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Dienogest

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Contents

Abstract

▲ The progestogen dienogest exhibits highly selective binding to the progesterone receptor. It has high progestational and significant antiandrogenic activity, but only moderate antigonadotrophic activity.

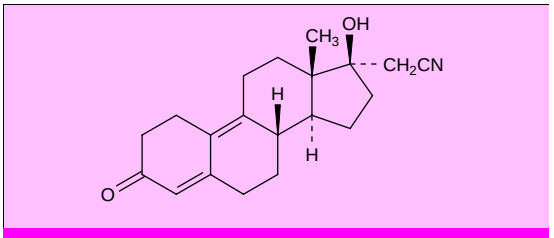
▲ Dienogest inhibits ovulation, produces secretory transformation of the endometrium and has antiproliferative effects.

▲ Oral dienogest 2 mg/day plus ethinylestradiol 30 μg/day provides effective contraception (Pearl Index approximately 0.2). Cycle stability is good during long term use of this combination; irregular vaginal bleeding was evident in 6% of women after 12 months' use.

▲ Androgenic symptoms (including hirsutism, seborrhoea, alopecia, acne vulgaris and hair and skin greasiness) improved in women treated with dienogest plus ethinylestradiol.

▲ The adverse events associated with dienogest are typical of those expected of a progestogen. The drug does not produce androgenic adverse effects and has little clinically significant effect on metabolic, lipid and haemostatic parameters.

Features and properties of dienogest (STS 557)	
Indication	
Oral contraception (in combination with ethinylestradiol)	Launched
Mechanism of action	
Progestogen	
Dosage and administration	
Usual oral dosage	2mg once daily
Pharmacokinetic profile (2 mg/day)	
Oral bioavailability (F)	90%
Proportion available as free active compound in plasma	≈10%
Volume of distribution	40L
Clearance (CL/F)	3 L/h
Elimination half-life	≈8 to 9h
Accumulation with repeated administration?	No
Endocrinological profile	
High progestational activity. Some antiprogestational activity	
Significant antiandrogenic activity. No androgenic activity	
Moderate antigonadotrophic activity	
Low estrogenic and antiestrogenic activity	
No glucocorticoid or mineralocorticoid activity	
Adverse events (when used in combination with ethinylestradiol)	
Irregular vaginal bleeding, headache, breast pain, nausea/vomiting, depression, decreased libido	



Dienogest

Progestogens are used in a number of indications including oral contraception, postmenopausal hormone replacement therapy and the treatment of endometriosis. The focus of this review is the use of the progestogen dienogest as a component of oral contraceptives.

Progestogens largely fall into 2 categories; the 19-nortestosterone derivatives (e.g. norethisterone, levonorgestrel, desogestrel, gestodene, norgestimate) and the progesterone derivatives (e.g. medroxyprogesterone acetate, cyproterone acetate). Dienogest is a hybrid progestogen that combines properties of both the 19-nortestosterone derivatives and the progesterone derivatives, as well as having unique pharmacodynamic and pharmacokinetic properties.[1,2] Dienogest is structurally distinct from conventional 19-nortestosterone derivatives by virtue of its 17α-cyanomethyl group.[1]

1. Pharmacodynamic Profile

Progestational, Antiprogestational and Antigonadotrophic Activity

- *In vitro*, dienogest has moderate affinity for the progesterone receptor in human uterus tissue, being about 10% of that of progesterone.[2,3]

- When measured by secretory transformation of estrogen-primed endometrium in immature rabbits (Clauberg/McPhail assay), dienogest had high progestational activity.[1,4,5] The 50% effective dose (ED_{50}) for oral (PO) dienogest was 0.11 mg/kg.[4] In postmenopausal women receiving PO ethinylestradiol 50 μg/day, a PO dienogest dose of 6.3mg given over 14 days (0.45 mg/day) was required for complete secretory transformation of the endometrium (according to the Kaufmann assay).[6] The dose of levonorgestrel required for full secretory transformation was 3.5mg.

- Dienogest (PO 1.5 mg/kg) had an antiprogestational effect in the Clauberg/McPhail assay in immature rabbits when it was administered 2 days before progesterone, but not when the 2 agents were given simultaneously.[5] Progesterone-induced deciduoma formation in immature or ovariectomised rats was dose-dependently inhibited by dienogest [subcutaneous (SC) 1 or 8 mg/day or PO 3 or 10 mg/kg/day].[7,8]

- The antigonadotrophic effect [shown by suppression of serum luteinising hormone (LH) levels in male gonadectomised immature rats] of dienogest is only moderate (effective SC dose 14mg over 14 days) and is less than that of levonorgestrel (effective SC dose 0.42mg).[9]

Inhibition of Ovulation

- A dose-finding study indicated that a minimum oral dienogest dose of 1 mg/day is required for inhibition of ovulation in cyclical women.[1,10]

- Dienogest inhibits ovulation primarily via peripheral actions, rather than via central action on gonadotrophin secretion.[1,11] During treatment with PO dienogest 2 mg/day in cyclical women, serum progesterone levels were reduced to anovulatory levels, but serum levels of LH and follicle-stimulating hormone were not greatly affected.[1,11]

- In 22 women (aged 20 to 34 years) with previously normal ovulatory cycles, ovulation was inhibited by treatment with PO dienogest 2 mg/day plus ethinylestradiol 30 μg/day for 3 treatment cycles (each comprising 21 consecutive days of active treatment followed by a 7-day pill-free period).[12] Residual ovarian activity was evident in few women in the first treatment cycle, but became evident in more women during later cycles (fig. 1).

- In healthy fertile women (aged 20 to 39 years), administration of a single oral dose of dienogest 0.6mg during the follicular phase of the menstrual cycle inhibited ovulation.[13] Administration of dienogest 2 days before the expected LH surge

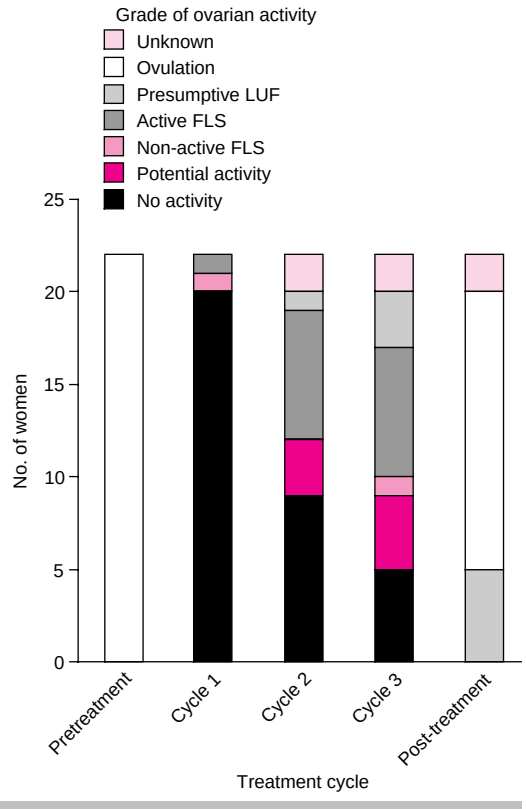


Fig. 1. Ovarian activity in women treated with dienogest plus ethinylestradiol.[12] 22 women (aged 20 to 34 years) with previously normal ovulatory cycles were treated with oral dienogest 2 mg/day plus ethinylestradiol 30 μg/day for 3 treatment cycles each comprising 21 consecutive days of treatment followed by a 7-day pill-free interval. Ovarian activity was graded by serum hormone levels and size of follicle-like structures (FLS), as follows: no activity (FLS ≤10mm); potential activity (FLS >10mm); non-active FLS (>13mm); active FLS (>13mm); presumptive luteinised unruptured follicle (LUF; persisting FLS >13mm); ovulation (ruptured FLS >13mm).

delayed the LH peak; a 2mg, but not a 0.6mg dose, prevented ovulation. When dienogest (0.6 or 2mg) was administered 1 day before or during the rising LH peak, the LH surge was lowered but ovulation was not affected. Corpus luteum function and ovulation were not affected when dienogest (0.6 or 2mg) was administered during the LH peak. The menstrual cycle was not affected when dienogest was administered after ovulation during the basal body temperature rise.

Androgenic/Antiandrogenic Activity

- Dienogest exhibits low competitive binding to the androgen receptor in rat prostate tissue *in vitro*.[2,3]

- The drug has no androgenic activity. Ventral prostate weight in gonadectomised immature male rats (Hershberger assay) was not significantly increased by treatment with PO dienogest doses ≤100 mg/kg/day or SC doses of 10 mg/day or 62.5mg over 7 days.[1,7,14]

- Dienogest (SC 2.5 to 62.5mg over 7 days) had antiandrogenic activity that was approximately 40% of that of cyproterone acetate in the modified Hershberger assay in immature gonadectomised male rats treated with testosterone.[1,14] The drug has greater antiandrogenic activity than chlormadinone acetate.

- An antiandrogenic effect has been shown in cyclical women treated with PO dienogest 2 mg/day plus ethinylestradiol 30 μg/day.[1,15] Serum levels of androstanediol glucuronide after 3 cycles of treatment (21 days of consecutive treatment followed by a 7-day pill-free interval) were 38% lower than at baseline. Serum total testosterone levels were reduced by 17 to 40%, free testosterone levels by 48 to 54% and dehydroepiandrosterone sulfate levels by 51%.

- In 18 women with hyperandrogenism, treatment with PO dienogest 2 mg/day plus ethinylestradiol 50 μg/day for up to 2 years improved androgenic signs and symptoms.[16] Hair follicle and sebaceous gland volume decreased significantly during treatment. Hirsutism was subjectively improved in 9 of 10 women moderately or extensively affected, and in 2 of 8 women with more mild cases. Seborrhoea was reported to be clearly improved by 9 of 13 affected women. In the 5 women with androgenic alopecia, hair growth, or no further hair loss, was reported.

- Antiandrogenic effects during contraceptive treatment with PO dienogest 2 mg/day plus ethinylestradiol 30 μg/day (21 days of consecutive treatment followed by a 7-day pill-free interval) were

evidenced by subjective effects on skin and hair in 10 718 women who received a total of 63 474 cycles of treatment.[17] In most women, hair became greasy less rapidly, skin was less greasy and acne vulgaris improved during the 6 months of treatment (fig. 2).

Other Activity

- Affinity of dienogest for estrogen receptors is negligible, according to *in vitro* studies in human and rabbit uterus tissue.[2,3] Slight estrogenic and antiestrogenic effects have been detected in animal models,[7,18,19] but not with clinically relevant doses in women.[1,10,11]

- Dienogest is not bound by the steroid transport proteins cortisol-binding globulin (CBG) or sex hormone-binding globulin (SHBG),[2,3] and does not interfere with ethinylestradiol-induced increases in levels of these proteins.[1,11] In cyclical women, treatment with PO dienogest 1 to 2 mg/day did not significantly affect serum prolactin, CBG and SHBG or renin levels.[1,10,11]

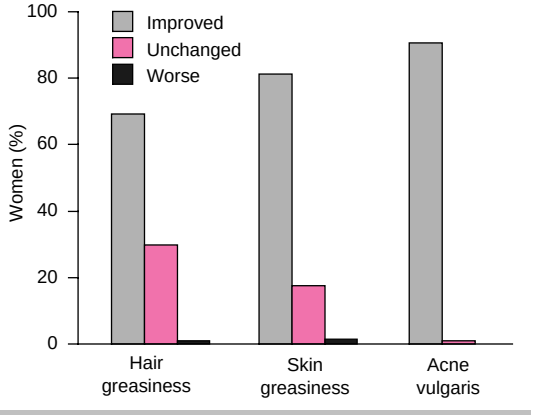


Fig. 2. Effects of dienogest plus ethinylestradiol on hair and skin.[17] 10 718 women received oral dienogest 2 mg/day plus ethinylstradiol 30 μg/day for 6 treatment cycles (total 63 474 treatment cycles, each comprising 21 consecutive days of active treatment followed by a 7-day pill-free interval). How rapidly hair became greasy and the extent of skin greasiness and acne vulgaris were compared with baseline. The improved category for acne vulgaris included 29.1% of women in whom acne was totally healed. The effect on acne was not reported for 8.6% of women.

- Affinity of dienogest for glucocorticoid and mineralocorticoid receptors is negligible, according to *in vitro* studies in rat tissue.[2,3] The drug has no glucocorticoid or mineralocorticoid activity.[1,7]

- Dienogest has demonstrated antiproliferative effects *in vitro* and *in vivo*.[1] In contrast to other progestogens, dienogest inhibited estrogen-stimulated tumour growth of HEC-88nu cells in mice.[20] The HEC-88nu cell line is derived from human endometrial carcinoma and expresses estrogen, but not progesterone, receptors. Dienogest also inhibited estrogen-stimulated tumour growth of Ishikawa and MCF-7 cells, which are derived from human endometrial and breast carcinomas, respectively; both of these cell lines express estrogen and progesterone receptors.

- *In vitro*, dienogest does not abolish the antioxidative or calcium channel blocking activity of 17β-estradiol.[1,21]

Animal Models of Contraceptive Activity

- Dienogest inhibited fertility and had an interceptive effect when administered postcoitally in a number of female animal models.[5,8,22-25] Relevant effects of dienogest in this respect include inhibition of egg fertilisation, inhibition of nidation, acceleration of tubal egg transport and morphological changes in the endometrium (including stromal hyperplasia and deep folding).[8,19,22,23]

- A contraceptive effect in male animal models has also been demonstrated.[26-31] Dienogest inhibited spermatogenesis, but in some studies undesirable effects on Leydig cell function, serum testosterone levels and libido occurred.

2. Pharmacokinetic Profile

- The pharmacokinetics of single oral doses of dienogest 1 to 4mg, alone or in combination with ethinylestradiol 30μg or 60μg, were assessed in male and female volunteers.[2] Oral bioavailability of dienogest was approximately 90%. Maximum serum dienogest concentrations were reached within approximately 2 hours.

• The pharmacokinetics of oral dienogest are linear.[2] In female volunteers who received single oral doses of dienogest in consecutive menstrual cycles, the mean maximum serum concentrations (C_{max}) were 28, 54, 101 and 212 μg/L after 1, 2, 4 and 8mg doses, respectively. The mean areas under the serum concentration curve ($AUC_{0-\infty}$) were 306, 577, 1153 and 2292 μg/L · h, respectively.[2]

• Almost 10% of the total concentration of dienogest after oral administration is available as free, nonprotein-bound compound in the plasma.[2] This biologically active fraction is relatively high compared with that normally observed with progestogens (0.5 to 4%).[2] The remaining 90% of the compound is bound to albumin.[2] The volume of distribution of dienogest is relatively low (40L after a single oral dose of 1mg).[2]

• Dienogest is eliminated relatively rapidly from plasma. The terminal elimination half-life ($t_{½\beta}$) of dienogest was 7.5 to 8.9h after single oral doses of dienogest 2 to 8mg alone or dienogest 2mg plus ethinylestradiol 30μg in male and female volunteers.[2] A slightly longer ($t_{½\beta}$) was observed when PO dienogest 4mg was administered in combination with ethinylestradiol 60μg to male volunteers (10.7h).[2]

• Unchanged dienogest predominates in the plasma but is subsequently converted to a number of metabolites, primarily via hydroxylation, hydrogenation and aromatisation reactions.[2,23,32] These metabolites are rapidly eliminated in the urine in the first 24 hours after administration, whereas unchanged dienogest appears to undergo renal reabsorption.

• The metabolites of dienogest generally show less affinity for the progesterone receptor than the parent compound.[2]

• In studies of repeated administration of oral dienogest, steady state was reached within 6 days and there was no accumulation of the drug.[2,33] After 21 days' administration of dienogest 2mg plus ethinylestradiol 30μg daily to female volunteers, C_{max} was 64 μg/L, AUC_{0-24} was 714 μg/L · h, clearance (CL_{tot}/F) was 2.9 L/h and ($t_{½\beta}$) was 9h; these values were not significantly different from those measured on day 1 of treatment.[2] In contrast, accumulation of levonorgestrel was evident in volunteers who received levonorgestrel 0.125mg plus ethinylestradiol 30μg daily.

• Dienogest is poorly absorbed through the skin.[2,34]

Drug Interactions

• Dienogest does not interfere with activity of cytochrome P450 3A4 *in vitro*.[35] In healthy volunteers, cytochrome P450-mediated metabolism of nifedipine,[36] caffeine and metamizol[37] was not affected by dienogest.

3. Therapeutic Trials

Contraception

For contraceptive use, dienogest is combined with ethinylestradiol in 28-day treatment cycles during which active treatment is given orally for 21 consecutive days followed by a 7-day pill-free interval. The studies described in this section used such a regimen.

• The combination of dienogest 2 mg/day plus ethinylestradiol 30 μg/day was determined to be optimal for contraceptive purposes in phase II and III trials.[1] With a low dienogest dose (0.225 mg/day) but high ethinylestradiol dose (50 μg/day), 2 pregnancies occurred during 372 treatment cycles. Effective contraception was attained with dienogest 2 mg/day combined with ethinylestradiol 30 μg/day and fewer bleeding disturbances occurred than with ethinylestradiol 50 μg/day.

• Contraceptive efficacy was assessed in 2291 healthy women (aged 18 to 40 years) who each received dienogest 2 mg/day plus ethinylestradiol 30 μg/day for 1 to 21 treatment cycles (total 24 719 cycles).[38] 15 pregnancies occurred during treatment. The adjusted Pearl Index was 0.2 [equivalent to the failure rate per 100 woman years; approximated by the number of pregnancies (for the adjusted index, pregnancies occurring in association with interfering factors such as tablet omission,

drug interactions and vomiting are excluded) divided by the total number of months of exposure and multiplied by 1200; a Pearl index lower than approximately 0.5 indicates highly effective contraception[39]].

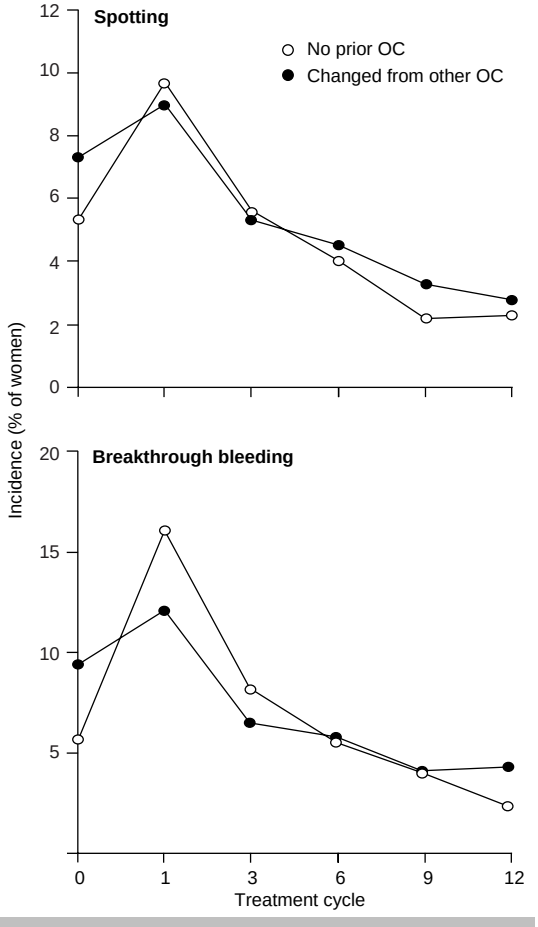


Fig. 3. Incidence of irregular vaginal bleeding during treatment with dienogest plus ethinylestradiol.[38] 2291 women received oral dienogest 2 mg/day plus ethinylestradiol 30 μg/day for 1 to 21 treatment cycles. Each 28-day treatment cycle comprised 21 consecutive days of active treatment followed by a 7-day pill-free interval. Data for women who were not receiving an oral contraceptive (OC) before the initiation of dienogest/ethinylestradiol and for those who were changed from another OC are presented separately; percentages shown are those for each group rather than for the total number of women. Bleeding was classified as spotting (requiring ≤1 tampon or sanitary pad per day) or breakthrough (menstrual period severity).

- A Pearl Index of 0.14 was reported from a 6-month postmarketing study in which 16 087 women received dienogest 2 mg/day plus ethinylestradiol 30 μg/day for a total of 92 146 treatment cycles.[17]

- Dienogest reduces the risk of pregnancy when administered after sexual intercourse, but the effect is not adequate for the drug to be used alone as a postcoital contraceptive.[40] 58 women ingested PO dienogest 2mg immediately after sexual intercourse an average of 3 times per cycle during a total of 302 menstrual cycles (872 reported episodes of sexual intercourse). Pregnancy occurred in 14 women, giving a Pearl index of 55.6. The observed pregnancy rate per episode of sexual intercourse was 1.6%, whereas the expected pregnancy rate in the absence of contraceptive intervention would be 4.04%.

Cycle Control in Contraceptive Users

- In 2291 women receiving contraceptive dienogest 2 mg/day plus ethinylestradiol 30 μg/day (active treatment for 21 consecutive days followed by a 7-day pill-free interval), irregular vaginal bleeding was common in the first cycle of treatment, but declined thereafter to be lower than before initiation of the contraceptive (fig. 3).[38] This occurred both in women who were not receiving another oral contraceptive before initiation of dienogest/ethinylestradiol and in those who changed from another oral contraceptive. Overall, approximately 22% of the women had irregular bleeding during the first treatment cycle. By the 12th treatment cycle, only about 6% of women experienced irregular bleeding.

- Withdrawal vaginal bleeding during the pill-free interval of the treatment cycle occurred in >95% of women in the above study.[38] By the 12th treatment cycle, the average duration of bleeding was 4 days, compared with 5 days before initiation of the contraceptive. Cycle length did not change significantly during treatment. Bleeding was less severe during treatment with dienogest plus ethinyl-

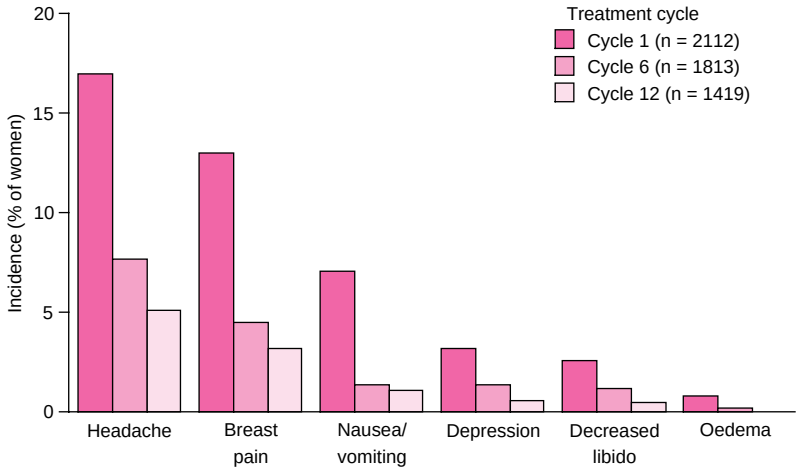


Fig. 4. Adverse events during dienogest plus ethinylestradiol treatment.[38] Incidence of evaluated adverse events in women (aged 18 to 40 years) receiving dienogest 2 mg/day plus ethinylestradiol 30 μg/day for contraceptive purposes. Each 28-day treatment cycle comprised 21 consecutive days of active treatment followed by a 7-day pill-free interval.

estradiol than before treatment; during the 12th treatment cycle bleeding was slight in 48% of women, moderate in 50% and severe in 2%. The incidence of dysmenorrhoea was reduced from 29% before the initiation of dienogest/ethinylestradiol to 5% by treatment cycle 12.

• In a postmarketing study of contraceptive dienogest 2 mg/day plus ethinylestradiol 30 μg/day (active treatment for 21 consecutive days followed by a 7-day pill-free interval) involving 16 087 women who received 92 146 treatment cycles, spotting occurred in 5% of women and breakthrough bleeding occurred in 3.4% of women during the first treatment cycle.[41] Withdrawal bleeding occurred in all but 2% of cycles. Among women reporting dysmenorrhoea, an improvement was recorded by 70% during treatment.

4. Tolerability

General Adverse Events

• Adverse events generally occurred more frequently in the first few months of treatment with PO dienogest 2 mg/day (alone or in combination with ethinylestradiol 30 μg/day) than in later months in clinical studies.[38,42]

• In a study of the contraceptive use of PO dienogest 2 mg/day plus ethinylestradiol 30 μg/day that involved more than 2000 women, headache, breast pain and nausea/vomiting occurred in >5% of women during the first treatment cycle, but declined in incidence thereafter (fig. 4).[38]

• A small amount of information on the tolerability of dienogest alone (tested in women with endometriosis) is available. In 223 women treated with PO dienogest 2 mg/day for 6 months, the most common adverse event was a decrease in libido, which was reported by 28% of women.[42] Other adverse events that were reported included increased appetite (24%), hot flushes (12.5%), tiredness (12%), nausea (11%), headache (10%), nervousness (9%), reduced energy (9%), breast pain (5%) and hirsutism (2%). In contrast to other adverse events, the incidence of decreased libido did not decrease over time.

• In clinical studies of approximately 2500 women who received PO dienogest 2 mg/day, alone or in combination with ethinylestradiol 30 μg/day, mean bodyweight increased slightly, but not to a statistically significant extent, during 1 to 21 treatment cycles.[38,42] Nevertheless, a small number of women

had marked increases or losses of bodyweight. Mean blood pressure did not change significantly.

• Serious adverse events considered probably related to treatment that occurred among 2291 women receiving PO dienogest 2 mg/day plus ethinylestradiol 30 μg/day were ovarian cysts (n = 2), lower leg thrombophlebitis (n = 1) and other vein complaints (n = 1).[38] Treatment was discontinued because of adverse events in 11.2% of the women.

• Animal studies indicate that dienogest does not have embryotoxic, teratogenic or mutagenic effects.[43-45]

Metabolic and Biochemical Parameters

• As demonstrated in women receiving monotherapy with PO dienogest 2 mg/day (to treat endometriosis), dienogest caused no significant changes in mean lipid levels during 6 months' treatment.[46] Glucose tolerance was not adversely affected, although fasting blood glucose levels and the insulin response to glucose load tended to increase slightly.[47] Biochemical parameters of liver function did not deviate from normal ranges, but statistically significant decreases in mean aspartate aminotransferase and alanine aminotransferase levels, and statistically significant increases in lactate dehydrogenase and total bilirubin levels occurred.[48]

• Other studies in women receiving PO dienogest 2 mg/day plus ethinylestradiol 30 or 50 μg/day confirm that the drug does not affect serum lipid or lipoprotein levels, blood clotting parameters, carbohydrate metabolism or immunological function to a clinically significant extent.[1,49]

• Treatment with PO dienogest 2 mg/day plus ethinylestradiol 30 μg/day in healthy women slightly stimulated both procoagulant and fibrinolytic activity, producing a balanced effect on haemostatic function.[50]

5. Dienogest: Current Status

Dienogest is a progestogen that is available for use in combination with ethinylestradiol as an oral contraceptive. It has antiandrogenic activity and thus and can improve androgenic symptoms.

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