Bayer HealthCare

**SCHEDULING STATUS:** S3

**PROPRIETARY NAME AND DOSAGE FORM:**

## VISANNE
Tablets

**COMPOSITION**:

Active: Each tablet contains 2 mg dienogest.
Excipients: Crospovidone lactose monohydrate, magnesium stearate, microcrystalline cellulose, potato starch, povidone, talc.

**PHARMACOLOGICAL CLASSIFICATION:**

A 21.8.2 Progesterones with or without oestrogens (ATC Code: G03D)

**PHARMACOLOGICAL ACTION:**

**Pharmacodynamic properties:**

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.

**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.

**INDICATION:**

Treatment of endometriosis.
Safety and efficacy beyond 24 months have not been established.

**CONTRA-INDICATIONS:**

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:

- 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.
- Hypersensitivity to the active substance or to any of the excipients.

**WARNINGS:**

**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.

**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.

**INTERACTIONS:**

**Effects of other medicines on VISANNE:**

*Individual enzyme-inducers or inhibitors (CYP3A4):*

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 with enzyme-inducing properties:*

Interaction can occur with medicines (e.g. phenytoin, barbiturates, primidone, carbamazepine, rifampicin and possibly oxcarbazepine, topiramate, felbamate, griseofulvin, nevirapine and products containing St. John's wort) that induces microsomal enzymes (e.g. cytochrome P450 enzymes) which can result in increased clearance of sex hormones.

Maximum enzyme induction is generally not seen for 2 to 3 weeks but may then be sustained for at least 4 weeks after cessation of therapy.

*Substances with enzyme-inhibiting properties:*

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.

**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 progestogens may influence the results of certain laboratory tests.

**PREGNANCY AND LACTATION:**

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

VISANNE should not be used during lactation.

**DOSAGE AND DIRECTION FOR USE:**

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.

**SIDE EFFECTS AND SPECIAL PRECAUTIONS:**

**Side effects:**

Side effects are more common during the first month after start of intake of VISANNE. In addition to effects listed under "Warnings" the following undesirable effects have been reported in users of VISANNE. 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<br>Increased appetite |
| **Psychiatric disorders** | Depressed mood<br>Sleep disorder<br>Nervousness<br>Loss of libido<br>Mood altered | Anxiety<br>Depression<br>Mood swings |
| **Nervous system disorder** | Headache<br>Migraine | Autonomic nervous system imbalance<br>Disturbance in attention |
| **Eye disorders** | | Dry eyes |
| **Ear and labyrinth disorders** | | Tinnitus |
| **Cardiac disorders** | | Unspecified circulatory system disorder<br>Palpitations |

| | | |
|---|---|---|
| **Vascular disorders** | | Hypotension |
| **Respiratory, thoracic and mediastinal disorders** | | Dyspnoea |
| **Gastrointestinal disorders** | Nausea<br>Abdominal pain<br>Flatulence<br>Abdominal distention<br>Vomiting | Diarrhoea<br>Constipation<br>Abdominal discomfort<br>Gastrointestinal inflammation<br>Gingivitis |
| **Skin and subcutaneous tissue disorders** | Acne<br>Alopecia | Dry skin<br>Hyperhidrosis<br>Pruritus<br>Hirsutism<br>Onychoclasis<br>Dandruff<br>Dermatitis<br>Hair growth abnormal<br>Photosensitivity reaction<br>Pigmentation disorder |
| **Musculoskeletal and connective tissue disorders** | Back pain | Bone pain<br>Muscle spasm<br>Pain in extremity<br>Heaviness in extremities |
| **Renal and urinary disorders** | | Urinary tract infection |
| **Reproductive system and breast disorders** | Breast discomfort<br>Ovarian cyst<br>Hot flush<br>Uterine/vaginal bleeding including spotting | Vaginal candidiasis<br>Vulvovaginal dryness<br>Genital discharge<br>Pelvic pain<br>Atrophic vulvovaginitis<br>Breast mass<br>Fibrocystic breast diseases<br>Breast induration |
| **General disorders and administration site conditions** | Asthenic conditions<br>Irritability | Oedema |

*Uterine bleeding irregularities:*

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

**Special precautions:**

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.

**Effects on ability to drive and use machine:**

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

**KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:**

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 “Side effects and special precautions”.

There is no specific antidote, treatment is symptomatic and supportive.

**IDENTIFICATION:**

White to off-white, round, flat-faced bevelled tablets.

**PRESENTATION:**

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. Pack sizes are 2 X 14', 6 X 14', and 12 X 14'.

**STORAGE INSTRUCTIONS:**

Store at or below 30 °C.
KEEP OUT OF REACH OF CHILDREN.

**REGISTRATION NUMBER:**

44/21.8.2/0159

**NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:**

Bayer (Pty) Ltd
Reg. No.: 1968/011192/07
27 Wrench Road
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**DATE OF PUBLICATION OF THE PACKAGE INSERT**

1 March 2013