is a nortestosterone derivative with no androgenic activity. Dienogest binds to the progesterone receptor of the human uterus with only 10 % of the relative affinity of progesterones. Despite its low affinity to the progesterone receptor, dienogest has a strong progestogenic effect *in vivo*. Dienogest has no significant androgenic, mineralocorticoid or glucocorticoid activity *in vivo*.

Dienogest acts on endometriosis by abolishing the trophic effects of estradiol on both the eutopic and ectopic endometrium. When given continuously, dienogest leads to a hypoestrogenic, hypergestagenic endocrine environment and decidualisation of endometrial tissue.

5.2 Pharmacokinetic properties

Absorption

Orally administered dienogest is almost completely absorbed. Peak serum concentrations of 47 ng/ ml are reached at about 1,5 hours after ingestion of a 2 mg tablet. A standardised high fat meal did not affect the bioavailability of dienogest. Bioavailability is about 91 %. The pharmacokinetics of dienogest are dose-proportional within the dose range of 1 to 8 mg.

Distribution

Dienogest is bound to serum albumin and does not bind to sex hormone binding globulin (SHBG) or corticoid binding globulin (CBG). 10 % of the total serum concentration of the active substance is present as free steroid, 90 % is non- specifically bound to albumin. The apparent volume of

distribution (Vd/F) of dienogest is 40 litres.

Biotransformation

Dienogest is completely metabolised by the known pathway of steroid metabolism, with the formation of inactive metabolites. Based on the *in vivo* and *in vitro* studies, CYP3A4 is the major enzyme involved in the metabolism of dienogest. The metabolites are rapidly excreted so that in plasma, unchanged dienogest is the dominating fraction. The metabolic clearance rate from serum Cl/ F is 64 ml/ min.

Elimination

Dienogest serum levels decrease in two phases. The terminal disposition phase is characterised by a half-life of approximately 9 to 10 hours. Dienogest is excreted in the form of metabolites which are excreted at a urinary to faecal ratio of about 3:1 after oral administration of 0,1 mg/ kg. The half-life of urinary metabolites excretion is 14 hours. Following oral administration, approximately 86 % of the dose administered is eliminated within 6 days; the bulk of this amount is excreted within the first 24 hours, mostly with the urine.

Steady-state condition

The pharmacokinetics of dienogest after repeated administration of DIENOGEST 2 mg PHARMC can be predicted from single dose pharmacokinetics.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate

Maize starch

Povidone K-30

Vegetable magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 25 °C.

Store in the original package in order to protect from light.

6.5 Nature and contents of container

DIENOGEST 2 mg PHARMC is packaged in PVC/PVDC/aluminium blisters. Aluminium foil is a foil of aluminium push-through with a dull side lacquered, and a bright side heat sealable lacquered for sealing to PVC. One blister calendar pack with 28 tablets, is packed into a carton box.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

7 HOLDER OF CERTIFICATE OF REGISTRATION

PHARMACORP (PTY) LTD

29 Victoria Link

Route 21 Corporate Park

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RSA

8 REGISTRATION NUMBER: 55/21.8.2/0725

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION: May 2023

10 DATE OF REVISION OF THE TEXT