SCHEDULING STATUS: **S3**

1 NAME OF THE MEDICINE

VISANNE
2 mg dienogest
Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active: Each tablet contains 2 mg dienogest.

Each tablet contains 63 mg lactose monohydrate

For full list of excipients see "section 6.1"

3 PHARMACEUTICAL FORM

White to off-white, round, flat-faced, bevelled tablets, marked with the letter "B" on one side and no marking on the other side and a diameter of 7 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of endometriosis.
VISANNE is indicated in the long-term treatment of endometriosis in adolescents after menarche from 12 years of age onward and adults

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 VISANNE 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 VISANNE 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.

Special populations

Paediatric

VISANNE is not indicated in children prior to menarche. The efficacy of VISANNE has been demonstrated in the treatment of endometriosis – associated pelvic pain in adolescent patients (12-18 years), with an overall favourable safety and tolerability profile.

The use of VISANNE in adolescents over a treatment period of 12 months was associated with a mean decrease in Bone Mineral Density (BMD) in the lumbar spine of 1.2 %. After cessation of treatment, BMD increased again in these patients.

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.

Therefore, the treating physician should weigh the benefits of VISANNE against the possible risks of use in each individual adolescent patient (see "section 4.4" and "section 5.1').

Geriatric patients

There is no relevant indication for use of VISANNE in the geriatric population.

Patients with hepatic impairment

VISANNE is contraindicated in patients with present or past severe hepatic disease. (see "section "4.3").

Patients with renal impairment

There are no data to suggesting the need for a dosage adjustment in patients with renal impairment.

4.3 Contraindications

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

- 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.
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Circulatory disorders:

Some epidemiological studies indicate a trend, but not statistically significant increased risk of venous thromboembolism (deep venous thrombosis, pulmonary embolism) associated with the use of progestogen-only preparations as in VISANNE. 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 young age), age, obesity, prolonged immobilisation, major surgery or major trauma. In case of long-term immobilisation, it is advisable to discontinue the use of VISANNE (in the case of elective surgery at least four weeks in advance) and not to resume treatment until two weeks after complete remobilisation.

Tumours:

There is a risk of having breast cancer diagnosed in patients using VISANNE.

Cases of benign liver tumours and, even more rarely, malignant liver tumours have been reported in users of hormonal substances such as the one contained in VISANNE. In isolated cases, these tumours have led to life-threatening intra-abdominal haemorrhages.

Changes in Bone Mineral Density (BMD)

The use of VISANNE in adolescents (12 to 18 years) over a treatment period of 12 months was associated with a mean decrease in bone mineral density (BMD) in the lumbar spine of 1.2%. After cessation of treatment, BMD increased again in these patients.

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 “section 5.1”)

Therefore, the treating physician should weigh the benefits of VISANNE against the possible risks of use in each individual adolescent patient also taking into account the presence of significant risk factors for osteoporosis (e.g. metabolic bone disease, family history of osteoporosis, low body mass index or eating disorders, such as anorexia nervosa or bulimia, chronic use of drugs that can reduce bone mass, e.g. anticonvulsants or corticosteroids, previous low trauma fracture, alcohol abuse and/or smoking).

Adequate intake of calcium and Vitamin D, whether from the diet or from supplements, is important for bone health in women of all ages.
No BMD decrease was observed in adults (see “section 5.1”).

Other conditions:

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

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

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

Pregnancies that occur among users of progestogen-only preparation are more likely to be ectopic than are pregnancies among users of combined oral contraceptives.

Therefore, in women with history of extra-uterine pregnancy or an impairment of tube function, the use of VISANNE should be decided 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.

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

Persistent ovarian follicle (often referred to as functional ovarian cyst) may occur during the use of VISANNE. Most of these follicles are asymptomatic, although some may be accompanied by pelvic pain.

Each VISANNE tablet contains 63 mg lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption who are on a lactose-free diet should consider the amount contained in VISANNE.

4.5 Interaction with other medicines and other forms of interaction

Effects of other medicines on VISANNE:

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

An increased clearance of sex hormones due to enzyme induction may reduce the therapeutic effect of VISANNE and may result in undesirable effects e.g. change in bleeding profile.

A reduced clearance of sex hormones due to enzyme inhibition may increase the therapeutic effects of VISANNE 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 oxcarbazepine, topiramate, felbamate, griseofulvin and products containing St. John's wort.

Enzyme induction can already be observed after a few days of treatment. Maximum enzyme induction is

generally seen within a few weeks. After the cessation of drug therapy enzyme induction may be sustained for about 4 weeks.

Substances with variable effects on the clearance of sex hormones, e.g.:
When co-administered with sex hormones, many HIV/HCV protease inhibitors and non-nucleoside reverse transcriptase inhibitors can increase or decrease plasma concentrations of the progestin. These changes may be clinically relevant in some cases.

Substances decreasing the clearance of progestins (enzyme inhibitors) Dienogest is a substrate of cytochrome

Strong and moderate CYP3A4 inhibitors such as azole antifungals (e.g. itraconazole, voriconazole, fluconazole), verapamil, macrolides (e.g. clarithromycin, erythromycin), diltiazem and grapefruit juice can increase plasma concentrations of the progestins.

Effects of VISANNE on other medicines:

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

Other forms of interactions:

The use of progestins may influence the results of certain laboratory tests.

4.6 Fertility, pregnancy and lactation

There are limited data from the use of dienogest in pregnant women. Animal studies and data from women exposed to dienogest during pregnancy reveal no special risks on pregnancy, embryonic/ foetal development, birth or development after birth for humans (see “section 5.3”). However, Visanne should not be administered to pregnant women because there is no need to treat endometriosis during pregnancy.

Breastfeeding

Treatment with Visanne during lactation is not recommended. Physiochemical properties and animal data indicate excretion of dienogest in breast milk.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

a) Summary of safety profile

Side effects are more common during the first month after start of intake of VISANNE. In addition to effects listed under “section 4.4” the following undesirable effects have been reported in users of VISANNE.

b) Tabulated summary of adverse reactions

Table below reports side effects by MedDRA system organ classes. The frequencies are based on pooled data of four clinical trials including 332 patients:

System organ class	Common (≥ 1/ 100 and < 10/ 100)	Uncommon (≥1/ 1000 and <1/100)
Metabolism and nutrition disorders	Weight increased	Weight decreased Increased appetite
Psychiatric disorders	Depressed mood Sleep disorder Nervousness Loss of libido Mood altered	Anxiety Depression Mood swings
Nervous system disorder	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 distention 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 disorders
Musculoskeletal and connective tissue disorders	Back pain	Bone pain Muscle spasm Pain in extremity Heaviness in extremities
Renal and urinary disorders		Urinary tract infections
Reproductive system and breast disorders	Breast discomfort Ovarian cyst Hot flush	Vaginal candidiasis Vulvovaginal dryness Genital discharge

	Uterine/vaginal bleeding including spotting	Pelvic pain Atrophic vulvovaginitis Breast mass Fibrocystic breast diseases Breast induration
General disorders and administration site conditions	Asthenic conditions Irritability	Oedema

c) Description of selected adverse reaction

Uterine bleeding irregularities:
The following bleeding patterns were observed: amenorrhea, infrequent bleeding, frequent bleeding, irregular bleeding, prolonged bleeding, and normal bleeding.

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 professionals 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: http://www.sahpra.org.za/Publications/index/8 .

4.9 Overdose

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

Pharmacological classification: A 21.8.2 Progesterones with or without oestrogen
ATC Code: G03D
Pharmacotherapeutic properties: Progestogens

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 oestradiol on both the eutopic and ectopic endometrium. When given continuously, dienogest leads to a hypoestrogenic, hypergestagenic endocrine environment and decidualisation of endometrial tissue.

The efficacy of VISANNE was demonstrated in the treatment of endometriosis related symptoms (pelvic pain,

dysmenorrhea, and dyspareunia) in a 12-month study with 111 female adolescents (after menarche between 12 and 18 years of age).

Endogenous oestrogen levels are only moderately suppressed during treatment with VISANNE.

Bone mineral density (BMD) was assessed in 21 adult patients before and after 6 months of treatment and there was no reduction in mean BMD. Currently, long-term data on bone mineral density (BMD) and risk of fractures in users of Visanne are not available.

In a 12-months study involving 103 adolescents the mean relative change in BMD of the lumbar spine (L2-L4) from baseline was -1.2 %. In a subset of the patients with decreased BMD a follow-up measurement was performed 6 months after end of treatment and showed an increase in BMD to – 0, 6 %.

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 (V_d/F) of dienogest is 40 litres.

Metabolism:

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 VISANNE can be predicted from single dose pharmacokinetics.

5.3 Preclinical safety data

Preclinical data reveal no special risks for humans based on conventional studies pf safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction. However, it should be borne in mind that sex steroids can promote the growth of certain hormone-dependent tissue and tumours.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Crospovidone
Lactose monohydrate,
Magnesium stearate,
Microcrystalline cellulose,
Potato starch,
Povidone,
Talc.

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

60 months in PVC/Al blister
36 months in PVC/Al/Pouch

6.4 Special precautions for storage

Store at or below 30 °C.

6.5 Nature and contents of container

- The tablets are packed into blisters consisting of a transparent, green-coloured polyvinyl chloride (PVC) film sealed onto aluminium foil and containing 14 white uncoated tablets.
- The tablets are packed into blisters consisting of a transparent, green-coloured polyvinyl chloride (PVC) film sealed onto aluminium foil and containing 14 white uncoated tablets. The blisters are then packed in a hermetic pouch

6.6 Special precautions for disposal

Not Applicable

7 HOLDERS OF CERTIFICATE OF REGISTRATION

Bayer (Pty) Ltd
Reg. No.: 1968/011192/07
27 Wrench Road
ISANDO
1609

8 REGISTRATION NUMBER

44/21.8.2/0159

9 DATE OF FIRST AUTHORISATION

01 March 2013

10 DATE OF REVISION OF THE TEXT

01 March 2022