PRODUCT MONOGRAPH

PrVISANNE®

dienogest tablets

2 mg

Progestin

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PrVISANNE®

dienogest

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Table 1 – Product Information Summary

Route of Administration	Dosage Form, Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Tablet, 2 mg	Lactose monohydrate *For a complete listing see* **DOSAGE FORMS, COMPOSITION AND PACKAGING** *section.*

INDICATIONS AND CLINICAL USE

VISANNE (dienogest) is indicated for the management of pelvic pain associated with endometriosis.

Efficacy of VISANNE has not been tested beyond 15 months.

Geriatrics (> 65 years of age)

VISANNE is not indicated for use in the geriatric population.

Pediatrics (< 18 years of age)

VISANNE is not intended for use prior to menarche.

VISANNE has not been tested beyond 12 months in adolescents. VISANNE has been associated with plateauing and loss of bone mineral density (BMD) in adolescents. Therefore, the treating physician should weigh the benefits of VISANNE against the possible risks of use in each individual adolescent patient (see **WARNINGS AND PRECAUTIONS, Endocrine and Metabolism**).

CONTRAINDICATIONS

VISANNE should not be used in women with any of the conditions listed below, which are partially derived from information on other progestin-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, past or present (eg, myocardial infarction, cerebrovascular accident, ischemic 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 tumors (benign or malignant)
- Known or suspected sex hormone-dependent malignancies
- Undiagnosed abnormal vaginal bleeding
- Any ocular lesion arising from ophthalmic vascular disease, such as partial or complete loss of vision or defect in visual fields
- Current or history of migraine with focal aura
- Hypersensitivity to dienogest or to any ingredient in the formulation or component of the container. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

In adolescent patients, the use of VISANNE has been associated with plateauing and loss of bone mineral density (BMD) which may not be completely reversible. BMD loss or plateauing in adolescents is of particular concern, as this is a critical period of bone accretion.

BMD loss may be greater with increasing duration of use. It is unknown if the use of VISANNE during adolescence will reduce peak bone mass and increase the risk of osteoporosis.

The risks and benefits of this treatment in adolescents should be re-evaluated on a regular basis (see **WARNINGS AND PRECAUTIONS, Endocrine and Metabolism**).

General

Before initiating treatment with VISANNE, pregnancy must be excluded (see **CONTRAINDICATIONS**).

During treatment, patients are advised to use non-hormonal methods of contraception (eg, barrier method) if contraception is required. Hormonal methods of contraception should not be used in combination with VISANNE.

As VISANNE is a progestin-only therapy, it can be assumed that special warnings and special precautions for use of other progestin-only therapies are 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.

Cigarette smoking increases the risk of serious adverse effects on the heart and blood vessels. Smoking may also increase the risk of bone mineral density decline. Women should be counseled not to smoke.

Carcinogenesis and Mutagenesis

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 estrogen-progestin 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 lifetime risk of breast cancer. The risk of having breast cancer diagnosed in progestin-only pill users is possibly of similar magnitude to that associated with COC. However, for progestin-only preparations, the evidence is based on much smaller populations of users and therefore is less conclusive than that for COCs. These studies do not provide evidence of causality. 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, however a small proportion of younger women appear to develop more aggressive cancers after using OCs than never-users.

Regular breast exams should be done in patients using VISANNE. Any irregularity or anomaly of the breast should be adequately investigated (eg, by mammography or ultrasound).

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

Cardiovascular

From epidemiological studies, there is little evidence for an association between progestin-only preparations and an increased risk of myocardial infarction or cerebral thromboembolism. The risk of cardiovascular and cerebral events is rather related to increasing age, hypertension, and smoking. In women with hypertension the risk of stroke may be slightly increased by progestin-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 progestin-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 cases of long-term immobilization it is advisable to discontinue the use of VISANNE (in the case of elective surgery, at least 4 weeks in advance) and not to resume treatment until 2 weeks after complete remobilization.

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

Treatment with VISANNE should be discontinued immediately if there is suspicion or symptoms of an arterial or venous thrombotic event (see **CONTRAINDICATIONS**).

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

Endocrine and Metabolism

Bone Mineral Density in Adult Women

In patients who are at an increased risk of osteoporosis a careful risk-benefit assessment should be performed before starting VISANNE because endogenous estrogen levels are moderately decreased during treatment with VISANNE. Currently, long-term data on bone mineral density (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 adult patients treated with leuprolide acetate (LA), a mean reduction of 4.04% ± 4.84% was noted after the same period (different between groups = 4.29%; 95% CI: 1.93 – 6.66; $P = 0.0003$) (see **ACTION AND CLINICAL PHARMACOLOGY**, **Pharmacodynamics**, and **ACTION AND CLINICAL PHARMACOLOGY**, **Bone Mineral Density**).

Bone Mineral Density in Adolescent Females (12 to < 18 years of age)

The use of VISANNE in adolescents (12 to <18 years) over a treatment period of 12 months was associated with a mean decrease in BMD in the lumbar spine of 1.2%. After cessation of treatment, BMD increased towards pre-treatment levels over a period of 6 months.

Plateauing or 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 **ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics**, and **ACTION AND CLINICAL PHARMACOLOGY**, **Bone Mineral Density**).

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. BMD monitoring should be considered in adolescent females using VISANNE, as clinically appropriate.

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

Hepatic

VISANNE is contraindicated in patients with present or past severe hepatic disease (see **CONTRAINDICATIONS**).

Pancreatic

VISANNE may slightly induce peripheral insulin resistance and glucose intolerance. Diabetic women, especially those with a history of gestational diabetes mellitus, should be carefully observed while taking VISANNE. (1)

Psychiatric

Patients who have a history of depression should be carefully observed. VISANNE should be discontinued if clinically relevant depression occurs or if pre-existing depression is aggravated during treatment.

Renal

VISANNE has not been studied in patients with impaired renal function. However, no special risk for these patients is expected since dienogest is almost completely metabolized before excretion and the metabolites are pharmacologically inactive.

Sexual Function/Reproduction

Although ovulation is inhibited in the majority of patients during treatment with VISANNE, it is not intended for use as a contraceptive. The menstrual cycle returns to pretreatment characteristics within 2 months after cessation of treatment with VISANNE.

If contraception is required, a non-hormonal method (eg, barrier method) should be used. Hormonal methods of contraception should not be used in combination with VISANNE.

Pregnancies that occur among users of progestin-only preparations for contraception are more likely to be ectopic than are pregnancies among users of combined oral contraceptives. (2) Therefore, in women with a history of extrauterine pregnancy or an impairment of fallopian tube function, the use of VISANNE should be considered only after carefully weighing the benefits against the risks.

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.

Changes in Bleeding Pattern

VISANNE treatment affects the menstrual bleeding pattern in the majority of women (see **ADVERSE REACTIONS**).

Uterine bleeding, for example in women with adenomyosis or uterine leiomyomas (fibroids), may be aggravated with the use of VISANNE. If bleeding is heavy and continues over time, this may lead to anemia (severe in some cases). Discontinuation of VISANNE should be considered in such cases.

VISANNE is expected to exhibit typical progestogenic effects on the endometrium by reducing estrogen levels which are the main growth stimulus for endometrial tissue. This may result in reduced endometrial thickness and an atrophic endometrium during treatment.

The menstrual cycle returns to pretreatment characteristics within 2 months after cessation of treatment with VISANNE.

Abnormal vaginal bleeding (eg, prolonged and/or heavy) should be thoroughly investigated by pelvic ultrasound, endometrial biopsy or hysteroscopy.

Skin

Recurrence of cholestatic jaundice and/or pruritus which first occurred during pregnancy or with previous use of sex steroids necessitates the discontinuation of VISANNE.

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 while taking VISANNE.

Special Populations

Pregnant Women

The administration of VISANNE during pregnancy is contraindicated (see **CONTRAINDICATIONS**). If pregnancy occurs during treatment with VISANNE, further intake must be stopped.

The data from a limited number of cases of exposure during pregnancy demonstrate that dienogest does not show adverse effects on pregnancy or on the health of the fetus/newborn. No significant epidemiological data have been obtained to date.

Preclinical data reveal no special risks on pregnancy, embryonic/fetal development, birth, or development after birth for humans (see **TOXICOLOGY**).

Nursing Women

VISANNE is contraindicated during lactation (see **CONTRAINDICATIONS**).

It is unknown if dienogest is excreted in human milk. Data in animals have shown excretion in rat milk (see **TOXICOLOGY**).

Geriatrics (> 65 years of age)

VISANNE is not indicated for use in the geriatric population.

Pediatrics (< 18 years of age)

VISANNE is not intended for use prior to menarche.

The use of VISANNE in adolescents (12 to <18 years) was studied over a treatment period of 12 months. VISANNE 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 in these patients over a period of 6 months.

Plateauing or loss of BMD is of particular concern during adolescence and early adulthood, as this is 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 **ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics**, and **ACTION AND CLINICAL PHARMACOLOGY**, **Bone Mineral Density**).

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. BMD monitoring should be considered in adolescent females using VISANNE, as clinically appropriate.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Undesirable effects are more common during the first months of treatment with VISANNE and subside with continued treatment.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

In clinical trials, VISANNE was generally well tolerated. The following adverse reactions have been reported in users of VISANNE.

The most frequent (> 5%) adverse drug reactions reported in pivotal trials with VISANNE were headache (6.6%) and breast discomfort including breast engorgement and breast pain (5.3%).

The following adverse drug reactions (reported to have a possible or probable relationship to VISANNE) were reported at a frequency of ≥ 1% in pivotal clinical trials based on pooled data from 3 clinical trials including 303 patients (see Table 2).

Table 2 – Adverse Drug Reactions With Frequency ≥ 1% in Pivotal Clinical Trials With VISANNE (N=303)

MedDRA System Organ Class	MedDRA Term	n	%
Metabolism and nutrition disorders	Weight increased	11	3.6
Psychiatric disorders	Depressed mood	9	3.0
	Sleep disorder	7	2.3
	Nervousness	4	1.3
	Loss of libido	5	1.7
Nervous system disorders	Headache	20	6.6
	Migraine	4	1.3
Gastrointestinal disorders	Nausea	11	3.6
	Abdominal pain	5	1.7
Skin and subcutaneous tissue disorders	Acne	6	2.0
	Alopecia	4	1.3
Reproductive system and breast disorders	Breast discomfort	16	5.3
	Ovarian cyst	8	2.6
	Uterine/vaginal bleeding including spotting	4	1.3
General disorders and administration site conditions	Asthenic conditions	7	2.3
	Irritability	4	1.3

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities, N = total number, n = number of subjects

Note: 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.

Menstrual Bleeding Patterns

In clinical trials, menstrual bleeding patterns were assessed systematically using daily patient diaries and were analyzed using the WHO 90 day reference period method. The following bleeding patterns were observed during the first 90 days (ie, first reference period) of treatment with VISANNE (n = 290): prolonged bleeding (38.3%), irregular bleeding (35.2%), infrequent bleeding (27.2%), normal bleeding (19.7%), frequent bleeding (13.4%), and amenorrhea (1.7%).

During the fourth reference period (day 271 to day 360), the following bleeding patterns were observed (n = 149): amenorrhea (28.2%), infrequent bleeding (24.2%), normal bleeding (22.8%), irregular bleeding (21.5%), prolonged bleeding (4.0%), and frequent bleeding (2.7%).

Changes in menstrual bleeding patterns were only occasionally reported as adverse events by the patients. In general, bleeding patterns were well tolerated and the discontinuation rate due to changes in bleeding pattern was below 1%. The bleeding parameters showed a clear and consistent pattern of reduced intensity over time following prolonged treatment with VISANNE (see Table 3).

Table 3 – Mean Days of Bleeding/Spotting and Spotting-Only With VISANNE Based on Pooled Data by WHO 90-Day Reference Periods – FAS (Studies 307041, 97085, and 307059)

	VISANNE (N=290)		
Reference Period	**n**	**No. of Bleeding/Spotting Days (Mean ± SD)**	**No. of Spotting-Only Days (Mean ± SD)**
1	281	25.1 ± 16.9	15.0 ± 13.2
2	248	13.3 ± 13.7	8.7 ± 9.8
3	156	12.7 ± 12.6	8.8 ± 9.3
4	146	10.2 ± 10.0	7.3 ± 7.8
5	60	8.5 ± 9.0	6.5 ± 7.5

Abbreviations: FAS = full analysis set; n = number of patients under observation; SD = standard deviation
Note: For those patients who received VISANNE in Study 307041, data from reference periods termed 1 − 4 in the follow-up Study 307059 actually correspond to periods 2 − 5 "on VISANNE" because these patients had already received VISANNE in reference period 1 of Study 307041.

Less Common Clinical Trial Adverse Drug Reactions (< 1%)

The following adverse drug reactions were seen at a frequency of < 1% in pivotal clinical trials with VISANNE.

Blood and lymphatic system disorders: Anemia.

Metabolism and nutrition disorders: Increased appetite

Psychiatric disorders: Anxiety, depression, mood altered, mood swings.

Nervous system disorders: Autonomic nervous system imbalance, disturbance in attention.

Eye disorders: Dry eye.

Ear and labyrinth disorders: Tinnitus.

Cardiac disorders: Palpitations, unspecified circulatory system disorder.

Gastrointestinal disorders: Abdominal discomfort, constipation, diarrhea, flatulence, gastrointestinal inflammation, vomiting.

Skin and subcutaneous tissue disorders: Dermatitis, dry skin, onychoclasis, photosensitivity reaction, pigmentation disorder, pruritus.

Musculoskeletal and connective tissue disorders: Back pain, bone pain, heaviness in extremities, muscle spasms, pain in extremity.

Renal and urinary disorders: Urinary tract infection.

Reproductive system and breast disorders: Breast induration, breast mass, fibrocystic breast disease, genital discharge, hot flush, pelvic pain, vaginal candidiasis, vulvovaginal dryness.

General disorders and administration site conditions: Edema.

DRUG INTERACTIONS

Overview

VISANNE should not be prescribed simultaneously with other steroids including danazol.

Progestins including dienogest are metabolized mainly by the cytochrome P450 3A4 system (CYP3A4). Therefore, inducers or inhibitors of CYP3A4 may affect progestin drug metabolism.

An increased clearance of sex hormones due to enzyme induction may reduce the therapeutic effect of VISANNE.

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

Drug-Drug Interactions

Substances increasing the clearance of sex hormones (diminished efficacy by enzyme induction)

Substances increasing the clearance of sex hormones include phenytoin, barbituates, primidone, carbamazepine, rifampicin, and possibly also oxcarbazepine, topiramate, felbamate, griseofulvin and products containing St. John's wort (see Table 4). (3-8)

Enzyme induction can 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

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 sex hormones (enzyme inhibitors)

Dienogest is a substrate of cytochrome P450 (CYP) 3A4. Strong and moderate CYP3A4 inhibitors such as azole antifungals (eg, ketoconazole, itraconazole, voriconazole, fluconazole), verapamil, macrolides (eg, clarithromycin, erythromycin), diltiazem and grapefruit juice can increase plasma concentrations of the progestin (see Table 4).

Effects of VISANNE on other medications

Based on in vitro inhibition studies, it is unlikely that VISANNE will have clinically relevant effects on the cytochrome P450 enzyme-mediated metabolism of other medications.

Table 4 – Established or Potential Drug-Drug Interactions

Proper Name	Ref	Effect	Clinical Comment
Anticonvulsants: phenytoin barbiturates primidone carbamazepine oxcarbazepine topiramate felbamate ethosuximide	T	↓dienogest	Induction of hepatic microsomal enzymes may decrease plasma levels of dienogest.
Anti-infective: rifampicin	CT	↓dienogest	Coadministration of a dienogest/estradiol valerate combination 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%.
erythromycin clarithromycin roxithromycin	CT	↑dienogest	Coadministration of a dienogest/estradiol valerate combination with erythromycin resulted in a 1.62-foldincrease of $AUC_{(0-24h)}$ at steady state for dienogest.
Antifungal: griseofulvin	T	↓dienogest	Induction of hepatic microsomal enzymes may decrease plasma levels of dienogest.
Calcium channel blocker: verapamil diltiazem nifedipine	T	↑dienogest	May increase plasma levels of dienogest.
Histamine receptor antagonist: cimetidine ranitidine	T	↑dienogest	May increase plasma levels of dienogest.
HIV/HCV protease inhibitors : ritonavir saquinavir indinavir nelfinavir atazanavir atazanavir / ritonavir tipranavir / ritonavir	T	↑dienogest	May increase plasma levels of dienogest.
HIV/HCV protease inhibitors : fos-amprenavir/ ritonavir boceprevir	T	↓dienogest	May decrease plasma levels of dienogest.
Non-nucleoside reverse transcriptase inhibitor: nevirapine efavirenz	T	↓dienogest	May result in an increased clearance of dienogest

Table 4 – Established or Potential Drug-Drug Interactions

Proper Name	Ref	Effect	Clinical Comment
Azole antifungal: ketoconazole itraconazole fluconazole voriconazole	CT	↑dienogest	Coadministration of a dienogest/estradiol valerate combination with ketoconazole resulted in a 2.86-fold increase of $AUC_{(0-24h)}$ at steady state for dienogest.
Grapefruit juice	T	↑dienogest	May increase plasma levels of dienogest.
Sedatives and hypnotics: benzodiazepines barbiturates chloral hydrate glutethimide meprobamate	T	↓dienogest	Induction of hepatic microsomal enzymes may decrease plasma levels of dienogest.
Other drugs: bosentan	T	↓dienogest	Induction of hepatic microsomal enzymes may decrease plasma levels of dienogest.

Legend: CT=Clinical Trial; T=Theoretical

Drug-Food Interactions

The bioavailability of VISANNE was unaffected by a high fat meal. VISANNE can be taken with or without food.

Drug-Herb Interactions

Herbal products containing St. John's wort (*Hypericum perforatum*) may induce CYP3A4 enzymes and can result in increased clearance of sex hormones.

Drug-Laboratory Interactions

The use of progestins may influence the results of certain laboratory tests (eg, gonadotropin, endogenous hormones).

The results of certain endocrine and liver function tests may be affected by progestin-containing products:

- Impaired glucose tolerance;
- Reduced serum folate concentration;
- Change in plasma lipoprotein levels.

The results of the above laboratory tests should not be considered reliable unless therapy has been discontinued for 2 to 4 weeks.

However, no significant impact on standard laboratory parameters, including hematology, blood chemistry, liver enzymes, lipids, and HbA1C was observed during treatment with VISANNE for up to 15 months (n = 168).

DOSAGE AND ADMINISTRATION

Dosing Considerations

VISANNE tablets are intended for continuous administration in women for the management of pelvic pain associated with endometriosis. Drug administration can be started on any day of the menstrual cycle.

Special Populations

Pediatrics (< 18 years of age)

The use of VISANNE in adolescent females (12 to < 18 years) over a 12 month period of time is associated with a decrease in bone mineral density (BMD). After cessation of treatment, BMD increases towards pre-treatment levels.

Plateauing or loss of BMD is of particular concern during adolescence and early adulthood, as this is critical period of bone accretion. 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. BMD monitoring should be considered in adolescent females using VISANNE, as clinically appropriate.

Recommended Dose and Dosage Adjustment

The dosage of VISANNE is 1 tablet taken orally every day without a break, preferably at the same time each day, with some liquid as needed. Tablets must be taken continuously regardless of any vaginal bleeding. When a pack is finished, the next one should be started the next day.

VISANNE may be taken with or without food.

Missed Dose

In the event of a missed tablet, a patient should take 1 tablet only as soon as possible and then continue to take the next tablet at her usual time the next day. The efficacy of VISANNE may be reduced in the event of missed tablets, vomiting and/or diarrhea (if occurring within 3 to 4 hours after the tablet is taken). A tablet not absorbed due to vomiting or diarrhea should likewise be replaced by 1 tablet.

OVERDOSAGE

A clinical study has shown that 20 to 30 mg dienogest per day (10 to 15 times the recommended dose of VISANNE) over 24 weeks of use in women was generally well tolerated. (9) There is no specific antidote to a VISANNE overdose and further treatment should be symptomatic, based on the pharmacological action of dienogest (see **TOXICOLOGY**, **Acute Toxicity**).

For management of a suspected overdose please contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Dienogest is a novel nortestosterone derivative with no androgenic but rather an antiandrogenic activity of approximately one third that of cyproterone acetate. (10) 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.

Pharmacodynamics

Dienogest reduces 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 hyperprogestogenic and moderately hypoestrogenic endocrine environment causing initial decidualization of endometrial tissue. (11)

Additional direct antiproliferative, immunologic and antiangiogenic effects seem to contribute to the inhibitory action of dienogest on cell proliferation (11-13) and to the reduction of pelvic pain associated with endometriosis.

Bone Mineral Density

The pharmacologic action of dienogest results in suppression of the hypothalamic-pituitary-ovarian axis, causing a moderate suppression of serum estrogen concentrations. This may lead to a decrease in bone mineral density, including during adolescence, a critical period of bone accretion. The potential risk for a future fracture, however, is not known (see **WARNINGS AND PRECAUTIONS**, **Endocrine and Metabolism**, and **WARNINGS AND PRECAUTIONS**, **Special Populations**).

Ovarian Function

In a study in 20 healthy women, a daily dose of 2 mg dienogest has been shown to induce an anovulatory state after 1 month of treatment. VISANNE has not been tested for contraceptive efficacy.

VISANNE is not intended for use as a contraceptive. If contraception is required, a nonhormonal method should be used (see **WARNINGS AND PRECAUTIONS, General**).

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

Based on available data, the menstrual cycle returns to pretreatment characteristics within 2 months after cessation of treatment with VISANNE.

Hypothalamo-Hypophyseal Function

Administered exogenously and continuously, progestins reduce the frequency and increase the amplitude of pulsatile GnRH release, which results in a reduction of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) secretion.

VISANNE does not increase the incidence or intensity of hot flushes.

Pharmacokinetics

Pharmacokinetics of dienogest are not influenced by sex hormone binding globulin (SHBG) or corticoid binding globulin (CBG) 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. The pharmacokinetics of dienogest are dose-proportional and linear within the dose range of 1 to 8 mg. There is minimal accumulation with repeated administration (accumulation ratio 1:24) and neither the time to maximum concentration nor the terminal half-life are altered compared to single-dose administration.

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 of 2 mg. 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). Ten percent (10%) of the total serum drug concentrations are present as free steroid; 90% are nonspecifically bound to albumin.

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

Metabolism

Dienogest is completely metabolized by the known pathways of steroid metabolism, with the formation of metabolites which are mostly inactive endocrinologically. 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; therefore in plasma, unchanged dienogest is the dominating fraction.

The metabolic clearance rate from serum (Cl/F) is 64 mL/min.

Excretion

Dienogest serum levels decrease in 2 phases. The terminal disposition phase is characterized by a half-life of approximately 9 to 10 hours. Dienogest is excreted in the form of inactive metabolites which are excreted at a urinary to fecal 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, most of the drug is excreted in the urine within the first 24 hours. Approximately 86% of the administered dose is eliminated within 6 days.

Special Populations and Conditions

Geriatrics (> 65 years of age)

VISANNE is not indicated for use in the geriatric population.

Pediatrics (< 18 years of age)

VISANNE is not intended for use prior to menarche.

VISANNE has been studied in the treatment of pelvic pain associated with endometriosis in adolescent patients (12 to <18 years) (see **WARNINGS AND PRECAUTIONS**, **Endocrine and Metabolism** and **WARNINGS AND PRECAUTIONS**, **Special Populations**). The systemic exposure (AUC(0-24h)) of dienogest at steady state in adolescents (12 to <18 years of age) (693 µg·h/L) is comparable to that in adults (616 µg·h/L).

Race

No clinically relevant interethnic differences among Caucasian and Japanese patients were observed with respect to the pharmacokinetics and pharmacodynamics of dienogest.

Hepatic Insufficiency

VISANNE is contraindicated in patients with present or past severe hepatic disease (see also **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS**, **Hepatic**). VISANNE has not been studied in patients with impaired liver function.

Renal Insufficiency

VISANNE has not been studied in patients with impaired renal function. However, no special risk for these patients is expected since dienogest is almost completely metabolized before excretion and the metabolites are pharmacologically inactive.

STORAGE AND STABILITY

VISANNE should be stored in the original packaging between 15°C and 30°C.

SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions.

DOSAGE FORMS, COMPOSITION AND PACKAGING

VISANNE (dienogest) is available as white to off-white, round, flat-faced, beveled-edged tablets with an embossed “B” on one side and a diameter of 7 mm.

Each tablet contains 2 mg dienogest and the following nonmedicinal ingredients: crospovidone, lactose monohydrate, magnesium stearate, microcrystalline cellulose, potato starch, povidone K 25, and talc.

VISANNE is available in blister packs of 28 tablets.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Common name: Dienogest

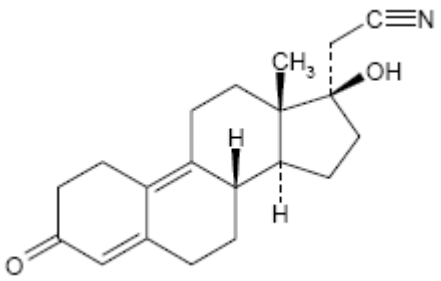
Chemical name: 17-hydroxy-3-oxo-19-nor-17α-pregna-4,9-diene-21-nitrile (IUPAC)

19-norpregna-4,9-diene-21-nitrile, 17-hydroxy-3-oxo-17α-cyanomethyl-17β-hydroxy-estra-4,9-dien-3-one (CAS Index Name)

Molecular formula: $C_{20}H_{25}NO_2$

Molecular weight: 311.43

Structural formula:



Physicochemical properties: White to off-white crystalline powder. Practically insoluble in water and neutral within the physiologically relevant pH range. Melting range is 210°C to 218°C. Dienogest is a neutral molecule within pH 2-12.

CLINICAL TRIALS

Study Demographics and Trial Design

Three pivotal trials (Studies 307041, 307059, and 97085) evaluated the efficacy of VISANNE in the management of pelvic pain associated with endometriosis using a visual analog scale (VAS) (0-100 mm). Patients with a confirmed diagnosis of endometriosis assessed by laparoscopy or laparotomy prior to treatment were included. These studies included patients with all stages of disease severity based on the rAFS or rARSM (revised American Society for Reproductive Medicine) classification systems.

The placebo-controlled study (Study 307041) was a multicenter, double-blind, randomized trial designed to prove the superiority of VISANNE compared to placebo. A total of 198 patients with endometriosis were treated over a period of 3 months. The frequency distribution of patients according to rASRM stages was comparable at baseline: 45.1% and 25% of VISANNE patients (and 44.8% and 26% of placebo patients) had moderate (stage III) and severe (stage IV) endometriosis, respectively. (14)

An open-label extension to this placebo-controlled study included a total of 168 women to assess the long-term efficacy of continued VISANNE treatment (Study 307059). Patients previously treated with either placebo or VISANNE in Study 307041 received VISANNE for an additional 52 weeks. (15)

Pelvic pain associated with endometriosis was also assessed in a 6-month noninferiority trial comparing VISANNE and leuprorelin acetate in 252 patients with endometriosis (Study 97085). Moderate (stage III) and severe (stage IV) endometriosis was present in 32.5% and 15% of VISANNE patients at baseline, respectively. (16)

Table 5 – Summary of Pivotal Studies for the Management of Pelvic Pain Associated With Endometriosis With VISANNE (Dienogest 2 mg)

Report (Study) / Phase (Study Design)	Primary Endpoint	Treatment Regimen	Treatment Duration	No. of Patients (Full Analysis Set)	Mean Age (Years)
A32473 (307041) / phase 3 (Multicenter, double-blind, randomized, placebo-controlled, parallel-group)	Pelvic pain associated with endometriosis assessed by VAS and change in pain medication[a]	VISANNE oral once daily Placebo	12 weeks	102 96	31.5 (18-44) 31.4 (19-46)
A39700 (307059) / phase 3; extension of Study 307041 (Multicenter, open-label, one-arm)	Pelvic pain associated with endometriosis assessed by VAS	VISANNE oral once daily	52 weeks	168 (87 previously treated with VISANNE and 81 previously treated with placebo in Study 307041)	31.9 (18-46)

Table 5 – Summary of Pivotal Studies for the Management of Pelvic Pain Associated With Endometriosis With VISANNE (Dienogest 2 mg)

Report (Study) / Phase (Study Design)	Primary Endpoint	Treatment Regimen	Treatment Duration	No. of Patients (Full Analysis Set)	Mean Age (Years)
AU19 (97085) / phase 3 (Multicenter, open-label, randomized, active-controlled, parallel-group)	Pelvic pain associated with endometriosis assessed by VAS	VISANNE oral once daily Leuprorelin acetate 3.75 mg intramuscular every 4 weeks	24 weeks	120 128	30.6 (18-47) 31.0 (18-45)

Abbreviations: VAS = visual analog scale
a Pain medication allowed ibuprofen tablets up to 1,200 mg/day

Study Results

Pelvic Pain Associated With Endometriosis - Studies 307041, 307059, 97085

Treatment with VISANNE produced clinically significant reductions in pelvic pain from baseline in all 3 pivotal studies.

Study 307041

Superiority of VISANNE over placebo was demonstrated in the placebo-controlled trial (Study 307041). The mean reduction in VAS score with VISANNE was more pronounced and statistically significant in comparison to placebo (difference = 12.3 mm; 95% CI = 6.4-18.1; $P < 0.0001$). After 3 months of treatment with VISANNE, the mean reduction of pain compared to baseline was 27.4 ± 22.9 mm. Pain improvement was not related to the use of pain medication which actually decreased over time (see Table 6).

Reduction of pelvic pain by at least 50% without a relevant increase of concomitant pain medication was achieved in 32.4% of patients on VISANNE (placebo: 13.5%); a reduction by at least 75% without a relevant increase in pain medication was achieved in 18.6% of patients on VISANNE (placebo: 5.2%).

Table 6 – Results for Study 307041, Comparison of VISANNE and Placebo for the Management of Pelvic Pain Associated With Endometriosis, Determined by VAS (mm) and Intake of Pain Medication (Number of Tablets)[a] Over 12 Weeks (Full Analysis Set)

	VISANNE N=102 mean ± SD	**Placebo N=96 mean ± SD**
VAS Baseline	56.8 ± 18.0	57.0 ± 17.8
VAS week 4	41.2 ± 22.0	50.8 ± 19.6
VAS week 8	30.6 ± 20.6	44.2 ± 20.5
VAS week 12	27.6 ± 20.4	39.4 ± 22.1
Difference: week 12 *minus* baseline, LOCF[b]	-27.4 ± 22.9	-15.1 ± 16.4
Difference between treatments: VAS (placebo *minus* VISANNE)	**12.272[c]**	
P-value (95% CI)	*P*<0.0001 (6.403 to 18.140)	
Pain medication at baseline[a]	9.9 ± 7.4	9.4 ± 8.6
Pain medication at week 12[a]	5.5 ± 5.8	5.7 ± 5.8
Difference: week 12 *minus* baseline, LOCF[b]	-4.4 ± 6.4	-3.7 ± 8.2
Difference between treatments: intake of pain medication (placebo *minus* VISANNE)	**0.741[c]**	
P-value (95% CI)	*P*=ns (-1.412 to 2.895)	

Abbreviations: VAS = visual analog scale, 100 mm, LOCF = last observation carried forward, N = number of patients, SD = standard deviation, CI = confidence interval, ns = not significant

a Cumulative number of tablets for the preceding 28 days.

b Negative difference reflects improvement from baseline.

c Positive value reflects difference in favor of VISANNE.

Note: Statistical analysis according to testing procedure described by Roehmel et al. 2006. (17)

Study 307059

The open label extension to the placebo-controlled trial showed continued improvement of pelvic pain associated with endometriosis for treatment up to 15 months duration (mean reduction at end of treatment = 41.9 ± 19.7 mm after 3 months treatment with placebo plus 12 months treatment with VISANNE and 44.2 ± 23.3 mm after 15 months treatment with VISANNE) (see Table 7).

Table 7– Results of Study 307059, Time Course of Pelvic Pain Associated With Endometriosis Assessed by VAS (mm) Over 64 Weeks (Historic Data From Study 307041 for 12 Weeks and Data During Extension Study 307059 for 52 Weeks) (Full Analysis Set)

	Previous Treatment: VISANNE N=87 VAS(mm) Mean ± SD	**Previous Treatment: Placebo N=81 VAS (mm) Mean ± SD**
Study 307041		
Baseline	56.4 ± 17.8	57.5 ± 16.7
Week 4	42.7 ± 21.9	52.0 ± 18.7
Week 8	31.4 ± 20.8	45.3 ± 19.6
Week 12[a]	27.9 ± 20.2	40.7 ± 21.1
Study 307059		
Baseline	27.9 ± 20.2	40.7 ± 21.1
Week 4	25.6 ± 18.8	35.4 ± 20.7
Week 16	19.2 ± 14.3	24.5 ± 16.1
Week 28	16.1 ± 13.4	19.5 ± 12.6
Week 40	13.1 ± 9.9	14.8 ± 10.9
Week 52	9.7 ± 7.4	13.5 ± 14.1
Change Week 12: start of Study 307041 to end of Study 307041	-28.5 ± 24.7	-16.7 ± 16.3
Change Week 52: end of Study 307041 to end of Study 307059	-17.0 ± 20.4	-25.6 ± 22.2
Change Week 64: start of Study 307041 to end of Study 307059	-44.2 ± 23.3	-41.9 ± 19.7

Abbreviations: N = number of patients, VAS = visual analog scale, SD = standard deviation, mm = millimeter
a Equivalent to baseline value for extension Study 307059

Study 97085

In the pivotal Study 97085 the efficacy of VISANNE was compared to the gonadotropin releasing hormone (GnRH) analog leuprorelin acetate in 120 patients. VISANNE demonstrated efficacy similar to leuprorelin acetate in the reduction of pelvic pain associated with endometriosis ($P < 0.0001$ for non-inferiority). After 6 months of treatment, similar reductions of pain were observed in both treatment groups (VISANNE: 47.5 ± 28.8 mm, leuprorelin acetate: 46.0 ± 24.8 mm) (see Table 8).

After 6 months of treatment, reduction of pelvic pain associated with endometriosis by 50% or more was achieved in 82.2% of patients treated with VISANNE (leuprorelin acetate: 85.4%); a reduction by 75% or more was achieved in 74.4% of patients treated with VISANNE (leuprorelin acetate: 69.8%).

Table 8– Results of Study 97085, Comparison Between VISANNE and Leuprorelin Acetate in the Management of Pelvic Pain Associated With Endometriosis, Determined by VAS (mm) Over 24 Weeks

	PPS		FAS	
	VISANNE N=90 VAS (mm) Mean ± SD	**Leuprorelin acetate N=96 VAS (mm) Mean ± SD**	**VISANNE N=118 VAS (mm) Mean ± SD**	**Leuprorelin acetate N=127 VAS (mm) Mean ± SD**
VAS baseline	60.2 ± 24.2	57.9 ± 21.0	53.3 ± 29.1	55.4 ± 24.2
Week 4	35.7 ± 23.7	32.6 ± 27.0	32.7 ± 24.7	31.5 ± 27.8
Week 8	24.2 ± 22.5	21.7 ± 23.0	22.1 ± 22.3	20.2 ± 22.5
Week 12	19.7 ± 23.2	18.7 ± 23.0	18.0 ± 22.5	17.9 ± 22.5
Week 16	16.2 ± 20.2	14.6 ± 19.5	15.6 ± 20.2	14.3 ± 19.5
Week 20	12.5 ± 18.0	12.8 ± 19.0	12.2 ± 18.3	14.4 ± 21.5
Week 24	12.7 ± 20.3	11.9 ± 16.9	12.1 ± 19.9	13.0 ± 19.4
Difference: week 24 *minus* baseline[a]	-47.5 ± 28.8	-46.0 ± 24.8	-40.2 ± 32.0	-41.8 ± 28.6
Difference between treatments (VISANNE *minus* leuprorelin acetate)[b]	**-1.50**		**1.58**	
P-value (one-sided for noninferiority) (95% CI)	*P* < 0.0001 (-9.25 to 6.25)		*P* = 0.0004 (-6.41 to 9.58)	

Abbreviations: PPS = per protocol set, FAS = full analysis set, VAS = visual analog scale, mm = millimetre, SD = standard deviation, N = number of patients, CI = confidence interval

a Negative difference reflects improvement

b Negative value in favor of VISANNE, positive value in favor of leuprorelin acetate.

Pelvic Pain Associated With Endometriosis in Adolescents - Study 13788

Study 13788

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).

The study showed continued improvement of pelvic pain associated with endometriosis. At baseline, the mean VAS for pelvic pain associated with endometriosis was 64.3 ± 19.1 mm. After 4 and 8 weeks of treatment, the mean VAS had decreased by 28.2 ± 29.5 mm and by 39.0 ± 32.1 mm, respectively, compared to baseline. Thereafter, further decreases were slower, and reached a minimum score at week 48 with a mean of 9.0 ± 13.9 mm (change from baseline -56.3 ± 25.5 mm). The end of treatment score was 12.1 ± 19.1 mm (change from baseline -53.0 ± 28.2 mm).

After 24 weeks of treatment, reduction of pelvic pain associated with endometriosis of at least 30% in the VAS was achieved in 81% of patients treated with VISANNE.

DETAILED PHARMACOLOGY

Animal Pharmacology

Primary Pharmacodynamics

Dienogest showed a low binding affinity to the uterine progesterone receptor in rats. Compared to progesterone, the relative binding affinity of dienogest was less than 20%. In human uterine cytosol, the relative binding affinity of dienogest to the progesterone receptor was about one order of magnitude less than that of progesterone.

The progesterone receptor mediated activity (alkaline phosphatase induction) of dienogest was tested in human breast carcinoma T47D cells and revealed a 2-fold weaker progestogenic activity than progesterone.

In bonnet monkeys, dienogest effectively blocked ovulation from the lowest tested dose of 0.3 mg/kg/day and higher when given subcutaneously. Equally strong effects on menstrual cycling and/or inhibition of ovulation were observed in the repeated-dose toxicity studies in other monkey species after oral dosing.

Effects of dienogest on the differentiation and proliferation of human endometrial stroma cells were assessed in vitro. Dienogest induced a dose-dependent inhibition of cell proliferation in the presence of estradiol. Changes typical of decidualization were observed. The antiprogestin RU-486 antagonized the effects of dienogest. (11) Dienogest statistically significantly reduced proliferation of endometriotic stromal cells isolated from human endometriotic lesions. (18)

The influence of dienogest on experimental endometriosis in rats revealed a reduced endometrial implant volume at oral doses ≥ 0.1 mg/kg of dienogest without affecting bone mineral density. A 100 mg/kg dose of danazol had a comparable effect on the endometrial implants but also decreased the bone mineral density. (19)

In contrast to some other progestins, dienogest was unable to maintain pregnancy in rats ovariectomized on day 3 of pregnancy. In rabbits, pregnancy was maintained at low dosages of dienogest, indicating that rabbits are very sensitive to the progestational activities of dienogest.

Antiandrogenic, Androgenic and Anabolic Activities

Dienogest possesses antiandrogenic activities. In the Hershberger assay in rats, dienogest showed clear antiandrogenic properties. (20) The antiandrogenic potency of dienogest was 40% that of cyproterone acetate. (21)

The fertility of male mice and male rabbits was reduced dose-dependently by dienogest.

Unlike other 19-nortestosterone derivatives, dienogest has no androgenic activity.

Antiprogestational Activities

Dienogest, itself, has no antiprogestogenic activity, but the major rodent plasma metabolite aromatic dienogest has antiprogestogenic activity. Therefore, in rodents dienogest can also act as an antiprogestin when given orally or subcutaneously. This finding of antiprogestogenic activity has no relevance for primates as this aromatic metabolite does not occur in relevant amounts in monkey or human plasma.

Estrogenic and Antiestrogenic Activities

Dienogest does not bind to the estrogen receptor. In a transactivation assay in the human breast cancer cell line MCF-7/2A, dienogest did not induce estrogen receptor-dependent transactivation.

Dienogest itself has no estrogenic activity, but the major rodent plasma metabolite, aromatic dienogest, has estrogenic activity. Therefore, in rodents, dienogest acts as an estrogen when given orally or subcutaneously. This finding of estrogenicity has no relevance for primates as this aromatic metabolite does not occur in relevant amounts in monkey or human plasma.

Glucocorticoid and Mineralocorticoid Activities

There was only low binding to the glucocorticoid receptor in rat liver and rat thymus and to the mineralocorticoid receptor in rat kidney. (21) Dienogest did not affect hepatic glycogen content in adrenalectomized rats. Dienogest-medicated rats failed to exhibit any changes in either urine volume or the urinary Na/K ratio, even when the dose was as high as 100 mg/kg orally. This indicates no glucocorticoid or mineralocorticoid activity. (20)

Summary of Endocrinological Activities

Competition experiments were performed with several receptors and ligands. Dienogest exhibited only low binding to the mineralocorticoid and the estrogen receptors. There was a slight binding to the androgen and the glucocorticoid receptors.

The conclusion drawn from the detailed endocrinological characterization of dienogest is that this drug substance has a potent progestational activity on the endometrium and a medium antigonadotrophic activity. A moderate antiandrogenic activity was observed in rats and mice. The estrogenic activity of dienogest observed in rats and mice was considered to represent a species-specific response related to the presence of an aromatic dienogest metabolite that occurs only in these species.

General Pharmacodynamics

In rats, dienogest did not influence general symptoms and behavior at doses up to 30 mg/kg. Effects on the central nervous system in mice, rats, and rabbits revealed effective doses after oral or parenteral administration as high as 100 mg/kg, with the exception of a slight decrease in body temperature in mice which was observed after 10 mg/kg injected intraperitoneally.

Some temporary effects of dienogest on body temperature or kidney function in rats were noted at lower doses (≥ 10 mg/kg), which are at least 2 orders of magnitude above the intended therapeutic dose in humans.

Cardiovascular effects of dienogest were studied in vitro on the isolated heart atrium of rats and guinea pigs and revealed changes of spontaneous contraction parameters only at high concentrations of about 3 x 10^{-4} mol/L. In vivo studies in rabbits did not reveal effects on blood pressure, heart rate, blood flow, arterial oxygen partial pressure, arterial carbon dioxide pressure, and ECG after intraduodenally administered dienogest at a dose of 30 mg/kg. In addition, studies to investigate particular cardiovascular effects on the duration of the action potential in isolated papillary muscles of guinea pigs did not show effects on action potential parameters up to a dienogest concentration of 10^{-5} mol/L. The effect of dienogest on the human hERG potassium channel was also investigated. Dienogest was tested at concentrations of 10^{-6} mol/L, 10^{-5} mol/L and 10^{-4} mol/L. The outward current amplitudes of the hERG-mediated potassium current were not significantly reduced during application of 10^{-6} mol/L and 10^{-5} mol/L. At a concentration of 10^{-4} mol/L dienogest showed a significant but reversible current reduction.

In vivo, in conscious monkeys, ECG parameters (PR interval, QRS widths, or QT interval) were not affected by oral administration of dienogest up to a dose of 30 mg/kg. The measurement of blood pressure and heart rate did not reveal any effects.

Effects on the autonomic and somatic nervous system were studied in vitro and revealed changes related to dienogest treatment only at high concentrations in the 10^{-4} mol/L range.

Safety pharmacology studies with dienogest concluded that compound-related changes were observed for the majority of investigated parameters only at very high doses (≥ 30 mg/kg) or at dienogest in vitro concentrations in the 10^{-4} mol/L range. In humans, a maximum concentration of about 80 ng/mL of dienogest in blood plasma (ca 2 x 10^{-7} mol/L) was determined during clinical studies. Therefore, no impact of dienogest on cardiovascular or ECG parameters in humans is expected in the therapeutic range.

Human Pharmacology

Pharmacodynamics

Dienogest reduces 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 hyperprogestogenic and moderately hypoestrogenic endocrine environment causing decidualization of endometrial tissue.

In addition to the estradiol-mediated effects dienogest also has direct antiproliferative, immunologic and antiangiogenic effects that contribute to the reduction of endometriosis-associated symptoms. (11-13)

Ovulation is inhibited at a daily dose of 2 mg but ovarian activity is not completely suppressed. Circulating estradiol levels during treatment with 2 mg dienogest/day are similar to those in the early follicular phase of the menstrual cycle. Clinical studies have not shown signs and

symptoms of a hypoestrogenic state in women using VISANNE. In particular, 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. (16)

The use of VISANNE 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 the start of treatment 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 that after cessation of treatment, BMD increased towards pre-treatment levels in these patients.

The menstrual cycle returns to pretreatment characteristics within 2 months after cessation of treatment with VISANNE.

Pharmacokinetics

Absorption and Bioavailability

Pharmacokinetic studies have shown that orally administered dienogest is rapidly and almost completely absorbed. The absolute bioavailability of dienogest from a film-coated, gelatin-containing tablet formulation was determined to be 90.6%. Maximum dienogest concentrations in serum or plasma were observed on average 1 to 2 hours after oral administration. Post-maximum dienogest concentrations declined biphasically with mean terminal half-lives of about 8 to 10 hours.

Pharmacokinetic dose linearity was observed in young Caucasian women following single oral administration of 1 to 8 mg dienogest. The observed C_{max} and AUC values were proportional to the administered dose.

After repeated administration of dienogest, only minimal accumulation was observed and neither the time to maximum nor the terminal half-life were altered compared to single-dose administration. In a combined single-multiple dose study in 16 young women, it could be shown that steady state was reached after 4 days of treatment and that the pharmacokinetics of dienogest after multiple dosing is predictable from single-dose pharmacokinetics as indicated by $AUC_{(0\text{-}24h)steady\ state}/AUC_{single\ dose}$ ratio of 1.03.

Distribution

A 10% fraction of circulating dienogest is present in the free form with approximately 90% being bound nonspecifically to albumin. (22) Dienogest does not bind to the specific transport proteins SHBG and CBG. (20) Thus, the pharmacokinetics of dienogest are not influenced by changes of SHBG or CBG concentrations and displacement of testosterone from SHBG or cortisol from CBG by dienogest is unlikely.

The volume of distribution at steady state (V_{ss}) of dienogest was 46 L after the intravenous administration of 85 µg ^{3}H-dienogest.

Metabolism

Studies in women with ^{3}H-labelled dienogest showed that the main fraction of radioactivity in plasma represented unchanged dienogest. In the first 24 hours after oral administration of 0.1 mg dienogest/kg body weight (bw) to women, about 60% of the total radioactivity in plasma represented the parent compound and no major peak was found besides unchanged dienogest.

Dienogest is extensively metabolized in humans by phase I reactions. In women only about 6% to 8% of the parent compound was renally excreted as unchanged or conjugated dienogest. The most prominent phase-I metabolites in human urine were hydroxylated metabolites, mainly 6β-OH-DNG, 1α-OH-DNG and 11β-OH-DNG. All other metabolites were minor in quantity. In plasma the main metabolite is 6β-OH-DNG; 4 other metabolites formed in humans are represented in plasma only to a minor extent.

CYP3A4 was found to be the most relevant CYP isoform for the metabolism of dienogest.

Overall, the metabolite pattern in humans was similar to that in monkeys and mice and, to a lesser extent, that in rats and dogs.

Pharmacological Activity of the Metabolites

Based on in vitro receptor binding and transactivation assays, none of the metabolites formed in humans is expected to exhibit direct steroid hormone-receptor-related pharmacological effects in vivo. Dienogest is not a prodrug and its pharmacologic activity does not depend on transformation into active metabolites.

Excretion

Dienogest is extensively metabolized and only trace amounts are excreted unchanged. The main route of excretion in women as well as in female rats, monkeys and rabbits is via urine. Excretion is fast and largely complete after 5 to 6 days.

The renal elimination half-life of total radioactivity after oral administration of 0.1 mg/kg bw was 14.4 ± 2.4 hours. The ratio of renal to fecal elimination was 6.7 after an oral dose of 101 µg (dienogest/volunteer, 5.4 after an IV dose of about 80 µg dienogest/volunteer and 3.2 after an oral dose of 0.1 mg/kg bw).

Special Populations

Race

No clinically relevant interethnic differences among Caucasian and Japanese patients were observed regarding pharmacokinetics and pharmacodynamics.

TOXICOLOGY

Acute Toxicity

Single-dose toxicity studies were conducted in several species including mice, rabbits, rats, and dogs. All of the studies revealed a very low toxicity of dienogest after single oral or parenteral administration. Nonlethal doses were between 1000 and 4000 mg/kg with the exception of male rabbits where it was below but close to 1000 mg/kg. Toxic signs observed at high doses were central depression in mice, none in rats, anorexia, weight loss, convulsions in rabbits, and a transient increase in GPT in dogs without histopathological findings.

Repeated-Dose Toxicity

Repeated-dose systemic toxicology studies of dienogest were conducted for various durations up to 13 weeks in mice, 12 months in rats, 6 months in dogs, and up to 12 months in monkeys.

In general, the principle findings observed in all studies were pharmacological or exaggerated pharmacological effects associated with the repeated administration of high dose levels of a progestogenic compound to laboratory animals.

In mice, dienogest was well tolerated when given orally at dose levels up to 125 mg/kg/day for 13 weeks. Principle changes were pharmacological in nature (lower uterus and cervix weights at dose levels of 25 mg/kg/day and higher ovary and lower seminal vesicle weights at dose levels of 125 mg/kg/day). At the high-dose level (125 mg/kg/day), increased absolute and relative liver weights were observed in male and female mice and were accompanied by periacinar hepatocyte hypertrophy in males. When given at a dose of 60 mg/kg to female mice, a depression of body weight gain and of hematopoiesis were the major additional findings. Toxicokinetic studies in mice were performed first in a separate 5-day study as well as in the 13-week study after the 60 mg/kg dose and later during the carcinogenicity study in this species. Up to an 18-fold multiple of human exposure to dienogest was studied in this species in terms of $AUC_{(0\text{-}24h)}$.

Repeated-dose systemic toxicity studies were conducted in female rats for 3, 6, and 12 months. In these studies, dienogest was well tolerated and not lethal when orally administered daily for 3 months at dose levels up to 30 mg/kg or for 6 and 12 months at doses up to 10 mg/kg/day. In the 3-month study, 3.0 mg/kg/day was identified as the NOAEL. In the 12-month study, 1.0 mg/kg/day was identified as the NOAEL. Body weights were unaffected in the 3-month study in animals given doses as high as 30 mg/kg/day, but were 9% and 12% higher than controls after daily oral administration of 0.1 and 1.0 mg/kg/day, respectively, for 12 months. Compared with controls, changes observed across the rat studies were predominantly pharmacological in nature and included persistent diestrus (30 mg/kg/day), lower average serum total cholesterol (≥ 3 mg/kg) and alanine and/or aspartate aminotransferase values (≥ 10 mg/kg/day), slightly higher serum triglyceride and nonesterified fatty acid values (≥ 0.1 mg/kg/day), alterations in coagulation parameters (higher platelet counts, fibrinogen values or longer prothrombin times after administration of doses ≥ 10 mg/kg), higher absolute and relative liver weights (≥ 1.0 mg/kg/day), and microscopic changes in target organs (ovaries, uterus and vagina) at most dose levels ≥ 1.0 mg/kg/day. Slightly lower erythrocytic parameters (typically erythrocyte counts, hemoglobin, and hematocrit), compared with controls were also observed in some of the studies. Microscopic liver changes including basophilic foci of cellular

alteration, periportal fat deposition, and vacuolated hepatocytes were observed after oral administration of 10 mg/kg/day for 12 months. The liver changes seen only in this chronic study most likely reflect earlier onset of age-related changes in female rats, and similar findings have been described after high dose levels of progestins were administered in chronic toxicity studies in rodents. Toxicokinetic investigations showed that up to a 29-fold multiple of human exposure to dienogest was achieved in the 3-month studies in female rats and a 12-fold exposure was achieved in the pivotal 1-year study in terms of multiples of $AUC_{(0-24h)}$.

In another non-GLP, supportive study, dienogest or levonorgestrel was administered to rabbits in their daily diet for 19 to 20 months at concentrations intended to deliver 0.14 or 0.70 mg/day. No intrinsic organ toxicity was observed following dietary administration of dienogest or levonorgestrel. In general, changes observed were limited to pharmacologic or exaggerated pharmacologic effects of progestins.

Dienogest was orally administered to female Beagle dogs in 3 studies. In the first supportive study, dienogest was administered as powder in gelatin capsules once daily for 1 month at doses of 0.1 to 10 mg/kg/day. In the second study, dienogest, as a liquid suspension in gelatin capsules, was administered once daily for 3 months at doses of 0.3 to 3.0 mg/kg/day. In a second supportive study, dienogest was administered as coated tablets once daily for 6 months at doses of 0.01 to 1 mg/kg/day. In general, dienogest was well tolerated and nonlethal. Pharmacological changes observed in the female dogs included slight increases in body weight, enlargement of the mammary gland accompanied microscopically by lobular hyperplasia, and histopathological changes in the ovaries, vagina, pituitary, and uterus. Clinical pathology changes included lower-than-control erythrocytic parameters (erythrocyte counts, hemoglobin, hematocrit) which were sometimes accompanied by alterations in lipid parameters and/or alterations in coagulation parameters. Sulfobromophthalein (BSP)-retention showed a slight, dose-dependent increase under dienogest in female animals at the mid- and high-dose level which was prominent in 1 animal in the second BSP test performed during the study. However, there was no morphological correlate in the liver of this dog.

Dienogest was orally administered to female Cynomolgus monkeys, once daily for 13 weeks at dose levels of 0.4, 2.0, and 10.0 mg/kg. Drug-induced cessation of menses occurred at all dose levels. No signs of intolerance or organ toxicity were observed at any dose level tested. $AUC_{(0-24h)}$ values for the high dose (10 mg/kg) in this GLP compliant study were ca 118 times higher than systemic exposure in women administered repeated 2 mg doses of dienogest.

In repeated-dose studies in female Rhesus monkeys, dienogest was orally (intragastrically) administered at dose levels of 0.1, 1, and 10 mg/kg/day for 3 or 12 months. An additional dose level of 0.3 mg/kg/day was also evaluated in the 12-month study. No compound-related mortality, effects on body weight, food consumption, ECG, ophthalmology, or urinalysis parameters were observed in either study. The NOAEL was identified as 1 mg/kg/day. Pharmacological effects, such as cessation of menstruation (all dose levels, and shown to be reversible in the 3-month study), serum biochemistry changes (lower than control alkaline phosphatase values after administration of 10 mg/kg/day), alterations in coagulation parameters (such as increases in fibrinogen and plasminogen activity but without effect on coagulation times or thromboelastograms), and intimal thickening and hypertrophy of the uterus were observed in each study. Furthermore, apart from a 2-fold increase in GPT in a single high-dose monkey and

only in week 4 (as compared to the mean in controls) of the 3-month study, there was no indication of liver toxicity in any of the 3 monkey studies. The highest dose of 10 mg/kg in the pivotal 1-year monkey study resulted in 75 times the human dienogest exposure.

Carcinogenicity

Slightly increased incidences of malignant lymphomas and pituitary adenomas were seen in male mice during a 2-year carcinogenicity study. Female mice showed an increased incidence of uterine stromal polyps at the highest tested dose level. These findings are considered to be related to the weak estrogenic partial activity of dienogest in rodents. In 1 of the 2 rat carcinogenicity studies, there was an increased incidence of pituitary adenomas and fibroepithelial tumors of the mammary gland in male animals. There was no change in tumor incidence in female rats in both studies. These observations do not suggest particular human risks apart from those which are generally assumed for the use of progestogenic compounds.

In vitro studies have shown varied and dose-dependent effects of progestins, including dienogest, on the proliferation of primary human breast cancer cell lines (HCC1500 and MCF-7). These effects appear to differ from those of progesterone. Dienogest alone has not been shown to stimulate cell proliferation in normal breast cell lines (MCF10A), but it demonstrated a minor stimulatory effect on malignant estrogen-receptor positive breast cells (HCC1500). While in vitro findings cannot be extrapolated to in vivo or clinical situations, dienogest is a novel progestin with a distinct pharmacological profile compared to progesterone or other progestins. (23-25)

Reproductive Toxicology

Reproductive toxicity studies with dienogest gave no indication of a teratogenic potential up to embryolethal doses. The inhibition of implantation in rats might be due to an estrogenic effect and the impairment of tubal transport of ova and the postimplantational losses further indicate a disturbance of the endocrine milieu. The fertility of female offspring was impaired after high doses of dienogest given during late pregnancy and lactation. Taken together, the results of reproductive toxicity testing with dienogest do not differentiate this drug from other progestins. (26)

Mutagenesis

Two reverse mutation tests in bacteria (Ames test) were conducted. In both tests, dienogest was negative up to a dose of 5 mg per plate. Furthermore, dienogest in concentrations up to a cytotoxic dose of 500 µg/mL (with and without metabolic activation) did not induce mutations in the TK locus in L5178Y mouse lymphoma cells.

Dienogest also did not induce chromosomal aberrations in Chinese hamster lung cells in culture up to a cytotoxic dose of 110 µg/mL (without metabolic activation) and 220 µg/mL (with metabolic activation). In a chromosomal aberration test in human lymphocytes, dienogest was negative.

Oral doses up to 2 g/kg did not induce micronuclei of polychromatic erythrocytes in the bone marrow of female mice above the control level in 2 studies.

In a rat liver initiation-promotion model in vivo, dienogest did not induce preneoplastic enzyme-altered foci up to a dose of 140 mg/kg for 5 consecutive days followed by treatment with clophen A50 over 11 weeks. In the same test, diethylnitrosamine was clearly positive.

Dienogest did not induce chromosomal aberrations in the bone marrow cells of pregnant baboons or in the lymphocytes of their newborns up to a dose of 1.6 mg dienogest. (27, 28)

A dose of 100 mg/kg dienogest injected intraperitoneally to mice slightly suppressed the incorporation of radioactively labeled thymidine into DNA of the kidney and somewhat more of the liver. However, the difference was not significant at the specified significance limit of 1%.

Other negative tests briefly reported by Schöneich et al (29) included the rec-type repair test with *Proteus mirabilis*, another Ames test, a host-mediated assay with *Salmonella typhimurium* in the rat, the cytogenetic assays with ascites tumor or bone-marrow cells in mice, and a dominant lethal test with male and female mice. In all tests performed (which exceeded the extent requested by international guidelines), dienogest showed no mutagenic potential.

Additionally, a UDS (unscheduled DNA synthesis) test was conducted in primary hepatocytes of female rats in vitro. Two independent experiments were performed in which freshly isolated hepatocytes were exposed to dienogest for 18 hours in the presence of methyl-^{3}H-thymidine. The uptake of radioactivity was determined by autoradiography. In the first series of experiments, a significant increase in net grains was found with 2 AAF and 10 or 15 µg/mL CMA, but also with the dienogest concentrations evaluated between 1.72 and 220 µg/mL. In the second experiment, 2 AAF was positive, but to a much lesser degree, and dienogest was only positive at the highest concentration of 220 µg/mL, which was slightly cytotoxic. Dienogest showed a weak genotoxic potential only in this UDS test of the female rat. In a second UDS test in male rat hepatocytes, dienogest did not induce UDS at concentrations up to a cytotoxic dose of 250 µg/mL in either of two independent experiments.

To support the evaluation of the above-mentioned UDS results in female rat hepatocytes, an in vivo/in vitro UDS assay in female rats was performed. Dienogest was given orally at extremely high dosages of 2000 mg/kg and 200 mg/kg. The animals were anesthetized and sacrificed by enzymatic liver perfusion 2 and 16 hours after dosing. Primary hepatocyte cultures were established and exposed for 4 hours to methyl-^{3}H-thymidine. The maximal dose of 2000 mg/kg bw corresponds to 60,000-fold of the daily human dienogest dose. Dienogest was considered noneffective in inducing DNA damage, leading to increased repair synthesis in this in vivo/in vitro UDS assay.

Dienogest was tested for its potential to generate DNA adducts in human liver slices after in vitro incubation over 6 hours. After incubation with dienogest or spironolactone, DNA-adduct levels were below or at the level of quantification. No DNA-adducts were observed in any female livers after incubation with dienogest up to concentrations of 5000 ng/mL. In 2 of 3 male livers no adducts were found and in only one liver a very low DNA adduct level ($3.94/10^{9}$ nucleotides) at the limit of quantification was found at an extremely high dienogest concentration of 5000 ng/mL. It was concluded that dienogest did not produce DNA-adducts in human liver slices to a relevant degree.

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PART III: CONSUMER INFORMATION

PrVISANNE®

dienogest

This leaflet is Part 3 of a three-part "Product Monograph" published when VISANNE was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about VISANNE. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

VISANNE is a treatment for the painful symptoms caused by endometriosis in women who have had the first menstrual cycle (menarche).

What it does:

VISANNE works to help reduce pelvic pain associated with endometriosis (endometrium-like tissues outside the uterus which cause a chronic inflammation).

When it should not be used:

You should not use VISANNE if you:

- are pregnant
- are breastfeeding
- are suffering from a medical condition related to a blood clot (thromboembolic disorder). This may occur, for example, in the blood vessels of the legs (deep vein thrombosis) or the lungs (pulmonary embolism).
- have or have ever had a disease affecting the arteries, including cardiovascular disease, such as a heart attack, stroke, or heart disease which causes a reduced blood supply (angina pectoris)
- have diabetes with blood vessel damage
- have or have ever had severe liver disease (and your liver function values have not returned to normal). Symptoms of liver disease may be yellowing of the skin and/or itching of the whole body.
- have or have ever had a benign or malignant liver tumor
- have ever suffered from a malignant tumor such as cancer of the breast or the reproductive organs
- have any unexplained vaginal bleeding
- loss of vision due to blood vessel disease of the eye
- migraine headache
- are allergic to dienogest or any of the other ingredients of VISANNE (see **What the medicinal ingredient is** and **What the nonmedicinal ingredients are**)

If any of these conditions appear for the first time while you are using VISANNE, stop taking it at once and consult your doctor.

What the medicinal ingredient is:

dienogest

What the nonmedicinal ingredients are:

Crospovidone, lactose monohydrate, magnesium stearate, microcrystalline cellulose, potato starch, povidone K 25, and talc.

What dosage forms it comes in:

VISANNE (dienogest) tablets are available in 28 tablet blister packs.

Each white to off-white, round tablet is embossed “B” on one side and contains 2 mg dienogest.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

VISANNE can decrease the bone mineral density (BMD) in adolescent girls (12 to < 18years). This effect may not be completely reversible once treatment is stopped.

Effects on BMD may be greater with increasing duration of use. It is unknown if the use of VISANNE during adolescence will reduce peak bone mass and increase the risk of developing osteoporosis (brittle bones).

The risks and benefits of this treatment in adolescents should be re-evaluated on a regular basis.

Before starting VISANNE, you must be sure that you are not pregnant and must stop taking any form of birth control that contains hormones such as the pill, patch, intrauterine system, injection, or ring.

While using VISANNE you must use a nonhormonal birth control method such as condoms or a diaphragm. DO NOT use any form of birth control that contains hormones.

VISANNE is not a birth control method and will not prevent pregnancy.

VISANNE should not be used in women who have not had their first menstrual cycle.

Cigarette smoking increases the risk of serious adverse effects on the heart and blood vessels. Smoking may also increase adverse effects on bone density. You should not smoke while taking VISANNE.

BEFORE you use VISANNE, talk to your doctor or pharmacist if you:

- have ever had a medical condition related to a blood clot (thromboembolic disorder) or anyone in your immediate family has had a blood clot at a relatively early age
- have a close relative who has had breast cancer
- suffer or have suffered from depression
- have uncontrolled high blood pressure
- have a history of liver disease. Symptoms may include yellowing of the skin or eyes or itching all over your body. Inform your doctor also if such symptoms occurred during a previous pregnancy.
- have diabetes or had diabetes temporarily during a previous pregnancy
- have ever had chloasma (golden-brown patches on the skin, particularly on the face)
- have lactose intolerance. VISANNE tablets contain lactose.

<u>The Risks of Using VISANNE</u>

1. Circulatory Disorder (including blood clots in the legs, lungs, heart, eyes, or brain)

Some studies have suggested that women who use progestin-only medications might have a slightly higher risk of blood clots; however, the results are not certain. You should discuss risk factors for blood clots with your doctor.

Be alert for the following symptoms and signs of serious adverse effects associated with blood clots. Call your doctor immediately if they occur:

- Sharp pain in the chest, coughing blood, or sudden shortness of breath.
- Pain and/or swelling in the calf.
- Crushing chest pain or heaviness.
- Sudden, severe, or worsening headache or vomiting, dizziness or fainting, disturbances of vision or speech, or weakness or numbness in an arm or leg.
- Sudden partial or complete loss of vision.

2. Breast Cancer

The most significant risk factors for breast cancer are increasing age and a strong history of breast cancer in the family (mother or sister). Other established risk factors include onset of menstrual periods before age 12 years, never having children, having your first full-term pregnancy after the age of 30 years, never having breastfed a child, and daily alcohol consumption.

Some studies have shown that the risk of developing breast cancer does not appear to be increased by using progestin-only therapies like VISANNE. However, more thorough studies are needed to confirm that there is no increased risk. You should also discuss breast self-examination with your doctor and report any breast lumps. A yearly breast examination by a health care professional is recommended for all women.

3. Diabetes

Patients with diabetes who use VISANNE should have their blood glucose levels closely monitored.

4. Ectopic Pregnancy

If you become pregnant while taking VISANNE, you are at a slightly increased risk of having an ectopic pregnancy (the embryo develops outside the womb). Before you start taking VISANNE, tell your doctor if you had an ectopic pregnancy in the past or have an impaired function of the fallopian tubes.

5. Liver Tumors

In rare cases, benign liver tumors, and in even fewer cases malignant liver tumors, have been reported in women taking hormones. Contact your doctor if you have unusually severe stomach pain.

6. Changes in Bone Mineral Density

The long-term use of VISANNE may decrease the bone mineral density of adolescents (12 to < 18 years) and, therefore, your doctor will carefully weigh the benefits of using VISANNE against other potential risks for bone loss. Your doctor may decide that your bone mineral density should be monitored.

If you use VISANNE, it will help your bones if you engage in regular weight-bearing exercise and have a healthy diet, including an adequate intake of calcium (e.g. in dairy products) and vitamin D (e.g. in oily fish such as salmon).

INTERACTIONS WITH THIS MEDICATION

Some medicines may interact with VISANNE. Let your healthcare professional know what other medicines you are taking.

Drugs that may interact with VISANNE include:

- Antifungals (eg, ketoconazole, itraconazole, fluconazole, voriconazole),
- Antibiotics (eg, erythromycin, clarithromycin, rifampicin)
- Anticonvulsants (eg, phenytoin, primidone, carbamazepine)
- Antacids (eg, cimetidine, ranitidine)
- Blood pressure medication (eg, diltiazem, verapamil)
- Drugs used for the treatment of HIV/Hepatitis C Virus infections (eg, ritonavir, saquinavir, indinavir, nelfinavir, boceprevir)

Herbal or food products that may interact with VISANNE include:

- St. John's wort
- Grapefruit juice

See also **ABOUT THIS MEDICATION**: When it should not be used, and **SIDE EFFECTS AND WHAT TO DO ABOUT THEM**.

PROPER USE OF THIS MEDICATION

Usual dose

One tablet should be swallowed daily, preferably at the same time, with some liquid as needed. VISANNE can be taken with or without food.

Overdose

In cases of drug overdose talk to your doctor, or a poison control centre, or go to the emergency room of a hospital near you.

Missed Dose

VISANNE will be less effective if you miss a tablet or have vomiting or diarrhea. If you miss one or more tablets or in case of vomiting or diarrhea within 3-4 hours of taking a tablet, take a tablet as soon as you remember and then continue taking the tablet the next day at your usual time. Do not take more than one tablet per day.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, VISANNE can cause side effects. These effects are more common during the first months after you start VISANNE and usually disappear or lessen with continued use. You may also experience changes in your menstrual bleeding pattern, such as spotting, irregular bleeding, or your periods may stop completely. You should consult your physician if your periods become longer or heavier.

Common (may affect up to 1 in 10 users)

- weight gain
- depressed mood, problems sleeping, nervousness, or loss of interest in sex
- headache or migraine
- nausea or abdominal pain
- acne or hair loss
- breast discomfort
- ovarian cyst
- uterine/vaginal bleeding including spotting
- generalized weakness
- irritability

Uncommon (may affect up to 1 in 100 users)

- increase in appetite
- anxiety, depression, changed mood, or mood swings
- disturbed attention
- dry eyes
- ringing in the ears
- palpitations
- diarrhea, constipation, abdominal discomfort, gas, vomiting, inflammation of the stomach and intestines
- dry skin, severe itching of the whole body, brittle nails, dermatitis, light sensitivity or problems with skin pigmentation
- pains in your bones, back pain, muscle spasms, pains and/or a sensation of heaviness in your arms and hands or legs and feet
- urinary tract infection
- vaginal yeast infection, dryness of the genital area, vaginal discharge, pelvic pain, hot flushes, or a lump or lumps in the breast
- swelling due to fluid retention

If any of the side effects become serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom/ Effect		Talk with your doctor or pharmacist		Stop taking drug and seek emergency medical treatment
		Only if severe	In all cases	
Common	Abdominal pain or nausea		✓	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

	Unexpected vaginal bleeding		✓	
Uncommon	Persistent sad mood		✓	
	Breast lump		✓	
	Vomiting		✓	
Rare	Pain or swelling in the leg			✓
	Unusual swelling of the extremities			✓

This is not a complete list of side effects. For any unexpected effects while taking VISANNE, contact your doctor or pharmacist.

HOW TO STORE IT

Store VISANNE in the original packaging between 15°C and 30°C. Keep out of reach of children and pets.

REPORTING SUSPECTED SIDE EFFECTS

Canada Vigilance Program

You can report any suspected adverse reactions associated with the use of heath products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701E
    Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, please contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

For more information, please contact your health professional or pharmacist first, or Bayer Medical Information at 1-800-265-7382 or canada.medinfo@bayer.com.

This document plus the full product monograph, prepared for health professionals can be found at http://www.bayer.ca or by contacting the manufacturer at the above-mentioned phone number and email address.

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