Professional Information

SCHEDULING STATUS

S3

1 NAME OF THE MEDICINE

VISAFEM (2 mg tablets)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2 mg dienogest (micronised).

Excipient with known effect: VISAFEM contains sugar (lactose monohydrate) 62,81 mg per tablet.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablets

VISAFEM is white to slightly yellowish round tablet marked with “D2” on one side and without marking on the other side, with a diameter of approximately 7 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 VISAFEM 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 VISAFEM 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 the next day to take tablet 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

VISAFEM should not be used in the presence of any condition listed below. Should any of the conditions appear during the use of VISAFEM, the use of VISAFEM must be discontinued immediately.

- Hypersensitivity to dienogest or to any of the excipients listed in 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 VISAFEM 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 VISAFEM although not all of the warnings and precautions are based on respective findings in the clinical studies with VISAFEM.

If any of the conditions/risk factors mentioned below is present or deteriorates, an individual risk-benefit analysis should be done before treatment with VISAFEM 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 VISAFEM. If bleeding is heavy and continuous over time, this may lead to anaemia (severe in some cases). In the event of anaemia, discontinuation of VISAFEM should be considered.

Changes in bleeding pattern

The majority of patients treated with VISAFEM 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.

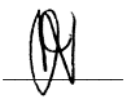
Although not statistically significant, some studies indicate that there may be a slightly increased risk of venous thromboembolism (deep venous thrombosis, pulmonary embolism) associated with the use of progestogen-only preparations. Generally recognised risk factors for venous thromboembolism (VTE) include a positive personal or family history (VTE in a sibling or a parent at a relatively early age), age, obesity, prolonged immobilisation, major surgery or major trauma. In case of long-term immobilisation, it is advisable to discontinue the use of VISAFEM (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

There is a risk of having breast cancer diagnosed in women who are currently using oral contraceptives (OCs), mainly using estrogen-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.

Signed: 

Benign liver tumours, and malignant liver tumours have been reported in users of hormonal substances such as the one contained in VISAFEM. 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 VISAFEM.

Osteoporosis

Changes in bone mineral density (BMD).

The use of VISAFEM 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). 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 (see sections 4.2 and 5.1).

In patients who are at an increased risk of osteoporosis a careful risk-benefit assessment should be performed before starting VISAFEM because endogenous estrogen levels are moderately decreased during treatment with VISAFEM (see section 5.1).

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 medicine should be discontinued if the depression recurs to a serious degree.

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VISAFEM generally does not appear to affect blood pressure in normotensive women. However, if a sustained clinically significant hypertension develops during the use of VISAFEM, it is advisable to withdraw VISAFEM 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 VISAFEM.

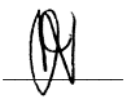
VISAFEM may have a slight effect on peripheral insulin resistance and glucose tolerance. Diabetic women, especially those with a history of gestational diabetes mellitus, should be carefully observed while taking VISAFEM.

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 VISAFEM.

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 VISAFEM 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 VISAFEM. Most of these follicles are asymptomatic, although some may be accompanied by pelvic pain.

VISAFEM contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take VISAFEM.

Signed: 

4.5 Interaction with other medicines and other forms of interaction

Effects of other medicines on VISAFEM

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 drug metabolism.

An increased clearance of sex hormones due to enzyme induction may reduce the therapeutic effect of VISAFEM 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 VISAFEM and may result in undesirable effects.

- Substances 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 products 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 medicine 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 estradiol valerate/dienogest tablets led to significant decreases in steady state concentrations and systemic exposures of dienogest and estradiol. The systemic exposure of dienogest and estradiol at steady state, measured by AUC(0-24h), were decreased by 83 % and 44 %, respectively.

- Substances 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.

- Substances decreasing the clearance of sex hormones (enzyme inhibitors):

Dienogest (e.g. VISAFEM) 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 VISAFEM on other medicines

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

Interaction with food

A standardised high fat meal did not affect the bioavailability of VISAFEM.

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

Women of childbearing potential / Contraception in males and females

If contraception is required a non-hormonal method should be used (e.g. barrier method).

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

Pregnancy

The administration of VISAFEM during pregnancy is contraindicated. If pregnancy occurs during the use of VISAFEM, further intake should be stopped.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

Breastfeeding

VISAFEM should not be used during lactation.

It is unknown whether VISAFEM is excreted in human milk. Data in animals have shown excretion of dienogest such as VISAFEM in rat milk.

Fertility

Based on the available data, ovulation is inhibited in the majority of patients during treatment with VISAFEM. However, VISAFEM is not a contraceptive.

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 such as VISAFEM.

4.8 Undesirable effects

a. Summary of the safety profile

Presentation of undesirable effects is based on MedDRA.

Undesirable effects are more frequent during the first months after the start of treatment with VISAFEM 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 VISAFEM. The most frequently reported undesirable effects under treatment with 2 mg dienogest are headache (9,0 %), breast discomfort (5,4 %), depressed mood (5,1 %) and acne (5,1 %).

b. Tabulated list of adverse reactions

Table 1

System Organ Class (MedDRA)	**Frequent**	**Less frequent**
Blood and lymphatic system disorders		anaemia
Metabolism and nutrition disorders	increased weight	decreased weight, increased appetite
Psychiatric disorders	depressed mood, sleep disorder, nervousness, loss of libido, altered mood	anxiety, depression, mood swings
Nervous system disorders	headache, migraine	autonomic nervous system imbalance, disturbance in attention
Eye disorders		dry eyes
Ear and labyrinth disorders		tinnitus

Cardiac disorders		unspecified circulatory system disorder, palpitations
Vascular disorders		hypotension
Respiratory, thoracic and mediastinal disorders		dyspnoea
Gastrointestinal disorders	nausea, abdominal pain, flatulence, abdominal distension, vomiting	diarrhoea, constipation, abdominal discomfort, gastrointestinal inflammation, gingivitis
Skin and subcutaneous tissue disorders	acne, alopecia	dry skin, hyperhidrosis, pruritus, hirsutism, onychoclasis, dandruff, dermatitis, abnormal hair growth, photosensitivity reaction pigmentation disorder
Musculoskeletal and connective tissue disorders	back pain	bone pain, muscle spasms, pain in extremity, heaviness in extremities

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Renal and urinary disorders		urinary tract infection
Reproductive system and breast disorders	breast discomfort, ovarian cyst, hot flushes, uterine / vaginal bleeding including spotting	vaginal candidiasis, vulvovaginal dryness, genital discharge, pelvic pain, atrophic vulvovaginitis, breast mass, fibrocystic breast disease, breast induration
General disorders and administration site conditions	asthenic conditions, irritability	oedema

Decrease of bone mineral density

Reports have shown in an uncontrolled clinical trial with 111 adolescent women (12 to <18 years) who were treated with 2 mg dienogest, 103 had BMD measurements.

Approximately 72 % of these study participants experienced a decrease in BMD of the lumbar spine (L2-L4) after 12 months of use (see section 4.4).

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. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form"**, found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

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4.9 Overdose

Acute toxicity studies performed with VISAFEM did not indicate a risk of acute adverse effects in case of inadvertent intake of a multiple of the daily therapeutic dose. Daily intake of 20 – 30 mg dienogest (10 to 15 times higher dose than in VISAFEM) over 24 weeks of use was very well tolerated. However, overdosage may potentiate the adverse effects reported under section 4.4 and 4.8. There is no specific antidote, treatment is symptomatic and supportive.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: progestogens, ATC code: G03DB08

A21.8.2 Progesterones with or without oestrogens

Pharmacodynamic properties

Dienogest is a nortestosterone derivative with no androgenic but rather an antiandrogenic activity of approximately one third of that of cyproterone acetate. Dienogest binds to the progesterone receptor of the human uterus with only 10 % of the relative affinity of progesterone. 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 reducing the endogenous production of estradiol and thereby suppresses the trophic effects of estradiol on both the eutopic and ectopic endometrium. When given continuously, dienogest leads to a hypoestrogenic, hypergestagenic endocrine environment causing initial decidualisation of endometrial tissue followed by atrophy of endometriotic lesions.

5.2 Pharmacokinetic properties

Absorption

Orally administered dienogest is rapidly and almost completely absorbed. Peak serum concentrations of 47 ng/mL are reached at about 1,5 hours after single ingestion. 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 – 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 medicine concentration is present as free steroid, 90 % is non-specifically bound to albumin.

The apparent volume of distribution (V_d/F) of dienogest is 40 L.

Biotransformation

Dienogest is completely metabolised by the known pathways of steroid metabolism, with the formation of endocrinologically mostly inactive metabolites. Based on *in vitro* and *in vivo* studies, CYP3A4 is the major enzyme involved in the metabolism of dienogest. The metabolites are excreted very quickly 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 9-10 hours. Dienogest is excreted in 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 excreted within the first 24 h, mostly with the urine.

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Steady-state conditions

Pharmacokinetics of dienogest are not influenced by SHBG levels. Following daily ingestion medicine serum levels increase about 1,24 fold reaching steady-state conditions after 4 days of treatment. The pharmacokinetics of dienogest after repeated administration of dienogest 2 mg tablets can be predicted from single dose pharmacokinetics.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Crospovidone, Type A

Lactose monohydrate

Magnesium stearate

Microcrystalline cellulose

Povidone K30

Pregelatinised maize starch

Silica colloidal anhydrous

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store at or below 30 °C.

Store in the outer carton box packaging to protect from light.

6.5 Nature and contents of container

VISAFEM are packaged in blister packs of green polyvinyl chloride (PVC) coated with polyvinylidene chloride (PVDC) and push-through heat-sealed aluminium (Alu) foil, packed into carton boxes.

Pack sizes are 2 x 14, 6 x 14, and 12 x 14.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Adcock Ingram Limited

1 New Road

Erand Gardens

Midrand 1685

South Africa

8 REGISTRATION NUMBER(S)

550034

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

28 February 2022

10 DATE OF REVISION OF THE TEXT

Signed: 

Date: 28 Feb 2022