

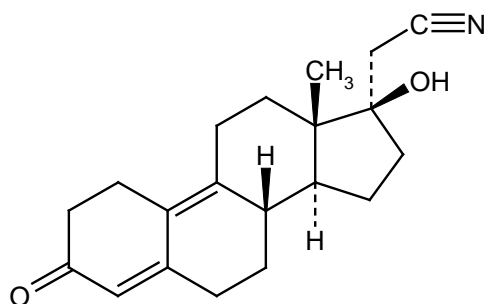
PRODUCT INFORMATION

VISANNE®

DESCRIPTION

Each Visanne tablet contains 2 mg of dienogest. The tablets are white to off-white, round, flat-faced, bevelled edge marked with the letter "B" on one side and have a diameter of 7 mm.

The chemical structure of dienogest is as follows:



INN	Dienogest
IUPAC / WHO	17 α -Hydroxy-3-oxo-19-norpregna-4,9-diene-21-nitrile (IUPAC)
CAS No	65928-58-7
Molecular formula	C ₂₀ H ₂₅ N O ₂
Molecular weight	311.43
Appearance	White to off-white crystalline powder

In addition Visanne contains the following inactive ingredients: lactose, potato starch, microcrystalline cellulose, povidone, talc-purified, crospovidone, magnesium stearate, water-purified.

PHARMACOLOGY

Pharmacotherapeutic group: Progestogens

ATC code: G03D

Dienogest is a nortestosterone derivative with 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 oestradiol and thereby suppressing the trophic effects of oestradiol 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. Additional properties, like

immunologic and antiangiogenic effects, seem to contribute to the inhibitory action of dienogest on cell proliferation.

Pharmacokinetic properties

Absorption

Orally administered dienogest is rapidly and almost completely absorbed. Peak serum concentrations of approximately 47 nanograms per mL are reached at about 1.5 hours after single ingestion. 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 drug concentrations are present as free steroid, 90% are non-specifically bound to albumin.

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

Metabolism

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 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 h, mostly with the urine.

Steady-state conditions

Pharmacokinetics of dienogest are not influenced by SHBG levels. Following daily ingestion, drug serum levels increase about 1.24 fold reaching steady-state conditions after 4 days of treatment. The pharmacokinetics of dienogest after repeated administration of Visanne can be predicted from single dose pharmacokinetics.

CLINICAL TRIALS

Efficacy

Superiority of Visanne over placebo with regard to reduction of endometriosis-associated pelvic pain (EAPP) and clinically meaningful reduction of pain compared to baseline were demonstrated in a 3-month study including 102 patients on Visanne. EAPP was measured on a Visual Analog Scale (VAS) (0 – 100 mm). After 3 months of treatment with Visanne, a statistically significant difference compared to placebo ($\Delta = 12.3$ mm; 95% CI: 6.4 – 18.1; $p < 0.0001$) and a clinically meaningful reduction of pain compared to baseline (mean reduction = 27.4 mm \pm 22.9) were demonstrated.

After 3 months of treatment, reduction of EAPP by 50% or more without relevant increase of concomitant pain medication was achieved in 37.3% of patients on Visanne (placebo: 19.8%); a reduction of EAPP by 75% or more without relevant increase of concomitant pain medication was achieved in 18.6% of patients on Visanne (placebo: 7.3%).

The open-label extension to this placebo-controlled study showed a continued improvement of endometriosis-associated pelvic pain for a treatment duration of up to 15 months (mean reduction at end of treatment = 43.2 ± 21.7 mm).

In addition, efficacy on EAPP was shown in a 6-months comparative trial of Visanne versus the GnRH analogue leuprorelin acetate (LA) including 120 patients on Visanne. EAPP was measured on a VAS (0 – 100 mm). A clinically meaningful reduction of pain compared to baseline and statistical non-inferiority versus LA were demonstrated (Visanne 47.5 ± 28.8 mm, LA 46.0 ± 24.8 mm). Non-inferiority versus LA based on a pre-defined non-inferiority margin of 15 mm was demonstrated ($p < 0.0001$).

Three studies including a total of 252 patients who received a daily dose of 2 mg dienogest demonstrated a substantial reduction of endometriotic lesions after 6 months of treatment.

A randomised, double-blind, parallel-group study ($n = 20$ to 23 per dose group) investigated pharmacodynamic effects of four dienogest doses (0.5, 1.0, 2.0 or 3.0 mg/day) for a maximum of 72 days. Ovulations were observed in 14% and 4% of women of the 0.5 mg and 1 mg groups, respectively. No ovulations occurred in the 2 mg and 3 mg groups. Visanne has not been tested for contraceptive efficacy in larger studies.

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).

Safety

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 the mean BMD. In a 12 month study involving 103 adolescents the mean relative change in BMD of the lumbar spine (L2-L4) from baseline to the end of treatment (EOT) was -1.2% (95% CI: -1.70% and -0.78%). In a subset of patients with decreased BMD at the EOT ($n = 60$), a follow-up measurement performed 6 months after cessation of treatment showed an increase in BMD towards baseline levels (mean relative change from baseline: -2.3% at EOT and -0.6% at 6 months after EOT [95% CI: -1.20% and 0.06%]).

No significant impact on standard laboratory parameters, including haematology, blood chemistry, liver enzymes, lipids, and HbA1C was observed during treatment with Visanne for up to 15 months ($n = 168$).

INDICATIONS

Treatment of endometriosis

CONTRAINDICATIONS

Visanne should not be used in the presence of any of the conditions listed below, which are partially derived from information on other progestogen-only preparations. Should any of the conditions appear during the use of Visanne, treatment must be discontinued immediately.

- Known or suspected pregnancy
- Lactation
- Active venous thromboembolic disorder
- Arterial and cardiovascular disease, present or in history (e.g. myocardial infarction, cerebrovascular accident, ischaemic heart disease)
- Diabetes mellitus with vascular involvement
- Present or history of severe hepatic disease as long as liver function values have not returned to normal
- Present 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.

PRECAUTIONS

General

Before starting Visanne treatment, pregnancy must be excluded. During treatment, patients are advised to use non-hormonal methods of contraception (e.g. barrier contraception such as condom) to prevent unwanted pregnancies.

Pregnancies that occur among users of progestogen-only preparations used for contraception (e.g. minipill) 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 Visanne should be decided on only after carefully weighing the benefits against the risks.

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

If any of the conditions/risk factors mentioned below is present or deteriorates, an individual risk-benefit analysis should be done before Visanne is started or continued.

Circulatory disorders

From epidemiological studies there is little evidence of an association between progestogen-only preparations and an increased risk of myocardial infarction or cerebral thromboembolism. 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.

Some studies indicate that there may be a slightly, but not statistically significant 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 Visanne (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 or suspicion of an arterial or venous thrombotic event.

Effects on fertility

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

If contraception is required a non-hormonal method should be used (e.g. condom). Based on available data, the menstrual cycle returns to normal within 2 months after cessation of treatment with Visanne.

Use in pregnancy (Category B3)

The administration of Visanne during pregnancy is contraindicated. If pregnancy occurs during use of Visanne, use of the product must be discontinued.

There are limited data from the use of dienogest in pregnant women. To date, no significant epidemiological data has been obtained. 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. However, Visanne must not be administered to pregnant women because there is no need to treat endometriosis during pregnancy.

Oral treatment of rats and rabbits with dienogest during organogenesis caused an increase in post implantation loss at systemic exposure levels (based on *AUC*) similar to that anticipated clinically. No teratogenicity was evident in either species at systemic exposure levels up to ten-fold higher than that expected at the clinical dose, based on *AUC*. Oral treatment of rats with dienogest during late pregnancy and lactation was shown to impair fertility in the offspring at maternal systemic exposure levels (based on *AUC*) approximately one-third of that anticipated clinically.

Changes in bleeding pattern

Visanne treatment affects the menstrual bleeding pattern in the majority of women (see ADVERSE EFFECTS). Uterine bleeding, for example in women with adenomyosis uteri or uterine leiomyomata, may be aggravated with the use of Visanne. If bleeding is heavy and continuous over time this may lead to anaemia (severe in some cases). In the event of anaemia, discontinuation of Visanne should be considered.

Chloasma

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 Visanne.

Osteoporosis and Changes in Bone Mineral Density (BMD)

Currently, long-term data on BMD and risk of fractures in users of Visanne are not available. BMD was assessed in 21 adult patients before and after 6 months of treatment with Visanne and there was no reduction of mean BMD. In 29 patients treated with leuprorelin acetate (LA), a mean reduction of 4.04% \pm 4.84 was noted after the same period (Δ between groups = 4.29%; 95%CI: 1.93 – 6.66; $p < 0.0003$). In patients who are

at an increased risk of osteoporosis a careful risk-benefit assessment should be performed before starting Visanne because endogenous oestrogen levels are moderately decreased during treatment with Visanne (see CLINICAL TRIALS, Safety).

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 towards pre-treatment levels over a period of 6 months in a subset of patients with decreased BMD (mean change from baseline -0.6%) see CLINICAL TRIALS.

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 Paediatric use and CLINICAL TRIALS).

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 medicines 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.

If clinically warranted, BMD may be monitored and the results used in the risk-benefit assessment of use of Visanne.

Other

Patients who have a history of depression should be carefully observed and the drug 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.

Persistent ovarian follicles (often referred to as functional ovarian cysts) 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 of lactose. 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.

Diabetes

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

Use in lactation

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

A decision must be made whether to discontinue breast feeding or to abstain from Visanne therapy, taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Paediatric use

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).

The use of Visanne in adolescent patients 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 towards pre-treatment levels over a period of 6 months in a subset of patients with decreased BMD (mean change from baseline -0.6%) see CLINICAL TRIALS.

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 CLINICAL TRIALS and PRECAUTIONS, Osteoporosis and Changes in Bone Mineral Density).

Geriatric use

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

Patients with hepatic impairment

Visanne is contraindicated in patients with present or past severe hepatic disease.

Patients with renal impairment

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

Carcinogenicity

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 oestrogen-progestogen preparations. The excess risk gradually disappears during the course of the 10 years after cessation of combined oral contraceptives (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 progestogen-only pill users is possibly of similar magnitude to that associated with COC, i.e. the pill. However, for progestogen-only preparations, the evidence is based on much smaller patient numbers and so is less conclusive than 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 ever-users tend to be less advanced clinically than the cancers diagnosed in never-users.

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 Visanne. 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 Visanne.

Long-term studies in rats and mice with dienogest showed increased incidences of pituitary adenomas, fibroepithelial mammary tumours, stromal polyps of the uterus and malignant lymphoma, at doses corresponding to exposure levels about 10 times that anticipated at the maximum recommended clinical dose, based on area under the plasma concentration time curve (AUC). Similar tumours have been shown to develop with other oestrogenic/ progestogenic compounds. The tumours are thought to result from marked species differences in the optimal oestrogen:progestogen ratio for reproductive function. Dienogest showed no tumour promotion activity in the rat liver foci assay at exposure levels corresponding to >100 times the estimated human exposure at the clinical dose, based on AUC.

Genotoxicity

Dienogest did not exhibit any evidence of genotoxic potential in assays for gene mutations in bacterial or mammalian cells, *in vitro* and *in vivo*.

Medical examination

A complete medical history and physical and gynaecological examination should be taken prior to the initiation or reinstatement of Visanne, guided by the **CONTRAINDICATIONS** and **PRECAUTIONS**, and should be repeated at least annually during the use of Visanne. The frequency and nature of these assessments should be adapted to the individual woman but should generally include special reference to blood pressure, breasts, abdomen and pelvic organs and should also include cervical cytology.

INTERACTIONS WITH OTHER MEDICINES

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 Visanne 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.

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.

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 therapy enzyme induction may be sustained for about 4 weeks.

The effect of the CYP3A4 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. The systemic exposure of dienogest at steady state, measured by AUC (0 – 24h), was decreased by 83%.

Substances with variable effects on the clearance of sex hormones, (e.g. nevirapine):

When co-administered with sex hormones, many HIV/HCV protease inhibitors (e.g. ritonavir, saquinavir, indinavir, nelfinavir) and non-nucleoside reverse transcriptase inhibitors can increase or decrease plasma concentrations of the progestogen. These changes may be clinically relevant in some cases.

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

Dienogest is a substrate of cytochrome P450 (CYP) 3A4.

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

In a study investigating the effect of CYP3A4 inhibitors (ketoconazole, erythromycin) on the combination of oestradiol valerate/dienogest, steady state dienogest plasma levels were increased. Co-administration with the strong inhibitor ketoconazole resulted in a 186% increase of AUC (0 – 24h) at steady state for dienogest. When co-administered with the moderate inhibitor erythromycin, the AUC (0 – 24h) of dienogest at steady state was increased by 62%. The clinical relevance of these interactions is unknown.

Effects of Visanne on other medicinal products

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

Drug food interactions

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

Effects on 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. lipid/lipoprotein fractions, parameters of carbohydrate metabolism and parameters of coagulation and fibrinolysis. Changes generally remain within the normal laboratory range.

Effects on ability to drive or use machines

Not known.

ADVERSE EFFECTS

Undesirable effects are more common during the first months after start of intake of Visanne, and subside with duration of treatment (see PRECAUTIONS). The following undesirable effects have been reported in users of Visanne.

The most frequently reported undesirable effects during treatment that were considered at least possibly related to Visanne were 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 Visanne are summarised in Table 1. Within each frequency grouping, undesirable effects are presented in order of decreasing frequency. Frequencies are defined as common ($\geq 1/100$ to $< 1/10$) and uncommon ($\geq 1/1000$ to $< 1/100$). The frequencies are based on pooled data of four clinical trials including 332 patients (100.0%).

Table 1: Categorised relative frequency of women with ADRs, by MedDRA SOC, 2 mg dienogest group – based on pooled data of four clinical trials including 332 patients

System Organ Class	Common	Uncommon
Blood and lymphatic system disorders		Anaemia (1; 0.3%)
Metabolism and nutrition disorders	Weight increased (12; 3.6 %)	Weight decreased (1; 0.3%) Increased appetite (1; 0.3%)
Psychiatric disorders	Depressed mood (17; 5.1%) Sleep disorder ^I (7; 2.1%) Nervousness (5; 1.5%) Loss of libido (5; 1.5%) Mood altered (4; 1.2%)	Anxiety (2; 0.6%) Depression (2; 0.6%) Mood swings (1; 0.3%)
Nervous system disorders	Headache (30; 9.0%) Migraine (4; 1.2%)	Autonomic nervous system imbalance (3; 0.9%) Disturbance in attention (2; 0.6%)
Eye disorders		Dry eye (1; 0.3%)
Ear and labyrinth disorders		Tinnitus (1; 0.3%)
Cardiac disorders		Unspecified circulatory system disorder (1; 0.3%) Palpitations (1; 0.3%)
Vascular disorders		Hypotension (1; 0.3%)
Respiratory, thoracic and mediastinal disorders		Dyspnoea (1; 0.3%)
Gastrointestinal disorders	Nausea (14; 4.2%) Abdominal pain ^{II} (12; 3.6%) Flatulence (10; 3.0%) Abdominal distension (4; 1.2%) Vomiting (4; 1.2%)	Diarrhoea (2; 0.6%) Constipation (2; 0.6%) Abdominal discomfort (2; 0.6%) Gastrointestinal inflammation ^{III} (2; 0.6%) Gingivitis (1; 0.3%)
Skin and subcutaneous tissue disorders	Acne (17; 5.1%) Alopecia (5; 1.5%)	Dry skin (3; 0.9%) Hyperhidrosis (2; 0.6%) Pruritus (2; 0.6%) Hirsutism (1; 0.3%) Onychoclasia (1; 0.3%) Dandruff (1; 0.3%) Dermatitis (1; 0.3%)

System Organ Class	Common	Uncommon
		Hair growth abnormal (1; 0.3%) Photosensitivity reaction (1; 0.3%) Pigmentation disorder (1; 0.3%)
Musculoskeletal and connective tissue disorders	Back pain (4; 1.2%)	Bone pain (1; 0.3%) Muscle spasms (1; 0.3%) Pain in extremity (1; 0.3%) Heaviness in extremities (1; 0.3%)
Renal and urinary disorders		Urinary tract infection ^{IV} (2; 0.6%)
Reproductive system and breast disorders	Breast discomfort ^V (18; 5.4%) Ovarian cyst ^{VI} (10; 3.0%) Hot flush (9; 2.7%) Uterine / Vaginal bleeding including Spotting ^{VII, VIII} (5; 1.5%)	Vaginal candidiasis (3; 0.9%) Vulvovaginal dryness ^{IX} (3; 0.9%) Genital discharge ^X (2; 0.6%) Pelvic pain (2; 0.6%) Atrophic vulvovaginitis (1; 0.3%) Breast mass (1; 0.3%) Fibrocystic breast disease (1; 0.3%) Breast induration (1; 0.3%)
General disorders and administration site conditions	Asthenic conditions ^{XI} (10; 3.0%) Irritability (5; 1.5%)	Oedema ^{XII} (2; 0.6%)

The most appropriate MedDRA term (version 11.0) to describe a certain adverse reaction is listed. Synonyms or related conditions are not listed, but should be taken into account as well.

- I Sleep disorder consists of sleep disorder (5; 1.5%), insomnia (2; 0.6%).
- II Abdominal pain consists of abdominal pain (5; 1.5%), abdominal pain lower (5; 1.5 %), abdominal pain upper (2; 0.6%).
- III Gastrointestinal inflammation consists of gastrointestinal inflammation (1; 0.3%), gastritis (1; 0.3%).
- IV Urinary tract infection consists of urinary tract infection (1; 0.3%), cystitis (1; 0.3%)
- V Breast discomfort consists of breast discomfort (11; 3.3%), breast engorgement (4; 1.2%), breast pain (3; 0.9%).
- VI Ovarian cyst consists of ovarian cyst (9; 2.7%), haemorrhagic ovarian cyst (1; 0.3 %).
- VII Uterine/ Vaginal bleeding including spotting consists of dysfunctional uterine bleeding (1; 0.3%), metrorrhagia (1; 0.3%), menorrhagia (1; 0.3%), uterine haemorrhage (1; 0.3%), vaginal haemorrhage (1; 0.3%).
- VIII According to bleeding diaries, irregularities in menstrual bleeding occurred more often but were usually not reported as adverse drug reaction by the patients. Please refer to text below the table for further information.
- IX Vulvovaginal dryness consists of vulvovaginal dryness (2; 0.6%), mucosal dryness (1; 0.3%).
- X Genital discharge consists of genital discharge (1; 0.3%) and vaginal discharge (1; 0.3%).

- XI Asthenic conditions consists of fatigue (6; 1.8%), asthenia (2; 0.6%), malaise (2; 0.6 %).
XII Oedema consists of oedema (1; 0.3%), face oedema (1; 0.3%).

Uterine bleeding irregularities

Menstrual bleeding patterns were assessed systematically using patient diaries and were analysed using the WHO 90 day reference period method.

During the first reference period (i.e. first 90 days of treatment with Visanne): The following bleeding patterns were observed (n = 290; 100%): amenorrhoea (1.7%), infrequent bleeding (27.2%), frequent bleeding (13.4%), irregular bleeding (35.2%), prolonged bleeding (38.3%), normal bleeding, i.e. none of the previous categories (19.7%)[‡].

During the fourth reference period the following bleeding patterns were observed (n = 149; 100%): amenorrhoea (28.2%), infrequent bleeding (24.2%), frequent bleeding (2.7%), irregular bleeding (21.5%), prolonged bleeding (4.0 %), normal bleeding, i.e. none of the previous categories (22.8%)[‡].

Changes in menstrual bleeding patterns were only occasionally reported as adverse event by the patients (see Table 1).

DOSAGE AND ADMINISTRATION

Tablet taking can start on any day of the menstrual cycle. 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 continuously without regard to vaginal 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 3-4 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 on the next day to take the tablet at her usual time. A tablet not absorbed due to vomiting or diarrhoea should likewise be replaced by one tablet.

If a short acting, e.g. oral, hormonal treatment was prescribed before starting treatment with dienogest, treatment may be started on the first day of menstrual bleeding after cessation of treatment.

If a long-acting, i.e. injectable, hormonal treatment was administered before starting treatment with dienogest, then dienogest may be started once metabolism/excretion of the previously administered drug is expected to be completed.

There is no experience with Visanne treatment for more than 15 months in patients with endometriosis.

OVERDOSAGE

Acute toxicity studies performed with Visanne did not indicate a risk of acute adverse effects in case of inadvertent multiple daily therapeutic dose. There is no specific antidote. 20 - 30 mg dienogest per day (10 to 15 times higher dose than in Visanne) over 24 weeks of use was well tolerated.

[‡] Sums up to more than 100% because one patient may fall into more than one category at the same time, e.g. "frequent bleeding" and "irregular bleeding".

PRESENTATION AND STORAGE

Visanne tablets are contained in blister packs. Each blister contains 14 white tablets containing dienogest 2 mg.

Carton containing blister packs of 2 x 14, 6 x 14 or 12 x 14 tablets. Not all pack sizes may be marketed.

Shelf life is 5 years when stored below 25°C.

NAME AND ADDRESS OF SPONSOR

Made in Germany for:

Bayer Australia Ltd
ABN 22 000 138 714
875 Pacific Highway
PYMBLE NSW 2073

POISONS SCHEDULE

S4: Prescription Only Medicine

DATE OF FIRST INCLUSION IN THE ARTG

11 June 2010

DATE OF MOST RECENT AMENDMENT

21 September 2016

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