1. NAME OF THE MEDICINAL PRODUCT

Visanne 2 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2 mg dienogest.
Excipients: each tablet contains 63mg lactose monohydrate.

For a full list of excipients, see section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Tablet

White to off-white, round, flat-faced, bevelled-edge tablets, marked with the letter with a "B" on one side and a diameter of 7 mm.

4. CLINICAL PARTICULARS

4.1 Indication(s)

Treatment of endometriosis.

4.2 Dosage and method of administration

Method of Administration:

For oral use.

Dosage Regimen

Tablet-taking can be started 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 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 complete.

Additional information on special populations

Paediatric population

Visanne is not indicated in children prior to menarche.

The efficacy of Visanne has been demonstrated in the treatment of endometriosis – associated pelvic pain in adolescent patients (12-18 years), with an overall favorable safety and tolerability profile.

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

Loss of BMD is of particular concern during adolescence and early adulthood, a critical period of bone accretion. It is unknown if BMD decrease in this population will reduce peak bone mass and increase the risk for fracture in later life.

Therefore, the treating physician should weigh the benefits of Visanne against the possible risks of use in each individual adolescent patient (see sections 'Special warnings and precautions for use', 'Pharmacodynamic properties'). If clinically warranted, BMD may be monitored and the results used in the risk-benefit assessment of use of Visanne.

Geriatric population

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 (see section Contraindications).

Patients with renal impairment

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

4.3 Contraindications

Visanne should not be used in the presence of any 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.

- Active venous thromboembolic disorder
- Arterial and cardiovascular disease, present or in history (e.g. 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 vaginal bleeding
- Hypersensitivity to the active substance or to any of the excipients

4.4 Special warnings and precautions for use

Before starting Visanne treatment, pregnancy must be excluded (see 'Pregnancy and Lactation'). During treatment, patients are advised to use non-hormonal methods of contraception (e.g. barrier method) if contraception is required.

Pregnancies that occur among users of progestogen-only preparations used for contraception (eg. 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 for an association between progestogen-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 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 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 case of long-term immobilization 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 remobilization.

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

Treatment should be stopped at once if there are symptoms of an arterial or venous thrombotic event or suspicion thereof.

Tumors

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-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. However, for progestogen-only preparations, the evidence is based on much smaller populations of users and so is less conclusive than that for COCs. These studies do not provide evidence for causation. The observed pattern of increased risk may be due to an earlier diagnosis of breast cancer in OC users, the biological

effects of OCs or a combination of both. The breast cancers diagnosed in ever-users tend to be less advanced clinically than the cancers diagnosed in never-users.

In rare cases, benign liver 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. A hepatic tumor should be considered in the differential diagnosis when severe upper abdominal pain, liver enlargement or signs of intra-abdominal hemorrhage occur in women taking Visanne.

Changes in bleeding pattern

Visanne treatment affects the menstrual bleeding pattern in the majority of women (see 'Undesirable 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 anemia (severe in some cases). Discontinuation of Visanne should be considered in such cases.

Changes in Bone Mineral Density (BMD)

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

Loss of BMD is of particular concern during adolescence and early adulthood, a critical period of bone accretion. It is unknown if BMD decrease in this population will reduce peak bone mass and increase the risk for fracture in later life. (see sections 'Pediatric Population' and 'Pharmacodynamic Properties')

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.

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

Other conditions

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.

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

Medical examination

A complete medical history should be taken and a physical and gynecological examination should be performed prior to the initiation or reinstitution of the use of Visanne, guided by the contraindications (see Contraindications) and warnings (see Special warnings and precautions for use), and these should be repeated regularly 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.

4.5 Interaction with other medicinal products and other forms of interaction

Note: The prescribing information of concomitant medications should be consulted to identify potential interactions.

- **Effects of other medicaments on Visanne**

Progestins including dienogest are metabolized 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 drug therapy enzyme induction may be sustained for about 4 weeks.

  The effect of the CYP 3A4 inducer rifampicin was studied in healthy postmenopausal women. Co-administration of rifampicin with estradiol valerate/dienogest tablets led to significant decreases in steady state concentrations and systemic exposures of dienogest. 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**

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 (e.g itraconazole, voriconazole , fluconazole), verapamil, macrolides (e.g clarithromycin, erythromycin), diltiazem and grapefruit juice can increase plasma concentration of the progestin.

  In a study investigating the effect of CYP3A4 inhibitors (ketoconazole, erythromycin) on the combination of Estradiol valerate/dienogest, steady state dienogest plasma levels were increased. Co-administration with the strong inhibitor ketoconazole resulted in a 2.86-fold increase of AUC (0-24h) of dienogest at steady state was increased 1.62-fold. 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 standardized high fat meal did not affect the bioavailability of Visanne.

- **Other forms of interactions**

The use of progestins 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.

4.6 Fertility, pregnancy and lactation

Pregnancy

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

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.

Fertility

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

Visanne was not studied for contraceptive efficacy, but DNG 2 mg has been shown in a study involving 20 women to inhibit ovulation after 1 month of treatment. If contraception is required a non-hormonal method should be used (see section ' Special warnings and precautions for use').

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

4.7 Effects on ability to drive or use machines

Not known.

4.8 Undesirable effects

Undesirable effects are more common during the first months after start of intake of Visanne, and subside with duration of treatment. 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 %).

Table 1, the frequencies of adverse drug reactions (ADRs) by MedDRA system organ classes (MedDRA SOCs) reported with Visanne are summarized in the table below. Within each frequency grouping, undesirable effects are presented in order of decreasing frequency. Frequencies are defined as common (≥1/100 to <1/10) and uncommon (≥1/1000 to <1/100).* The frequencies are based on pooled data of four clinical trials including 332 patients (100.0%).

Table 1: Categorized 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		Anemia
Metabolism and nutrition disorders	Weight increased	Weight decreased Increased appetite
Psychiatric disorders	Depressed mood Sleep disorder Nervousness Loss of libido Mood altered	Anxiety Depression Mood swings
Nervous system disorders	Headache Migraine	Autonomic nervous system imbalance Disturbance in attention
Eye disorders		Dry eye
Ear and labyrinth disorders		Tinnitus
Cardiac disorders		Unspecified circulatory system disorder

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

*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.

Uterine bleeding irregularities

Menstrual bleeding patterns were assessed systematically using patient diaries and were analysed using the WHO 90 days 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%): Amenorrhea (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

%).[1] During the fourth reference period the following bleeding patterns were observed (n=149; 100%): Amenorrhea (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 %).[13] Changes in menstrual bleeding patterns were only occasionally reported as adverse event by the patients (See Table 1).

4.9 Overdose

Acute toxicity studies performed with Visanne did not indicate a risk of acute adverse effects in case of inadvertent intake of a multiple of the daily therapeutic dose. 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 were very well tolerated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Progestogens

ATC code: G03D

Mechanism of action

Dienogest acts on endometriosis by reducing the endogenous production of estradiol and thereby suppressing the trophic effects of estradiol on both the eutopic and ectopic endometrium. When given continuously, dienogest leads to a hypoestrogenic, hypergestagenic endocrine environment causing initial decidualization 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.

Pharmacodynamics effects

Dienogest is a nortestosterone derivative with no androgenic but rather an antiandrogenic activity of approximately one third of that of cyproterone acetate. Dienogest binds to the progesterone receptor of the human uterus with only 10% of the relative affinity of progesterone. Despite its low affinity to the progesterone receptor, dienogest has a strong progestogenic effect in vivo. Dienogest has no significant androgenic, mineralocorticoid or glucocorticoid activity in vivo.

Clinical efficacy and safety

Data on 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 (Δ = 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 ± 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 endometriosis-associated pelvic pain was shown in a 6-month 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 was observed in both treatment groups (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 randomized, double-blind, parallel-group study (n=20 to 23 per dose group) investigated pharmacodynamics effects of four dienogest doses (0.5, 1.0, 2.0, or 3.0mg/day) for a maximum of 72 days. Ovulations were observed in 14% and 4% of women of the 0.5mg and 1mg groups, respectively. No ovulation occurred in the 2mg and 3mg groups. In the 2mg group, ovulation was confirmed in 80% of women within 5 weeks after cessation of therapy. 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)

Data on safety

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

Bone mineral density (BMD) was assessed in 21 adult patients before and after 6 months of treatment and there was no reduction in mean BMD. In a 12-months study involving 111 female adolescents, 103 had BMD measurements. The mean relative change in BMD of the lumbar spine (L2-L4) from baseline was -1.2 %. In a subset of the patients with decreased BMD a follow-up measurement was performed 6 months after end of treatment and showed an increase in BMD towards baseline levels.

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).

Long-term safety

A long-term post-approval observational active surveillance study was conducted to investigate the incidence of first-time occurrence or worsening of clinically relevant depression and occurrence of anemia. A total of 27,840 women with a newly prescribed hormonal therapy for endometriosis were enrolled in the study and followed up for up to 7 years.

A total of 3,023 women started with a prescription for dienogest 2 mg and 3,371 patients started with other approved endometriosis drugs. The overall adjusted hazard ratio for new occurrences of anemia comparing the dienogest patients with the patients on other approved endometriosis drugs was 1.1 (95% CI: 0.4 – 2.6). The adjusted hazard ratio for depression risk comparing dienogest and other approved endometriosis drugs was 1.8 (95% CI: 0.3-9.4). A slightly increased risk of depression in dienogest users compared with users of other approved endometriosis drugs could not be excluded."

The proportion of DNG users reporting "side effects" or "medication ineffective" as reasons for stopping the treatment was higher compared to other approved endometriosis drugs (e.g. Danazol, GnRH-a) and was more comparable to non-approved endometriosis drugs (e.g. CHCs, other progestins).
Overall, it is difficult to interpret the results owing to the heterogeneity of reasons for treatment discontinuation; the large inter-country variance in prescribed endometriosis treatment; the difference between (sub-)cohorts in the indicated duration of use; and in the methods of administration (e.g. injectable three-month Depo which does not allow for immediate discontinuation by the patient).

5.2 Pharmacokinetic properties

- Absorption

Orally administered dienogest is rapidly and almost completely absorbed. Peak serum concentrations of 47 ng/ml are reached at about 1.5 hours after single ingestion. 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 / Biotransformation

Dienogest is completely metabolized 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 / Excretion

Dienogest serum levels decrease in two phases. The terminal disposition phase is characterized by a half-life of approximately 9-10 hours. Dienogest is excreted in form of 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 approximately 86% of the dose administered is eliminated within 6 days, the bulk of this amount excreted within the first 24 h, mostly with the urine.

- 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.

5.3 Preclinical safety data

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Potato Starch
Microcrystalline cellulose (E460)
Povidone K 25 (E1201)
Talc (E553b)
Crospovidone (E1202)
Magnesium stearate (E572)

6.2 Incompatibilities

None.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store below 30°C. Protect from light.

6.5 Nature and contents of container

PVC/Al blister packaged into a hermetic pouch.

6.6 Instructions for use / handling

None.

6.7 Manufacturer:

Bayer Weimar GmbH und. Co. KG
Döbereinerstr. 20,
99427 Weimar Germany

7. Date of Last Revision

14 December 2021

If you would like to report a side effect for any Bayer Pharmaceutical or Consumer Health product, you can do it easily using our online reporting portal: https://safetrack-public.bayer.com/ or scan the QR code available below. Please also remember to seek medical advice directly from your doctor or pharmacist.

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