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Visanne[®] Product Monograph



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Visanne® Product Monograph

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Foreword

Endometriosis is characterized by the presence of functional endometrium-like tissue ('endometriotic lesions') outside the uterus (e.g. on the ovaries and on other pelvic structures). Endometriosis is a prevalent condition that affects approximately 5–10% of reproductive female population. Symptoms typically include recurrent episodes of dysmenorrhea, dyspareunia, and pelvic pain, while sub-fertility or infertility are frequent. The painful and long-lasting symptoms of endometriosis can have a profound, debilitating impact on a woman's quality of life.

A definitive diagnosis of endometriosis based on symptoms alone can be difficult. The typical symptoms are non-specific and similar to those of other conditions which often delays diagnosis by many years. Laparoscopy is the gold standard for definitive diagnosis, but this is an invasive technique that may not be suitable for all patients.

Surgery is a common treatment choice, although recurrence of endometriosis post-operatively is common. Approved medical therapies, such as gonadotropin-releasing hormone agonists, danazol, and certain progestins, may offer symptom relief but are often associated with suboptimal tolerability and safety which limit their long-term use. To reduce the substantial burden of endometriosis, an effective, safe, and well-tolerated medical therapy is required that is suitable for long-term treatment.

Visanne® is a progestin that uniquely combines the pharmacological properties of 19-norprogestins and progesterone derivatives, offering a potent effect on endometrial tissue. Visanne® is the only oral progestin that has been systematically investigated for the treatment of endometriosis through a comprehensive study program. The clinical experience from this program demonstrates that Visanne® provides highly effective pain relief in endometriosis that is comparable to the current efficacy standard (GnRH agonists), combined with a favorable safety and tolerability profile that allows for long-term use.

1. Endometriosis

Endometriosis at a glance

- Endometriosis is a prevalent, chronic, and debilitating condition in women of reproductive age.
- There are many symptoms of endometriosis, with dysmenorrhea and pelvic pain being the most common.
- Accurate and timely diagnosis remains a challenge which can lead to delays in treatment.
- Surgery and a range of medical therapies are available, but no single treatment approach is ideal for all patients.
- To reduce the substantial burden of endometriosis, an effective, safe, and well-tolerated medical therapy is needed that allows for long-term use.

1.1 Epidemiology of endometriosis

Endometriosis can be defined as the presence of endometrium-like tissue ("endometriotic lesions") outside the uterus which induces a chronic inflammatory reaction.¹

Endometriosis is a prevalent condition among women of reproductive age. Although precise estimates are difficult to establish from the literature, in part because of differences in the populations studied and the diagnostic tools used, the prevalence of endometriosis is believed to be 5–10% of the female population. Based on several sources using different methodologies, approximately 5.5 million women in the U.S. and 16 million women in Europe are estimated to be affected by endometriosis.^{2–8}

Endometriosis affects women primarily during their reproductive years. While the peak age for diagnosis is between 25 and 34 years, the onset of disease may be considerably earlier in life. In recent years, endometriosis has increasingly been diagnosed in adolescents.^{9,10} The prevalence of endometriosis is higher in certain groups, such as women with dysmenorrhea (40–60%) and those reporting chronic pelvic pain (75%).^{11–13} All ethnic and social groups of women are affected.

Reflecting the complex causes that are believed to underlie endometriosis, the natural course of the condition is highly variable and difficult to predict for individual women. In most women, however, endometriosis follows a progressive course that is characterized by a worsening of symptoms in the absence of effective treatment.¹⁴ A younger age at symptom onset indicates a more severe disease course.¹⁵

1.2 Diagnosing endometriosis

The most typical symptoms of endometriosis are dysmenorrhea, premenstrual pain, dyspareunia, and diffuse pelvic pain (Table 1).¹⁶ These symptoms are often present together. Endometriosis can also interfere with the functioning of the bowel, bladder, or muscle tissue, depending on the site where the endometriotic lesions develop.

Table 1: Symptoms associated with endometriosis

Most typical symptoms:	Dysmenorrhea
	Premenstrual pain
	Dyspareunia
	Diffuse/chronic pelvic pain
Other symptoms include:	Bowel-associated or bladder-associated symptoms (frequently perimenstrual)
	Back pain
	Chronic fatigue
Note:	A proportion of women with endometriosis are asymptomatic.

Due to the variable presentation of symptoms, there is frequently a delay between the first appearance of symptoms and an accurate diagnosis. An international survey reported that the average delay is 8.3 years.¹⁷

Endometriosis is commonly associated with infertility. Approximately 25–40% of infertile women have endometriosis.¹⁸ Women suffering infertility, but with no or only non-specific symptoms of endometriosis, may first become aware that they have endometriosis after visiting a fertility specialist.

A definitive diagnosis of endometriosis requires laparoscopy, ideally combined with confirmatory histology, to identify the presence of endometriotic lesions.^{1,19} Physicians and patients may, however, agree that it is not appropriate to perform this invasive procedure, with its associated risks, according to the individual circumstances. In this situation, a physician may make a presumptive diagnosis based on the symptoms alone.¹ In the future, new techniques may offer the potential for less invasive diagnosis than offered by laparoscopy, such as the detection of nerve fibers in eutopic endometrium.²⁰

1.3 Current treatment options

There is no permanent cure for endometriosis. The aim of treatment is to alleviate pain and other symptoms, reduce endometriotic lesions and improve the quality of life in affected individuals. A range of medical therapies and surgery—often in combination—are used in the management of endometriosis, but no single treatment approach is ideal for all patients. As noted recently by the American Society for Reproductive Medicine, "Endometriosis should be viewed as a chronic disease that requires a life-long management plan with the goal of maximizing the use of medical treatment and avoiding repeated surgical procedures".¹³ The treatment that is chosen should reflect the particular symptoms or needs of each patient.

Surgical therapies

Surgery is a common treatment option. Surgical intervention, usually performed via laparoscopy, involves excision or ablation of endometriotic lesions, removal of endometriotic cysts, and the division of adhesions, frequently combined with follow up medical therapy. The success of surgical intervention reflects the skill of the practitioner, and recurrence of endometriosis is common (e.g. the 5-year recurrence rate is approximately 40–50%).²¹

Medical therapies

A range of medical therapies may be used in endometriosis. These medications can be categorized into:

- Non-specific therapies that are not specifically approved in endometriosis or are used off-label, including non-steroidal anti-inflammatory drugs (NSAIDs) and combined oral contraceptives (COCs).
- Specific therapies approved for the treatment of endometriosis (e.g. gonadotropin-releasing hormone or GnRH agonists, danazol, and certain progestins).

Notably, few of the approved medications have demonstrated effectiveness in controlled clinical trials, particularly in placebo-controlled studies. Demonstration of significant superiority in placebo-controlled studies represents an important proof of efficacy for a medication in endometriosis because of the large known placebo effect. The Visanne® clinical development program is notable for including dose-range, placebo-controlled, active comparator-controlled, and long-term studies. These studies are described in Chapter 4.

Non-specific therapy

NSAIDs

NSAIDs may provide general, non-specific pain relief in endometriosis. There is no evidence to show whether any individual NSAID is more effective than another.²² A particular concern with the long-term use of NSAIDs is their well-known propensity to cause adverse effects in the gastrointestinal tract.²²

COCs

Although COCs are widely used in clinical practice to treat the symptoms of endometriosis, these agents are not approved for this indication in most countries. Guidelines offer limited guidance on COC regimens in endometriosis because of the lack of solid clinical trial evidence.²³ As a putative mode of action for hormonal therapies in endometriosis is via counteracting the effects of estrogen at the uterus, the inclusion of estrogen in a medication may appear counter-productive. Debate also continues on whether COCs may mask the development of the condition.⁵

Specific therapy

Hormonal therapies

Hormonal therapies induce atrophy of an endometriotic lesion by utilizing its hormonal responsiveness,^{5,24} presumably by suppressing the production of and/or counteracting the effects of endogenous estrogen. Classes of hormonal therapies that are widely approved for use in endometriosis include GnRH agonists, androgens (i.e. danazol) and certain progestins. The list of GnRH agonists and progestins approved for use in endometriosis varies between countries.

GnRH agonists

GnRH agonists are established as a standard therapy for endometriosis because of their high efficacy in pain relief, but their use is limited by adverse effects.^{24,25} GnRH agonists promote atrophy of endometriotic lesions and induce amenorrhea by strongly reducing estrogen production, but these agents consequently give rise to typical symptoms of estrogen deprivation (e.g. hot flushes, vaginal dryness, headache and decreased libido).²⁵ A particular safety concern with GnRH agonists is the acceleration of bone mass loss due to low estrogen levels, which elevates the risk for osteoporosis, and limits the use of GnRH agonists to 6 months in the absence of add-back estrogen therapy.^{12,24} Although add-back therapy can prolong the duration of GnRH therapy, optimal regimens have not been established.^{12,26} In younger women who have not reached maximum bone density, the risk of bone mass loss requires especially careful consideration before GnRH agonists are used.¹

Danazol

Danazol is an androgenic steroid that is effective in treating the symptoms of endometriosis, but its use is limited by the typical adverse effects of androgenic steroids on lipid metabolism and by unpleasant effects that include weight gain, edema, acne, vaginal dryness, hot flushes, oily skin, hirsutism, and liver toxicity.^{24,27} Because of these effects, danazol has largely been superseded by newer agents in many countries.

Progestins

Progestins have been used to treat endometriosis for decades, but most have not been developed for the treatment of endometriosis, and the acceptance of many of these agents as an effective therapy is based on clinical experience without supportive evidence from controlled (especially placebo-controlled) trials. The scarcity of clinical data also hampers the selection of one progestin over another. Dienogest (the active ingredient of Visanne®) is the only oral progestin that has been systematically investigated for the treatment of endometriosis through a comprehensive clinical study program.

Vercellini *et al.*²⁸ reviewed data for progestins in the treatment of symptomatic endometriosis, citing only four randomised controlled trials, and concluded from this evidence that: 'the efficacy of progestins for temporary relief of endometriosis-associated pelvic pain (EAPP) is good and comparable to that of other, less safe treatments'.

Among the few controlled trials performed on progestins, dydrogesterone only at a dose of 60 mg (but not 40 mg) significantly reduced pain, but failed to show an effect on the revised American Fertility Society (rAFS) score compared with placebo.²⁹ Depot medroxyprogesterone acetate (MPA), at a dose of 104 mg or 150 mg every 90 days for 12 months, has demonstrated efficacy equivalent to danazol or GnRH agonists for reducing symptoms.^{30,31} However, for depot MPA, there is a concern that long-term use has an adverse impact on bone mineral density (BMD), while the delay in resumption of ovulation that follows discontinuation of therapy is a contraindication to use in women who wish to conceive in the near future.^{32,33}

A number of progestins are also associated with androgenic effects and weight gain, which can be related to their pharmacological profile (see Chapter 3).^{5,26,32} Among the progestins, Visanne® possesses a unique pharmacological profile which confers characteristics—including anti-androgenic activity and only mild hypoestrogenic effects—that are beneficial for safety and compliance in the treatment of endometriosis (see Chapter 3).

The place of therapies in treatment guidelines

Current treatment approaches in endometriosis vary widely, reflecting both physician and patient preferences. A number of guidelines have been developed with the aim of providing standardized, evidence-based guidance on optimal treatment approaches.

The European Society of Human Reproduction and Endocrinology (ESHRE) guideline for the diagnosis and treatment of endometriosis has been widely adopted.¹ This guideline recommends GnRH agonists, danazol, COCs or progestins as hormonal treatments in women with confirmed endometriosis. For the empirical treatment of symptoms without a definitive diagnosis of endometriosis, COCs or progestins are recommended. The ESHRE guideline (updated online, 2007³⁴) states that progestins "can be considered as a first choice for the treatment of endometriosis because they are as effective in reducing (laparoscopy) scores and pain as danazol or GnRH agonists and have a lower cost and a lower incidence of adverse effects".

2. Visanne®: Specifically Developed to Treat Endometriosis

Visanne® at a glance

- Visanne® is formulated as a tablet containing 2 mg of the active ingredient, dienogest.
- Visanne® has been developed specifically for the treatment of endometriosis through a comprehensive clinical study program.
- The Visanne® study program includes:
 - A dose-range study³⁵
 - A placebo-controlled study³⁶
 - An active comparator-controlled study versus leuprolide acetate (LA)³⁷
 - A long-term, open-label extension study.³⁸
- In preclinical studies, dienogest demonstrates a strong progestational effect, anti-androgenic activity and no mineralocorticoid or glucocorticoid activity *in vivo*.
- Experience from the study program confirms that Visanne® offers an efficacy, safety and tolerability profile that allows for long-term use in endometriosis (see Chapter 4).

2.1 What is Visanne®?

Visanne® is a targeted therapy with a pronounced local endometrial effect that has been developed specifically to treat endometriosis. Visanne® is formulated as a tablet containing 2 mg dienogest to be taken orally, once a day.

2.2 What does Visanne® do?

The active ingredient of Visanne®—dienogest—is a progestin that uniquely combines the pharmacological advantages of 19-norprogestins and progesterone derivatives. Preclinical studies have characterized the pronounced effect of dienogest on the endometrium, which is combined with negligible binding affinities for estrogen, glucocorticoid, and mineralocorticoid receptors.³⁹ A significant characteristic that distinguishes dienogest from danazol and from other agents in the 19-norprogestin class is its lack of clinically relevant androgenic effects.

The Visanne® clinical study program has demonstrated that Visanne® is an effective therapy for relieving pain related to endometriosis, with an efficacy significantly superior to placebo and equivalent to current standard therapy with GnRH agonists. Visanne® also provides substantial lesion reduction, demonstrated by laparoscopic studies. The symptom improvements associated with Visanne® in placebo- and active comparator-controlled trials are accompanied by a favorable safety and tolerability profile. Treatment-related adverse effects are low in frequency, generally mild to moderate in intensity, and associated with low rates of treatment discontinuation. As predicted by its pharmacological profile, Visanne® in clinical trials is not limited by androgenic or hypoestrogenic effects, unlike GnRH agonists (see Chapter 4).

Clinical trial experience in which patients were treated for up to 15 months confirms that Visanne® maintains a favorable safety, tolerability, and efficacy profile. Therefore, Visanne® represents a treatment option for the sustainable alleviation of the painful, debilitating symptoms of endometriosis.

3. Pharmacological Profile of Dienogest

Pharmacology of dienogest at a glance

- Dienogest is a 19-norprogesterin that differs from other 19-norprogestins by possessing a cyanomethyl group instead of an ethinyl group at the 17 α position.
- Dienogest combines the advantages of 19-norprogestins with the benefits of progesterone derivatives.
- Dienogest has a pronounced effect on the endometrium, which underlies its efficacy in endometriosis.
- A significant characteristic of dienogest is its lack of androgenic activity. Rather, dienogest has anti-androgenic activity, unlike other norprogestins, and demonstrates no mineralocorticoid or glucocorticoid activity *in vivo*.
- Inducers or inhibitors of cytochrome P450 3A4 (CYP3A4) may affect the metabolism of progestins, including dienogest.

3.1 Chemistry of dienogest

One Visanne® tablet contains 2 mg of the progestin, dienogest (17 α -cyanomethyl-17 α -hydroxy-estra-4,9(10)-dien-3-one) (Figure 1).

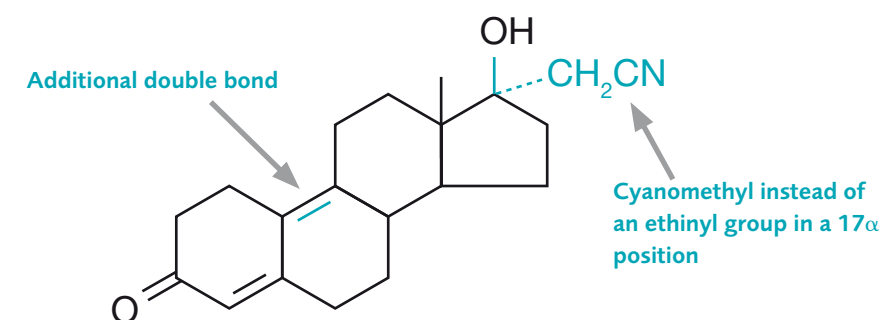


Figure 1: Chemical structure of dienogest.⁴⁰

Dienogest is a 19-norprogesterin that is derived from the steroid 19-nortestosterone.⁴⁰ Dienogest differs from other 19-norprogestins by possessing a cyanomethyl group instead of an ethinyl group at the 17 α position. Through this unique molecular structure, dienogest combines the advantages of the 19-norprogestins (e.g. relatively short plasma half-life of approximately 10 hours, strong progestational effect on the endometrium, and high oral bioavailability >90%) with the benefits of progesterone derivatives (e.g. anti-androgenic activity and relatively moderate inhibition of gonadotropin secretion).^{39,41,42}

A significant characteristic of dienogest is its lack of androgenic activity—despite being related to testosterone.^{40,42} In contrast, many other progestins are characterized by adverse effects that are androgenic in nature. The unique pharmacology of dienogest underlies the favorable efficacy and tolerability profile of Visanne® in the treatment of endometriosis, as described in Chapter 4.

3.2 Formulation of Visanne®

Product description

White to off-white, round, flat-faced, beveled-edge tablets with an embossed 'B' on one side.

Inactive components

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

Package description

Blister packs, each containing 28, 84, or 168 tablets.

3.3 Pharmacokinetic profile of dienogest

Dienogest is almost completely absorbed and shows high bioavailability after oral administration. The half-life of dienogest is relatively short, which translates to almost unchanged serum concentrations after repeated once-a-day administration. The high circulating levels of free dienogest ($\approx 10\%$) explain the extensive penetration of the molecule into different tissues. Elimination is primarily via the kidney.³⁹

Table 2: Pharmacokinetics of dienogest

Absorption	• Rapid and almost completely absorbed after oral administration • Peak serum concentration: 47 ng/ml, reached approximately 1.5 hours after single ingestion • Bioavailability: approximately 91% • Pharmacokinetics: dose-proportional within 1–8 mg dose range • No clinically relevant impact of concomitant intake of food.
Distribution	• Of total serum drug concentration, 10% is present as free steroid and 90% is non-specifically bound to albumin. • Does not bind to SHBG or CBG • Apparent volume of distribution: 40 l
Metabolism	• Dienogest is hydroxylated and conjugated • Major enzyme involved in metabolism: CYP3A4 • Metabolites: - Not endocrinologically active - Excreted very quickly so that unchanged dienogest is the predominant fraction in plasma. - Metabolic clearance rate from serum (Cl/F): 64 ml/min.
Excretion	• Two-phase serum level decrease • Terminal disposition phase half-life: approximately 9–10 hours • Metabolites excreted at a urinary to fecal ratio of about 3:1 after oral administration of 0.1 mg/kg • Half-life of urinary metabolite excretion: 14 hours • Following oral administration, approximately 86% of dose is eliminated within 6 days, the majority excreted within the first 24 hours, mostly in urine.

SHBG, sex hormone binding globulin; CBG, corticoid binding globulin.

Under steady-state conditions, the pharmacokinetics of dienogest are not influenced by sex hormone binding globulin (SHBG) levels. Following daily ingestion, drug serum levels increase by about 1.24-fold, reaching steady-state conditions after 4 days of treatment.

The pharmacokinetics of dienogest after repeated administration can be predicted from the single-dose pharmacokinetics.

Progestins, including dienogest, are metabolized mainly by the CYP3A4 system located in the intestinal mucosa and liver.⁴⁰ Therefore, inducers or inhibitors of CYP3A4 may affect progestin drug metabolism. For further details, please see the Chapter Summary of Product Characteristics.

3.4 Pharmacodynamics of dienogest

3.4.1 Introduction

Progestins may be classified based on their molecular structure and associated functional characteristics. Progesterone derivatives, such as MPA and megestrol acetate, offer a range of progestogenic and androgenic actions. Newer 19-norprogestins (which are not approved in endometriosis) have a strong progestogenic effect on the endometrium, with little androgenic, estrogenic or glucocorticoid activity.⁴³

Dienogest combines the pharmacodynamic advantages of progesterone derivatives with the pharmacological benefits of 19-norprogestins (see Chapter 3.1). In addition, dienogest has anti-androgenic activity, which is approximately one-third that of the progesterone derivative, cyproterone acetate. Dienogest has no mineralocorticoid or glucocorticoid activity *in vivo* (Table 3).

Table 3: Biological activities of progesterone, dienogest, and selected other progestins (Adapted from Schindler *et al.*, 2003⁴⁴)

	Progestogenic activity	Glucocorticoid activity	Androgenic activity	Anti-andro-genic activity	Anti-mineralo-corticoid activity
Progesterone	+	–	–	(+)	+
Dienogest	+	–	–	+	–
Drospirenone	+	–	–	+	+
Levonorgestrel	+	–	+	–	–
Gestodene	+	–	(+)	–	(+)
MPA	+	+	+	–	–
Norgestimate	+	–	(+)	–	–
NETA	+	–	(+)	–	–
Desogestrel	+	–	(+)	–	–
Cyproterone acetate	+	(+)	–	+	–

MPA, medroxyprogesterone acetate; NETA, norethisterone acetate. + = relevant activity; (+) = activity not clinically relevant; – = no activity.



3.4.2 Receptor binding affinities

Dienogest binds to the progesterone receptor with high specificity but with relatively low affinity, at 10% that of progesterone. Despite its low affinity for the progesterone receptor, dienogest has a pronounced progestogenic effect *in vivo* which can be attributed to the high circulating levels of the unbound molecule.³⁹

Dienogest has a low binding affinity for androgen receptors and little or no affinity for estrogen, aldosterone, or glucocorticoid receptors.^{40,42,45} These binding affinities of dienogest are relatively similar to those of progesterone.

3.4.3 Endometrial activity

The potent action of dienogest on endometrial tissue has been demonstrated by assessments of endometrial transformation activity in humans (Kaufmann assay)⁴¹ and rabbits (McPhail test),⁴² and by comparing the individual transformation doses and ovulation inhibition doses of different progestins.⁴⁶ Dienogest demonstrates strong activity on the endometrium relative to its inhibitory effect on ovulation. This characteristic of dienogest results in a higher ratio of ovulation inhibition dose to endometrial transformation dose than for other progestins.^{40,42}

The pronounced endometrial effect of dienogest may also be an explanation for its effective lesion reduction. This has been demonstrated in *in vitro* and animal studies,^{45,47} while the effect of Visanne® on endometrial lesions has been confirmed at laparoscopy in the clinical development program (Köhler *et al.*, 2010;³⁵ see Chapter 4).

3.5 Mechanism of action

Dienogest reduces endometriotic lesions through a number of biological mechanisms.

Dienogest is associated with relatively moderate inhibition of gonadotropin secretion, reducing the endogenous production of estradiol and thereby suppressing the trophic effects of estradiol on both eutopic and ectopic endometrium.^{41,42} When given continuously, dienogest leads to a hypoestrogenic, hypergestagenic endocrine environment, causing initial decidualization of endometrial tissue followed by atrophy of endometriotic lesions. Animal studies indicate that dienogest may additionally reduce plasma estradiol levels by directly inducing apoptosis of granulosa cells in the ovary.⁴⁸

Dienogest also demonstrates a direct inhibitory effect on the proliferation of endometrium-like tissue which is independent of its progestational effects via the progesterone receptor.^{47,49–51}

Other areas of research into the inhibitory actions of dienogest on endometrial cell proliferation have suggested that dienogest modulates the expression of matrix metalloproteinases, which are involved in regulating the response of endometrium-like tissue to estrogen at the paracrine level.³² A further potential mechanism of action explored for dienogest in endometriosis is inhibition of angiogenesis.⁵²

3.6 Effects on ovarian function

Dienogest at 2 mg/day induces an anovulatory state with complete inhibition of ovulation as assessed by Hoogland scores. In addition, mean E2 concentrations were in the range of 20-50 pg/ml showing only moderate suppression of estrogen production.⁵³ In combination with ethinyl estradiol (0.03 mg), dienogest 2 mg reliably inhibits ovulation and is an established contraceptive regimen.⁴¹

Visanne® has not been directly studied for contraceptive efficacy and, therefore, women are advised to use non-hormonal methods of contraception (e.g. barrier method) as a precaution to prevent unwanted pregnancies.

Based on the available information, normal menstrual and ovarian activity resume rapidly after cessation of treatment with Visanne®, and there are case reports of women becoming pregnant shortly after ceasing treatment, including those with a prior history of infertility.³⁸

3.7 Toxicology of Visanne®

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

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

For further details, please see the Chapter Summary of Product Characteristics.

4. Clinical Experience with Visanne®

Clinical experience with Visanne® at a glance

Visanne® for pain relief

- Visanne® is an effective therapy for reducing the painful symptoms of endometriosis, including dysmenorrhea, premenstrual pain, dyspareunia, and diffuse pelvic pain.
- Visanne® demonstrates an efficacy that is significantly superior to placebo and equivalent to the current standard therapy with GnRH agonists, but has a more favorable side-effect profile.
- Visanne® provides sustained pain relief over the long term. In clinical studies, a continuous improvement was shown up to 15 months.

Visanne® for lesion reduction

- Visanne® effectively reduces endometriotic lesions.

Safety of Visanne®

- Clinical evidence extending up to 15 months shows that Visanne® is generally well tolerated and is associated with low incidences of treatment-related adverse events and low dropout rates.
- Visanne® does not produce relevant hypo-estrogenic side effects, such as decrease in BMD and menopausal symptoms (e.g. hot flashes) associated with GnRH agonists.
- Visanne® is not associated with clinically relevant androgenic effects and has no negative impact on lipid levels, unlike danazol and some progestins.
- Bleeding irregularities—a known characteristic of progestins—were common in patients treated with Visanne®. Experience from clinical trials demonstrates that there is a progressive reduction in frequency and intensity of bleeding during long-term treatment and that bleeding patterns are generally well tolerated and associated with low rates of treatment withdrawal. To enhance treatment compliance in clinical practice, it is recommended that women are advised on the likely changes in bleeding pattern during treatment with Visanne®.

Overview of key clinical studies

Progestins have been used in the treatment of endometriosis for a number of years, although there is limited evidence from controlled studies (particularly placebo-controlled studies) to support the efficacy of many agents in this class. Dienogest is the only oral progestin that has been specifically investigated for the treatment of endometriosis in a comprehensive study program (see Table 4). This program shows that Visanne® possesses efficacy in the treatment of endometriosis, combined with a safety profile that enables long-term use.

Table 4: Summary of key clinical studies of Visanne®

Study design	Summary of findings	Reference
Dose-range (1, 2 and 4 mg dienogest daily); 24 weeks	Efficacy - Numbers of patients reporting pelvic pain, dyspareunia, dysmenorrhea and premenstrual pain were significantly reduced by dienogest. - Similar, substantial reductions in lesion score were achieved with dienogest. Safety and tolerability - Moderate suppression of estrogen levels - Trend to decreased bleeding intensity over study, with no dropouts due to altered bleeding 2 mg offered slightly better tolerability, and was recommended as optimal dose.	Köhler <i>et al.</i> , 2010 ³⁵
Dienogest (2 mg) versus placebo, double-blind; 12 weeks	Efficacy - Dienogest was significantly superior to placebo for reducing endometriosis-associated pelvic pain. Safety and tolerability - Adverse event profile similar to placebo - Moderate suppression of estrogen levels - No relevant alteration in plasma lipid levels - No relevant change in mean body weight, equivalent to placebo - Mean numbers of bleeding/spotting days and episodes and mean duration of episodes similar for dienogest and placebo. Less regular bleeding pattern with dienogest, but no dropouts due to altered bleeding	Strowitzki <i>et al.</i> , 2010 ³⁶
Dienogest (2 mg) versus LA; 24 weeks	Efficacy - Dienogest was equivalent (non-inferior) in efficacy to LA. - Progressive reductions in pain occurred with both dienogest and LA. Safety and tolerability - Moderate suppression of estrogen production with dienogest - Lower frequency of hot flushes with dienogest than LA - Mean BMD decreased with LA (-4.04%), unchanged with dienogest (+0.25%; <i>P</i>=0.0003). - No relevant effect of dienogest on mean body weight, equivalent to LA - Mean numbers of bleeding/spotting days and episodes decreased in both groups. Higher rate of amenorrhea in LA group. Less regular bleeding pattern with dienogest than LA, no dropouts due to altered bleeding or adverse events	Strowitzki <i>et al.</i> , 2010 ³⁷

Table 4 (continued)

Study design	Summary of findings	Reference
Dienogest (2 mg), long-term extension of placebo study; up to 53 additional weeks	Efficacy - Dienogest progressively decreased EAPP during long-term treatment. Safety and tolerability - No relevant hypoestrogenic effects - No relevant alteration in plasma lipid levels - No relevant change in mean body weight - Mean frequency and intensity of bleeding decreased during treatment; only two of 168 patients dropped out due to altered bleeding	Seitz <i>et al.</i> , 2009 ³⁸

BMD, bone mineral density; LA, leuprolide acetate.

4.1 Clinical efficacy of Visanne®

The efficacy of Visanne® in endometriosis has been assessed using a range of measures that may be conveniently divided into: (a) pain relief and (b) lesion reduction.

4.1.1 Efficacy for pain relief

Pain relief is the most relevant outcome for the symptomatic patient seeking treatment for endometriosis and should be a measure of success for any medication.^{54,55} Recent studies of Visanne® which included symptom assessments as an efficacy measure consistently show that Visanne® provides effective pain relief.

Open-label, dose-range study: dienogest 1, 2, and 4 mg daily

The optimal dose of dienogest was determined in a 24-week, randomized, open-label study in 68 women with endometriosis stage I, II, or III (rAFS scale). Women were randomly assigned to treatment with dienogest 1, 2, or 4 mg once daily.³⁵ Randomization to the 1 mg group was halted prematurely because of unsatisfactory bleeding patterns.

Dienogest at 2 mg and 4 mg daily was associated with improvements in patient-reported symptoms in substantial proportions of women. Proportions of women with dyspareunia decreased significantly from 51.7% at baseline to 6.9% at week 24 in the 2 mg group, and from 57.1% to 5.7% in the 4 mg group. Similar decreases were observed in the 2 mg and 4 mg groups for diffuse pelvic pain, dysmenorrhea and premenstrual pain (see Figure 2).



Painful examinations (i.e. at gynecological inspection, palpation, or colposcopy) were reported at baseline by 75.9% of women in the 2 mg group and by 73.2% in the 4 mg group. By 24 weeks, the proportions of women reporting painful examinations decreased to 44.8% and 21.4%, respectively.

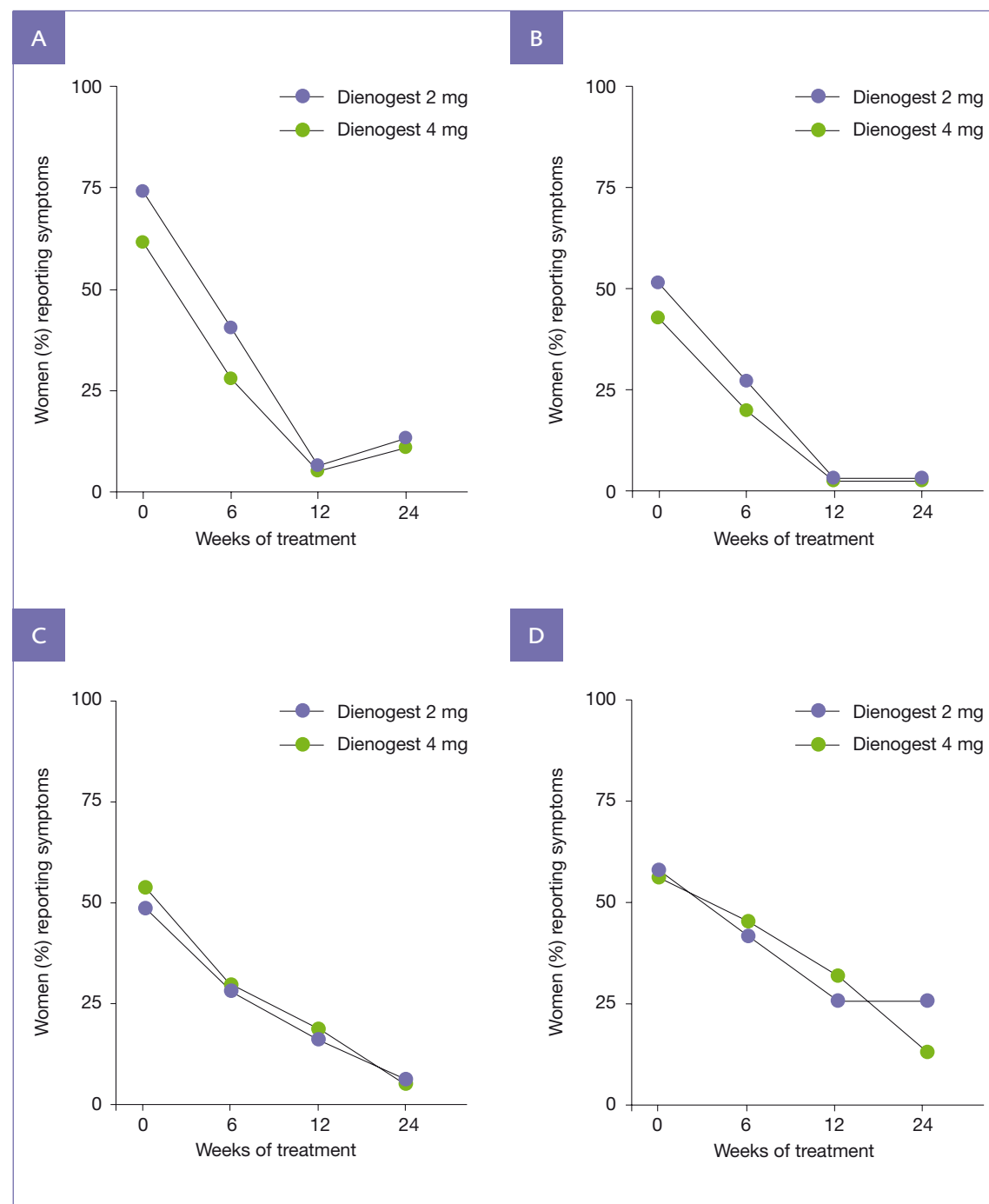


Figure 2: Proportions of women (%) reporting (A) Dysmenorrhea, (B) Premenstrual pain, (C) Dyspareunia and (D) Diffuse pelvic pain, at baseline and after treatment with dienogest 2 or 4 mg for 24 weeks.³⁵

Double-blind, placebo-controlled study

A placebo effect is well documented in studies of pain control and so novel treatments in endometriosis must demonstrate superiority over placebo in order to prove their efficacy for pain relief. The efficacy of dienogest 2 mg for providing pain relief was compared against placebo in a 12-week, randomized, double-blind trial of 188 women with endometriosis.³⁶ Inclusion criteria included histologically-confirmed endometriosis (stage I–IV, using revised American Society for Reproductive Medicine (rASRM) scoring, with laparoscopy done within 12 months before study start) and an EAPP score ≥ 30 mm on a 100 mm visual analogue scale (VAS) at baseline. The VAS is a validated tool that is widely used in clinical trials for the measurement of pain.⁵⁶

The mean VAS score (measured on a scale 0–100 mm) decreased by 27.4 mm in the dienogest group and by 15.1 mm in the placebo group during the 12-week study, representing a statistically significant between-group difference of 12.3 mm in favor of dienogest (95% confidence interval, 6.4 to 18.1; $P < 0.0001$) (Figure 3).

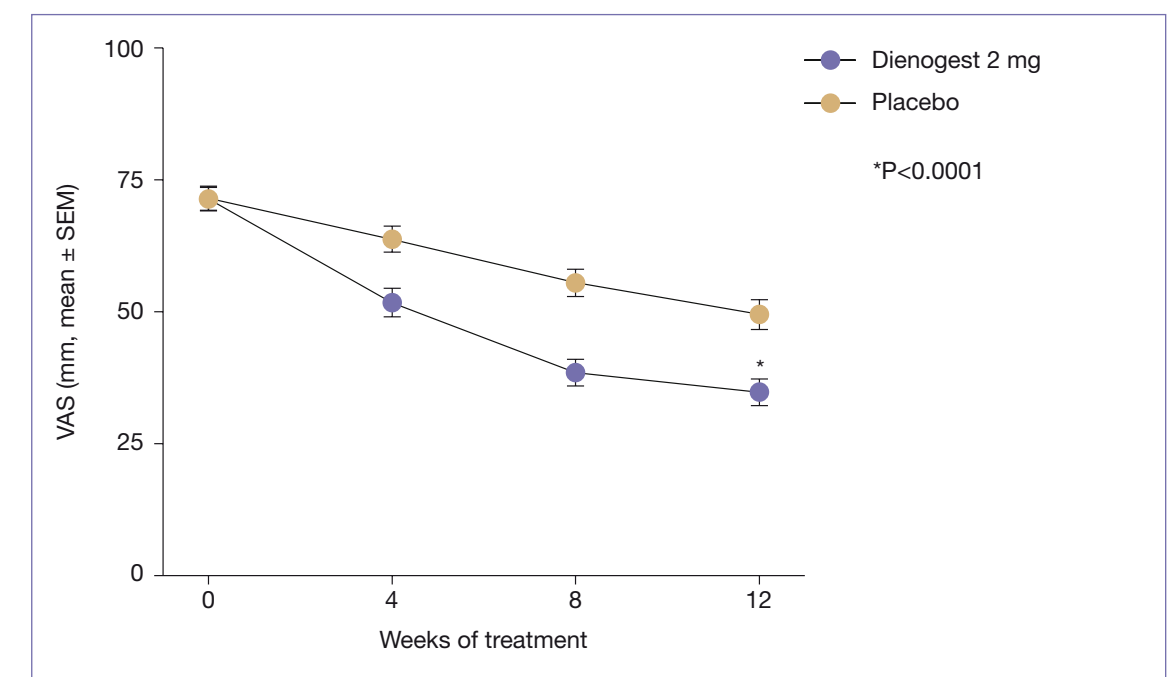


Figure 3: Change in VAS score (mm, mean $\pm$ SEM) during treatment with dienogest 2 mg versus placebo.³⁶

The Biberoglu and Behrman (B&B) severity profile scoring system for symptoms and physical findings was a secondary efficacy assessment in the placebo-controlled study.⁵⁷ B&B analyses confirmed the results of the primary end-point, by demonstrating greater reductions in symptoms and signs in the dienogest than placebo group.

The Clinical Global Impression (CGI) scale was used as a measure of overall improvement.⁵⁸ The proportion of patients assessed by physicians to be 'very much improved/much improved' at week 12 on the CGI was 52.9% for dienogest and 22.9% for placebo.

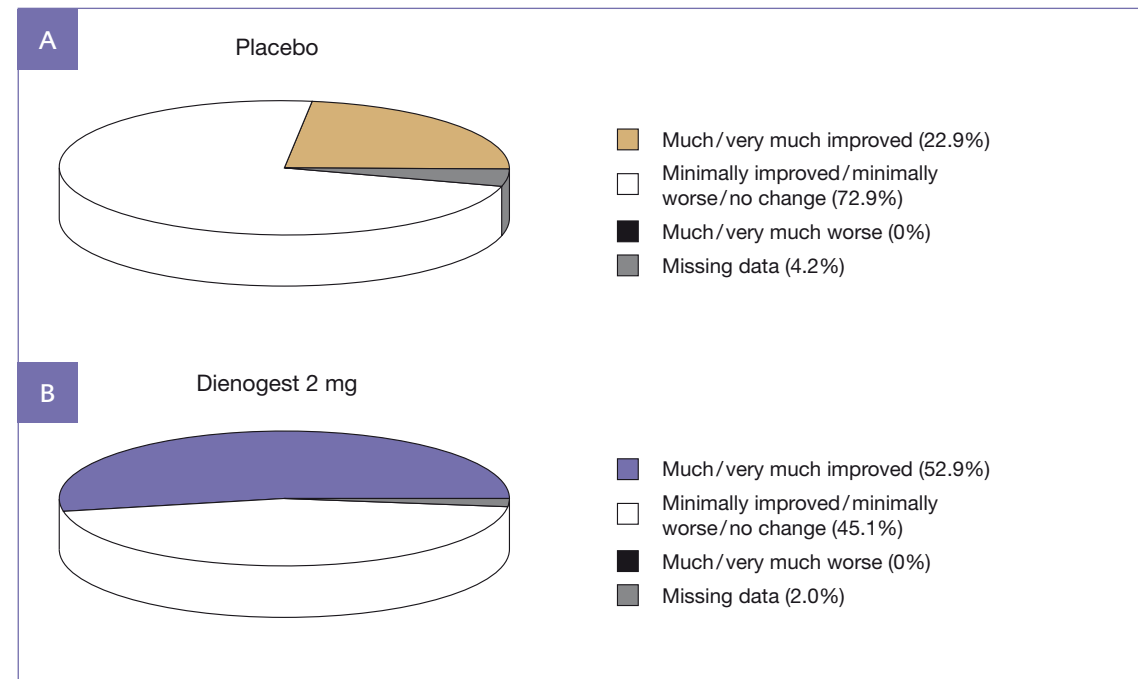


Figure 4: Frequency of patients (%) with global improvement assessed by investigators according to CGI scale and category after 12 weeks of treatment with (A) Placebo or (B) Dienogest 2 mg.³⁶

In quality of life analyses using the SF-36 Health Survey Questionnaire (a non-disease-specific tool widely used in clinical trials, including endometriosis studies), there was significantly greater improvement in the dienogest than placebo group for the sub-domain 'bodily pain'. As may have been expected from this non-specific tool, mental and physical sum scale scores showed similar improvements and only minimal differences in the two treatment groups.

In summary, a range of tools used in this study for the assessment of painful symptoms consistently showed superior efficacy for dienogest compared with placebo in the treatment of endometriosis.

Long-term extension study

A total of 168 women who completed the 12-week, placebo-controlled study (described above) participated in an open-label extension study to investigate dienogest 2 mg daily for up to 53 additional weeks. Together, the placebo-controlled plus open-label study therefore included an overall treatment period of up to 65 weeks.³⁸

The mean VAS score in this population decreased progressively during the overall treatment period, from 56.9 mm at baseline of the placebo-controlled study, to 34.1 mm at baseline of the extension study, to 11.5 mm at the end of the extension study. The changes in VAS score in the groups treated with dienogest or placebo during the placebo-controlled study are shown in Figure 5.

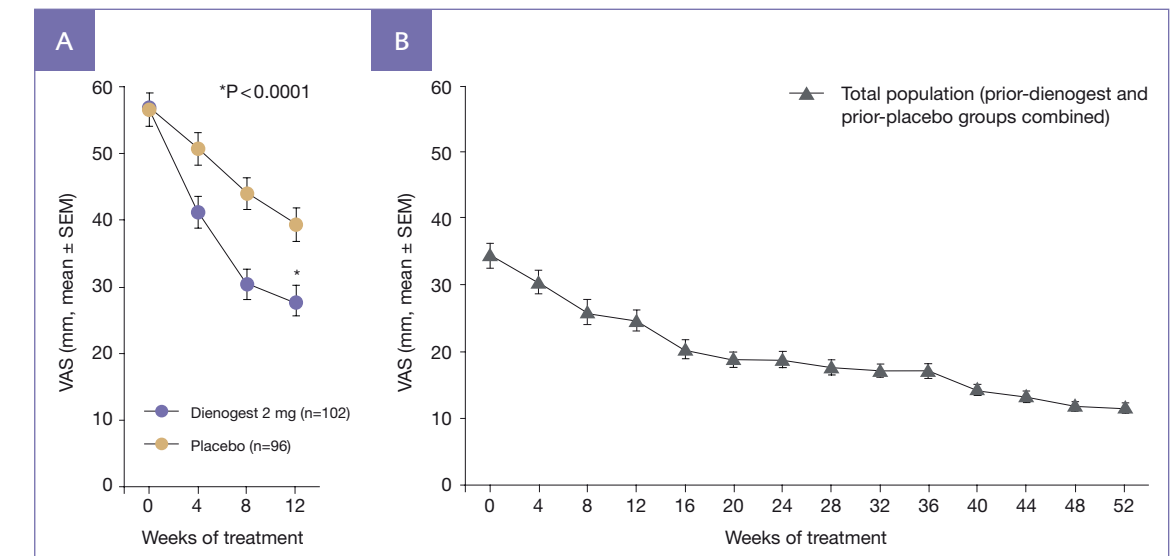


Figure 5: Change in VAS score (mean ± SEM) during (A) the placebo-controlled study in groups categorised by treatment and (B) open-label treatment with dienogest 2 mg in the extension study.³⁸

Open-label, comparative study of dienogest versus LA

Dienogest was compared against the GnRH agonist, LA (3.75 mg intramuscularly (IM) every 4 weeks), in a 24-week, randomized, phase III, non-inferiority study of 252 women with laparoscopically-confirmed endometriosis; laparoscopy was performed within 12 months of study commencement.³⁷ A GnRH agonist was chosen as the active comparator because these agents represent a standard medical therapy in the treatment of endometriosis.

Dienogest and LA both provided continuous and comparable reductions in pelvic pain measured by VAS score. By the end of the 24-week study, the reduction in mean VAS score was 47.5 mm with dienogest and 46.0 mm with LA, representing a between-group difference of -1.5 mm in favor of dienogest (95% confidence interval, -9.26 to 6.25) (see Figure 6). The non-inferiority of dienogest relative to LA was therefore demonstrated ($P < 0.0001$), based on the prespecified non-inferiority margin of 15 mm.

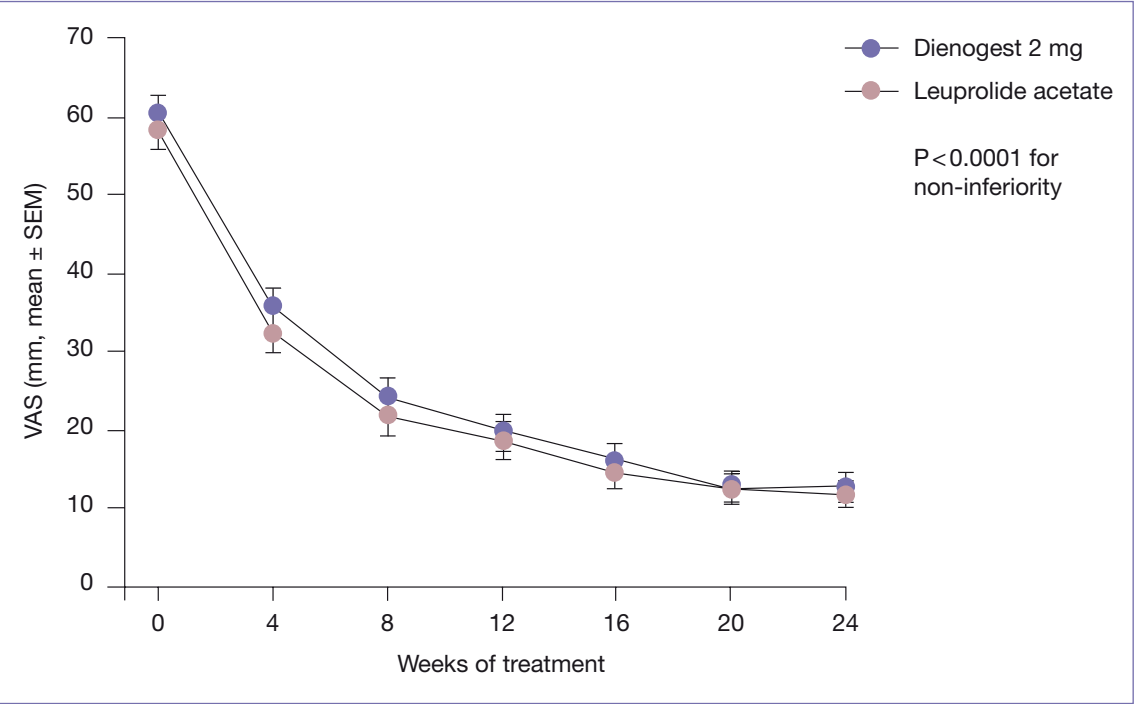


Figure 6: Change in VAS score (mean ± SEM) for pelvic pain during treatment with dienogest 2 mg versus LA.³⁷

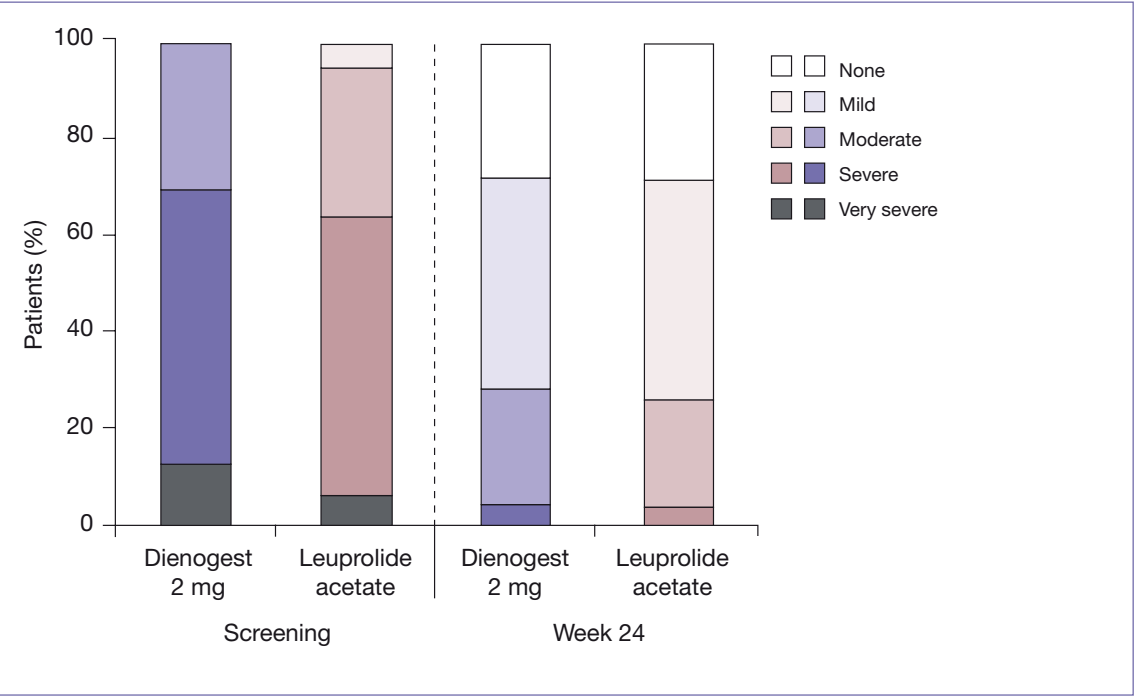


Figure 7: Total symptom and sign severity score profile (B&B) at baseline and week 24 in the dienogest and LA groups.³⁷

Consistent with the equivalent VAS score changes in the two groups, dienogest and LA were also associated with similar decreases in the intensity of symptoms and physical findings, summarized by B&B total symptom and sign scores (Figure 7).

Additional studies on the efficacy of dienogest for pain relief

Additional data from clinical trials that used a range of designs provide further evidence for the efficacy of dienogest in relieving the pain related to endometriosis (Table 5).

Table 5: Additional clinical studies investigating pain relief in endometriosis

Study design	Study drugs	Patients	Outcomes relating to pain relief	Reference
Open-label, 24 weeks Primary outcome: change in endometriotic lesions and symptoms	Dienogest 2 x 1 mg/day	n=84 women with diagnosed endometriosis	- Global improvement rating: 83% for all subjective symptoms - Dysmenorrhea, premenstrual pain, and dyspareunia improved in 85, 84 and 86%, respectively	Köhler <i>et al.</i> , 1989 ⁶³
Randomised, multicentre, 16 weeks Primary outcome: changes in rAFS score	Dienogest 2 x 1 mg/day versus triptorelin 3.75 mg/month IM	n=142 women with stage II to IV endometriosis; surgically treated	- No significant group difference in rAFS score changes - Symptoms and signs generally comparable in dienogest and triptorelin groups. Pelvic pain more common in triptorelin (67.8%) than dienogest group (47.5%, <i>P</i>=0.03)	Cosson <i>et al.</i> , 2002 ⁶⁴
Open-label, pilot study, 24 weeks Primary outcome: change in rAFS score	Dienogest 2 x 10 mg/day	n=21 women with stage I to IV endometriosis	- Reduction in mean symptom score from 6.2 to 1.8 (<i>P</i>=0.0001) - Marked improvements in dysmenorrhea and premenstrual pain; moderate improvements in pelvic pain and dyspareunia	Schindler <i>et al.</i> , 2006 ⁶⁵

Table 5 (continued)

Study design	Study drugs	Patients	Outcomes relating to pain relief	Reference
Randomized, multicenter, double-blind, 24 weeks Primary outcome: global improvement rating for subjective and objective signs and symptoms	Dienogest 1, 2 and 4 mg/day (two divided doses per day)	n=171 women with diagnosed endometriosis	- Global improvement rating: similar improvements with all dosages of dienogest - Marked or moderate improvement in subjective symptoms during menstruation were similar across doses - All baseline symptoms disappeared in 27.6, 35.1 and 26.8% of women receiving 1, 2 and 4 mg dienogest, respectively - Only 2 mg/day dose maintained serum estradiol levels within therapeutic window (30–50 pg/mL) predicted to provide reduction of endometriosis lesions while minimizing hypoestrogenic effects	Momoeda <i>et al.</i> , 2007 ⁶⁶
Randomized, multicenter, double-blind, 24 weeks Primary outcome: change in scores for subjective symptoms and objective findings	Dienogest 2 x 1 mg/day versus buserelin 3 x 300 µg/day, intranasal	n=271 women with diagnosed endometriosis	- VAS score for lower abdominal pain and lumbago improved in both dienogest and buserelin groups - Mean reduction in lower abdominal pain: –30.2 (SD 31.8) for dienogest and –27.3 (SD 33.8) for buserelin - Mean reduction in lumbago: –15.7 (SD 28.7) for dienogest and –17.3 (SD 24.8) for buserelin - Significant reductions in subjective symptom scores with both dienogest and buserelin, during and outside menstruation	Harada <i>et al.</i> , 2008 ⁷¹

SD, standard deviation; rAFS, revised American Fertility Society VAS, visual analogue scale.

Open-label, dose-range study: dienogest 1, 2, and 4 mg daily

Changes in rAFS score and in stage of endometriosis at laparoscopy were assessed in the 24-week, dose-range study of dienogest.³⁵ Dienogest at 2 mg and 4 mg daily produced significant reductions in the rAFS score between baseline and study end. Mean rAFS scores decreased from 11.4 to 3.6 ($P=0.0003$) in the 2 mg group and from 9.7 to 3.9 ($P<0.0001$) in the 4 mg group (Figure 8).

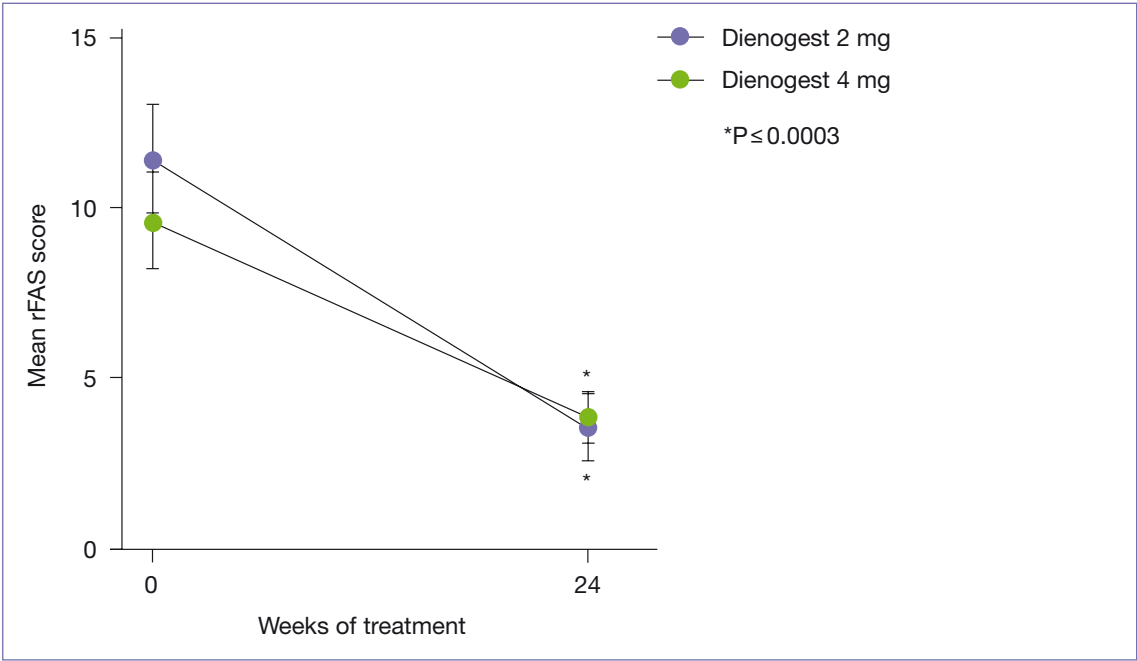


Figure 8: Mean (±SEM) rAFS score at baseline and after treatment with dienogest 2 or 4 mg for 24 weeks.³⁵

The severity of disease by the rAFS classification decreased in both 2 mg and 4 mg dienogest groups (Figure 9). For example, in the 2 mg group, 34.5%, 37.9%, and 27.6% of women had stage I, II, and III endometriosis, respectively, at baseline. After 24 weeks, 23.8% of women had a classification of no endometriosis and 52.4%, 9.5%, and 4.8% had stage I, II, and III endometriosis, respectively (missing data in 9.5%).

4.1.2 Efficacy for lesion reduction

Assessment of lesion reduction by laparoscopy provides additional evidence for the efficacy of Visanne® in endometriosis. Although pain relief is now established as the primary efficacy measure in endometriosis studies, and the correlation between pain relief and lesion reduction is not robust,^{19,54,59–61} the availability of laparoscopic data is important in demonstrating that Visanne® addresses the underlying pathology in addition to the most important clinical symptoms of endometriosis.

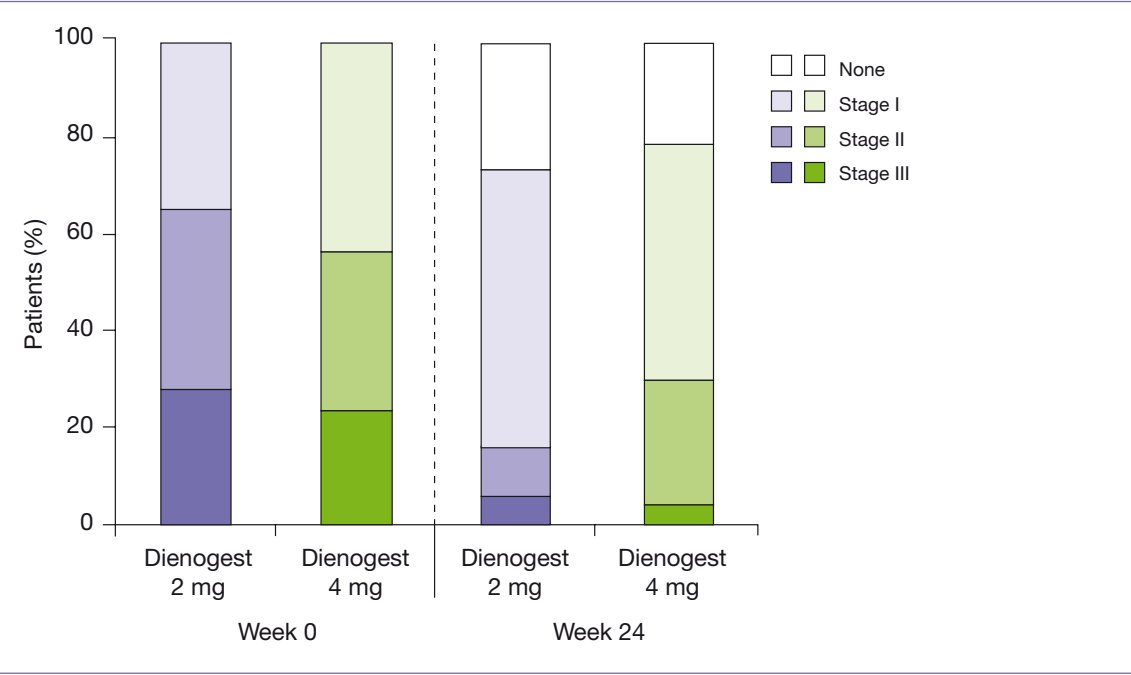


Figure 9: Change in endometriosis severity (proportions of women, %) by rAFS classification at baseline and after treatment with dienogest 2 or 4 mg for 24 weeks. Percentages based on full-analysis set, excluding patients with missing data. ³⁵

Additional studies on the efficacy of dienogest for lesion reduction

Additional evidence for the efficacy of dienogest to reduce lesions in endometriosis is provided by a number of clinical studies^{62–66} (Table 6).

Table 6: Supportive clinical studies investigating lesion reduction in endometriosis

Study design	Study drugs	Patients	Efficacy outcomes relating to lesion reduction	Reference
Open-label, 24 weeks Primary outcome: change in endometriotic lesions and symptoms	Dienogest 2 x 1 mg/day	n=58 women with diagnosed endometriosis	Repeat laparoscopy (n=51) revealed endometriotic lesions had disappeared in 66.7%. A marked improvement was noted in 80.4% and no visible effect in 19.6%.	Köhler <i>et al.</i> , 1987 ⁶²
Open-label, 24 weeks Primary outcome: effect on lipid metabolism	Dienogest 2 x 1 mg/day	n=84 women with diagnosed endometriosis	Repeat laparoscopy revealed endometriotic lesions had disappeared in 62%. A marked improvement was noted in 80% and no visible effect in 18%.	Köhler <i>et al.</i> , 1989 ⁶³

Table 6 (continued)

Study design	Study drugs	Patients	Efficacy outcomes relating to lesion reduction	Reference
Randomized, multicenter, 16 weeks Primary outcome: change in rAFS score	Dienogest 2 x 1 mg/day versus triptorelin 3.75 mg/month IM	n=142 women with stage II to IV endometriosis; surgically treated	- Total rAFS score: 38 in both groups at baseline and 4 in both groups at 16 weeks - Components of rAFS score (implant, adhesion and posterior cul-de-sac obliteration scores) similar in the two groups - No significant group differences in implants/adhesions, tubal/ovarian localization	Cosson <i>et al.</i> , 2002 ⁶⁴
Open-label, pilot study, 24 weeks Primary outcome: change in rAFS score	Dienogest 2 x 10 mg/day	n=21 women with stage I to IV endometriosis	- Repeat laparoscopy revealed improvement in mean AFS score from 2.9 to 1.7 (P=0.0001) - Proportions of patients with stage III/IV disease decreased from 70% to 30% - Total disease regression in 5 patients - Significant reductions in total AFS score, endometriosis score, and adhesion score	Schindler <i>et al.</i> , 2006 ⁶⁵
Randomized, multicenter, double-blind, 24 weeks Primary outcome: global improvement rating for subjective and objective signs and symptoms	Dienogest 1, 2, and 4 mg/day (two divided doses per day)	n=171 women with diagnosed endometriosis	Endometriosis-related ovarian cysts decreased in size (P<0.05)	Momoeda <i>et al.</i> , 2007 ⁶⁶

IM, intramuscular; rAFS, revised American Fertility Society.

4.2 Clinical safety of Visanne®

4.2.1 Review of safety database for Visanne®

In nine phase II and III studies included in the clinical development program of Visanne®, more than 724 women have received dienogest for treatment periods extending up to



15 months (see Table 7). When also including the COC that contains 2 mg dienogest with 0.030 mg ethinyl estradiol (Valette®), and the hormone replacement therapy (HRT) that contains 2 mg dienogest with 1 or 2 mg estradiol valerate (Climodien®), more than 10 million women-years of experience with dienogest are available.⁶⁷⁻⁷⁰

Table 7: Exposure data from trials in the clinical development program of Visanne®

Duration of treatment	Number of women	Cumulative number of women
>60 and <72 weeks	73	73
>48 and ≤60 weeks	73	146
>24 and ≤48 weeks	122	268
>12 and ≤24 weeks	394	662
>4 and ≤12 weeks	54	716
≤4 weeks	8	724

4.2.2 Adverse event profile of Visanne®

See also special warnings and precautions for use in the Chapter Summary of Product Characteristics.

The most frequently reported adverse drug reactions during treatment with Visanne® in clinical trials were headache (9.0%), breast discomfort (5.4%), depressed mood (5.1%), and acne (5.1%). The continuous administration of progestins in general leads to endometrial regression, with irregular endometrial breakthrough bleeding, particularly during the first weeks of use. Therefore changes in bleeding pattern, such as spotting, irregular bleeding, or amenorrhea, occurred during treatment with Visanne®. Clinical trial experience extending up to 65 weeks demonstrated that there is a progressive reduction in the frequency and intensity of bleeding during continued treatment with Visanne®. In these trials, the changes in bleeding pattern associated with Visanne® did not impact on patient acceptability or persistence.

The adverse drug reactions that were recorded in the most recent clinical trials of Visanne®, categorized by MedDRA system organ class, are shown in the Chapter Summary of Product Characteristics.

In support of preclinical studies, which demonstrated that dienogest has only weak affinity for androgen receptors combined with anti-androgenic activity,^{42,45} clinical trials confirm that Visanne® is not associated with clinically relevant androgenic effects and has no negative impact on lipid levels.^{35,40,44,66}

4.2.3 Hypoestrogenic effects

Dienogest causes a hypoestrogenic endocrine environment in endometrial tissue, but produces only moderate reductions in plasma estrogen concentrations which tend to stabilize at the lower end of normal limits over time.^{66,71} The moderate suppression of plasma estrogen concentrations is apparent in the clinical trials of Visanne®.

- In the 24-week, dienogest versus LA comparator study, mean estradiol levels (subgroup measurements) decreased by only 6.9 ± 331.8 pmol/L (1.88 ± 90.39 pg/ml) with dienogest, but by 226.0 ± 182.8 pmol/L (61.56 ± 49.80 pg/ml) with LA (Figure 10).³⁷

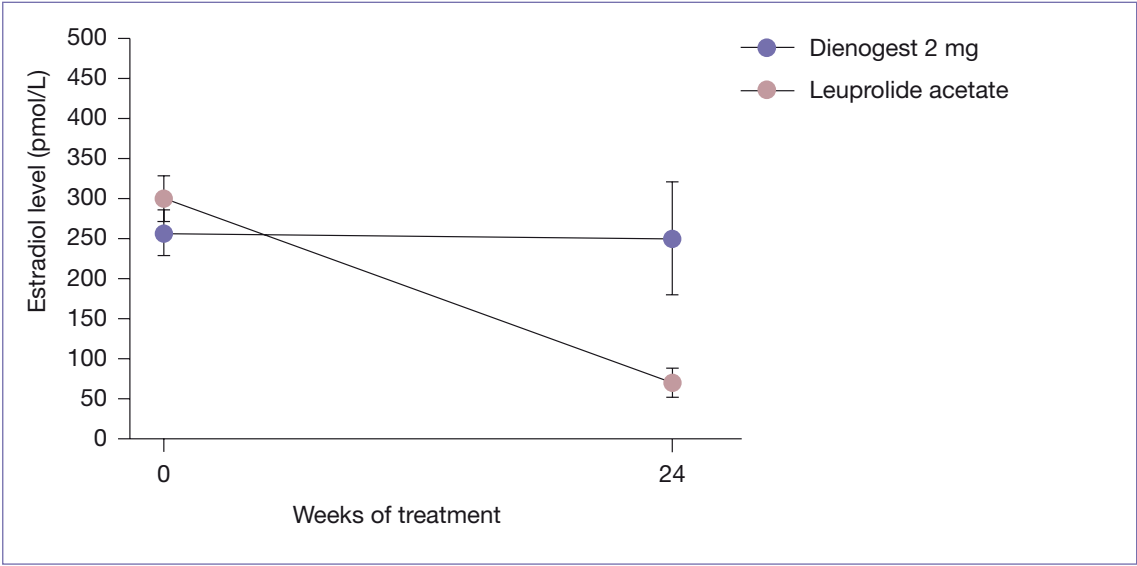


Figure 10: Mean (±SEM) estradiol levels during treatment with dienogest 2 mg versus LA.³⁷

- In the 12-week, placebo-controlled study, mean estradiol levels decreased by 70 ± 282 pmol/L (19 ± 77 pg/ml) with dienogest and increased by 70 ± 554 pmol/L (19 ± 151 pg/ml) with placebo.³⁶ The increase in mean estradiol levels in the placebo group can be explained by the fluctuation in their natural cycle, which was not suppressed.
- In the 1-year extension study, mean estradiol levels showed minimal changes (i.e. 18.7 ± 439.3 pmol/L (5.1 ± 119.7 pg/ml)) during continued dienogest treatment.³⁸
- Compared with LA in the 24-week comparator study, dienogest did not produce significant hypo-estrogenic side effects, such as BMD decrease and menopausal symptoms such as hot flushes, sleep disorder, decreased libido, and vaginal dryness.³⁷



The mean number of days/week with hot flushes during the comparator study was 0.89 in the dienogest group and 4.23 in the LA group. The mean frequency of hot flushes remained low and stable during dienogest treatment but increased in the LA group (Figure 11). In the last treatment week, 19 women in the dienogest group reported hot flushes, compared with 83 women in the LA group.³⁷

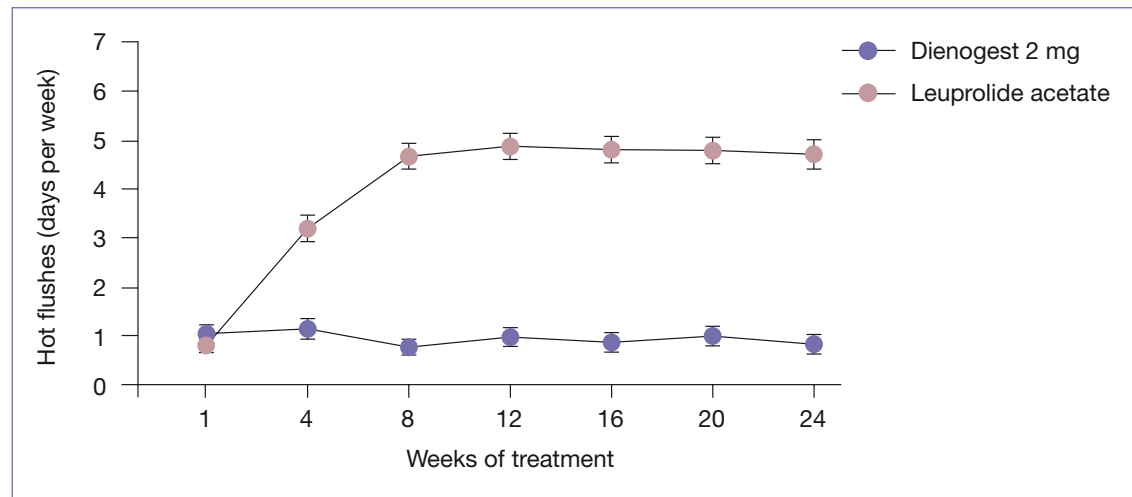


Figure 11: Mean (±SEM) number of days/week with hot flushes during treatment with dienogest 2 mg versus LA.³⁷

Further evidence for the lower incidence of hot flushes associated with dienogest than GnRH agonists comes from a 16-week randomized trial that compared dienogest 2 x 1 mg/day versus triptorelin 3.75 mg/month IM following surgical treatment. The proportion of patients with hot flushes was 9.6% with dienogest and 61.2% with triptorelin.⁶⁴

Mean lumbar BMD measured by dual energy X-ray absorptiometry (DEXA) was unchanged over 24 weeks in a patient subgroup treated with dienogest in the LA comparator study.³⁷ As would be expected from the known hypoestrogenic effects of GnRH agonists, there was a significant reduction in mean lumbar BMD in the LA group. Statistically significant between-group differences in mean BMD in favor of dienogest were apparent by study end ($P=0.0003$) (Figure 12). Consistent with these observations on BMD, markers of bone metabolism indicated increases in bone resorption in the LA group but no relevant change in the dienogest group.

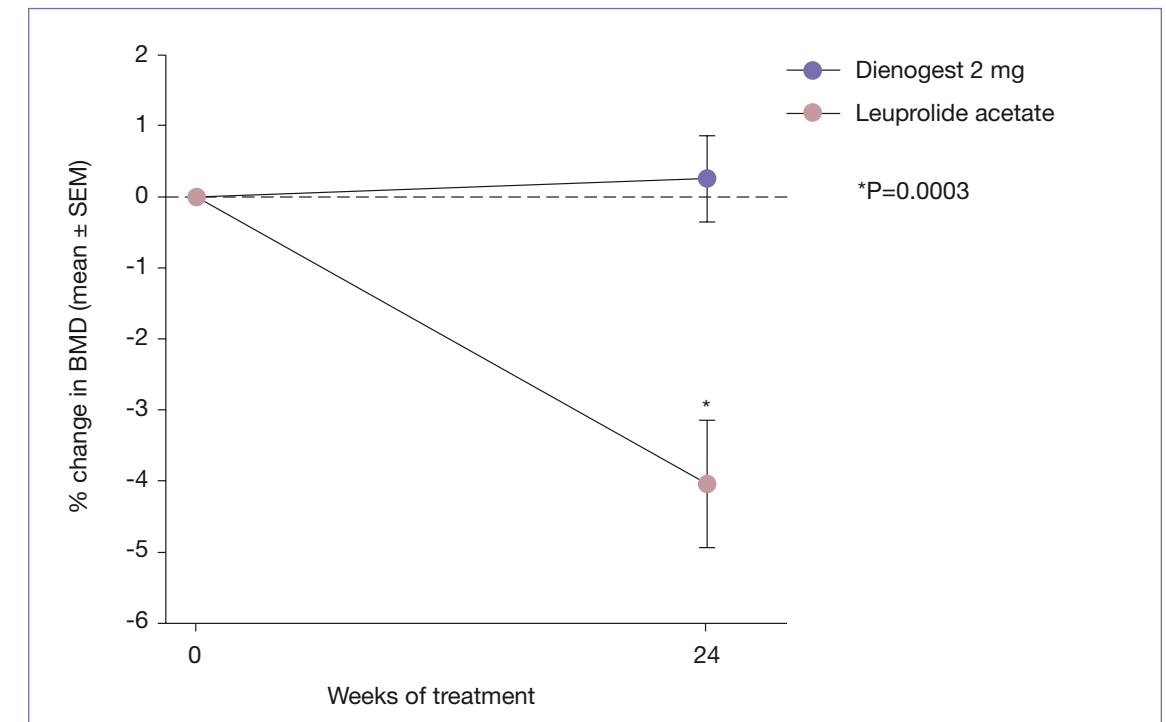


Figure 12: Change in mean (±SEM) bone mineral density (BMD) with dienogest compared with LA after 24 weeks (subgroup analyses).³⁷

Currently, long-term data on BMD beyond 15 months are not available.

4.2.4 Metabolic effects

Dienogest has little effect on plasma lipid levels and on carbohydrate metabolism.^{63,72} Even at a high dienogest dose of 20 mg/day, plasma lipid levels remained within the normal reference range throughout 24 weeks of treatment.⁶⁵ The Visanne® study program, including the placebo-controlled trial,³⁶ the comparator trial versus LA,³⁷ and the long-term extension study,³⁸ confirm the lack of a relevant effect of dienogest on lipid levels.

- In the 12-week, placebo-controlled study, lipid parameters including total, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) cholesterol and triglycerides showed minimal changes in both treatment groups. For example, mean (SD) total cholesterol levels increased by 0.10 ± 0.93 mmol/L in the dienogest group and decreased by 0.01 ± 0.87 mmol/L in the placebo group, while mean triglyceride levels increased by 0.14 ± 0.53 mmol/L and 0.07 ± 0.48 mmol/L, respectively.³⁶

- In the 24-week comparator trial versus LA, mean (SD) LDL-cholesterol levels increased by 0.02 ± 0.57 mmol/L in the dienogest group compared with 0.19 ± 0.48 mmol/L in the LA group.³⁷
- The 1-year extension study of dienogest reported minimal changes in lipid parameters from baseline to study end. For example, mean (SD) total cholesterol levels decreased by 0.05 ± 0.93 mmol/L and mean triglyceride levels increased by 0.03 ± 0.57 mmol/L.³⁸

Measurement of glucose concentrations in the 24-week dose-range study of dienogest indicated no clinically relevant changes in any patient.³⁵

4.2.5 Body weight

An increase in body weight is a common effect of therapy with a number of agents in the progestin class. However, Visanne® is not associated with relevant changes in body weight, based on individual studies and on a pooled analysis of data from the clinical study program^{36–38} (Figure 13).

- In the 24-week dose-range study, there were minimal changes in body weight with dienogest at 2 and 4 mg daily.³⁵
- In the 24-week LA comparator study, changes in body weight were similar for dienogest 2 mg and LA, at +1.21 kg and +1.15 kg, respectively.³⁷
- The long-term extension study showed little alteration in body weight over 1 year of dienogest treatment. In patients who had body weight assessments at baseline and after 1 year of treatment ($n=124$), the mean change in body weight was +0.58 kg.³⁸

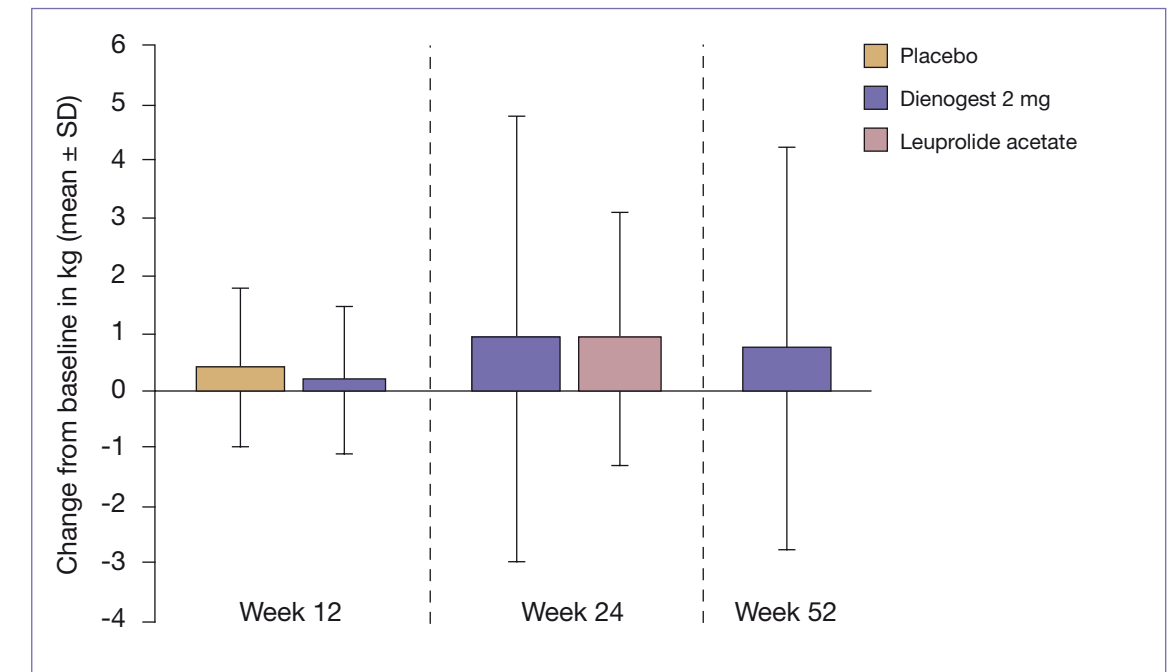


Figure 13: Change in mean ($\pm$ SD) body weight, dienogest in comparison with placebo and LA (pooled dienogest data at 12, 24 and 52 weeks^{36–38}; placebo data at 12 weeks³⁶; and LA data at 24 weeks³⁷).

4.2.6 Bleeding patterns

Irregular uterine bleeding is a known adverse effect of treatment with progestins. The menstrual bleeding pattern associated with Visanne® has been assessed systematically in a pooled analysis of data from the clinical development program,^{36–38} using the method published by Gerlinger *et al.*⁷³ By this method, bleeding patterns are analyzed in reference periods of 90 days' duration, in accordance with recommendations by the World Health Organization. Analyses of the proportions of women with clinically important bleeding patterns, summarized in Table 8, demonstrate that the regularity of bleeding improves with continued dienogest treatment. Data on bleeding patterns during placebo treatment in the placebo-controlled trial are added in Table 8 for comparison.³⁶

Table 8: Proportions of women with each menstrual bleeding pattern during dienogest treatment (numbers add up to more than 100% because each patient could fall into more than one category)

Menstrual bleeding pattern	First 90-day treatment period		Fourth 90-day treatment period
	Dienogest (n=290)*	Placebo (n=92)**	Dienogest (n=149)***
Amenorrhea	1.7%	0%	28.2%
Infrequent bleeding	27.2%	0%	24.2%
Frequent bleeding	13.4%	9.8%	2.7%
Irregular bleeding	35.2%	28.3%	21.5%
Prolonged bleeding	38.3%	5.4%	4.0%
Normal bleeding	19.7%	60.9%	22.8%

*Data pooled from clinical trials.
**From Strowitzki *et al.*, 2010³⁶.
***From Seitz *et al.*, 2009³⁸ (no placebo data available).

The long-term extension study of dienogest treatment for up to 15 months in 168 women assessed bleeding patterns as the primary target variable. This study demonstrated that the mean numbers of bleeding/spotting days and episodes and the mean duration of bleeding/spotting episodes decreased during treatment, as EAPP progressively improved (Figure 14).³⁸

In the Visanne® clinical trial program, changes in bleeding pattern were only occasionally reported as adverse events and were associated with low discontinuation rates, indicating a high rate of acceptance. In the long-term extension study, only two of 168 women withdrew from treatment due to a change in bleeding patterns.³⁸

To enhance treatment compliance in clinical practice, it is recommended that women are advised on the likely changes in bleeding pattern during treatment with Visanne®.

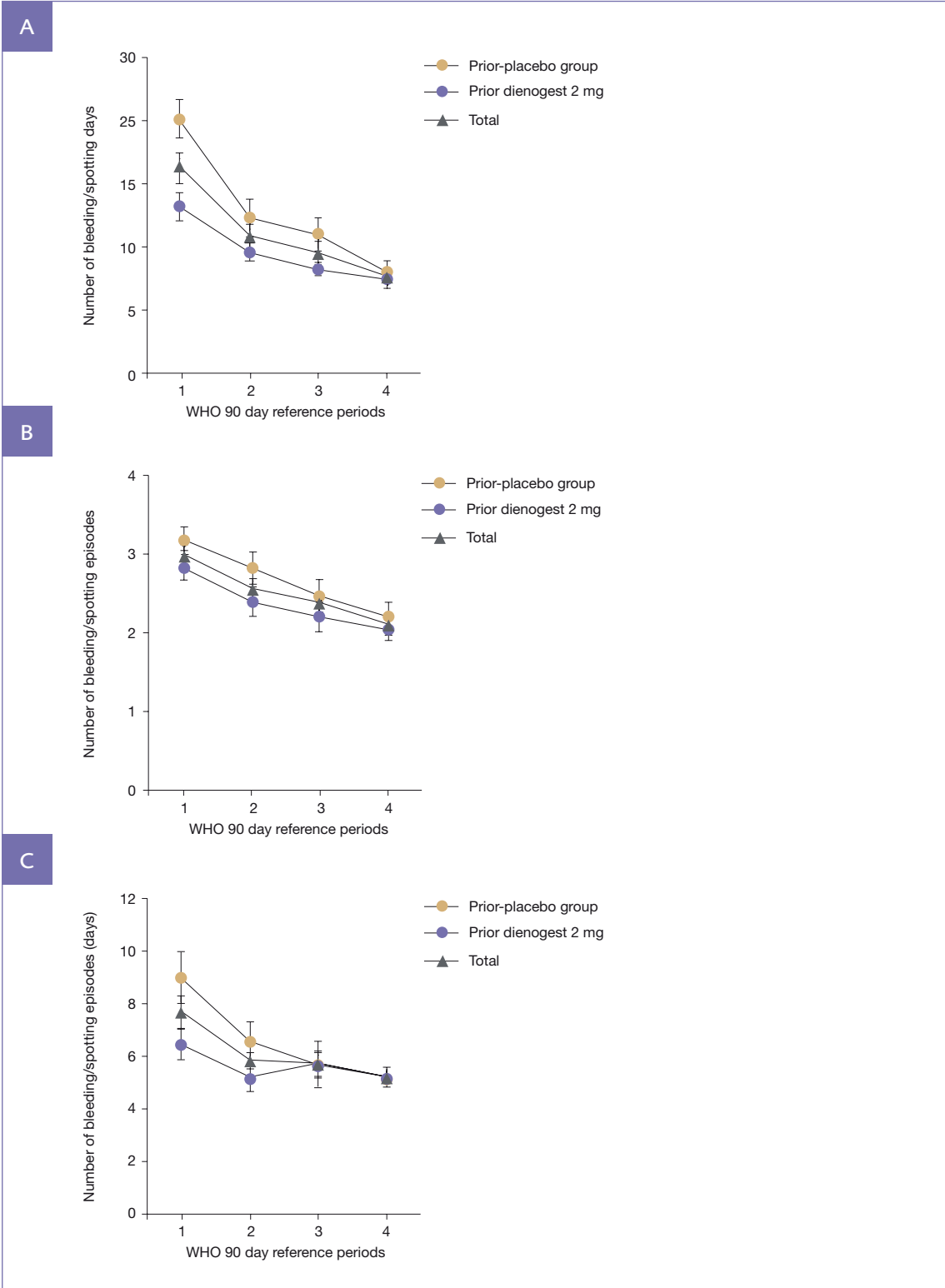


Figure 14: Mean (± SEM) numbers of (A) bleeding/spotting days, (B) bleeding/spotting episodes and (C) individual mean length of bleeding/spotting episodes in the open-label study. Total patient group and patient subgroups previously treated with dienogest 2 mg/day or placebo in the placebo-controlled study.³⁸



5. Visanne®: Frequently Asked Questions and Answers

5.1 Background on endometriosis

What is endometriosis?

The endometrium is a layer of mucous tissue which lines the uterine cavity and undergoes hormone-dependent changes during the menstrual cycle. Endometriosis is a chronic gynecological condition defined by the presence of endometrium-like tissue ("endometriotic lesions") developing outside the uterus. The development of endometriotic lesions (usually in the pelvic cavity) induces a chronic, inflammatory reaction that typically causes painful symptoms. Endometriosis is also associated with reduced fertility. The major medical needs of women with endometriosis are a reduction of endometriosis-associated pain and/or improvement of fertility.

What are the symptoms of endometriosis?

The typical symptoms of endometriosis include cramping menstrual pain (dysmenorrhea), premenstrual pain, painful sexual intercourse (dyspareunia), and severe abdominal and chronic pelvic pain. Often, these symptoms occur together. Other symptoms associated with endometriosis include pain during ovulation, pain in the bowel or bladder, and chronic fatigue. Endometriosis can also present with a wide range of additional, atypical, symptoms.

How can endometriosis be diagnosed?

Endometriosis may be suggested by the presence of typical symptoms, but establishing an accurate diagnosis based on symptoms alone can be difficult, as these may be non-specific and can overlap with symptoms related to other conditions. Currently, a definitive diagnosis of endometriosis is possible only via surgery (i.e. laparoscopy), ideally combined with confirmatory histology. Due to this surgical hurdle and the lack of other, more convenient diagnostic measures, there may be a delay between the first appearance of symptoms and an accurate diagnosis. An international survey reported that the average delay is 8.3 years.¹⁷ Due to the risks associated with laparoscopy, physicians and patients may agree that it is not appropriate to perform this invasive procedure based on the individual circumstances. In this situation, a physician may make a presumptive diagnosis based on the symptoms alone.¹

How many women are affected by endometriosis?

Endometriosis is a prevalent condition among women of reproductive age. Although precise estimates are difficult to establish, the prevalence of endometriosis is believed to be 5–10% of the female population, affecting an estimated 5.5 million women in the U.S. and 16 million women in Europe.^{2–8} The prevalence of endometriosis is higher in certain groups, such as infertile women (25–40%), women with dysmenorrhea (40–60%), and those reporting pelvic pain (75%).^{9,12,13}

What are the therapeutic options in endometriosis?

A range of therapeutic options are available, including medical therapies, surgery, or a combination of approaches. GnRH agonists are an effective medical therapy, but these agents can be used only for the short-term relief of symptoms, as safety concerns (particularly bone demineralization) limit their use to 6 months without estrogen add-back therapy. Danazol is used infrequently today due its unpleasant androgenic adverse effects. Certain progestins may be associated with androgenic effects and weight gain. Other medical therapies are used off-label (e.g. oral contraceptives) or on-demand as only symptomatic treatment (such as NSAIDs). For many women, surgery represents a final treatment option. However, surgery is only as effective as the skill of the surgeon and recurrence of symptoms is common (the 5-year recurrence rate is approximately 40–50%).²¹ As endometriosis is a long-lasting condition, there is a need for a well tolerated medical treatment that can be used long term, with an efficacy that has been proven in controlled clinical trials—particularly in placebo-controlled studies, which are important because of the large known placebo effect.

5.2 Visanne®

What is new about Visanne®?

Visanne® is the first therapy that has been specifically developed for the treatment of endometriosis. Extensive preclinical and clinical trial evidence confirms that Visanne® offers a pronounced effect on the endometrium that translates to an effective treatment for endometriosis.^{35–38} In contrast to the current standard therapy in endometriosis (i.e. GnRH agonists), long-term use of Visanne® is not restricted by safety or tolerability concerns. Only Visanne® has demonstrated in a comprehensive development program: effective pain relief; lesion reduction, and a safety and tolerability profile suited for long-term use in endometriosis.

What is the recommended dose of Visanne®?

Visanne® should be administered as a 2 mg tablet of dienogest, once daily, orally. A 2 mg dose of dienogest once-daily has been identified as optimal in the treatment of endometriosis.³⁵

What is the clinical trial experience with Visanne®?

The potential of dienogest to be an effective progestin in the treatment of endometriosis was recognised a number of years ago, based on its favorable pharmacological profile.⁶² Two open-label studies followed, which explored the metabolic effects of dienogest in women with endometriosis.^{63,74}

Following these early studies, the efficacy and safety of Visanne® in the treatment of endometriosis were explored in a comprehensive clinical development program that included a dose-range,³⁵ placebo-controlled,³⁶ active comparator-controlled (versus leuprolide acetate),³⁷ and long-term open-label study.³⁸ In these studies, Visanne® demonstrated efficacy for reducing endometriotic lesions and improving endometriosis-associated pain, including diffuse pelvic pain, dyspareunia, dysmenorrhea, and premenstrual pain. In the treatment of endometriosis-associated pain, Visanne® was significantly superior to placebo and was equivalent to the current therapeutic standard (a GnRH agonist), while offering superior safety and tolerability.^{36,37} Studies from Japan which investigated dienogest at a dose of 2 mg daily in divided doses, confirm the efficacy of this medication to relieve the pain symptoms and reduce the lesions in endometriosis.^{66,71} For example, in the randomized, double-blind study by Harada *et al.*,⁷¹ dienogest 2 x 1 mg/day was equivalent to intranasal buserelin 3 x 300 µg/day for reduction of pain after 24 weeks.

The clinical development program for Visanne® has now been completed. More than 700 women have received dienogest for periods extending up to 15 months and these data confirm that Visanne® has characteristics that allow for the long-term treatment of endometriosis.

Who can use Visanne®?

Visanne® is suitable for the treatment of women with endometriosis which should be diagnosed according to local medical standards.

How long can a woman use Visanne®?

Visanne® demonstrated continuous symptom improvement together with a favorable safety and tolerability profile over 15 months in a long-term extension study.³⁸ The mode of action of Visanne® indicates that this favorable profile would not deteriorate over longer term use. By contrast, GnRH agonists are limited by the risk of bone demineralization to 6 months of treatment in the absence of add-back therapy.^{24,25}

What are the common side effects that a women may experience when taking of Visanne® for the first time?

Visanne® has a favorable safety and tolerability profile. The most frequently reported adverse drug reactions during treatment with Visanne® in clinical trials were headache (9.0%), breast discomfort (5.4%), depressed mood (5.1%) and acne (5.1%) (see the Chapter Summary of Product Characteristics). The prolonged administration of progestins in general leads to endometrial regression, with irregular endometrial breakthrough bleeding. Therefore changes in bleeding pattern, such as spotting, irregular bleeding or amenorrhea, may occur during treatment with Visanne®. Clinical trial experience extending up to 15 months demonstrates that there is a progressive reduction in the incidence and intensity

of bleeding during continued treatment with Visanne®. In these trials, the changes in bleeding pattern associated with Visanne® did not impact on patient acceptability or persistence. To enhance treatment compliance in clinical practice, it is recommended to counsel patients about likely changes in bleeding pattern during treatment with Visanne®.

Who should not take Visanne®?

Visanne® is not indicated in children prior to menarche. The safety and efficacy of Visanne® in adolescents (i.e. menarche to 18 years) has not been established. There is no relevant indication for the use of Visanne® in the elderly. As Visanne® is a progestin preparation, it can be assumed that the special warnings and precautions for the use of oral progestins are also valid for the use of Visanne®, although not all of these warnings and precautions are based on respective findings in the clinical studies with Visanne®. Warnings that relate to the androgenic effects of certain progestins are not applicable to Visanne®.

Visanne® should not be used in the presence of any of the conditions listed below which are partially derived from information on other progestin-only preparations (see the Chapter Summary of Product Characteristics). Should any of the conditions appear during the use of Visanne®, treatment must be discontinued immediately:

- Active venous thromboembolic disorder
- Arterial and cardiovascular disease, past or present (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

Does Visanne® also have a contraceptive effect?

The majority of women suffering from endometriosis are of reproductive age and many of these women will therefore require contraception. As part of its mode of action, Visanne® inhibits ovulation.⁵³ However, no studies have directly assessed the contraceptive efficacy of Visanne®. Due to this lack of evidence, women taking Visanne® as treatment for endometriosis are advised to use non-hormonal contraception as a precaution to prevent unwanted pregnancies.

Many women with endometriosis will desire pregnancy once sufficient pain relief is achieved. Based on the available information, normal menstrual and ovarian activity resume rapidly after cessation of treatment with Visanne®, and there are case reports of women become pregnant shortly after ceasing treatment, including those with a prior history of infertility.³⁸

Visanne® should not be administered to pregnant women because there is no need to treat endometriosis during pregnancy.

Are there any risks if Visanne® is taken by mistake during pregnancy?

There are limited data on the use of dienogest in pregnant women. Available data from women exposed to dienogest during pregnancy and animal studies reveal no special risks on pregnancy, embryonic/fetal development, birth, or development after birth for humans. Reproduction toxicological studies are not suggestive of any teratogenic effects. There is no evidence of mutagenic and carcinogenic activities *in vitro* and *in vivo*, including carcinogenicity studies performed in Wistar rats and in mice.³⁹ However, Visanne® should not be administered to pregnant women because there is no need to treat endometriosis during pregnancy. Please also see the Chapter Summary of Product Characteristics.

Visanne®: Summary and Conclusions at a Glance

- Visanne® has been developed specifically for the treatment of endometriosis through a dedicated study program.
- Visanne® is an effective therapy for reducing the painful symptoms of endometriosis, with an efficacy significantly superior to placebo and equivalent to current standard therapy with GnRH agonists, such as leuprolide acetate and buserelin.
- Visanne® is suitable for long-term use due to its favorable safety and tolerability profile. Study data over 15 months show low incidences of treatment-related adverse events and low rates of treatment withdrawal.
- Visanne® effectively reduces endometriotic lesions.
- Visanne® does not produce relevant hypo-estrogenic side effects, such as decrease in BMD and menopausal symptoms (e.g. hot flushes) associated with GnRH agonists.
- Visanne® is not associated with clinically relevant androgenic effects and has no negative impact on lipid levels, unlike danazol, and some progestins.
- The most common adverse effects that occurred in clinical studies with Visanne® include headache, breast discomfort, acne, and depressed mood.
- The bleeding pattern becomes less regular after initiation of treatment with Visanne®. During continued treatment, there is a progressive reduction in the frequency and intensity of bleeding. To enhance treatment compliance in clinical practice, it is recommended to counsel patients about likely changes in bleeding pattern during treatment with Visanne®.
- Visanne® is formulated as a once-daily tablet of dienogest (2 mg)
- Visanne® is concluded to be a specific treatment option for alleviating the painful, debilitating symptoms of endometriosis and is suitable for long-term use.

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References

1. Kennedy S, Bergqvist A, Chapron C et al. ESHRE guideline for the diagnosis and treatment of endometriosis. *Hum Reprod* 2005; 20: 2698–2704.
2. Eskenazi B, Warner ML. Epidemiology of endometriosis. *Obstet Gynecol Clin North Am* 1997; 24: 235–258.
3. Wheeler JM. Epidemiology of endometriosis-associated infertility. *J Reprod Med* 1989; 34: 41–46.
4. Taylor MM. Endometriosis – a missed malady: *AORN J* 2003; 77: 298–303.
5. Crosignani P, Olive D, Bergqvist A, Luciano A. Advances in the management of endometriosis: an update for clinicians. *Hum Reprod Update* 2006; 12: 179–189.
6. Greene R, Stratton P, Cleary SD, Ballweg ML, Sinaii N. Diagnostic experience among 4,334 women reporting surgically diagnosed endometriosis. *Fertil Steril* 2009; 91: 32–39.
7. National Institutes of Health: <http://www.nichd.nih.gov/publications/pubs/endometriosis> (accessed January 2010).
8. European Network on Endometriosis. www.endonetwork.eu/ (accessed January 2010).
9. Farquhar C. Endometriosis. *BMJ* 2007; 334: 249–253.
10. Laufer MR, Sanfilippo J, Rose G. Adolescent endometriosis: diagnosis and treatment approaches. *J Pediatr Adolesc Gynecol* 2003; 16: S3–S11.
11. Farquhar CM. Extracts from the "clinical evidence". *Endometriosis. BMJ* 2000; 320: 1449–1452.
12. Mounsey AL, Wilgus A, Slawson DC. Diagnosis and management of endometriosis. *Am Fam Phys* 2006; 74: 594–600.
13. The Practice Committee of the American Society for Reproductive Medicine. Treatment of pelvic pain associated with endometriosis. *Fertil Steril* 2008; 90: S260–S269.
14. Koninckx PR, Meuleman C, Demeyere S, Lesaffre E, Cornillie FJ. Suggestive evidence that pelvic endometriosis is a progressive disease, whereas deeply infiltrating endometriosis is associated with pelvic pain. *Fertil Steril* 1991; 55: 759–765.
15. Ballweg ML. Big picture of endometriosis helps provide guidance on approach to teens: comparative historical data show endo starting younger, is more severe. *J Pediatr Adolesc Gynecol* 2003; 16 (Suppl): S21–S26.
16. Sinaii N, Plumb K, Cotton L et al. Differences in characteristics of 1,000 women with endometriosis based on extent of disease. *Fertil Steril* 2008; 89: 538–545.
17. Hummelshoj L, Prentice A, Groothuis P. Update on endometriosis. *Women's Health* 2006; 2: 53–56.
18. Ozkan S, Murk W, Arici A. Endometriosis and infertility: epidemiology and evidence-based treatments. *Ann NY Acad Sci* 2008; 1127: 92–100.
19. American Society for Reproductive Medicine. Revised American Society for Reproductive Medicine classification of endometriosis: 1996. *Fertil Steril* 1997; 67: 817–821.
20. Al-Jefout M, Dezarnaulds G, Cooper M et al. Diagnosis of endometriosis by detection of nerve fibres in an endometrial biopsy: a double blind study. *Hum Reprod* 2009; 24: 3019–3024.
21. Guo SW. Recurrence of endometriosis and its control. *Hum Reprod Update* 2009; 15: 441–461.
22. Allen C, Hopewell S, Prentice A. Nonsteroidal anti-inflammatory drugs for pain in women with endometriosis. *Cochrane Database of Systematic Reviews* 2009, Issue 2. Art. No.: CD004753.
23. Davis LJ, Kennedy SS, Moore J, Prentice A. Oral contraceptives for pain associated with endometriosis. *Cochrane Database Syst Revs* 2007; 3: CD001019.
24. Winkel CA, Scialli AR. Medical and surgical therapies for pain associated with endometriosis. *J Womens Health Gend Based Med* 2001; 10: 137–162.
25. Sagsveen M, Farmer JE, Prentice A, Breeze A. Gonadotrophin-releasing hormone analogues for endometriosis: bone mineral density. *Cochrane Database Syst Revs* 2003; 4: CD001297.
26. Mahutte NG, Arici A. Medical management of endometriosis-associated pain. *Obstet Gynecol Clin North Am* 2003; 30: 133–150.
27. Selak V, Farquhar C, Prentice A, Singla AA. Danazol for pelvic pain associated with endometriosis. *Cochrane Database of Systematic Reviews* 2007, Issue 4. Art. No.: CD000068.
28. Vercellini P, Cortesi I, Crosignani PG. Progestins for symptomatic endometriosis: a critical analysis of the evidence. *Fertil Steril* 1997; 68: 393–401.

29. Overton CE, Lindsay PC, Johal B et al. A randomized, double-blind, placebo-controlled study of luteal phase dydrogesterone (Duphaston) in women with minimal to mild endometriosis. *Fertil Steril* 1994; 62: 701–707.
30. Vercellini P, De Giorgi O, Oldani S, Cortesi I, Panazza S, Crosignani PG. Depot medroxyprogesterone acetate versus an oral contraceptive combined with very-low-dose danazol for long-term treatment of pelvic pain associated with endometriosis. *Am J Obstet Gynecol* 1996; 175: 396–401.
31. Crosignani PG, Luciano A, Ray A, Bergqvist A. Subcutaneous depot medroxyprogesterone acetate versus leuprolide acetate in the treatment of endometriosis-associated pain. *Hum Reprod* 2006; 21: 248–256.
32. Vercellini P, Fedele L, Pietropaolo G, Frontino G, Somigliana E, Crosignani PG. Progestogens for endometriosis: forward to the past. *Hum Reprod Update* 2003; 9: 387–396.
33. Physician Information. depo-subQ provera 104 medroxyprogesterone acetate injectable suspension 104 mg/0.65 mL. http://209.85.229.132/search?q=cache:pp1KgMPaQuol:www.pfizer.com/files/products/uspi_depo_subq_provera.pdf+depot+medroxyprogesterone+acetate+prescribing+information+usa&cd=2&hl=en&ct=clnk&gl=uk (accessed January 2010).
34. ESHRE Guideline for the Diagnosis and Treatment of Endometriosis. <http://guidelines.endometriosis.org/pain.html>. Updated 30 June 2007 (accessed January 2010).
35. Köhler G, Faustmann TA, Gerlinger C, Seitz C, Mueck AO. A dose-ranging study to determine the efficacy and safety of 1, 2, and 4mg of dienogest daily for endometriosis. *Int J Gynaecol Obstet* 2010; 108: 21–25.
36. Strowitzki T, Faustmann T, Gerlinger C, Seitz C. Dienogest in the treatment of endometriosis-associated pelvic pain: a 12-week, randomized, double-blind, placebo-controlled study. *Eur J Obstet Gynecol Reprod Biol* 2010.
37. Strowitzki T, Marr J, Gerlinger C, Faustmann T, Seitz C. Dienogest is as effective as leuprolide acetate in treating the painful symptoms of endometriosis: a 24-week, randomized, multicentre, open-label trial. *Hum Reprod* 2010; 25(3): 633–641.
38. Seitz C, Gerlinger C, Faustmann T, Strowitzki T. Safety of dienogest in the long-term treatment of endometriosis: a one-year, open-label, follow-up study. *Fertil Steril* 2009; 92: S107 (abstract).
39. Oettel M, Breitbarth H, Elger W et al. The pharmacological profile of dienogest. *Eur J Contracept Reprod Health Care* 1999; 4 (Suppl 1): 2–13.
40. Oettel M, Carol W, Elger W et al. A 19-norprogesterone without 17a-ethinyl group II: dienogest from a pharmacodynamic point of view. *Drugs Today* 1995; 31: 517–536.
41. Foster RH, Wilde MI. Dienogest. *Drugs* 1998; 56: 825–833.
42. Sasagawa S, Shimizu Y, Kami H et al. Dienogest is a selective progesterone receptor agonist in transactivation analysis with potent oral endometrial activity due to its efficient pharmacokinetic profile. *Steroids* 2008; 73: 222–231.
43. Sitruk-Ware R. New progestagens for contraceptive use. *Hum Reprod Update* 2006; 12: 169–178.
44. Schindler AE, Campagnoli C, Druckmann R et al. Classification and pharmacology of progestins. *Maturitas* 2003; 46 (Suppl 1): S7–S16.
45. Katsuki Y, Sasagawa S, Takano Y et al. Animal studies on the endocrinological profile of dienogest, a novel synthetic steroid. *Drugs Exp Clin Res* 1997; 23:45–62.
46. Kuhl H. Comparative pharmacology of newer progestogens. *Drugs* 1996; 51: 88–215.
47. Okada H, Nakajima T, Yoshimura T, Yasuda K, Kansaki H. The inhibitory effect of dienogest, a synthetic steroid, on the growth of human endometrial stromal cells in vitro. *Mol Hum Reprod* 2001; 7: 341–347.
48. Sasagawa S, Shimizu Y, Nagaoka T, Tokado H, Imada K, Mizuguchi K. Dienogest, a selective progestin, reduces plasma estradiol level through induction of apoptosis of granulosa cells in the ovarian dominant follicle without follicle-stimulating hormone suppression in monkeys. *J Endocrinol Invest* 2008; 31: 636–641.
49. Katsuki Y, Takano Y, Futamura Y et al. Effects of dienogest, a synthetic steroid, on experimental endometriosis in rats. *Eur J Endocrinol* 1998; 138: 216–226.
50. Fu L, Osuga Y, Morimoto C et al. Dienogest inhibits BrdU uptake with G0/G1 arrest in cultured endometriotic stromal cells. *Fertil Steril* 2008; 89: 1344–1347.
51. Shimizu Y, Takeuchi T, Mita S et al. Dienogest, a synthetic progestin, inhibits the proliferation of immortalized human endometrial epithelial cells with suppression of cyclin D1 gene expression. *Mol Hum Reprod* 2009; 15: 693–701.
52. Nakamura M, Katsuki Y, Shibutani Y, Oikawa T. Dienogest, a synthetic steroid, suppresses both embryonic and tumor-cell-induced angiogenesis. *Eur J Pharmacol* 1999; 386: 33–40.
53. C. Klipping, I. Duijkers, T. A. Faustmann, S. F. Klein, B. Schuett et al. Pharmacodynamic study of four oral dosages of dienogest. *Fertil Steril* 2010; 94(4): S181.
54. Sinaii N, Cleary SD, Younes N, Ballweg ML, Stratton P. Treatment utilization for endometriosis symptoms: a cross-sectional survey study of lifetime experience. *Fertil Steril* 2007; 87: 1277–1286.
55. Somigliana E, Vigano P, Barbara G, Vercellini P. Treatment of endometriosis-related pain: options and outcomes. *Front Biosci* 2009; 1: 455–465.
56. Gallagher EJ, Liebman M, Bijur PE. Prospective validation of clinically important changes in pain severity measured on a visual analog scale. *Ann Emerg Med* 2001; 38: 633–638.
57. Vincent K, Kennedy S, Stratton P. Pain scoring in endometriosis: entry criteria and outcome measures for clinical trials. Report from the Art and Science of Endometriosis meeting. *Fertil Steril* 2010; 93: 62–67.
58. Guy W. Clinical Global Impressions. In: *ECDEU Assessment Manual for Psychopharmacology*, Revised. DHEW Pub. (ADM). Rockville, MD: National Institute for Mental Health, 1976; 218–222.
59. Vercellini P, Trespidi L, De Giorgi O, Cortesi I, Parazzini F, Crosignani PG. Endometriosis and pelvic pain: relation to disease stage and localization. *Fertil Steril* 1996; 65: 299–304.
60. Rodgers AK, Falcone T. Treatment strategies for endometriosis. *Expert Opin Pharmacother* 2008; 9: 243–255.
61. Vercellini P, Somigliana E, Vigan P et al. Surgery for endometriosis-associated infertility: a pragmatic approach. *Hum Reprod* 2009; 24: 254–269.
62. Köhler G, Göretzlehner G, Amon I. Therapy of endometriosis with dienogest (article in German). *Zentralbl Gynakol* 1987; 109: 795–801.
63. Köhler G, Göretzlehner G, Brachmann K. Lipid metabolism during treatment of endometriosis with the progestin dienogest. *Acta Obstet Gynecol Scand* 1989; 68: 633–635.
64. Cosson M, Querleu D, Donnez J et al. Dienogest is as effective as triptorelin in the treatment of endometriosis after laparoscopic surgery: results of a prospective, multicenter, randomized study. *Fertil Steril* 2002; 77: 684–692.
65. Schindler AE, Christensen B, Henkel A, Oettel M, Moore C. High-dose pilot study with the novel progestogen dienogest in patients with endometriosis. *Gynecol Endocrinol* 2006; 22: 9–17.
66. Momoeda M, Taketani Y et al. Randomized, double-blind, multicentre, parallel-group dose-response study of dienogest in patients with endometriosis. *J Pharmacol Ther* 2007; 35: 769–783.
67. Palombo-Kinne E, Schellschmidt I, Schumacher U, Gräser T. Efficacy of a combined oral contraceptive containing 0.030 mg ethinylestradiol/2 mg dienogest for the treatment of papulopustular acne in comparison with placebo and 0.035 mg ethinylestradiol/2 mg cyproterone acetate. *Contraception* 2009; 79: 282–289.
68. Zimmermann T, Dietrich H, Wisser KH, Hoffmann H. The efficacy and tolerability of Valette: a postmarketing surveillance study. *Eur J Contracept Reprod Health Care* 1999; 4: 155–164.
69. von Schoultz B. Clinical efficacy and safety of combined estradiol valerate and dienogest: a new no-bleed treatment. *Climacteric* 2003; 6 (Suppl 2): 24–32.
70. Gräser T, Römer T, Wiedey KD, Janaud A. Climodien (estradiol valerate 2 mg plus dienogest 2 mg) is safe and effective in the treatment of postmenopausal complaints. *Climacteric* 2001; 4: 332–342.
71. Harada T, Momoeda M, Taketani Y et al. Dienogest is as effective as intranasal buserelin acetate for the relief of pain symptoms associated with endometriosis - a randomized, double-blind, multicenter, controlled trial. *Fertil Steril* 2009; 91: 675–681.
72. Schindler AE, Henkel A, Moore C, Oettel M. Effect and safety of high-dose dienogest (20 mg/day) in the treatment of women with endometriosis. *Arch Gynecol Obstet* 2009; (in press).
73. Gerlinger C, Endrikat J, Kallschnigg G, Wessel J. Evaluation of menstrual bleeding patterns: a new proposal for a universal guideline based on the analysis of more than 4500 bleeding diaries. *Eur J Contracept Reprod Health Care* 2007; 12: 203–211.
74. Nikschick S, Köhler G, Mannchen E. Carbohydrate metabolism during treatment of endometriosis with the progestin dienogest. *Exp Clin Endocrinol* 1989; 94: 211–214.

Visanne®: Summary of Product Characteristics

(Based on Europe approved Labelling.)

1. Name of the medicinal product

Visanne® 2 mg tablets.

2. Qualitative and quantitative composition

Each tablet contains 2 mg dienogest.

Excipient: each tablet contains 62.8 mg lactose monohydrate.

For a full list of excipients, see section 6.1 in the Chapter Summary of Product Characteristics.

3. Pharmaceutical form

Tablet

White to off-white, round, flat-faced, bevelled-edge tablets with an embossed 'B' on one side and a diameter of 7 mm.

4. Clinical particulars

4.1 Therapeutic indications

Treatment of endometriosis.

4.2 Posology and method of administration

Method of administration

For oral use.

Posology

The dosage of Visanne® is one tablet daily without any break, taken preferably at the same time each day with some liquid as needed. The tablet can be taken with or without food.

Tablets must be taken continuously without regard to vaginal bleeding. When a pack is finished the next one should be started without interruption.

There is no experience with Visanne® treatment >15 months in patients with endometriosis.

Treatment can be started on any day of the menstrual cycle.

Any hormonal contraception needs to be stopped prior to initiation of Visanne®. If contraception is required, non-hormonal methods of contraception should be used (e.g. barrier method).

Management of missed tablets:

The efficacy of Visanne® may be reduced in the event of missed tablets, vomiting and/or diarrhea (if occurring within 3–4 hours after tablet taking). In the event of one or more missed tablets, the woman should take one tablet only, as soon as she remembers, and should then continue the next day at her usual time. A tablet not absorbed due to vomiting or diarrhea should likewise be replaced by one tablet.

Additional information on special populations

Paediatric population

Visanne® is not indicated in children prior to menarche. The safety and efficacy of Visanne® in adolescents (menarche to 18 years) has not yet been established.

Geriatric population

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

Patients with hepatic impairment

Visanne® is contraindicated in patients with present or past severe hepatic disease (see section 4.3 in the Chapter Summary of Product Characteristics).

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, past or present (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 tumours (benign or malignant)
- Known or suspected sex hormone-dependent malignancies
- Undiagnosed vaginal bleeding
- Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use

As Visanne® is a progestogen-only preparation it can be assumed that the special warnings and precautions for use of 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 treatment with Visanne® can be started or continued.

Serious uterine bleeding

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). In the event of anemia, discontinuation of Visanne® should be considered.

Changes in bleeding pattern

The majority of patients treated with Visanne® experience changes in their menstrual bleeding pattern (see section 4.8 in the Chapter Summary of Product Characteristics).

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. Rather, the risk of cardiovascular and cerebral events is related to increasing age, hypertension and smoking. In women with hypertension the risk of stroke may be slightly enhanced by progestogen-only preparations.

Although not statistically significant, some studies indicate that there may be a slightly increased risk of venous thromboembolism (VTE; deep venous thrombosis, pulmonary embolism) associated with the use of progestogen-only preparations. Generally recognized risk factors for VTE include a positive personal or family history (VTE in a sibling or a parent at a relatively early age), age, obesity, prolonged immobilisation, major surgery, or major trauma. In case of long-term immobilisation it is advisable to discontinue the use of Visanne® (in the case of elective surgery at least 4 weeks in advance) and not to resume treatment until 2 weeks after complete remobilisation.

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

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

Tumours

A meta-analysis from 54 epidemiological studies reported that there is a slightly increased relative risk (relative risk = 1.24) of having breast cancer diagnosed in women who are currently using oral contraceptives, mainly using estrogen-progestogen preparations. The

excess risk gradually disappears during the course of the 10 years after cessation of 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 users of progestogen-only preparations 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 oral contraceptive users, the biological effects of oral contraceptives or a combination of both. The breast cancers diagnosed in users of oral contraceptives tend to be less advanced clinically than the cancers diagnosed in those who have never used oral contraceptives.

In rare cases, benign liver tumours, and even more rarely, malignant liver tumours have been reported in users of hormonal substances such as the one contained in Visanne®. In isolated cases, these tumours have led to life-threatening intra-abdominal haemorrhages. A hepatic tumour should be considered in the differential diagnosis when severe upper abdominal pain, liver enlargement or signs of intra-abdominal haemorrhage occur in women taking Visanne®.

Osteoporosis

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® (see section 5.1 in the Chapter Summary of Product Characteristics).

Other conditions

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

Dienogest 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®.

Dienogest 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®.

Pregnancies that occur among users of progestogen-only preparations used for contraception are more likely to be ectopic than are pregnancies among users of COCs. 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.

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.

Lactose

Each Visanne® tablet contains 62.8 mg of lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, lapp lactase deficiency, or glucose-galactose malabsorption who are on a lactose-free diet should consider the amount contained in Visanne®.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medication on Visanne®

Individual enzyme-inducers or inhibitors (CYP3A4)

Progestogens including dienogest are metabolised mainly by the CYP3A4 system 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 with enzyme-inducing properties

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

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

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 and estradiol. The systemic exposure of dienogest and estradiol at steady state, measured by AUC (0–24 hours) were decreased by 83% and 44%, respectively.

Substances with enzyme-inhibiting properties

Known CYP3A4 inhibitors such as azole antifungals (e.g. ketoconazole, itraconazole, fluconazole), cimetidine, verapamil, macrolides (e.g. erythromycin, clarithromycin and roxithromycin), diltiazem, protease inhibitors (e.g. ritonavir, saquinavir, indinavir, nelfinavir), antidepressants (e.g. nefazodone, fluvoxamine, fluoxetine), and grapefruit juice may increase plasma levels of progestogens and result in undesirable effects.

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 186% increase of AUC (0–24 hours) at steady state for dienogest. When co-administered with the moderate inhibitor erythromycin, the AUC (0–24 hours) of dienogest at steady state were increased by 62%.

The clinical relevance of these interactions is unknown.

Effects of dienogest on other medication

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

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

Interaction with food

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

Laboratory tests

The use of progestogens may influence the results of certain laboratory tests, including biochemical parameters of liver, thyroid, adrenal and renal function, plasma levels of (carrier) proteins (e.g. corticosteroid binding globulin and lipid/lipoprotein fractions), parameters of carbohydrate metabolism and parameters of coagulation and fibrinolysis. Changes generally remain within the normal laboratory range.

4.6 Pregnancy and lactation

Pregnancy

There is limited data from the use of dienogest in pregnant women.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see Chapter 5.3 in the Summary of Product Characteristics).

Visanne® must 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.

It is unknown whether dienogest is excreted in human milk. Data in animals have shown excretion of dienogest in rat milk.

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

Fertility

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

If contraception is required a non-hormonal method should be used (see section 4.2 in the Chapter Summary of Product Characteristics).

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 and use machines

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

4.8 Undesirable effects

Undesirable effects are more common during the first months after the start of treatment with Visanne®, and subside with continued treatment. There may be changes in bleeding pattern, such as spotting, irregular bleeding or amenorrhea. The following undesirable effects have been reported in users of Visanne®.

The most frequently reported undesirable effects under treatment with Visanne® are headache (9.0%), breast discomfort (5.4%), depressed mood (5.1%), and acne (5.1%).

In addition, the majority of patients treated with Visanne® experience changes in their menstrual bleeding pattern. Menstrual bleeding patterns were assessed systematically using patient diaries and were analyzed using the WHO 90-days reference period method. During the 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%). 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%). Changes in menstrual bleeding patterns were only occasionally reported as adverse event by the patients (see adverse event table).

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 (≥1/1,000 to <1/100). The frequencies are based on pooled data of four clinical trials, including 332 patients (100%).

Table 1: Adverse reactions table, phase III clinical trials, N=332

System Organ Class	Common	Uncommon
Blood and lymphatic system disorders		Anemia
Metabolism and nutrition disorders	Weight increase	Weight decrease Increased appetite
Psychiatric disorders	Depressed mood Sleep disorder Nervousness Loss of libido Altered mood	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		Unspecific circulatory system disorder Palpitations
Vascular disorders		Hypotension
Respiratory, thoracic and mediastinal disorders		Dyspnea
Gastrointestinal disorders	Nausea Abdominal pain Flatulence Abdominal distension Vomiting	Diarrhea Constipation Abdominal discomfort Gastrointestinal inflammation Gingivitis
Skin and subcutaneous tissue disorders	Acne Alopecia	Dry skin Hyperhidrosis Pruritus Hirsutism Onychoclasia Dandruff Dermatitis Abnormal hair growth Photosensitivity reaction pigmentation disorder

Table 1 (continued)

System Organ Class	Common	Uncommon
Musculoskeletal and connective tissue disorders	Back pain	Bone pain Muscle spasms Pain in extremities Heaviness in extremities
Renal and urinary disorders		Urinary tract infection
Reproductive system and breast disorders	Breast discomfort Ovarian cyst Hot flushes 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	Edema

4.9 Overdose

Acute toxicity studies performed with dienogest 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. A daily intake of 20–30 mg dienogest (10 to 15 times higher dose than in Visanne®) over 24 weeks of use was very well tolerated.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: progestogens; ATC code: G03D.

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

Dienogest acts on endometriosis by reducing the endogenous production of oestradiol and thereby suppresses 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.



Data on efficacy

Superiority of Visanne® over placebo was demonstrated in a 3-month study including 198 patients with endometriosis. EAPP was measured on a VAS (0–100 mm). After 3 months of treatment with Visanne® a statistically significant difference compared to placebo ($\Delta = 12.3$ mm; 95%CI: 6.4–18.1; $P < 0.0001$) and a clinically meaningful reduction of pain compared to baseline (mean reduction = $27.4 \text{ mm} \pm 22.9$) were demonstrated.

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

The open-label extension to this placebo-controlled study suggested a continued improvement of EAPP for a treatment duration of up to 15 months.

The placebo controlled results were supported by the results obtained in a 6-month, active-controlled study versus a GnRH agonist including 252 patients with endometriosis.

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.

In a small study ($n=8$ per dose group), a daily dose of 1 mg dienogest has been shown to induce an anovulatory state after 1 month of treatment. Visanne® has not been tested for contraceptive efficacy in larger studies.

Data on safety

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

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

No significant changes of the mean values of standard laboratory parameters (including haematology, blood chemistry, liver enzymes, lipids, and HbA1C) were observed during treatment with Visanne® for up to 15 months ($n=168$).

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 SHBG or corticoid binding globulin. 10% of the total serum drug concentration is present as free steroid, 90% is non-specifically bound to albumin.

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

Metabolism

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

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 faecal ratio of about 3:1 after oral administration of 0.1 mg/kg. The half-life of urinary metabolites excretion is 14 hours. Following oral administration approximately 86% of the dose administered is eliminated within 6 days, the bulk of this amount excreted within the first 24 hours, 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.

Pharmacokinetics in special populations

Visanne® has not been studied specifically in renally impaired subjects.

Visanne® has not been studied in subjects with hepatic impairment.

5.3 Preclinical safety data

Preclinical data reveal no special risks for humans based on conventional studies of 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 tumours.

NOTES

No special requirements

[illegible]

NOTES

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NOTES

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