J Med Drug Rev 2015;5:1–31

Gynaecological uses of dienogest alone and in combination with oestrogens

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SUMMARY

Dienogest is a hybrid synthetic gestagen which shares characteristics with 19-nortestosterone and progesterone derivatives, and also has advantageous substance specific pharmacological features. These include a high oral bioavailability, strong suppressive effect on the endometrium, lack of oestrogenic and androgenic effects, with a significant antiandrogenic efficacy component. Due to its reliable ovulation inhibiting effect, dienogest is a part of oral contraceptives in combination with ethinyl estradiol (Valette®, Maxim®) or is a part in a 4-phasic drug (Qlaira®) with dynamic dosage in combination with estradiol valerate (Qlaira®). Due to the specific efficacy profile of dienogest, Valette® and Maxim® can also be used for the treatment of moderate forms of acne, whereas Qlaira® is especially suitable for use as a contraceptive for women with heavy menstrual bleeding (hypermenorrhea). In the dosage of 2 mg in combination with estradiol valerate 1 or 2 mg a day (Lafamme® 1/2 mg or 2/2 mg), dienogest is tried and tested as a continuous hormone replacement therapy for postmenopausal women. During the therapy, the climacteric complaints improve quickly, with a positive impact especially on mood, sleep and mental functioning. As monotherapy (Visanne®), dienogest is used for the treatment of endometriosis. In terms of pain reduction, it was shown to be equal to the GnRH analogue leuprorelin acetate, but with a better tolerability. The lower abdominal pain typical for endometriosis, receded quickly and laparoscopies showed a clear regression of endometriosis lesions.

Key words: Acne · dienogest · endometriosis · estradiol · estradiol valerate · ethinyl estradiol · hormone replacement therapy · hypermenorrhea · contraception · contraceptives · Lafamme · Maxim · Qlaira · Valette · birth control · Visanne

Index

1. Introduction 2

2. Pharmacology of dienogest 2
2.1 Chemistry 2
2.2 Pharmacokinetics 2
2.3 Pharmacodynamics 3
2.3.1 Endocrinological effects 3
2.3.2 Endometrial activity 5
2.3.3 Other effects 5

3. Ethinyl estradiol and dienogest (Valette®/Maxim®) 6
3.1 Use as contraceptive 6
3.1.1 Methodology of the clinical trials 7
3.1.2 Contraceptive efficacy 7
3.1.3 Safety and tolerability 8
3.1.4 Cycle and bleeding control 9
3.1.5 Impact on lab results, coagulation system and blood pressure 9
3.1.6 Return of fertility after using Valette® 10
3.2 Use in women with acne 10

4. Estradiol valerate and dienogest (Qlaira®) 11
4.1 Use as a contraceptive 11
4.1.1 Efficacy 12
4.1.2 Safety and tolerability 12
4.1.3 Impact on metabolic and coagulation parameters 14
4.1.4 Cycle and bleeding control 14
4.2 Use as contraceptive for heavy menstrual bleeding 15
4.2.1 Efficacy for the treatment of hypermenorrhea 16
4.2.2 Benefits for work productivity and activities of daily living 17

5. Hormone replacement therapy with estradiol valerate anddienogest (Lafamme®) 18
5.1 Efficacy for climacteric complaints 19
5.1.1 Impact on hot flushes 19
5.1.2 Impact on insomnia 20
5.1.3 Antidepressive effect 20
5.1.4 Improvement of cognitive functioning 21
5.2 Cessation of menstrual bleeding 22
5.3 Impact on body weight and metabolic parameters 22
5.4 Safety 22
5.4.1 Endometrial protection 22
5.4.2 Tolerability 22

6. Therapy of endometriosis with dienogest (Visanne®) 22
6.1 Clinical efficacy 23
6.1.1 Dose-finding study 23
6.1.2 Pain relief 23
6.1.3 Reduction of endometriosis lesions 25
6.2 Safety and tolerability 25

Expert comment 26

Literature 27

1. Introduction

Progesterone as the main natural gestagen (corpus luteum hormone), prepares the organism for a pregnancy with its effects on the female reproductive organs during the second phase of the menstrual cycle. It creates an important basis for contraception and nidation and afterwards is responsible for protecting the subsequent gravidity. Synthetic analogues of progesterones, which are also known as gestagens, are used in combination with an oestrogen as hormonal contraceptives, for acne or hypermenorrhea, as hormone replacement therapy for postmenopausal women, but also as monotherapies, e.g. for treating endometriosis. The anti-contraceptive effect of hormonal combination drugs is mainly due to the ovulation inhibiting effect of the gestagen component, which is supplemented by the inhibiting effect of the oestrogen on the FSH release and follicle growth, and by gestagenic effects on the cervical mucus (increase of viscosity), endometrium (atrophy and stromal decidual change) and the motility of the fallopian tubes. The focus of the following overview is on the synthetic gestagen dienogest with its various substance combinations and indications. Dienogest has significantly different attributes compared to other gestagens. The emphasis lies on the discrepancy between its mild effects on the organism as a whole and its strong effects on the endometrium, as well as on the anti-androgenic partial effect. Dienogest is used as gestagen component in oral contraceptives, with a dosage of 2 mg/day (in combination with 30 μg/day ethinyl estradiol) or a maximum of 3 mg/day (in combination with 1–3 mg/day estradiol valerate), and as a hormone replacement therapy it is used in a dosage of 2 mg/day (in combination with 1 or 2 mg estradiol valerate per day). In the same dosage of 2 mg/day, dienogest is approved as a monotherapy for the treatment of endometriosis.

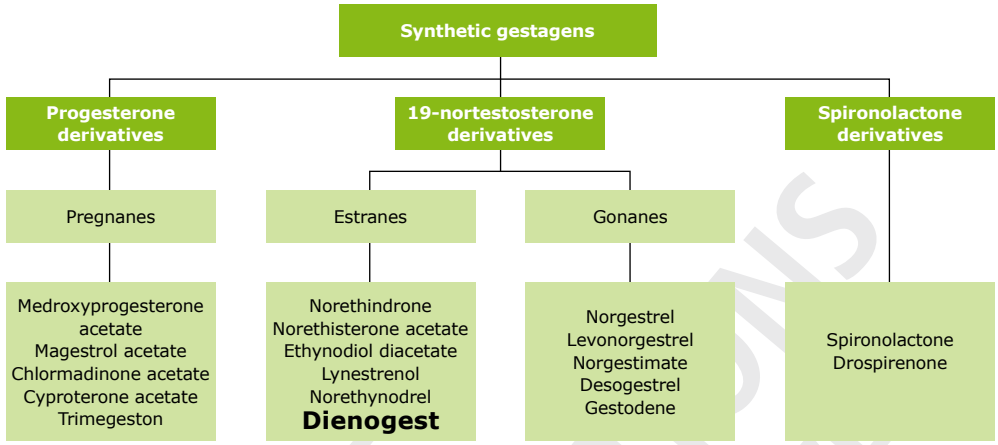


Figure 1. Chemical classification of synthetic gestagens (adapted from Ruan et al., 2012)

2. Pharmacology of dienogest

2.1 Chemistry

Synthetic gestagens are classified according to their chemical structure into C-21 bonds (progesterone derivatives, pregnanes) with a structure of 21 carbon atoms – which include also the natural progesterone – and in derivatives of the C-19 connection 19-nortestosterone; the latter include the estranes, with one methyl group in position C-13, and the gonanes with an ethyl group in C-13. Another gestagen group are the spironlactone derivatives (figure 1). Based on this classification, dienogest is an estrane and 19-nortestosterone derivative; however it does not have an ethinyl group at C-17α like the other 19-nortestosterone derivatives, but a cyanomethyl group (figure 2). The latter is significantly less reactive than the ethinyl group, i.e. it does not inhibit or inactivate the metabolising liver enzymes (Guengerich, 1990; Böcker & Kleingeist, 1995). Another chemically unique characteristic of dienogest is its double bond in the steroid ring B. The resulting system of conjugated double bonds in the steroid rings A and B is responsible for the high affinity of dienogest to the progesterone receptors. Therefore, dienogest has the active properties of both a 19-nortestosterone and a progesterone derivative.

2.2 Pharmacokinetics

The pharmacokinetic attributes of dienogest, based on the ADME classification (short for absorption, distribution, metabolism, excretion) are summarized in table 1.

Like other 19-nortestosterone derivatives – and as opposed to some progesterone derivatives – dienogest has a high oral

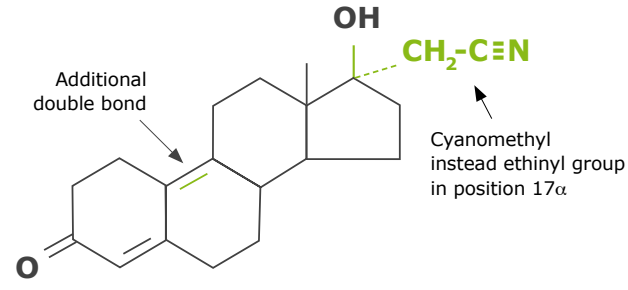


Figure 2. Chemical structure of dienogest

Table 1. Pharmacokinetics of dienogest
(adapted from Ruan et al., 2012)

Parameter	Attribute
Absorption	Fast and almost complete; bioavailability 90 %
Distribution	10 % free dienogest, 90 % unspecific and weak binding to albumin; no binding to SHBG and CBG
Metabolism	Hydroxylation and conjugation; metabolites are virtually inactive. Due to the fast elimination of metabolites, there is mainly unchanged dienogest in the plasma
Elimination	Renal with an elimination half-life from the plasma of ca. 10 hours
Steady State	Reached after 2 – 3 days, irrespective of SHBG level. No relevant accumulation

Abbreviations: SHBG = sex hormone-binding globulin, CBG = corticosteroid-binding globulin

bioavailability of over 90 %. Also in terms of the distribution parameters C_{max} (maximum concentration in the plasma) and t_{max} (time to reach C_{max}), dienogest is similar to the other 19-nortestosterone derivatives, whereas with regard to the overall volume of distribution, it correlates more with the gestagens of the progesterone line. Since the gestagenic active doses of dienogest are comparable with oral and subcutaneous administration, a relevant hepatic first pass effect is virtually impossible (Oettel et al., 1993).

As a consequence of the cyanomethyl group in the dienogest molecule, the active substance does not significantly impact on the specific mitochondrial P450 enzyme system in the liver mitochondria, as opposed to the gestagens which have an ethinyl substitute in C-17α (Böcker & Kleingeist, 1995).

This is a feature dienogest shares with estradiol (Mueck et al., 2000) which means that combination drugs with these two hormonal substances do not induce or inhibit cytochrome P450 (Ruan et al., 2012).

The pharmacokinetics of dienogest are between 1 and 8 mg/day linearly dosage dependent. The serum concentrations after the first oral dose of 2 mg are already over the minimum concentration of 4.0 ng/ml for the duration of 24 hours which is necessary to inhibit the ovulation (Oettel et al., 1999a). Steady state concentrations in the plasma are reached within only 2 to 3 days. The elimination half-life of dienogest is like those of the other 19-nortestosterone derivatives relatively short – it is between 8 and 10 hours in young women of reproductive age and between 11 to 12 hours in postmenopausal women (Oettel et al., 1999a). An accumulation of the active substance is therefore not expected. This is also due to the lack of affinity to the sex hormone-binding globulin (SHBG) which differentiates dienogest from other gestagens where an accumulation is possible as a result of the high binding affinity to SHBG. A practical advantage of the lack of SHBG affinity of dienogest is that the active substance does not release any testosterone from its protein bond. This also contributes to the fact that dienogest has no androgenic attributes as opposed to other gestagens (Oettel et al., 1999a).

Dienogest is mainly metabolized via the CYP3A4 system in the intestinal mucosa and the liver by reducing the ketone group, with various hydroxylation reactions and the elimination of the cyanomethyl group (Oettel et al., 1995b; Lippert & Mueck, 1995; Zimmermann et al., 2000a). Although dienogest itself does not have any relevant enzyme-inducing or -inhibiting effects, other CYP3A4 inductors or inhibitors can have an impact on the dienogest metabolism. The different metabolites of dienogest usually show a significantly lower affinity to the progesterone receptors than the mother substance and are very quickly eliminated by the kidney – within 24 hours after administration, whereas unchanged dienogest is apparently renally reabsorbed. The latter therefore makes up the main part of the active substance in the plasma.

In table 2, elimination half-life, distribution volume and plasma binding rates of dienogest are shown in comparison to other 19-nortestosterone derivatives.

2.3. Pharmacodynamics

2.3.1 Endocrinological effects

Table 3 shows the receptor specificity of different gestagens and the unique position of dienogest. In vitro, dienogest binds

Table 2. Pharmacokinetics of different 19-nortestosterone derivatives (adapted from Oettel et al., 1999a)

	Norethisterone	Levonorgestrel	3-Ketodesogestrel	Gestodene	Dienogest
Elimination half-life, h	7.6	14.8	11.2	11.2	9.1
Distribution volume, l	240	120	110	32	46
Plasma protein binding, %					
Albumin	61.0	50.0	63.5	24.1	91.0
SHBG	35.5	47.5	32.0	75.3	0
Free, not bound	3.5	2.5	4.5	0.6	9.0

Abbreviations: SHBG = sex hormone-binding globulin

fact box PHARMACOKINETICS

- High bioavailability after oral administration.
- Linear pharmacokinetics with daily administration.
- Short plasma half-life and therefore good controllability of the therapy and low risk of accumulation.
- After single doses of 2 mg, reliably high serum concentrations above the necessary levels for 24 hours, to achieve the inhibition of ovulation.
- No relevant first pass effect in the liver.
- Elimination primarily via the kidney.
- No binding to specific transport proteins for endogenous steroids (SHBG, CBG).
- High concentrations of the unbound active substance in the blood.
- The metabolites are virtually ineffective on an endocrinological level.

highly selectively to progesterone receptors in human uterus tissue, however with moderate binding affinity (Oettel et al., 1995a; Juchem et al., 1995). In the Clauberg-McPhail assay with young rabbits, used to test the secretory transformation of oestrogen-stimulating endometrium, dienogest showed a high gestagenic activity (Oettel et al., 1995b; Stölzner et al., 1983; Oettel & Kurischko, 1980). In the Kaufmann assay with postmenopausal women treated with 50 μg/day ethinyl estradiol, an oral dienogest dose of 0.45 mg/day corresponding to ca. 6 mg per cycle, was necessary to achieve a complete secretory transformation of the endometrium (Böhm et al., 1985).

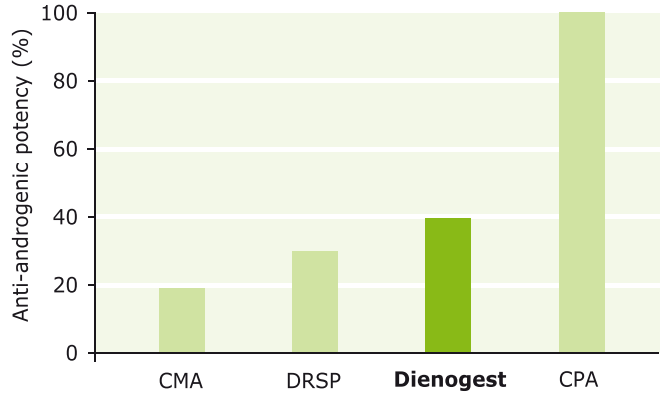
The fact that dienogest, despite its relatively low binding affinity on the progesterone receptors, has in vivo a potent gestagenic effect on the endometrium, can be explained by its advantageous pharmacokinetic attributes with high bioavailability and, compared to other gestagens, a significantly higher proportion of free, biologically active substance in the blood.

The binding of dienogest to the oestrogen and androgen receptors is negligible. As a result, dienogest in clinically relevant doses has no direct oestrogenic and androgenic activity in humans. The lack of any extragenital anti-oestrogenic partial effect has the advantage that positive oestrogen effects, e.g. on sleep, psyche, mental functioning and vessels are not antagonized. The lack of vasoconstrictive activity of dienogest could be proven, both in vitro due to its calcium antagonistic activity (Mueck et al., 1995), and in clinical trials (Mueck et al., 2001).

Receptor binding studies showed that apart from a potent gestagenic activity, dienogest like cyproterone acetate also has a pronounced anti-androgenic activity (Sasagawa et al., 2008a). The Hershberger assay, an in vivo model with infantile, testosterone treated, castrated rats, showed that the anti-androgenic potency of dienogest was approximately 40 % of the potency of cyproterone acetate (Stölzner et al., 1985; Oettel et al., 2001) **(figure 3)**.

In a dose-finding study, the ovulation inhibiting minimal dosage of oral dienogest for menstruating women was 1 mg/day (Oettel et al., 1995b; Moore et al., 1995). The inhibition of the ovulation was not based on a central anti-gonadotropic effect, i.e. a secretion inhibition of the follicle-stimulating hormone (FSH) and the luteinizing hormone (LH), but was primarily based on peripheral mechanisms (Oettel et al., 1995b; Moore et al., 1995) with an inhibition of the pre-ovulatory ovarian increase of 17ß-estradiol. For this reason, there is no positive feedback to the pituitary gland and the ovulatory FSH and LH peaks do not set in at all or set in with irregular delays (Oettel et al., 1997).

A glucocorticoid and mineralocorticoid effect of dienogest could also not be detected (Oettel et al., 1999; Sasagawa et al., 2008a). This may be clinically advantageous because in vitro studies have shown that other gestagens with their glucocorticoid-like



Abbreviations: CMA = chlormadinone acetate, CPA = cyproterone acetate, DRSP = drospirenone

Figure 3. Relative anti-androgenic potency of different gestagens in the Hershberger assay (Stölzner et al., 1985; Oettel et al., 2001)

Table 3. Receptor selectivity of different gestagens (adapted from Oettel et al., 1999a)

	Receptor				
Gestagen	**Progesterone**	**Oestrogen**	**Glucocorticoid**	**Mineralocorticoid**	**Androgen**
Progesteron	+	-	+	+	-
Gestodene	+	-	+	+	+
3-keto-desogestrel*	+	-	+	-	+
Levonorgestrel	+	-	+	+	+
Drospirenone	+	-	-	++	-
Dienogest	+	-	-	-	-

*3-Keto-desogestrel (etonogestrel) is the active from of desogestrel.
- No or low effect, + marked effect, ++ strong effect

Table 4. Endocrine partial effects of different gestagens (adapted from Oettel et al., 1999a)

Gestagen	oestrogenic effect	anti-oestrogenic effect	androgenic effect	anti-androgenic effect
Progesterone	-	+	-	-
Chlormadinone acetate	-	+	-	+
Cyproterone acetate	-	(+)	-	++
Norethisterone acetate	+	+	+	-
Levonorgestrel	-	++	+	-
Desogestrel	-	+	-	-
Gestodene	-	+	+	-
Dienogest	-	-	-	+/++

- No or low effect, + marked effect, ++ strong effect

effect increase the pro-coagulative activity of thrombin (Herkert et al., 2001; Oettel et al., 2001) which may be disadvantageous for the thrombotic risk.

Receptor selectivity and endocrine partial effects of dienogest and of several other gestagens are shown in table 3 and 4.

2.3.2 Endometrial activity

The most important physiological effect of natural progesterone on the endometrium is to transform the mucosa from the state of oestrogen-stimulating proliferation into the secretory state. With the decreasing hormone secretion, as a result of the corpus luteum regression at the end of the ovarian cycle, it comes to menstrual bleeding in the sense of withdrawal bleeding. A long-term exposition to gestagens however, results in an atrophy of the endometrium.

The most important reason for using dienogest in all its clinical applications and, most of all, for the treatment of endometriosis, is its extremely potent gestagenic activity in the endometrium. This was documented in various experimental studies (Oettel et al., 1999b) and in clinical studies on the endometrial safety of dienogest (Gräser et al., 2000a; Gräser et al., 2000b; Römer, 2009; Bitzer et al., 2011). The assessment of the ratio between the dosage for inhibiting the ovulation (mg/day) and the dosage for endometrial transformation (mg/cycle) with the Kaufmann assay, showed the extremely high level of 17 for dienogest (Oettel et al., 1999b) (figure 4). The endocrinological pharmacodynamics of dienogest are therefore characterized by its pronounced peripheral focus of activity on the endometrium which is very similar to natural progesterone.

2.3.3 Other effects

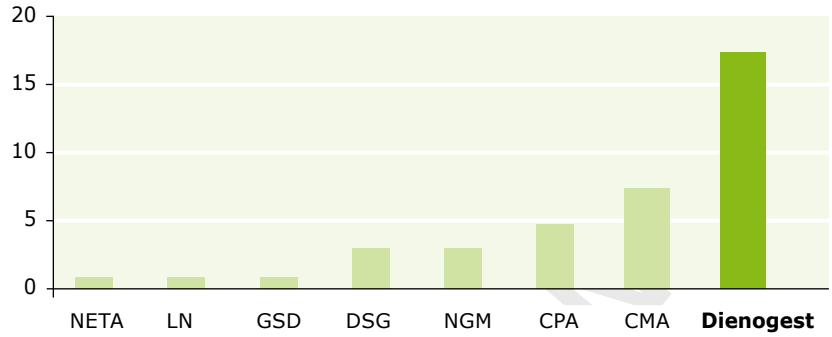
Dienogest showed in vitro and in vivo an anti-proliferative effect (Oettel et al., 1995b). As opposed to other gestagens, dienogest inhibited the oestrogen-dependent tumor growth of HEC-88nu cells in mice (Katsuki et al., 1997). This cell line derived from human endometrial cancer, expresses oestrogen receptors but no progesterone receptors. In the mouse model, dienogest also inhibited the oestrogen stimulated growth of the cell lines Ishikawa (endometrial cancer) and MCF-7 (breast cancer) which both express both oestrogen receptors and progesterone receptors (Katsuki et al., 1997).

Animal studies indicate that dienogest, via the immediate stimulation of the apoptosis of granulosa cells in the ovaries may also contribute to a reduction of estradiol levels in the plasma (Sasagawa et al., 2008b).

The angiogenesis is probably essential for the emergence and progression of an endometriosis. Therefore it is interesting that dienogest also has an anti-angiogenic effect. This effect could

be demonstrated both with embryonic chicken cells in the chorion-allantois-membrane test and with tumor cells of mice (S-180) in the mouse dorsal air sac assay (Nakamura et al., 1999). Furthermore, dienogest also has anti-inflammatory properties. It inhibited the aromatase and cyclooxygenase-2 expression, as well as the development of prostaglandin E2 in spheroid cultures of human endometriotic stroma cells and endometrial epithelial cells (Yamanaka et al., 2012; Shimizu et al., 2011).

Dienogest in the dosage of up to 20 mg/day over a treatment duration of 24 weeks, for women with endometriosis, had no clinically relevant effect on the lipid metabolism, liver enzymes, coagulation system and thyroid metabolism (Schindler, 2010).



Abbreviations: CMA = chlormadinone acetate, CPA = cyproterone acetate, DSG = desogestrel, GSD = gestodene, LNG = levonorgestrel, NETA = norethisterone acetate, NGM = norgestimate

Figure 4. Index of the endometrial efficacy as a ratio of the ovulation inhibiting dosage (mg/day) and the endometrial transformation dosage (mg/14 days) in the Kaufmann assay for different gestagens (adapted from Oettel et al., 1999a)

3. Ethinyl estradiol and dienogest (Valette®/Maxim®)

3.1 Use as a contraceptive

The combination of 30 μg ethinyl estradiol and 2 mg dienogest was launched in the German market in 1995 with the trade name Valette® and remains until today the most widely sold oral contraceptive in Germany. Nowadays, generics are also available, but only Maxim® is identical to Valette® in terms of active substances and excipients, as well as mode of administration. Maxim® has now superseded Valette® in its importance. It is a low dose monophasic combination drug with 21 coated tablets per cycle. After 21 administration days, follows a 7 day administration break.

The development of ethinyl estradiol/dienogest was the result of intensive efforts in pharmaceutical research in the early 1990s, with the goal of further improving the tolerability of oral contraceptives. Dienogest does not only have a clear ovulation inhibiting effect, but also – as opposed to many other gestagens – an anti-androgenic partial effect. This makes ethinyl estradiol/dienogest a very reliable oral contraceptive which hardly affects the lipid and carbohydrate metabolism, and it is also an effective therapy for women with moderate acne.

The contraceptive efficacy of ethinyl estradiol/dienogest relies on several mechanisms, where the ovulation inhibiting effect of dienogest is in the foreground. With 2 mg, the oral daily dose of dienogest in this combination drug is about double the minimal ovulation inhibiting dose of 1 mg/day (Oettel et al., 1995b; Moore et al., 1995). In addition, there is a synergy effect with ethinyl estradiol which results in a time-dependent reduction of the LH and FSH levels, causing a durable inhibition of follicular maturation, estradiol production and ovulation (Schleussner et al., 1995). Other contraceptive mechanisms are the gestagen-dependent inhibition of the cervical mucus production and the secretion of a highly viscous cervical mucus which sperm can hardly permeate (Endrikat et al., 2013; Rivera et al., 1999). Apart from that, dienogest, due to its strong gestagenic activity on the endometrium, reduces the proliferative effect of ethinyl estradiol and therefore reduces the risk of an endometrial hyperplasia, even after a longer term usage of the combination drug.

The contraceptive efficacy and safety of ethinyl estradiol/dienogest (Valette®) was examined in several clinical studies and documented extensively.

fact box PHARMACODYNAMICS

- Very strong gestagenic activity on the endometrium.
- The ovulation inhibiting minimal dose of oral dienogest for menstruating women is 1 mg/day.
- No noteworthy oestrogenic or androgenic effect and no noteworthy extragenital anti-oestrogenic partial effect.
- In-vivo, negligible glucocorticoid and mineralocorticoid effect.
- Clear anti-androgenic activity component.
- Anti-proliferative, anti-angiogenic and anti-inflammatory attributes.

3.1.1 Methodology in the clinical trials

- **Study I.** Open, non-controlled study with 22 healthy women with ovulatory cycles (aged 20–34 years) on the ovulation inhibiting effect of Valette®. Transvaginal ultrasound examinations of the ovaries and tests of the serum progesterone, 17ß-estradiol, FSH and LH levels were carried out. The ovarian activity of the study participants was documented over a control cycle before treatment, over three cycles during the administration and over another control cycle after the administration ended, based on an assessment scale **(table 5)** (Spona et al., 1997a).

- **Study II.** Open, randomized, multicenter, pilot study to examine the efficacy and safety of Valette® in 12 gynaecological practices with 93 women (Moore et al., 1999a). Assessed were one control cycle and 6 treatment cycles (531 cycles in total). In a subgroup of 27 women, the progesterone serum levels were also measured over the duration of 6 cycles.

- **Study III.** Main study on the efficacy and safety of Valette® (Moore et al., 1999a). The study was an open, non-controlled, multicenter, phase III study which included the calculation of the Pearl Index, which is required by the regulations of the European Commission of the European Community for testing oral contraceptives (directive from 1989). The study was carried out in 146 German centres with 2,290 healthy women (aged 18–40 years) and included the assessment of a total of 28,183 cycles. The individual treatment duration varied between 1 and 22 cycles. Participants kept a cycle diary where they noted anything exceptional, side-effects and bleeding behaviour. Clinical examinations were carried out every 3 months. 64 % of the participants had used a different contraceptive immediately before the trial (in 69 % a low dose drug), 14 % were first users and 22 % had used an oral contraceptive at some point in the past but had a longer pause before starting the trial. The compliance of the participants was excellent – for 97.2 % of the cycles a correct administration of the tablets was documented. In a subgroup of 29 women, the impact of Valette® on different hormonal and metabolic serum parameters was measured over 3 cycles. The results were compared with those of the hormone-free control cycle before the start of the treatment.

- **Study IV.** Controlled, randomised, comparative, monocenter, double-blind study on the impact of Valette® on the lipid metabolism, blood coagulation and several other blood levels vs. another contraceptive (0.02 mg ethinyl estradiol + 0.15 mg desogestrel) (Moore et al., 1999a). Both study groups included 20 women each (aged 18–40 years) and the duration of the administration of both contraceptives was 6 cycles, respectively.

- **Study V.** Placebo-controlled, double-blind study over the duration of one cycle, to examine the impact of Valette® on the coagulation system (Moore et al., 1999a). This study was completed according to the protocol with 36 healthy subjects (aged 19–35 years) with a regular menstrual cycle. On days 7, 14 and 21 of the previous cycle and during the administration, the following coagulation parameters were measured: Prothrombin fragment 1+2, fibrinogen, factor VII, thrombin-antithrombin complex, antithrombin III, protein C, protein S, plasminogen, tissue plasminogen activator (TPA), plasminogen activator inhibitor (PAI), D-dimer and plasmin-antiplasmin (PAP) complex.

- **Observational study.** Non-interventional study on the efficacy and tolerability of Valette® in gynaecological routine practice (Zimmermann et al., 1999a). 2,029 office-based gynaecologists from Germany took part and delivered data of 16,087 women with a total of 92,146 cycles, corresponding to 7,679 women-years.

- **Fertility trial.** Prospective, non-interventional, population-based (questionnaire) study in Germany on the fertility of women who wanted to get pregnant after discontinuing Valette® (Wiegratz et al., 2006). The questionnaires of 706 women were evaluable and 652 of these also delivered pregnancy data for the duration of the 1 year follow-up.

Table 5. Assessment scheme for the ovarian activity (adapted from Spona et al., 1997a)

Grade		FLS (mm)	Hormone level	
			Estradiol (nmol/l)	Progesterone (nmol/l)
1	No activity	≤ 10		
2	Possible activity	> 10		
3	Non-active FLS	> 13	≤ 0.1	
4	Active FLS	> 13	> 0.1	≤ 5
5	Suspected LUF	> 13, persisting	> 0.1	> 5
6	Ovulation	> 13, ruptured	> 0.1	> 5

Notes: 0.1 nmol/l estradiol = 30 pg/ml; 5 nmol/l progesterone = 1.6 ng/ml
Abbreviations: FLS = follicle-like structure, LUF = luteinized unruptured follicle

3.1.2 Contraceptive efficacy

In **study I**, Valette® delivered in all 22 women a reliable inhibition of ovulation. The follicular maturation was suppressed most effectively in the first administration cycle. In one woman, a luteinized unruptured follicle (LUF) syn-

drome was observed in the second cycle and in three women in the third cycle (figure 5). In the control cycle after the administration, 15 women ovulated and 5 showed a LUF syndrome (Spona et al., 1997a).

In study II, during a total of 531 cycles not a single pregnancy occurred. The serum progesterone level was almost completely suppressed (figure 6) (Moore et al., 1999a).

In study III with 2,290 women with up to 22 cycles (total number of cycles 28,183), there were 16 pregnancies. This corresponds with an unadjusted Pearl Index of 0.68. When missed tablet administrations, vomiting, drug interactions etc. and the resulting 11 pregnancies were taken into account, the adjusted Pearl Index was 0.21. In the life table analysis, the cumulative failure rates were 0.0052 after 6 cycles, 0.0076 after 12 cycles and 0.0089 after 18 and 22 cycles (Moore et al., 1999a). While the failure rates in everyday practice are probably higher due to frequent administration errors than under trial conditions, a Pearl Index of 0.21 nevertheless shows an extremely high contraceptive efficacy. The contraceptive efficacy of Valette® demonstrated in this study, was roughly comparable with the results of oral contraceptives containing levonorgestrel and gestodene (Brill et al., 1991; Corson, 1993). In an observational study with more than 16,000 participating women, there were only 11 unwanted pregnancies during the course of more than 92,000 menstrual cycles, which corresponds with an unadjusted Pearl Index of 0.14. At least 4 of these pregnancies were caused by usage errors.

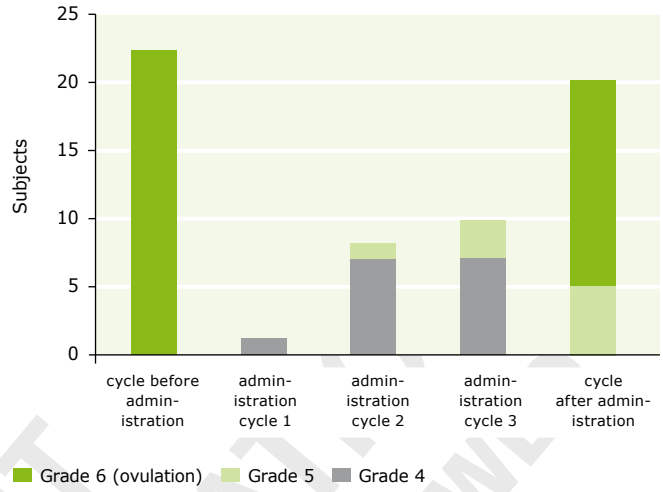


Figure 5. Follicle development (grade 4–6) before, during, and after contraceptive use of Valette® in 22 healthy women (study I) (adapted from Moore et al., 1999a)

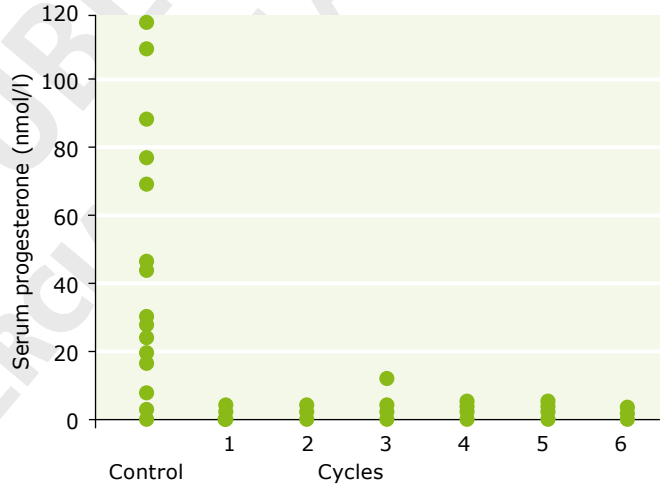


Figure 6. Serum progesterone levels in 27 healthy women during contraceptive use of Valette® (study II) (adapted from Moore et al., 1999a)

3.1.3 Safety and tolerability

The documented side-effects in studies II and III are shown in table 6. Headaches occurred sporadically and were usually mild. The incidence of headaches increased in the first administration cycle to 14–17 % and decreased subsequently. In the sixth cycle their incidence was already lower than in the cycles prior to the administration of Valette®. Also, the feeling of tension in the breasts was usually described as mild. Its incidence increased in the first cycle (10–13 %) and subsequently became rarer. Temporary nausea and vomiting were reported by 7 % of the women in study III. The frequency of these complaints decreased with the duration of the administration and went back to 0 by the 18th cycle. In study II, nausea and vomiting were only occasionally observed during the whole duration of the administration.

In both studies (II and III), the incidence of depressive moods did not increase vs. the precursor (control) cycle. In study II, it even decreased from previously 3.4 % in the control cycle to 1.2 % during the 6th administration cycle. Oedemas only occurred occasionally with a mild to moderate severity. Libido changes were very rare.

In an observational study, the most commonly reported side-effects were breast pain (1.4 % of all women), weight gain (1.1 %), headaches (0.9 %), nausea/vomiting (0.9 %), dysmenorrhea (0.3 %), libido loss (0.3 %) and depressive moods (0.2 %). Only 3.2 % of the women discontinued the treatment due to side-effects (Zimmermann et al., 1999a).

Serious side-effects. In the studies I to V, 34 adverse events occurred which were classified as serious (Moore et al., 1999a).

However, only in 7 of these cases a possible or likely connection with the usage of Valette® was made. These included 3 ovarian cysts, one benign dysplasia in the breast, one thrombophlebitis in the lower extremity, one hypermenorrhea and one

leiomyoma in the uterus. In the observational study, a serious side-effect occurred in 6 (0.03 %) women of the 16,267 women (2 thromboses, 1 suspected lung embolism, 2 liver dysfunctions, 1 cervical metaplasia) (Zimmermann et al., 1999a).

Thrombotic risk. It is an undisputed fact that according to current knowledge, combined hormonal contraceptives (CHC) increase the risk of thromboembolic events like venous thromboembolisms (VTE). Nevertheless, it still has not been finally clarified whether there are differences in the risk between the different CHCs and if so which. The same goes for the gestagen component of CHCs. The Committee for Medicinal Products for Human Use (CHMP) at the European Medicines Agency (EMA) only recently concluded that the benefit of low dosed (ethinyl estradiol < 50 μg) CHCs to prevent unwanted pregnancies still outweighs the risks and that the familiar VTE risk associated with all CHCs is low (European Medicines Agency, 2014). However, it is pointed out that physicians should inform women about the risk of VTE and its signs and symptoms, as well as the differences between the drugs in terms of their VTE risk. When prescribing a CHC, the individual risk factors of a woman should also be considered. Based on the current data, the CHMP classifies the VTE risk of CHC which contain levonorgestrel, norethisterone or norgestimate as lowest (ca. 5–7 of 10,000 women per year) and the risk of CHCs with drospirenone, gestodene or desogestrel as highest (9–12 of 10,000 women per year). The risk of CHC containing dienogest can currently not be finally determined. Limited epidemiological data indicate that the risk of VTE with ethinyl estradiol-dienogest-containing CHCs is similar to levonorgestrel-containing CHCs.

3.1.4 Cycle and bleeding control

Valette® in studies II and III (Moore et al., 1999a), as well as in another two studies in the Czech Republic and Poland (Golbs et al., 2002a, 2002b) achieved in the average of all women a decrease in the intensity and duration of menstrual bleeding. Despite the fact that sometimes an increase of dysmenorrhea can occur, it was shown in study III with over 2,000 women that the incidence of dysmenorrhea of 28.8 % before treatment was reduced to 12.9 % in the first treatment cycle and near zero in the 6th cycle (Moore et al., 1999a) (figure 7). Also in the observational study, a good cycle control was observed. Spotting and breakthrough bleeding occurred in 5.0 % and 3.4 % of women, respectively, during the first administration cycle and here too, the incidence decreased over the course of the treatment. No incidence of withdrawal bleedings ('silent menstruation') was reported in 2.0 % of the cycles on average and during the whole duration of administration in 5.9 % of women (figure 8) (Zimmermann et al., 1999a). This corresponds with the incidence of no withdrawal bleedings in the phase III study (3 % of the cycles) (Moore et al., 1999a) and in the Czech and Polish study (4.8 % and 3.7 % respectively during the 1st cycle, in subsequent cycles ca. 3 %) (Golbs et al., 2002a, 2002b).

3.1.5 Impact on lab results, coagulation system and blood pressure

Thyroid gland. In the beginning of the administration of Valette® there is an increase of thyroid hormone levels; within 3 months steady-state levels are reached (Sanger et al., 2008). Despite the increase of total T3 and T4 levels, the thyroid gland function remains unchanged because of the simultaneous increase of the transport protein TBG (thyroxine-binding globulin) (Sanger et al., 2008; Wiegratz et al., 2003a), so that the free thyroid gland hormones fT3 and fT4 do not increase (Sanger et al., 2008).

Carbohydrate metabolism. In a subgroup of 29 women in study III, the impact of Valette® on the carbohydrate metabolism was examined over the duration of 3 cycles (Moore et al., 1999a). Like with other low dose oral contraceptives, there was a slight increase of insulin levels and insulin resistance which, however, did not result in significant increases of blood glucose levels or HbA1c levels or the insulin/glucose ratio.

Table 6. Side-effect spectrum during the use of Valette® (ethinyl estradiol/dienogest) in studies II and III (Moore et al., 1999a)

			Symptom frequency (%)									
	Patients (n)		Headaches		Tension in the breasts		Nausea / vomiting		Depression		Oedemas	
Cycle	II	III	II	III	II	III	II	III	II	III	II	III
0	59	n/s	8.5	n/s	5.1	n/s	0	n/s	3.4	n/s	0	n/s
3	91	2072	11.0	12.3	7.7	8.8	2.2	3.9	4.4	1.5	0	0.5
6	84	1858	7.2	8.0	2.4	4.6	1.2	1.5	1.2	1.3	0	0.2
12	n/s	1612	n/s	5.2	n/s	3.4	n/s	1.0	n/s	0.5	n/s	0.1
18	n/s	569	n/s	3.5	n/s	1.8	n/s	0.2	n/s	0.5	n/s	0

Notes: II = study II, III = study III
Abbreviations: n/s = not stated

Lipid metabolism. The impact of three cycles with Valette® on various lipid metabolism parameters was examined in 20 women in study III (Moore et al., 1999a). A significant increase of triglycerides, VLDL and HDL cholesterol as well as apolipoprotein A1 was observed. Apolipoprotein B increased only slightly. Total cholesterol and lipoprotein(a) remained unchanged and LDL cholesterol even showed a decreasing trend. The results of another study with 25 women who received Valette® for 6 cycles were similar (Wiegratz et al., 2002). These women showed slight increases in HDL cholesterol, a significant increase of apolipoprotein A1 and a significant decrease of lipoprotein(a). These changes were more advantageous than those with the combination ethinyl estradiol/levonorgestrel. Since dienogest alone does not have a significant impact on the lipid metabolism (Kohler et al., 1989), the effects observed under Valette® are likely to be caused by the oestrogen component.

Coagulation system. Under Valette®, both the procoagulant and the fibrinolytic activity slightly increased (Spona et al., 1997b). Compared to placebo (Spona et al., 1997b), but also compared to the levels before treatment (Moore et al., 1999a; Wiegratz et al., 2008) significant increases of factor VII and protein C, as well as fibrinolytic activity were measured.

Blood pressure. Valette® did not generally lead to significant changes of blood pressure (Moore et al., 1999a) although it cannot be ruled out in individual cases. The blood levels relevant for blood pressure were also only marginally changed (Wiegratz et al., 2003b). After 6 cycles, cortisol serum levels were increased by 74–100 % compared to the control cycle, but angiotensin II remained unchanged during the first 3 cycles, and subsequently dropped significantly. The serum levels of endothelin-1 remained constant.

3.1.6 Return of fertility after Valette®

In a prospective observational study, 56 % of women who discontinued Valette® because they wanted to get pregnant, where pregnant within 3 subsequent menstrual cycles (figure 9) (Wiegratz et al., 2006). Within a year, the pregnancy rate in the 652 women for whom complete data were available was 94 %. By comparison, in a study with fertile women who wanted to get pregnant of whom more than two thirds had never used an oral contraceptive before, 64 % got pregnant within the next 3 cycles and 91 % within 12 cycles (Dunson et al., 2004; Colombo et al., 2000). These figures show that the fertility of women after discontinuing the therapy with Valette® is not impaired. The duration of the usage of the contraceptives seemed to have no impact on the time to conception (Wiegratz et al., 2006).

3.2 Use in women with acne

Acne is a multifactorial, chronic, inflammatory disease of the sebaceous gland follicles. Androgens, due to their stimulating effect on the activity of the sebaceous glands and the epithelial proliferation in the region of the sebaceous gland duct and the acro-infundibulum of follicles, play a pathogenetically important role. For those affected, acne can impede the quality of life severely, associated with the fear of social exclusion and even depression (Zouboulis, 2014). Valette®/Maxim®, as a result of the antiandrogenic effect of dienogest, have a proven advantageous impact on women with existing moderate acne. Both drugs are approved for the treatment of moderate acne if there are no contraindications for a therapy with COCs and suitable local treatments have failed. Based on this, they can be prescribed in this indication and will be reimbursed by the German statutory health insurances, even if the patient also uses the contraceptive effect of the drug.

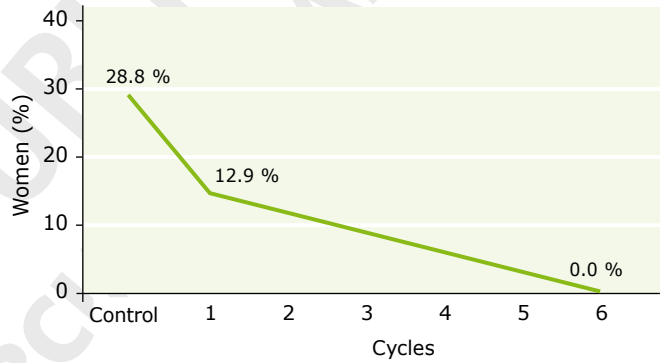


Figure 7. Incidence of dysmenorrhea during a 6 month administration of Valette® in the studies II and III (adapted from Moore et al., 1999a)

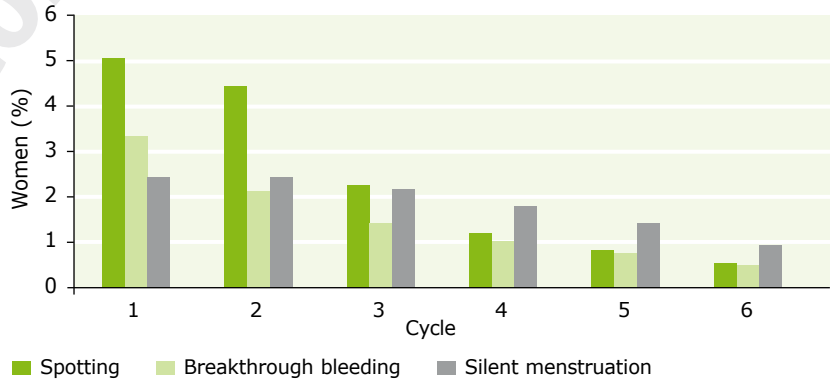
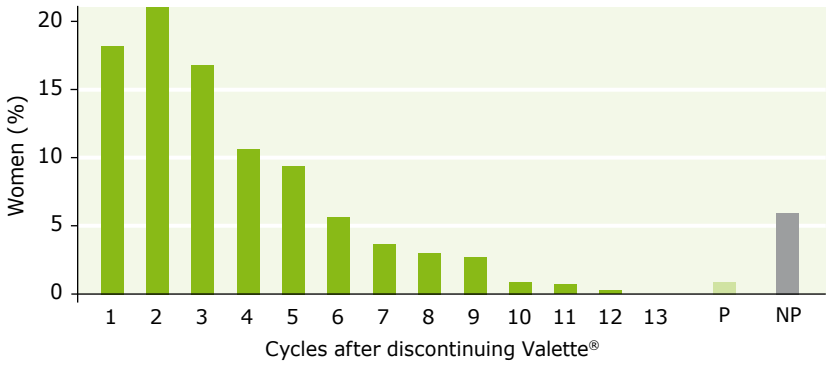


Figure 8. Incidence of bleeding dysfunctions during a 6 month therapy with Valette® in 16 087 women (adapted from Zimmermann et al., 1999a)



Abbreviations: P = pregnancy within a year without record of time point, NP = no pregnancy

Figure 9. Onset of pregnancy within the first 13 cycles after discontinuing Valette® in women who wanted to get pregnant (adapted from Wiegratz et al., 2006)

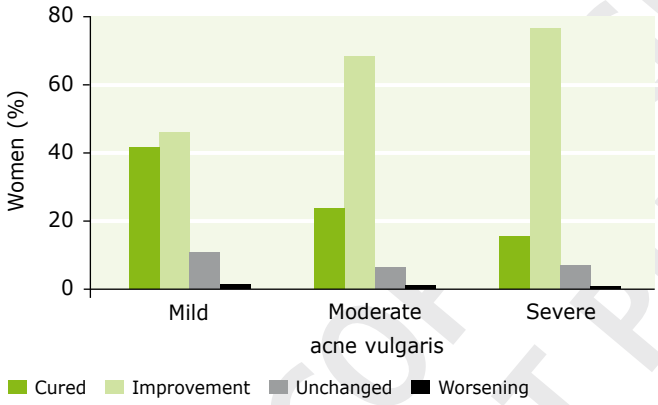


Figure 10. Impact of the treatment with Valette® over 6 cycles on acne symptoms of women with mild (n = 2173), moderate (n = 2802), and severe (n = 985) acne vulgaris, assessed with the IGA scale (Investigator Global Assessment) (adapted from Zimmermann et al., 1999b)

In a multinational, multicenter, randomized, double-blind study, 1,338 women with mild to moderate facial acne papulopustulosa (aged 16–45 years) were treated for 6 cycles, either with ethinyl estradiol/dienogest (Valette®) (n = 525), ethinyl estradiol/cyproterone acetate (n = 537) or placebo (n = 264) (Palombo-Kinne et al., 2009). Valette® improved the symptoms significantly compared to the placebo group, with regard to the number of inflammatory lesions (papules, pustules and nodules) and the total number of lesions. With regard to efficacy, Valette® was equal to the comparator drug cyproterone acetate. A definitive improvement of facial acne – assessed with the 6-point IGA scale (Investigator Global Assessment) – was achieved with Valette® in 91.9 % of the women, with ethinyl estradiol/ cyproterone acetate in 90.2 % and with placebo in 76.2 % of the women.

Of 6.004 women who suffered of acne vulgaris at the beginning of a prospective surveillance study, who were treated with Valette® for the duration of 6 cycles, in 29 % of the cases it came to a healing of acne; in 61 % of the women the acne improved (Zimmermann et al., 1999b). Even with severe forms of acne, more than 90 % of the patients benefited from Valette® (figure 10).

In post-marketing surveillance of Valette®, the impact of this contraceptive on other androgenic symptoms like greasy hair and greasy ('impure') skin was examined (Zimmermann et al., 1999b and 2000b). In the beginning, 70 % of the women reported greasy hair and 88 % reported greasy, impure skin. An acne of mild to severe form was diagnosed by gynaecologists in 58 % of the women. After 6 cycles Valette®, 70 % of affected women reported an improvement of their greasy hair (i.e. slower regreasing), 81% an improvement of their impure skin and 90% an improvement of their acne (29 % of these, a complete healing).

4. Estradiol valerate and dienogest (Qlaira®)

When Qlaira® was introduced on the German market in 2009, it was the first oral contraceptive on the basis of 'natural' estradiol. Estradiol valerate is the valerianic acid ester of estradiol (figure 11) and because the ester group is separated from estradiol valerate during the gastrointestinal absorption, 17ß-estradiol is created (Düsterberg et al., 1982).

The strong activity of dienogest on the endometrium was the reason why in Qlaira® it was used as the gestagen component. This way, irregular bleeding which frequently occur with other combination drugs on an estradiol or estradiol valerate basis, can be reduced to a minimum (Fruzetti & Bitzer, 2010).

Qlaira® is a novel 4-phasic drug with a dynamic dosage scheme, i.e. with a step by step dosage reduction of estradiol valerate from 3 to 1 mg/day and an increase of the dienogest dosage to 3 mg/day during the 28 day administration cycle (figure 12). This way, the risk of breakthrough bleeding is minimised. Due to the strong endometrial effect of dienogest, Qlaira® is also approved for the treatment of heavy menstrual bleeding (hypermenorrhea) without organic causes if women want oral contraception.

4.1 Use as contraceptive

The administration and dosing regimen of Qlaira® with both hormonal components was developed in two consecutive, prospective, randomized, open phase II dose-finding studies with young women. From four different variations of this 4-phasic regimen, one regimen was finally chosen which provided the best ovulation inhibiting effect and the highest cycle stability

fact box VALETTE®/ MAXIM®

- Highly effective contraception.
- Good cycle control, even after a few cycles, less spotting and breakthrough bleeding.
- Weaker and shorter menstrual bleeding, frequently improvement of dysmenorrhea.
- Only low impact on lipid and carbohydrate metabolism, the blood pressure remains unchanged in most cases.
- Fast return of fertility after discontinuation of administration.
- The thrombotic risk is ultimately unknown, but is probably comparable with levonorgestrel-containing contraceptives (caveat: informing patients is vital!).
- Therapeutic effects also in moderate acne after the failure of suitable local treatments (can in this indication be prescribed and are reimbursed by the statutory German health insurances, even if the patients also use the drug for contraception).

(Endrikat et al., 2008). In these studies, it was shown that under Qlaira® the serum levels of estradiol, progesterone, LH and FSH are suppressed over the whole cycle (Endrikat et al., 2013). Other findings indicate that the contraceptive effect of Qlaira® is not just based on an effective inhibition of ovulation, but also on an effective suppression of endometrial growth. Furthermore, Qlaira® reduces the pre-ovulatory cervical mucus production which impedes or prevents sperm ascension (Endrikat et al., 2013).

4.1.1 Efficacy

The contraceptive efficacy and safety of Qlaira® were examined in a large scale phase III study (Palacios et al., 2010). The study was an open, non-comparative study carried out in 50 European centres. The 1,377 participants were between 18 and 50 years old (average age 30.3 years). Over the course of this phase III study, 13 unwanted pregnancies occurred during the therapy, over a total of 23,368 cycles corresponds with an unadjusted Pearl Index of 0.73 (upper limit 95 % confidence interval [CI] 1.25). 6 of the pregnancies were due to the failure of the treatment so that the adjusted Pearl Index was 0.34 with an upper limit 95 % CI of 0.73. 12 of the pregnancies occurred in the younger age group (18–35 years) which results in an adjusted and unadjusted Pearl Index of 0.94 (upper limit 95 % CI 1.65) or 0.40 (upper limit 95 % CI 0.92), respectively.

In a large scale, randomized, double-blind study with the primary aim of assessing the bleeding attributes (also see below), data on the efficacy of Qlaira® were also collected (Ahrendt et al., 2009). In 399 women in the Qlaira® group over the administration duration of 7 cycles, it did not come to a single pregnancy. In the equally large comparator group with ethinyl estradiol/levonorgestrel, one unwanted pregnancy set in. The Pearl Index was not calculated in this study.

Nelson et al. (2013) assessed the pooled data from three studies on Qlaira® with healthy women (aged 18–50 years) with a BMI < 30 kg/m². The studies which were assessed, were the above mentioned European studies by Palacios et al. (2010) and Ahrendt et al. (2009), as well as an unpublished North-American study (open, non-comparative) with 490 women aged 18 to 35 years. The therapy duration was initially 13 cycles which was later extended to 28 cycles. The primary endpoint was the number of unwanted pregnancies. In total in the three studies, 2,266 women received contraception with Qlaira®. Over the course of 880,950 therapy days, there were 19 pregnancies. After deducting 10 pregnancies which were clearly down to usage errors (e.g. pills were not taken or taken in a wrong way), the pooled adjusted Pearl Index was 0.42 (0.51 among 18 to 35 year old women).

These results document the high contraceptive efficacy of Qlaira® which corresponds with the efficacy of ethinyl estradiol-containing oral contraceptives.

4.1.2 Safety and tolerability

In both phase II studies by Endrikat et al. (2008), 5 side-effects occurred during up to three cycles in 96 women with the latterly used dosage regimen for Qlaira® (depressive mood, headaches, worsening of acne, eye irritations). When all four tested estradiol valerate/dienogest regimens were analysed, the most common adverse events were headaches and abdominal pain, acne, breast pain, dysmenorrhea, emotional instability and nausea. Most of these complaints are typical for oral contraceptives.

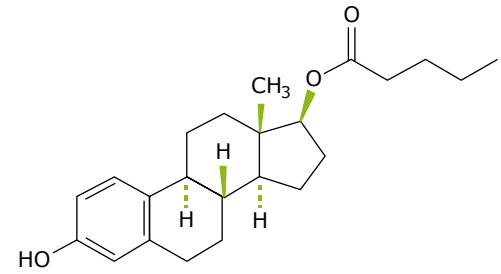


Figure 11. Estradiol valerate

In the phase III study by Palacios et al. (2010), 10.2 % of the 1,377 women discontinued the treatment due to side-effects. The most common reasons for discontinuation were intracycle or breakthrough bleeding (1.7 %), acne (1.0 %) and weight gain (0.9 %). 917 women (66.6 %) reported at least one adverse event during therapy and in 272 of those affected (19.8 %), the principal investigators made a possible, probable or clear link to the treatment. The most common treatment-related side-effects were breast pain (3.6 %), acne (2.6 %), headaches (1.9 %), intracycle bleeding (1.9 %), weight gain (1.5 %), and breast discomfort (1.2 %). Most of these side-effects were only mild, but 59 events in 43 women were classified as severe. For 5 of these events the principal investigators saw a possible connection with the treatment.

In the comparative study by Ahrendt et al. (2009), the women were not questioned directly about side-effects and instead, only spontaneously mentioned complaints were documented. In the Qlaira® group (n = 399), 108 women (27.1 %) reported 175 events; in the ethinyl estradiol/levonorgestrel group (n = 399), 102 women (25.6 %) reported 162 events. Under Qlaira®, breast pain (3.8 %), headache (2.5 %) and vaginal infections (2.5 %) were reported most commonly.

The side-effect spectrum of Qlaira® documented in these studies, highlights the good tolerability of combined oral contraceptives.

Dysmenorrhea. A randomized phase IIIb study in 44 centres especially examined the what the effect of Qlaira® (n = 253) vs. EE/LNG (n = 254) on dysmenorrheic pain (Petraglia et al., 2014). The treatment duration was 3 cycles, respectively. The symptoms were assessed subjectively every day by the women, and documented in a diary. The duration of dysmenorrheic pain – assessed over 2 control cycles and 2 cycles with contraception – decreased during treatment with Qlaira® by an average of 4.6 days, and with EE/LNG by an average of 4.2. days (difference not statistically significant) **(figure 13)**.

Hormone withdrawal symptoms during the cycle. The 21/7-day schedule of conventional oral contraceptives is supposed to simulate the average ‚natural' 28 day menstrual cycle. But many women experience a range of complaints during the 7 day hormone-free interval which – as in the normal menstrual cycle – can be classified as hormone withdrawal symptoms (headaches and lower abdominal pain, feeling of tension in the breast, flatulence). These can result in reduced compliance or complete discontinuation of the drug. Qlaira® was therefore developed as dynamically dosed contraceptive. The hormone-free phase was reduced to 2 days and over 4 days estradiol valerate alone is administered to safeguard continuous estradiol serum levels during the whole cycle (Zeun et al., 2009) **(figure 14)**.

In a randomized phase III study vs. a 21/7 day drug with ethinyl estradiol/levonorgestrel (EE/LNG), it could actually be confirmed that Qlaira® is associated with a lower incidence and intensity of hormone withdrawal symptoms, specifically headaches and lower abdominal pain (Macias et al., 2013). In this study, 449 women aged 18 – 50 years were randomized. 441 of these (223 in the Qlaira® and 218 in the EE/LNG group) received the study medication. Over the course of 6 cycles, the study participants assessed the intensity of their complaints on day 22 to 28 on a visual analogue scale (VAS) from 100 mm (0 = no pain to 100 = unbearable pain). Both drugs reduced the pain intensity compared to the baseline situation before starting the therapy, but Qlaira® significantly more (-47.7 mm) than EE/LNG (-34.5 mm). This difference was statistically significant ($p = 0.0001$) **(figure 15)**. In addition, in the Qlaira® group considerably more women were classified as therapy responders based on various criteria. Corresponding with the decrease of headaches and lower abdominal pain, the use of analgesics decreased among the participants over the course of the 6 cycles (-3.5 tablets with Qlaira® vs. -1.8 tablets with EE/LNG; $p < 0.05$).

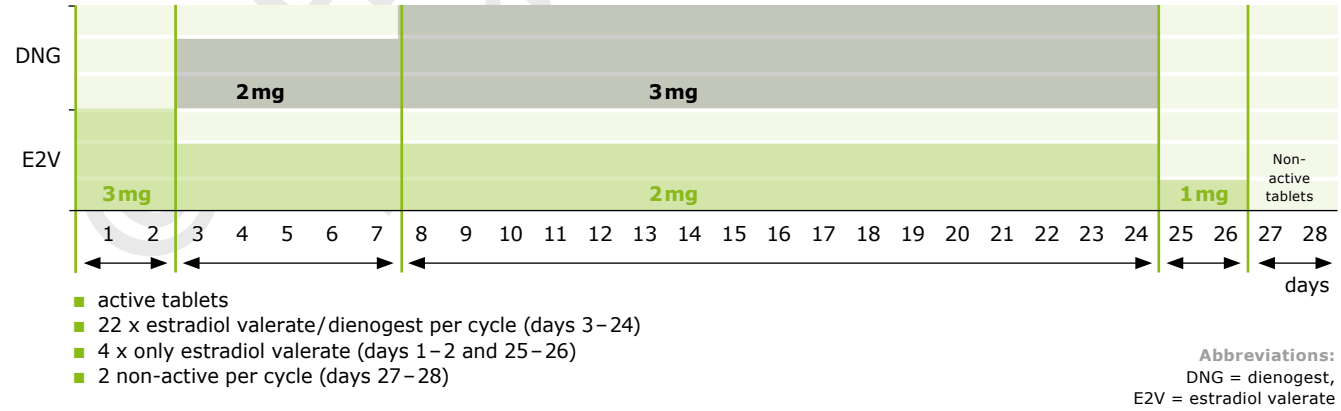


Figure 12. Dosing regimen of the 4-phasic contraceptive Qlaira® (estradiol valerate/dienogest)

Based on the results of this study, Qlaira® is a good therapeutic option especially for women who tend to have headaches and lower abdominal pain during menstruation.

Thrombotic risk. Large scale observational studies (phase IV) on the thrombotic risk of Qlaira® have been ongoing since the introduction of the drug, but have not been completed yet.

4.1.3 Impact on metabolic and coagulation parameters

Klipping et al. (2011) compared in an open, randomized, crossover study with 29 healthy women aged 18–50 years the hemostatic effect of Qlaira® vs. a mono-phasic contraceptive with 30 μg ethinyl estradiol and 150 μg levonorgestrel (EE/LNG). Each treatment lasted 3 cycles, with a wash-out phase of two cycles in between. Primary endpoints were the individual changes of the thrombin and fibrin turnover, measured with the activation markers prothrombin-fragment 1+2 and D-dimer. Apart from that, various other pro- and anticoagulatory parameters were determined. Qlaira® did not result in significant changes of the prothrombin fragment 1+2, whereas with EE/LNG a slight increase could be observed. However, the difference was not significant. D-dimer, on the other hand, increased significantly under Qlaira® (on average, from 203.0 to 237.4 ng/ml) vs. EE/LNG (on average, from 201.8 to 352.6 ng/ml) ($p = 0.01$). The mean levels of both contraceptives were still within normal limits. The increases of pro-coagulatory markers were usually lower with Qlaira® (e.g. fibrinogen, factor VII) than with EE/LNG, whereas most anticoagulatory markers (antithrombin III, protein C, protein S, resistance against activated protein C [APC]) were almost unchanged with both drugs. Only the APC sensitivity ratio in the EE/LNG group was slightly over the reference range, with a significant difference vs. Qlaira® ($p = 0.0006$) (table 7). Overall, in the 3rd cycle under the treatment with Qlaira® there was a lower percentage of women vs. EE/LNG who showed changes in several coagulation parameters which were outside the reference range.

Also in the randomized open study by Junge et al. (2011), the coagulation parameters were only marginally impacted by Qlaira®. 60 healthy women were randomized in this study, 58 were evaluable (aged 18–50 years). They received either Qlaira® or a triphasic drug with ethinyl estradiol and levonorgestrel (EE/LNG) for the duration of 7 cycles, respectively. Prothrombin fragment 1+2 and D-dimer on average remained unchanged with Qlaira®, whereas with EE/LNG they increased by 117 % and 63 %, respectively (significant with $p < 0.01$ for D-dimer). Also the procoagulation parameters fibrinogen (+8 %) and factor VIIc (+13.5 %) increased significantly less with Qlaira® than with the comparator drug (+28 % and +24 %, respectively); factor VIIIc remained relatively stable in both groups. The anticoagulation marker did not change significantly, however with Qlaira® clearly less than with EE/LNG.

In addition, several lipid and thyroid gland parameters, cortisol and sex hormone-binding proteins (CBG, SHBG), as well as blood glucose and insulin level were measured in this randomised study (Junge et al., 2011). Qlaira® had a beneficial impact on HDL (+8 %) and LDL cholesterol (-6.5 %) and caused – similar to EE/LNG – the triglyceride (+31.5 %) and VLDL cholesterol levels (+27 %) to increase. Lp(a) remained mainly unchanged. All thyroid gland parameters also stayed within the normal range with Qlaira® and in the oral glucose tolerance test neither insulin nor blood glucose levels were impacted. CBG and SHBG increased in the Qlaira® group (+28 % and +63 %, respectively), but this increase was lower than in the EE/LNG group (+146 % and 112 %, respectively). Body weight and blood pressure remained stable throughout.

Overall, these analyses of a broad range of laboratory parameters gave no evidence of negative changes under the treatment with Qlaira®. Qlaira® specifically seemed to have slightly lower impact on the individual coagulation parameters than the examined contraceptives with ethinyl estradiol (EE/LNG). This however does not allow for conclusions about the thrombotic risk. Such conclusions can only be drawn after the phase IV studies have been completed.

4.1.4 Cycle and bleeding control

A problem with oral contraceptives with estradiol or estradiol valerate often consists of irregularities or dysfunctions of the menstrual cycle with prolonged or more intense withdrawal bleeds and/or frequent spotting or frequent breakthrough bleeds during the course of a cycle. The dynamic dosage regimen of Qlaira® is targeted to minimise these precise problems. In a randomized double-blind study in 34 centres in Germany, the Czech Republic, and France, cycle stability and bleeding patterns with Qlaira® were examined over 7 cycles and compared

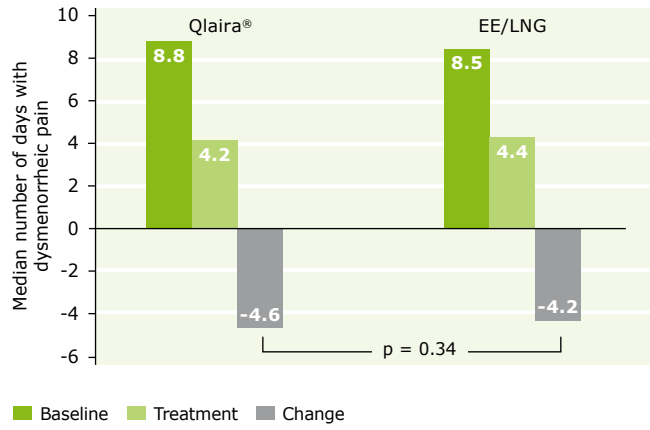


Figure 13. Impact of estradiol valerate/dienogest (Qlaira®) and ethinyl estradiol/levonorgestrel (EE/LNG) on dysmenorrheic pain (Petraglia et al., 2014)

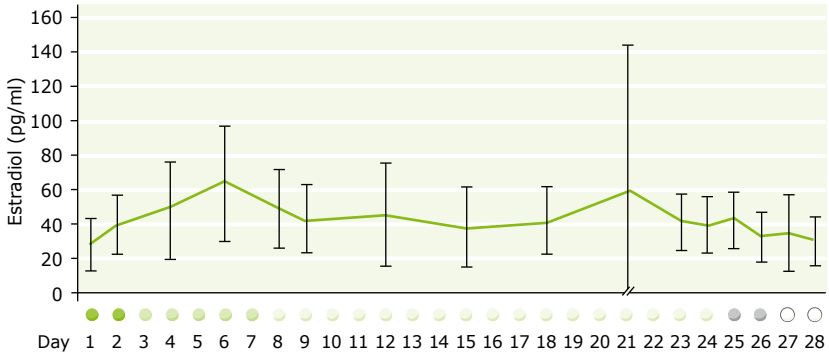


Figure 14. Estradiol levels over the course of a cycle during the administration of Qlaira®. Stated are the daily minimal levels (mean ± standard deviation). Adapted from Zeun et al., 2009

Table 7. Absolute and relative changes in coagulation parameters after 3 cycles Qlaira® or ethinyl estradiol/levonorgestrel (adapted from Klipping et al., 2011)

Parameter	absolute change (relative change, %)	
	Qlaira® (n = 29)	EE/LNG (n = 28)
Coagulatory		
Fibrinogen, g/l	0.32 (19.1)	0.76 (29.5)
Factor VII activity (VIIc), %	2.3 (4.0)	6.8 (7.9)
Factor VIII activity (VIIIc), %	-1.3 (-0.9)	2.6 (5.1)
Anticoagulatory		
Antithrombin III activity, %	-0.3 (0.1)	-3.0 (-2.7)
Protein C activity, %	-2.3 (-0.5)	5.7 (6.2)
Protein S activity, %	4.5 (6.3)	-0.8 (0.2)
APC resistance (ratio)	-0.04 (-0.9)	-0.08 (-1.9)
APC sensitivity (ratio)	0.09 (7.7*)	0.56 (39.3)

* p = 0,0006 vs. EE/LNG

Abbreviations: APC = activated protein C, EE/LNG = ethinyl estradiol/levonorgestrel

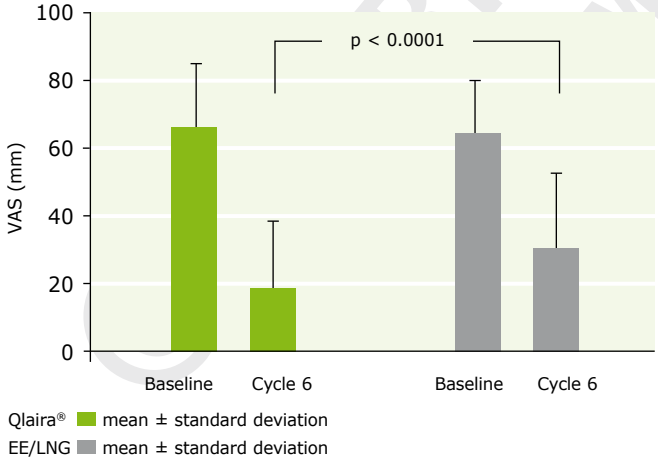


Figure 15. Decrease of headaches and lower abdominal pain during the administration of estradiol valerate/dienogest (Qlaira®) or ethinyl estradiol/levonorgestrel (EE/LNG) for 6 cycles (adapted from Macias et al., 2013)

with a mono-phasic contraceptive with 20 μg ethinyl estradiol and 100 μg levonorgestrel (EE/LG) (Ahrendt et al., 2009). In total, 798 women were randomized (399 per group). With Qlaira® the regular withdrawal bleed at the end of the cycle slightly more frequently did not occur (per cycle in 16.8 – 22.3 % of the women vs. 6.2 – 10.5 % in the EE/LNG group; $p < 0.0001$), but unplanned intracycle bleeds were equally frequent with both contraceptives (per cycle in 10.5 – 18.6 % of the women with Qlaira® vs. 9.9 – 17.1 % of the women with EE/LNG). The frequency of dysmenorrhea decreased from a baseline level of 9.5 % (Qlaira®) and 6.8 % (EE/LNG) of the women, respectively, to 0.5 % in both groups in the 7th cycle. Apart from that, under Qlaira® there were less days with bleeds or spotting during the cycle vs. the comparator drug – on average 16 vs. 21 days during the first treatment phase (day 1 – 90) and on average 12 vs. 15 days during the second treatment phase (day 91 – 180) ($p < 0.0001$, respectively). The withdrawal bleed was also shorter and weaker with Qlaira®. The duration of the withdrawal bleed per cycle was an average of 4 days in the Qlaira® group and in the EE/LNG group an average of 5 days ($p < 0.05$). The score for the bleeding intensity on a scale from 1 (none) to 5 (heavy) was 3 (low) on average for Qlaira® and for EE/LNG it was on average 4 (normal intensity). Accordingly, more women in the Qlaira® group had weaker bleeding that in the EE/LNG group (figure 16).

The results looking at bleeding attributes in the study of Nelson et al. (2013) were equally advantageous. The study was based on the pooled data from three efficacy studies with Qlaira® with a total of 2,266 women. 19 % to 24 % of the women did not have a withdrawal bleed in at least one of the cycles. The duration of the withdrawal bleed varied between an average of 4.0 and 4.6 days, with 59 % to 66 % of the women describing the bleed as low or as spotting. Intracycle bleeding occurred in cycles 2 – 13 in 13 % to 23 % of the women and generally the incidence was highest in the beginning and decreased in subsequent cycles. The duration of intracycle bleeding also receded after a longer term administration of Qlaira® (on average 1.4 days in the 2nd cycle, 0.7 days in the 13th cycle). 77 to 85 % of the women assessed the intensity of intracycle bleeding as spotting or as low.

4.2 Use as contraceptive for heavy menstrual bleedingn

Among the various menstrual dysfunctions, heavy menstrual bleeding (HMB) is one of the most common complaints which

drive women to consult a gynaecologist. HMB includes hypermenorrhea, menorrhagia and or polymenorrhea either alone or in combination. The vast majority of women included in the efficacy studies for Qlaira suffered from hypermenorrhea (table 8). Based on objective criteria, hypermenorrhea is defined as a blood loss of ≥ 80 ml per cycle (Hallberg et al., 1966). In clinical practice, heavier periods describe a blood loss that is so massive that the affected women are impaired physically, psychologically, socially, or in a material sense in their quality of life. Most heavy periods are idiopathic, i.e. no organic causes like myomas, polyps, miscarriages, vascular anomalies or coagulation dysfunctions can be detected. For the treatment of these idiopathic forms, there are several drug therapies available; surgical procedures (hysterectomy, endometrial ablation) are usually only an option after the failure of drug therapy attempts and after family planning has ended. Frequently, women with heavy periods were prescribed combined oral contraceptives off label in the last decades, without proof of their suitability in clinical trials (Iyer et al., 2000). With Qlaira® there is now a drug which can be used for reliable contraception with a proven efficacy for hypermenorrhea.

4.2.1 Efficacy for the treatment of hypermenorrhea

The approval of Qlaira® for the indication hypermenorrhea without organic cause (only in connection with contraception) is based on two randomised, placebo-controlled, double-blind phase III studies with identical design and analysis plan. One of the studies was carried out in the USA and Canada (Jensen et al., 2011), the other in Australia and Europe (Fraser et al., 2011b). In addition, both studies were examined together in a pooled analysis to increase the statistical meaningfulness of the results (Fraser et al., 2011a).

Patients and methodology. Both studies consisted of 4 sections – a 28 day screening phase, followed by a 90 day precursor phase, a 196 day treatment phase (at the end of which, the efficacy over 90 days was analysed) and a follow-up phase of 30 days. The active treatment consisted of Qlaira® or placebo for the duration of 196 days (7 cycles). In both studies together, 421 women were randomized in whom during the precursor phase an idiopathic menstrual dysfunction without detectable organic cause was confirmed. This could either be hypermenorrhea (≥ 2 episodes with a blood loss of ≥ 80 ml), menorrhagia (≥ 2 episodes of ≥ 8 days duration) and/or polymenorrhea (≥ 5 episodes with ≥ 20 bleeding days) (table 8). Primary efficacy criteria were changes in blood loss in ml, the number of sanitary towels/tampons used, and parameters of the iron metabolism.

Relative reduction of the blood loss. A reduced blood loss could already be observed during the end of the first cycle with Qlaira®. The effect increased during the next cycles and continued until the end of the study therapy (figure 17). At the end of the 7th administration cycle, the median blood loss in the Qlaira® group was 88 % lower than in the precursor phase. In the placebo group, the median reduction of 24 % was low. In the subgroup of women with hypermenorrhea (blood loss ≥ 80 ml per cycle; n = 227 in the Qlaira® group and n = 136 in the placebo group) who represented the majority of the trial population, the results were very similar (median reduction of blood loss 88 % with Qlaira® vs. 23 % with placebo).

When the treatment success was measured based on the number of sanitary towels/tampons used, the difference of efficacy between Qlaira® and placebo was also highly significant ($p < 0.0001$).

Absolute reduction of blood loss. Over the whole 90 day duration of the analysis phase, the menstrual blood loss in the Qlaira® group was on average 414 ± 373 ml lower than in the precursor phase – in the placebo group it was only 109 ± 300 ml lower. The difference was highly significant with $p < 0.0001$. In the subgroup of women with hypermenorrhea, the figures were 454 ± 375 ml and 118 ± 302 ml, respectively ($p < 0.0001$).

Overall, 92 % of the women benefited from the treatment with Qlaira® because their blood loss was reduced by 20 %; 80 % of the women had a reduction of 50 % and 46 % of the women even had a reduction of 80 %. In the placebo group, only 42 %, 14 %, and 2 % of the women achieved a corresponding improvement. A further increase in the menstrual blood loss during the assessment phase was observed in only 5 % of the women with Qlaira®, however in 20 % of the women with placebo.

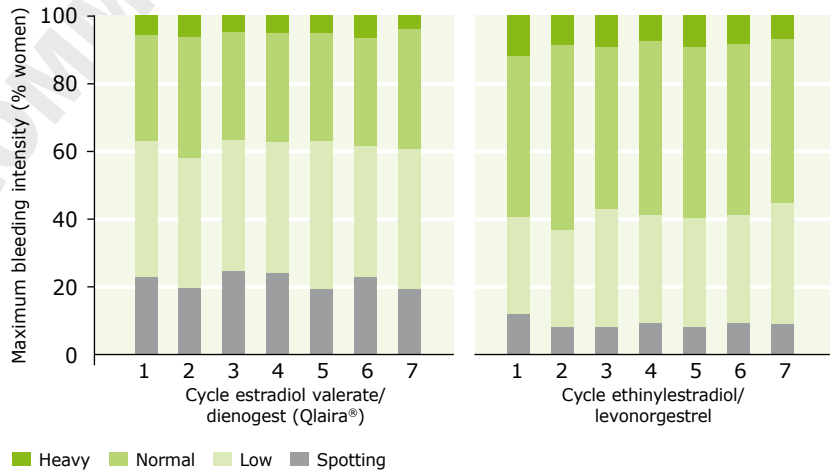
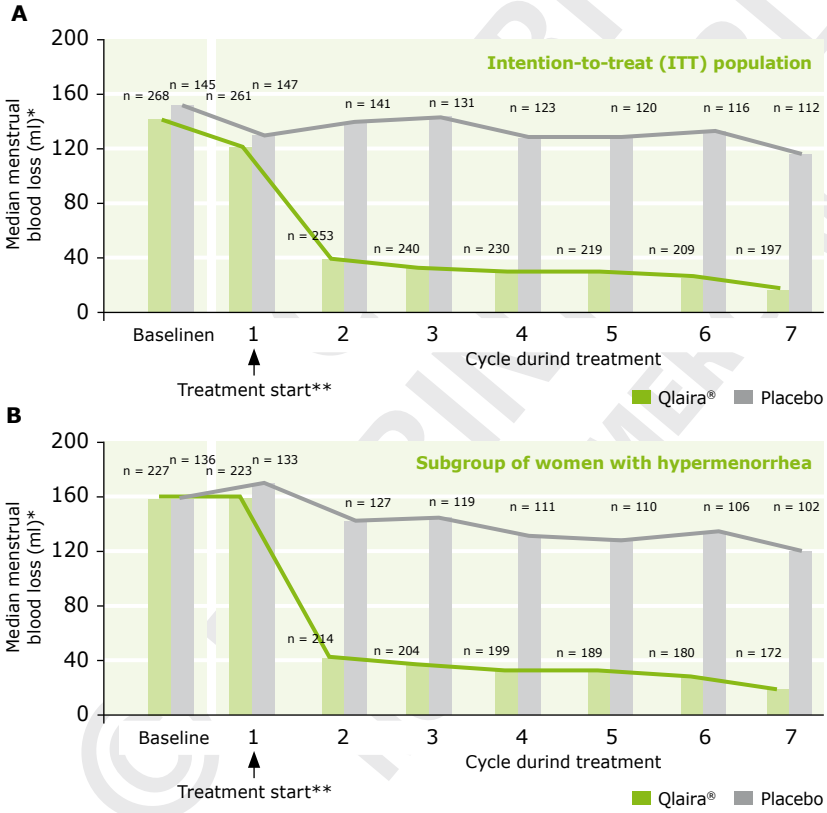


Figure 16. Maximum intensity of regular withdrawal bleeds in women using Qlaira® or ethinyl estradiol/levonorgestrel during 7 cycles (adapted from Ahrendt et al., 2009)

Table 8. Clinical and demographic baseline attributes of women with heavy menstrual bleeding in a pooled analysis of both placebo-controlled studies (Fraser et al., 2011a)

	Qlaira® (n = 269)	Plazebo (n = 152)
Age ± SD, years	38.3 ± 7.1	37.8 ± 7.2
Ethnic group, n (%)		
Caucasian	215 (79.9)	126 (82.9)
Black	39 (14.5)	14 (9.2)
Hispanic	8 (3.0)	6 (3.9)
Asian	3 (1.1)	3 (2.0)
Other	4 (1.5)	3 (2.0)
Body weight ± SD, kg	71.0 ± 11.5	71.0 ± 11.2
Body Mass Index ± SD, kg/m²	25.5 ± 3.7	25.9 ± 3.4
Type of menstrual dysfunction, n (%)		
Hypermenorrhea	227 (84.4)	136 (89.5)
Menorrhagia	46 (17.1)	22 (14.5)
Polymenorrhea	4 (1.5)	2 (1.3)

Abbreviations: SD = standard deviation



* Total blood loss during a 28 day cycle

** Blood loss in the first cycle corresponds with the physiological menstrual bleeding where the treatment was started, plus possible intracycle bleeding.

Figure 17. Median levels of the menstrual blood loss (MBL) during treatment with Qlaira® and placebo in **A** the intention-to-treat (ITT) analysis and **B** the subgroup of women with hypermenorrhea (MBL ≥ 80ml per cycle in the median of the precursor phase) (Fraser et al., 2011a)

Therapeutic effect in relation to the baseline situation. The relative bleeding reducing effect of Qlaira® was shown to be independent of the volume of menstrual blood loss before treatment. In absolute terms (in ml), the benefit of Qlaira® was even higher, if the menstrual bleeding before was heavier.

Changes of the iron metabolism. During the study, the subjects were allowed to take iron supplements. These were taken by 16.7 % of the women in the Qlaira® group and 25.7 % of women in the placebo group. Despite this, the improvement of all markers of the iron metabolism measured (haemoglobin, haematocrit, ferritin) during the treatment with Qlaira®, was significantly higher than in the placebo group (table 9).

Summary assessment of the treatment success. The principal investigators concluded that significantly more women in the Qlaira® group vs. the placebo group had a successful treatment, i.e. a good or very good improvement of their bleeding symptoms (83.0 % vs. 40.6 %; $p < 0.0001$). The patients themselves assessed their treatment success similar in the Qlaira® group and in the placebo group (improvement rate 79.2 % vs. 42.4 %; $p < 0.0001$).

4.2.2 Benefit for work productivity and activities of daily living

In both of the above phase III studies with Qlaira® vs. placebo which included women with heavy menstrual bleeding, not just the efficacy and safety, but also the impact on work productivity and activities of daily living of the patients were assessed prospectively and published separately (Wasiak et al., 2012 and 2013). The assessment was based on a modified version of the WPAI questionnaire (Work Productivity Impairment Questionnaire) which was answered by the patients after completing the precursor phase (= baseline level), on day 84 (after 3 cycles), and on day 196 (after 7 cycles, i.e. at the end of the treatment). The WPAI questionnaire is based on the Likert scale, i.e. an ordinal or range-scaled system with 10 graduations of an item, where higher scores indicate a higher grade of impairment. The assessment duration in this study was the past 12 weeks (in the original WPAI it is only

7 days). The impairment of work productivity in the questionnaire referred only to the so-called presenteeism which means the limited productivity when employees go to work despite being ill. Absenteeism, i.e. absence due to illness was excluded.

Until the end of the treatment, in all countries the work productivity and activities of daily living of trial participants in the Qlaira® group were improved much more pronounced than in the placebo group:

- The gain of work productivity over the course of 7 therapy cycles (Qlaira® vs. placebo) in the United States was 46.2 % vs. 13.1 %, in Canada 47.3 % vs. 16.1 %, in Germany 55.5 % vs. 27.2 %, and on average in all countries of the Australian-European study 46.0 % vs. 15.1 %.
- The activities of daily living also improved with Qlaira® more than with placebo: in the United States 53.0 % vs. 24.8 %, in Canada 56.2 % vs. 28.0 %, in Germany 60.7 % vs. 37.7 %, and on average in all countries of the Australian-European study 55.6 % vs. 30.8 %.
- These advantageous effects of Qlaira® could be converted into significant economic cost savings. For Germany (in 2008), the estimates equalled a monthly saving of 47.2 US$ (work productivity) and 45.6 US$ (activities of daily living) per working woman with heavy menstrual bleeding.

5. Hormone replacement therapy with estradiol valerate and dienogest (Lafamme®)

Due to the longer life expectancy, nowadays women after the menopause spend more than a third of their life in a phase with a hormone deficiency. The impact of the lack of oestrogen during this life phase can be diverse. Possible consequences are menopausal complaints like hot flushes, bleeding dysfunctions,

Table 9. Iron metabolism parameters (mean ± standard deviation) in the placebo-controlled study with Qlaira® in women with heavy menstrual bleeding (Fraser et al., 2011a)

Parameter	Qlaira®			Placebo		
	Baseline level	Day 196	Difference	Baseline level	Day 196	Difference
Haemoglobin, g/dl	n = 269	n = 245	n = 245	n = 152	n = 135	n = 135
	12.2 ± 1.3	12.8 ± 1.1	+0.64 ± 1.1***	12.0 ± 1.4	12.2 ± 1.3	+0.12 ± 1.0
Haematocrit, %	n = 269	n = 244	n = 244	n = 152	n = 135	n = 135
	38.7 ± 3.8	40.1 ± 3.7	+1.48 ± 3.7**	38.5 ± 4.3	38.7 ± 4.0	+0.08 ± 3.1
Ferritin, ng/ml	n = 269	n = 249	n = 249	n = 150	n = 137	n = 136
	17.9 ± 25.9	25.5 ± 24.4	+7.1 ± 28.8*	17.2 ± 16.9	18.7 ± 17.3	+1.2 ± 12.2

*p < 0.05 vs. difference under placebo; **p < 0.0002 vs. difference under placebo; ***p<0.0001 vs. difference under placebo.

fact box QLAIRA®

- First oral contraceptive with the effect of estradiol.
- Made possible with to the distinctive properties of dienogest and the dynamic dosage of both components (oestrogen emphasis in the beginning, gestagen emphasis at the end of the cycle, only 2 days hormone-free).
- Easy to use due to the 28 day blister without administration break.
- Evenly low estradiol serum levels throughout the whole cycle.
- Short, weak withdrawal bleeds and less hormone withdrawal symptoms (headaches and lower abdominal pain) at the end of the cycle.
- Is also approved for the therapy of hypermenorrhea, however always linked to contraception.
- Positive effects on the iron metabolism, work productivity and activities of daily living.
- Qlaira® with its many benefits is the preferred option for women who want an oral contraception, but also for women who suffer of heavy menstrual bleeding and/or do not manage with the ethinyl estradiol-containing pills.
- First data show a slightly lower impact on the relevant metabolic and coagulation parameters, but conclusions about the thrombotic risks are not yet possible - due to the lack of sufficient data from large scale post-marketing studies, so that the contraindications and risks are the same as those of ethinyl estradiol-containing oral contraceptives.

depressive moods, insomnia, concentration and memory problems, as well as atrophic changes in the urogenital area. Long-term negative consequences, like an increased morbidity due to cardiovascular diseases and osteoporosis can also develop.

Since the introduction of hormone replacement therapy about 50 years ago, new insights have made it necessary to develop new therapeutic solutions. To meet the current demands of science and also to meet the wishes of affected women in the postmenopause, it is necessary to provide drugs for treatment in doses that are as low as possible, while still being able to eliminate effectively and comprehensively all complaints of the menopausal syndrome.

Pharmacology. Lafamme® is a combined oestrogen/gestagen drug with the active substances estradiol valerate and dienogest. Estradiol valerate is already converted into the biologically active 'natural' 17ß-estradiol during gastrointestinal absorption or during the first liver passage. Lafamme® is available in two strengths with different oestrogen doses. Lafamme® 1 mg contains with 1 mg estradiol valerate an estradiol dose of 0.76 mg per tablet which is a very low oestrogen dose. Lafamme® 2 mg with 2 mg estradiol valerate contains 1.53 mg estradiol per tablet which is a medium oestrogen dose. The tablets of both strengths contain 2 mg dienogest.

After a single administration of Lafamme® 1 mg, maximum estradiol serum levels of 21 pg/ml are reached within approximately 6 hours. After daily administration, in 4 to 7 days a steady state is reached. The minimum and maximum estradiol serum concentrations in steady state are 21 and 43 pg/ml, respectively. The average estradiol serum concentration is 33 pg/ml. The half-life of estradiol is 20 hours.

A gestagen component is necessary for the hormone replacement therapy for non-hysterectomized women to protect the endometrium and to prevent hyperplasia as a result of the oestrogen input. Dienogest has an advantage in this respect because it has an extremely strong gestagenic effect on the endometrium, but as opposed to other gestagens, it has no anti-oestrogenic partial extragenital effects. This will not decrease the desired positive oestrogen effects, for example in the CNS. It has the advantage that in hormone replacement therapy Lafamme® 1 mg/2 mg with the lower estradiol dose of 0.76 daily is often already sufficient to eliminate the oestrogen deficiency and therefore to reduce the menopausal complaints effectively. Apart from that, Lafamme® also has an advantageous effect on the psyche, sleep and cognitive functioning because of dienogest and the additional antiandrogenic effect.

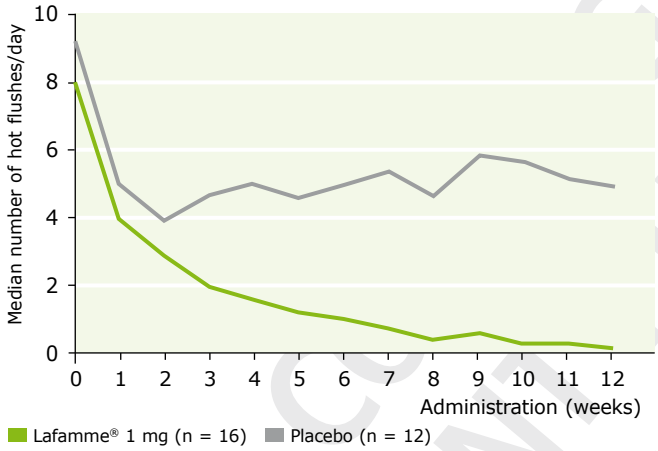
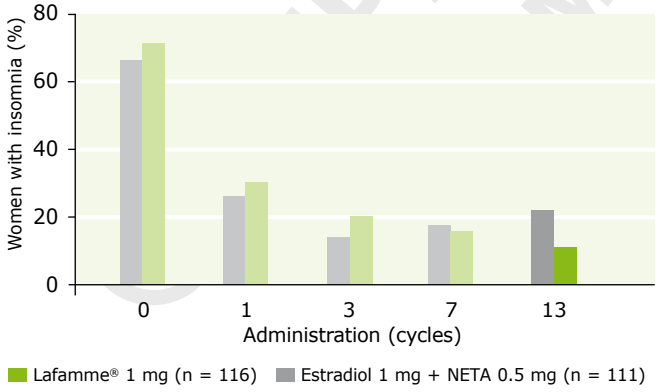


Figure 18. Incidence of **hot flushes** during a 12 week therapy with Lafamme® 1 mg or placebo



Abbreviations: NETA = norethisterone acetate

Figure 19. Incidence of **insomnia** during treatment with Lafamme® 1 mg and a comparator over 13 cycles

Usage. Lafamme® is used for the continuous hormone replacement therapy to treat oestrogen deficiency symptoms in postmenopausal women or postmenopausal non-hysteretomized women whose menopause was at least 1 year ago. There are only limited experiences with the treatment of women over the age of 65.

5.1 Efficacy for menopausal complaints

5.1.1 Impact on hot flushes

In a placebo-controlled double-blind study, the efficacy of Lafamme® 1 mg was examined in 28 women with menopausal complaints (Jenapharm research report A01000). One of the assessment criteria was the elimination of hot flushes **(figure 18)**. Before therapy, the median number of hot flushes in the Lafamme® group was 8 per day and in the placebo group 9 per day. After a 1 week hormone substitution, already a clear improvement of complaints could be observed. The number of hot flushes was already reduced by half. After 4 weeks of treatment, the number of hot flushes decreased by 79 % with Lafamme® and in the placebo group by just 45 %. At the end

of the 12 week treatment, the women in the Lafamme® group were virtually free of hot flushes, whereas the subjects in the placebo group still had an average of 5 hot flushes per day.

5.1.2 Impact on insomnia

Insomnia which occurs more frequently during the menopause is a burden for patients and can cause a significant impairment of the quality of life and general functioning, as well as memory, fine motor skills and reaction time (Löffler et al., 1998; Saletu et al., 1998). In a randomized, multicenter, double-blind study, the impact of Lafamme® 1 mg compared to another hormo nal combination drug with 1 mg estradiol and 0.5 mg norethisterone acetate (NETA) on insomnia was examined (Jenapharm research report A04274). The study included 227 postmenopausal women. Before the start of the therapy, 72 % of the women in the Lafamme® group suffered of insomnia. In the comparator group 67 % were affected.

Even after a 4 week hormone substitution, a significant symptom relief could already be observed in all women. In both groups, insomnia reduced by more than half. In the further course of the treatment it became clear that Lafamme® 1 mg – despite its low oestrogen dose of 0.76 mg estradiol – could equally achieve an efficient reduction of insomnia. This additional benefit can be explained with the effect of dienogest. In previous tests in the sleep laboratory it could be proven that dienogest supports the positive oestrogen effects on sleep (Saletu-Zyhlarz et al., 2003). Hence, after 13 administration cycles only 11 % of the women in the Lafamme® group were affected by insomnia, however with the comparator drug it was 22 % (figure 19).

The impact of the treatment on the severity of insomnia was also examined in this trial (Jenapharm research report A04274). Before the start of the treatment, 37 % of women who suffered of insomnia in the Lafamme® group had mild complaints and 63 % moderate to severe complaints. In the comparator group, 44 % had mild complaints and 56 % moderate to severe complaints. Also in terms of the severity, it was shown that Lafamme® 1 mg is an effective hormone replacement therapy despite its low oestrogen dosage. After 13 administration cycles, only 4 % of women in the Lafamme® group still had severe insomnia, the rest had mild to moderate complaints. In the comparator group after 13 administration cycles, 12 % of women were still affected by severe insomnia.

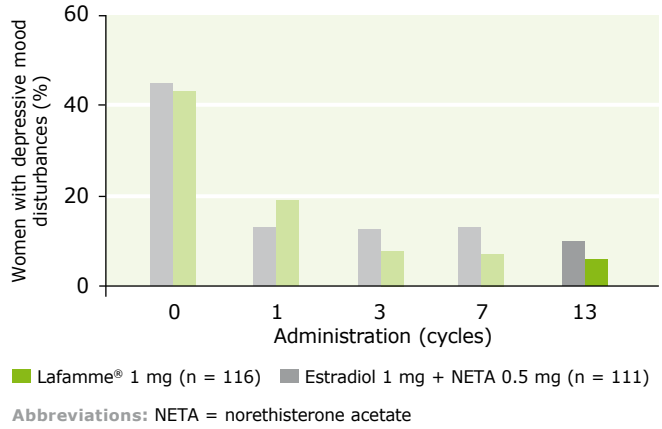
5.1.3 Antidepressive effect

Another assessment criterion for the efficacy of Lafamme® 1 mg in the randomized, multicenter, double-blind study vs. estradiol 1 mg/NETA 0.5 mg with 227 postmenopausal women was the severity of an existing depressive mood (Jenapharm research report A04274), which however does not preclude that in individual cases depression can also occur as an unwanted side-effect. Psychological symptoms like this are indeed quite common during the menopause and oestrogens can have a positive effect on the mood due to the increase of serotonin activity. At the start of the study, 43 % of the women in the Lafamme® group suffered of depressive moods and in the comparator group it was 45 % of the women. Already after the first administration cycle, there was a clear decrease in the incidence of depressivity, and during the further course of the hormone substitution this effect got even stronger. After 13 administration cycles with Lafamme® 1 mg, only 7 % of the women were affected by depressive moods – in the comparator group it was 10 % (figure 20).

Another randomized double-blind study, in this case placebo-controlled, confirmed the good efficacy of Lafamme® 2 mg for the treatment of postmenopausal depression (Rudolph et al., 2004). In this study, 129 women aged 48 to 65 years took part who were diagnosed with a mild to moderate depressive episode associated with a menopausal syndrome (score ≥ 16 on the Hamilton depression scale HAMD). The treatment had a duration of 24 weeks, either with Lafamme® in the higher potency (2/2 mg) (n = 65) or placebo (n = 64).

Lafamme® 2 mg resulted in a clear improvement of depression among the trial participants, despite a pronounced placebo effect which was highly significant both after 12 weeks ($p = 0.0003$) and after 24 weeks ($p = 0.0005$) vs. placebo. In 43.1 % of the women in the Lafamme® group, the HAMD score improved ≥ 50 % to absolute levels under 8; another 26.1 % had at least a gradual improvement, whereas in the placebo group most women (64.1 %) showed no change in their depressive symptoms (table 10).

The antidepressive effect of the hormone replacement therapy with Lafamme® 2 mg could only be partly explained by the simultaneous improvement of vasomotoric symptoms (hot flushes and night sweats) and insomnia because even



Abbreviations: NETA = norethisterone acetate

Figure 20. Incidence of depressive moods during treatment with Lafamme® 1 mg and a comparator for 13 cycles

if these accompanying effects were statistically taken into account, the antidepressive effect of Lafamme® 2 mg remained significant. There was also no significant link of the therapeutic effect to a history of premenstrual syndrome or postnatal depression. Most of the women in the Lafamme® group (80 %) and in the placebo group (81 %) had no side-effects during the treatment.

5.1.4 Improvement of cognitive functioning

The oestrogen deficiency during the postmenopause can impair the neurotransmitter metabolism in the brain, specifically that of acetylcholin, and reduce the oxygen supply to the brain. The consequences are disturbed general brain functioning, as well as forgetfulness, decreasing concentration, worsening of memory retention and recall. In a placebo-controlled study with 2 mg estradiol valerate alone or in combination with 2 or 3 mg dienogest with women with insomnia associated with a menopausal syndrome, it could be shown that the combined hormone therapy did not only improve the sleep quality subjectively and objectively but also the oxygen supply to the brain during sleep, measured with an increase in the apnoe- and apnoe-hypopnoea index. During daytime, vigilance and the overall cerebral performance of the women imp roved considerably. In addition, several cognitive functions like memory retention, concentration and recall could be increased significantly. Although the oestrogen monotherapy had advantageous neurophysiological effects, the combination with dienogest could significantly enhance these effects in individual areas (Saletu et al., 2002; Saletu, 2003; Saletu et al., 2005).

Table 10. Improvement of depressive symptoms in postmenopausal women during treatment with Lafamme® 2/2 mg or placebo over 24 weeks (adapted from Rudolph et al., 2004)

	Lafamme® 2/2 mg (n = 65)			Placebo (n = 64)		
Parameter	Baseline	Week 12	Week 24	Baseline	Week 12	Week 24
Severity of depression, med. HAMD score ± SD	18.9 ± 3.1	12.1 ± 6.4*	10.8 ± 7.2**	18.8 ± 3.9	15.8 ± 6.9	15.0 ± 7.7
HAMD response						
No response (HAMD ≥ 16), n (%)	-	-	20 (30.8)	-	-	41 (64.1)
Partial remission (HAMD 9 – 15), n (%)	-	-	17 (26.1)	-	-	6 (9.4)
Complete remission (HAMD ≤ 8), n (%)	-	-	28 (43.1)	-	-	17 (26.6)
CGI response			n = 60			n = 57
Not evaluated	-	-	1 (1.7)	-	-	4 (7.0)
No change/worsening	-	-	12 (20.0)	-	-	29 (50.9)
Minimal improvement	-	-	7 (11.7)	-	-	5 (8.8)
Moderate improvement	-	-	19 (31.7)	-	-	12 (21.1)
Significant improvement	-	-	21 (35.0)	-	-	7 (12.3)

*p = 0.0003 vs. placebo; **p = 0.0005 vs. placebo

Abbreviations: HAMD = Hamilton Depression Score, CGI = Clinical Global Impression

fact box LAFAMME®

- Lafamme® is a continuous combined oestrogen-gestagen drug (1 or 2 mg estradiol valerate + 2 mg dienogest per tablet) for the hormone replacement therapy in the menopause.
- As a result of the combination with the gestagen dienogest, Lafamme® relieves menopausal complaints quickly and effectively even with the low estradiol dose.
- Lafamme® can also sustainably improve mood and sleep in the context of a menopausal syndrome and can have a positive impact on cognitive functioning.
- With Lafamme®, the majority of users achieves a cessation of menses quickly.
- Lafamme® usually has no unfavourable effects on body weight and metabolic parameters, even after longer administration.

5.2 Cessation of menses

Many women expect of a hormone replacement therapy in the menopause apart from the elimination of menopausal complaints also a fast cessation of menses. To achieve this, dienogest as gestagen component of Lafamme® is particularly suitable because it has a strong transformatory effect on the endometrium. Corresponding to this, in the randomized, multicenter, double-blind study with postmenopausal women treated with Lafamme® 1 mg most women achieved a cessation of menses quickly. Already at the end of the first administration cycle, the menstrual bleeding stopped in 80 % of the women. After 13 cycles the success rate was 95 % (Jenapharm research report A04274). This is a good basis for high compliance with the Lafamme® therapy.

5.3 Impact on body weight and metabolic parameters

In a clinical study with 159 women, the body weight remained practically unchanged during the administration of Lafamme® 1 mg over 13 cycles, i.e. there was only a minor median change (Jenapharm research report A04274). Furthermore, no relevant changes in the parameters of the carbohydrate metabolism were observed. Total cholesterol, LDL-c and HDL-c levels decreased over the course of a year by 7.5 %, 6.5 % and 4.5 %, respectively. Triglyceride levels decreased temporarily (by 5 % after 7 cycles), but after 13 cycles they approximately reached baseline levels again. The coagulationsystem showed no relevant impact. Bone-specific alkaline phosphatase decreased by ca. 19 % which in connection with the simultaneously observed decrease of pyridinoline or desoxypyridinoline release indicates an inhibition of bone resportion (Jenapharm research report A04274).

5.4 Safety

5.4.1 Endometrial protection

In clinical studies with Lafamme®, the risk free usage for the endometrium also examined. For this purpose, the data of 498 postmenopausal women were analysed. The scan of the endometrial thickness with transvaginal sonography showed an average thickness of ≤ 5 mm; ca. 90 % of the users had an atrophic endometrium. During the whole duration of the treatment, none of the users had an endometrial hyperplasia (Jenapharm research report A01000, A02343, A04274 and A11355).

5.4.2 Tolerability

In clinical trials on the efficacy and innocuousness, Lafamme® 1 mg was shown to be a well-tolerated drug for the continuous combined hormone substitution. The adverse events reported in multicenter studies, were similar to those observed during the treatment with other hormone substitution drugs. Complaints like bleeding dysfunctions (8.9 %), headaches (9.5 %) and tension in the breasts (11.9 %), as well as hot flushes and nausea, were the most commonly reported adverse events. Adverse events which could possibly, probably or definitely be linked to the administration of the drug resulted over the course of one year only in 17.7 % of users in an early discontinuation of the treatment. These complaints mainly occurred in the first weeks of treatment.

6. Therapy of endometriosis with dienogest (Visanne®)

Endometriosis is a common chronic oestrogen related disease where endometrium-like tissue grows outside the uterus (uterine cavity). About 5 to 10 % of all women of reproductive age are affected. The symptoms typically include repeated dysmenorrhea, dyspareunia and lower abdominal pain, but dysuria and dyschezia can also be signs of the disease. Frequently, the result is a decreased fertility or infertility. The complaints which are often chronic can severely impair the quality of life of the women affected. For treatment, surgical and pharmacological measures can be considered. With a pharmacological treatment that is as long-term as possible, the recurrence risk can be reduced. The pharmacological therapies available are drugs like GnRH agonists and certain gestagens (dienogest). However, the duration of the use of GnRH agonists is limited due to the severe reduction of estradiol production.

Visanne® contains the gestagen dienogest (2 mg/tablet) which is extremely effective in the endometrium. Dienogest moderately inhibits the endogenous synthesis of estradiol and therefore reduces the trophic effects of estradiol on the eutopic and ectopic endometrium (Foster & Wilde, 1998; Sasagawa et al., 2008a). If used continuously, dienogest creates a hypo-oestrogenic, hyper-gestagenic, endocrine environment which leads to a decidualization of the endometrial stroma and a subsequent atrophy of endometriosis lesions. Independent of its gestagenic effect via the progesterone receptor, dienogest also inhibits the

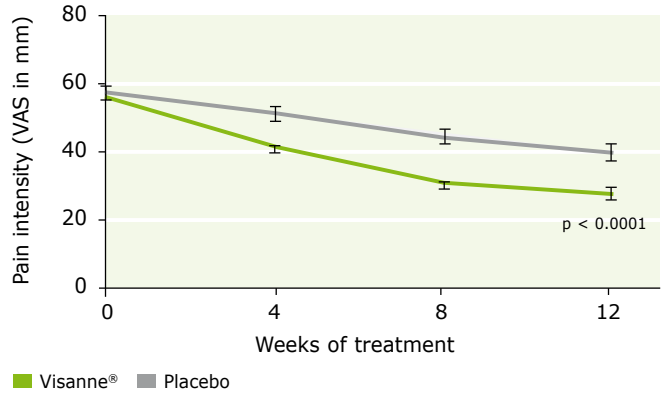


Figure 21. Intensity of lower abdominal pain in endometriosis patients during treatment with Visanne® or placebo. The scores are medians on a visual analogue scale (VAS) ± standard deviation (Strowitzki et al., 2010a)

proliferation of endometrium-like tissue (Okada et al., 2001; Katsuki et al., 1998; Fu et al., 2008; Shimizu et al., 2009).

Visanne® is the only orally administered gestagen drug which was systematically tested in an extensive trial programme and approved for the use in endometriosis. The clinical results from this programme show that Visanne® safeguards an effective pain relief for women with endometriosis which is comparable to the current standard therapy (GnRH agonists). The favourable safety and tolerability profile contributes to the view that Visanne® is also suitable for a longer term administration. At the moment, there are only limited published data available on the administration of Visanne® for more than 15 months or up to 36 months (Takagi et al., 2012).

6.1 Clinical efficacy

6.1.1 Dose-finding study

In a 24 week, randomized, open dose-finding study with 68 women with mild to moderate endometriosis (stage I – III), it was found that the lowest effective active dose of dienogest for the treatment of endometriosis is 2 mg/day (Köhler et al., 2010). In this dosage, until the end of the study a significant proportion of patients had an improvement of symptoms like dyspareunia, lower abdominal pain, dysmenorrhea, premenstrual pain and pain during the gynaecological examination. Doubling the dose to 4 mg/day was not associated with a further increase of efficacy (Köhler et al., 2010). The dienogest dose of 2 mg in Visanne® with daily administration of the drug is therefore absolutely sufficient.

6.1.2 Pain relief

For symptomatic patients who decide to have an endometriosis treatment, the pain relief has utmost priority for the success of the treatment (Sinaii et al., 2007; Somigliana et al., 2009). Current studies show consistently that Visanne® achieves an effective pain relief.

In a 12 week, multicenter, randomized, **placebo-controlled double-blind study** with 188 women who had a laparoscopic diagnosis of endometriosis in stage I to IV not longer than one year ago, the efficacy of Visanne® for pain relief was examined (Strowitzki et al., 2010a). All patients had lower abdominal pain at the beginning of the study, with an intensity of at least 30 mm on a visual analogue scale (VAS) with 100 mm. The median VAS score decreased over the course of the study in the Visanne® group by 27.4 mm and in the placebo group by 15.1 mm. This difference of 12.3 mm (95 % confidence interval 6.4 – 18.1) in favour of Visanne® was significant with $p < 0.0001$ **(figure 21)**.

The secondary efficacy criterion in this study was the symptom scale by Biberoglu and Behrman (B&B scale) which also showed a clear improvement of symptoms with Visanne® vs. placebo. On the CGI scale (Clinical Global Impression), the general well-being improved in 52.9 % of the patients with Visanne® clearly to very clearly. With placebo, this was only the case in 22.9 % of the patients. An assessment of the quality of life with the SF-36 questionnaire also showed a significant improvement vs. placebo in the category 'physical pain' with Visanne®.

Long-term results with Visanne® were gained from an **open extension study** (Petraglia et al., 2012) which was offered to the participants at the end of the 12-week, placebo-controlled, double-blind study (Strowitzki et al., 2010a). The continued treatment with Visanne® was planned for 53 weeks and 152 of 168 patients completed this extension therapy as planned (total active treatment duration 65 weeks for women who already

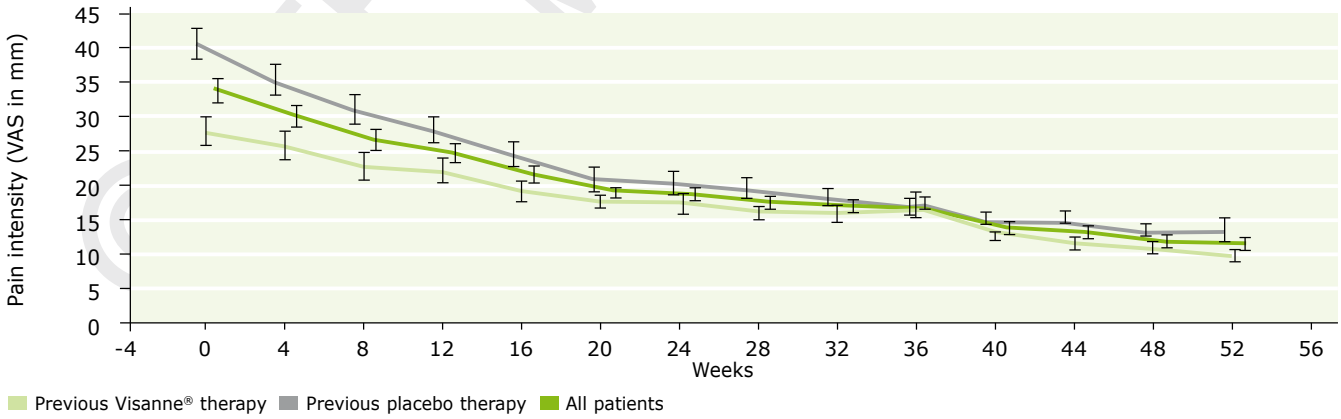


Figure 22. Intensity of lower abdominal pain in endometriosis patients during a 52 week follow-up treatment with Visanne®. The scores are medians on a visual analogue scale (VAS) ± standard deviation (Petraglia et al., 2012)

received Visanne® in the prior 12-week study). A subgroup of 34 patients was afterwards followed up for 24 weeks without treatment (total study duration 90 weeks). At the beginning of the extension study, the median intensity of lower abdominal pain in the women previously treated with Visanne® was 27.9 mm, while the previous placebo patients had a score of 40.7 mm and in the total study population it was 34.1 ± 21.6 mm on the VAS. The median pain score decreased steadily and significantly in the total population over the course of the follow-up treatment Visanne®, to a final VAS score of 11.5 ± 11.3 mm ($p < 0.001$) (figure 22). The frequency and duration of bleeds or spotting also decreased continuously with Visanne®, with levels going back to baseline within 4–6 weeks during the therapy-free follow-up phase.

In a 24 week, open, multicenter, randomised phase III study, the efficacy and safety of Visanne® were compared vs. the GnRH agonist leuprorelin acetate (LA) (Strowitzki et al., 2010b and 2012). The primary study objective was to prove non-inferiority of Visanne® vs. a standard therapy with regard to the efficacy attribute 'lower abdominal pain' – measured with a VAS of 100 mm. The study included 252 women with a laparoscopy-confirmed endometriosis diagnosis (stage I–IV) not longer than 1 year ago. LA was administered in a dosage of 3.75 mg/month via intramuscular depot injection. It was shown that the lower abdominal pain of trial participants (baseline levels 60.2 mm in the Visanne® group and 57.9 mm in the LA group) decreased continuously in both treatment groups. The extent of the reduction was comparable with 47.5 mm (Visanne®) and 46.0 mm (LA) (figure 23).

This result confirmed that Visanne® is equal to the GnRH agonist in terms of efficacy (confirmed non-inferiority with $p < 0.0001$). Very similar results on the efficacy of both therapies were shown with the B&B score – a measure for subjective complaints and gynaecological examination findings, as well as with the SF-36 questionnaire, while in the latter, Visanne® tended to show better results. Also with regard to tolerability, there were clear advantages in this study in favour of Visanne®. Since dienogest only moderately reduces the serum estradiol levels compared to GnRH analogues, the frequency of symptoms due to the lack of oestrogen, like headache (12.5 % vs. 19.5 %), hot flushes (0 % vs. 7 %), dry vaginal mucous membrane (1.7 % vs. 7 %), loss of libido (4.2 % vs. 6.3 %) and insomnia (1.7 % vs.

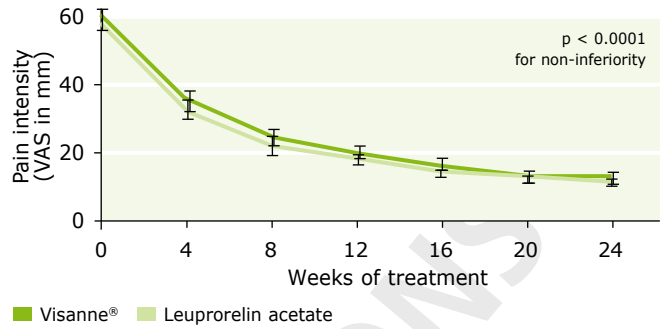


Figure 23. Intensity of lower abdominal pain in endometriosis patients in the randomised comparative study with Visanne® versus leuprorelin acetate. The score points are medians on a visual analogue scale (VAS) ± standard deviation (Strowitzki et al., 2010b)

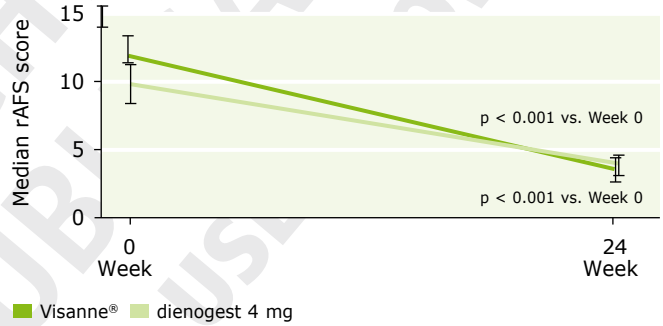


Figure 24. Regression of endometrial lesions during treatment with dienogest. The scores are medians ± standard deviation of the rAFS scores (Köhler et al., 2010)

fact box VISANNE®

- Due to the pharmacological characteristics of dienogest, Visanne® is an effective therapy for endometriosis.
- Durable relief of pain symptoms and significant regression of endometriosis lesions.
- Efficacy in pain reduction comparable with GnRH agonists with a better safety and tolerability profile.
- No clinically relevant negative impact on lipid parameters and bone density.
- Possible bleeding irregularities decrease with continued therapy.
- Can be used long-term.*
- Fast return of fertility after discontinuing Visanne®.

* At the moment, there are only limited published data about the administration of Visanne® for more than 15 months or up to 36 months available (Takagi et al., 2012)

7.8 %) in the Visanne® group was significantly lower than in the LA group (Strowitzki et al., 2010b). Furthermore, various markers of the bone metabolism indicated a higher bone resorption during treatment with LA, but not during Visanne® treatment (Strowitzki et al., 2010b). From several other studies with durations between 16 and 52 weeks, there are published results on the efficacy of dienogest on endometriosis-related pain which all confirm good treatment success with this substance (Köhler et al., 1989; Schindler et al., 2006; Momoeda & Taketani, 2007; Momoeda et al., 2009) and its therapeutic equality to GnRH agonists (Cosson et al., 2002; Harada et al., 2009).

6.1.3 Reduction of endometrial lesions

The laparoscopic proof of the reduction of endometrial lesions delivers valuable, objective, additional information on the efficacy of a drug therapy. In the 24 week dose-finding study with 1, 2, and 4 mg dienogest per day, changes in the endometriosis findings were examined based on the revised criteria of the American Fertility Society (rAFS) (Köhler et al., 2010). Dienogest resulted between the start and the end of the trial in a significant reduction of the rAFS score, on average from 11.4 ± 1.71 to 3.6 ± 0,95 ($p < 0.001$) in the group with 2 mg (Visanne®) and from 9.7 ± 1.34 to 3.9 ± 0.74 ($p < 0.001$) in the group with 4 mg **(figure 24)**. The disease stage improved correspondingly based on the rAFS classification, both with 2 mg dienogest and with 4 mg dienogest. In the 2 mg group, the distribution of stages at the beginning of the study were 34.5 % in stage I, 37,9 % in stage II, and 27.6 % in stage III. After 24 weeks of treatment, 23.8 % of the patients had no endometriosis at all, while 52.4 % had stage I, 9.5 % had stage II, and 4.8 % had stage III endometriosis.

In other studies too, in some cases a clear, and in many patients a complete regression of the laparoscopic endometriosis findings could be observed with Visanne® (Köhler et al., 1987 and 1989; Cosson et al., 2002; Schindler et al., 2006; Momoeda & Taketani, 2007).

6.2 Safety and tolerability

In clinical studies, the most common adverse events during treatment with Visanne® were headaches (9.0 %), breast discomfort (5.4 %), depressive mood (5.1 %), and acne (5.1 %). Apart from that, there were changes in the bleeding pattern with spotting, irregular bleeding or amenorrhea. Over the longer-term treatment, the frequency and intensity of bleeding decreased (excerpt – for a complete list of adverse events see Summary of Product Characteristics for Visanne® 2 mg, from June 2013).

In the 52 week open extension trial with Visanne®, the laboratory levels measured (haematology, lipid and carbohydrate metabolism, liver enzymes, estradiol) as well as the vital parameters and the body weight of patients remained almost unchanged (Petraglia et al., 2012).

In a subgroup of Visanne® treated patients in the comparative study with leuprorelin acetate, there was no change in the median bone mineral density in the lumbar spine (LS) based on dual-energy x-ray absorptiometry (DEXA) over the course of 24 weeks. Other markers of bone resorption did not change either (Strowitzki et al., 2010b). In a Japanese study, where 135 endometriosis patients were treated with Visanne® for 52 weeks, the DEXA scans showed a minimal but significant decrease of the bone mineral density of the LS by 1.6 ± 2.4 % after 24 weeks. This trend, however, did not continue afterwards

Conclusions for the clinical practice

- Due to its unique pharmacology with a high gestagenic effect in the endometrium and a clear antiandrogenic activity, dienogest is particularly suitable as gestagen component of oral contraceptives, and for the therapy of endometriosis.
- The combination dienogest/ethinyl estradiol (Valette®, Maxim®) is a highly efficacious and well tolerated contraceptive which can also be used for the treatment of moderate acne for women who have failed local therapy.
- Qlaira® is the first contraceptive on the basis of 'natural' estradiol. It is a 4-phasic drug with a dynamic dosage of dienogest and estradiol valerate which is easy to take with the 28 day blister. Due to the short hormone-free interval (2 days), there are usually no hormone withdrawal symptoms at the end of the cycle.
- Qlaira® is also well suited for contraception in women with heavy periods without organic cause because it significantly reduces the bleeding intensity and it relieves limitations in everyday life caused by hypermenorrhea to a large extent.
- The combination of dienogest (2 mg) and estradiol valerate (1 or 2 mg) (Lafamme®) was developed for the continuous hormone substitution in the menopause. Even with low estradiol doses, there is usually a rapid improvement of menopausal complaints, like improved sleep and better cognitive functioning.
- As a monotherapy (Visanne®), dienogest is a very effective drug for the treatment of endometriosis.
  In this indication it is equally effective as GnRH analogues, but better tolerated. Lower abdominal pain is normally relieved quickly and durably, the endometriosis lesions recede.

(1.7 ± 2.2 % at the end of the study). The authors state that the slight decrease of lumbar bone density with Visanne® was not significantly different to the spontaneous progression in this population group (Momoeda et al., 2009). However, since endogenous estradiol levels decrease moderately under Visanne® (e.g. Klipping et al., 2012), for women with an increased risk of osteoporosis, a thorough consideration of risks and benefits should be carried out.

Women with endometriosis are largely still of reproductive age and do indeed want contraception. Based on the current data, dienogest in a daily dose of 2 mg, offers a complete inhibition of ovulation (Oettel et al., 1999a; Moore et al., 1999c; Klipping et al., 2012). But since the efficacy of Visanne® as a contraceptive was not specifically tested, women who want to take the drug are advised to use non-hormonal contraceptives to prevent unwanted pregnancies (e.g. barrier methods). After the discontinuation of Visanne®, the menstrual cycle and the ovarian activity of the women normalized again within a few weeks (Klipping et al., 2012; Petraglia et al., 2012).

Based on the conventional studies on the toxicity after repeated administration, genotoxicity, reproduction toxicity and carcinogenic potential, the pre-clinical data do not indicate special risks for humans. But it should be considered that sex steroids can promote the growth of certain hormone-dependent tissues and tumors. Studies on the acute toxicity of dienogest do not indicate any risk of acute adverse events in case of unintentional wrong administration with several times the therapeutic daily dose (SmPC for Visanne® 2 mg, from June 2013).

Expert comment

by Prof. Dr. med. Thomas Römer, Evangelisches Krankenhaus Köln-Weyertal

Practice-relevant aspects for the gynaecological use of dienogest alone or in combination with oestrogens

Dienogest and dienogest-containing drugs are important components in the therapeutic armamentarium of gynaecologists because their range of uses, from the use as contraceptives to the treatment of important gynaecological conditions, like endometriosis or hypermenorrhea, or hormone substitution in the menopause. Dienogest and ethinyl estradiol-containing pills are used widely because, apart from providing reliable contraception, the antiandrogenic effect of the gestagen dienogest on the not uncommon androgenisation symptoms, can be used therapeutically at the same time. Apart from that, the ethinyl estradiol/dienogest combination with its high bleeding stability has also proven itself in practice in many gynaecological and in cycle-related conditions where the administration in a long cycle or a long-term administration can be an advantage. Qlaira® as a contraceptive with estradiol valerate, is increasingly considered. One of the reasons for this is that the tested and easily verifiable effect of the significantly decreasing monthly blood loss can be used for the therapy of hypermenorrhea in this substance combination for all age groups, while taking into account the increasing thromboembolic risk with increasing age. Qlaira® is therefore an effective oral alternative also to the intrauterine application of Mirena® and surgical interventions like endometrial ablation, especially in the light of the fact that the subject of hypermenorrhea and the associated impairment of the quality of life, and the available therapeutic options are in practice often underestimated.

Dienogest as a monotherapy is the most tested and most effective gestagen which is increasingly used for the endometriosis therapy. On one hand, its effectivity corresponds with the effectivity of GnRH analogues, and on the other hand, an equally effective and side-effect-reduced therapy is also possible in the longer-term, based on our experiences. In many situations, Visanne® even offers a pharmaceutical alternative to high risk endometrial surgery like intestinal or bladder resections which would necessitate multidisciplinary planning.

For the hormone substitution during the menopause, which currently sees a comeback, combinations of dienogest and estradiol valerate have proven themselves. For the practice, it is particularly valuable that two dosage of estradiol valerate are available with this drug, so that an individualized therapy is possible. At the beginning of the menopause, where the bleeding dysfunctions are in the foreground, the combination with 1 mg estradiol valerate is often preferred. When other climacteric symptoms, like severe vegetative and/or psychological complaints are in the foreground, like hot flushes and sleep dysfunctions, there is a tendency to use the 2 mg dose in practice.

Dienogest – good tolerability provided – can therefore be an effective pharmacological companion for many women – for contraception, the treatment of gynaecological conditions or the therapy of menopausal complaints. This option of continuity provided by a gestagen in gynaecological practice and therapy is valued hugely, both by patients and by treating gynaecologists.

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