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Estradiol Valerate/Dienogest

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Contents

Abstract

▲ Estradiol valerate 2mg/dienogest 2mg is an oral estrogen/progestogen formulation that has been approved throughout the European Union for the treatment of climacteric symptoms in postmenopausal women.

▲ Dienogest is a progestogen that combines the properties of both progesterone and 19-nortestosterone derivatives. It has moderate affinity for the progesterone receptor, significant antiproliferative and antiandrogenic activity, and produces secretory transformation of the endometrium.

▲ Estradiol valerate is an esterified form of natural 17β-estradiol, the most potent endogenous human ovarian estrogen, and is hydrolysed to estradiol soon after oral administration.

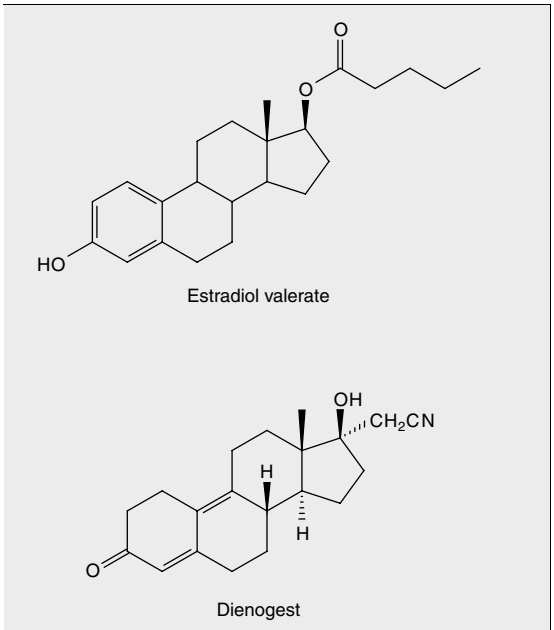
▲ Results from a randomised, double-blind, multicentre trial showed that oral estradiol valerate 2mg/dienogest 2mg and estradiol valerate 2mg/dienogest 3mg once daily for 1 year were each as effective as estradiol 2mg/estriol 1mg/norethisterone acetate 1mg in the treatment of climacteric symptoms in 581 postmenopausal women; reductions from baseline in Kupperman Index scores were 78.5, 74.5 and 75.0%, respectively.

▲ The number of days without any type of bleeding was lowest in patients treated with estradiol valerate 2mg/dienogest 2mg (8.7 days), and highest in the estradiol valerate 2mg/dienogest 3mg group (12.1 days). During the twelfth month of treatment with estradiol valerate 2mg/dienogest 2mg, the percentage of patients who reported bleeding was 14.5%.

▲ Endometrial biopsy results were similar in patients treated with estradiol valerate 2mg/dienogest 2mg, estradiol valerate 2mg/dienogest 3mg or estradiol 2mg/estriol 1mg/norethisterone acetate 1mg once daily for 1 year; 90.8, 87.4 and 87.5% of samples, respectively, contained atrophic material. Proliferative material was found in 4.2, 2.5 and 4.4% of the biopsies, respectively; there was no incidence of hyperplasia in any of the treatment groups.

▲ A noncomparative muticentre study in 1501 postmenopausal women demonstrated that adverse events associated with estradiol valerate 2mg/dienogest 2mg once daily for 48 weeks included breakthrough bleeding, mastalgia, headache, abdominal pain, hypertension, thrush, migraine, weight gain, increase in endometrial thickness and metrorrhagia.

Features and properties of estradiol valerate/dienogest		
Indication		
Treatment of climacteric symptoms in postmenopausal women		
Mechanism of action		
Estrogen/progestogen		
Dosage and administration		
Usual dosage in clinical trials	Estradiol valerate 2mg/dienogest 2mg	
Route of administration	Oral	
Frequency of administration	Once daily	
Pharmacokinetic profile of single-dose estradiol valerate 2mg/dienogest 2mg		
	Estradiol	**Dienogest**
Maximum plasma concentration	0.031 μg/L	53.68 μg/L
Area under the concentration-time curve	0.446 μg • h/L	482.6 μg • h/L
Time to peak plasma concentration	8h	1h
Route of elimination	Renal	Renal
Elimination half-life	17.2h	10.8h
Adverse events		
Breakthrough bleeding, mastalgia, headache, abdominal pain, hypertension, thrush, migraine, weight gain, increase in endometrial thickness and metrorrhagia		



Estradiol valerate/dienogest

The mean age at menopause is about 50 years worldwide.[1] In about 75 to 80% of women, symptoms associated with menopause usually begin during the climacteric, which starts about 4 years before menopause.[2] During this period, levels of follicle-stimulating hormone (FSH), luteinising hormone (LH), estradiol and estrone vary unpredictably. Climacteric symptoms typically include vasomotor changes (hot flushes and night sweats) and urogenital complications, such as atrophic vaginal irritation and dryness, dyspareunia and atrophic urethral epithelium leading to micturition disorders. However, women can also experience irritability, joint pain, sleep disturbances and mood swings.[1] In about 65% of women passing the menopause, climacteric symptoms persist; of these women, approximately 30% have symptoms severe enough to warrant medical attention.[3]

Oral hormone replacement therapy (HRT) is a well established means for relieving climacteric symptoms, as well as for reducing the long-term risk of osteoporosis. In women who have not undergone hysterectomy, estrogen-only HRT is associated with an increased risk of endometrial hyperplasia and cancer;[4] therefore, a progestogen is added to the regimen in order to prevent this occurrence.[5] Progestogens decrease estrogen-induced endometrial proliferation and lead to the development of a secretory endometrium[6] or, if used continuously, atrophic tissue.[7] Sequential HRT, in which postmenopausal women are treated sequentially with estrogens followed by an estrogen/progestogen combination, is associated with regular withdrawal bleeding. In contrast, continuous treatment with a combined estrogen/progestogen combination causes endometrial atrophy and subsequent amenorrhoea.[7]

This review examines the use of an oral formulation containing estradiol valerate and dienogest for continuous-combined HRT in postmenopausal women.

1. Pharmacodynamic Profile

Estradiol valerate is an esterified form of natural 17β-estradiol (estradiol), the most potent endogenous human ovarian estrogen, and is rapidly hydrolysed to estradiol after oral administration.[7] The pharmacodynamics of orally administered estradiol valerate are comparable to those of orally administered micronised estradiol.[8] The pharmacodynamics of estradiol and dienogest have been reviewed previously in *Drugs & Aging*[9] and *Drugs*,[10] respectively, and elsewhere.[6,11,12] The pharmacological profile of estradiol valerate has also been reviewed previously.[13] Therefore, this review provides only a brief overview of the pharmacodynamic profile of estradiol and dienogest. Results of three studies that evaluated the effects of the estradiol valerate/dienogest combination on vasoactive markers,[14] serum levels of insulin-like growth factor I (IGF-I), sex hormone-binding globulin (SHBG) and placental protein 14 (PP14),[15] and on coagulation, the lipid profile and glucose metabolism[16] in postmenopausal women are also discussed. While there have been two reports concerning the effects of estradiol valerate/dienogest on insomnia,[17] and on performance, mood and

personality[18] in postmenopausal women, these studies will not be discussed further.

Estradiol

• Estrogens, including orally administered estradiol, passively diffuse through cellular membranes and bind to estrogen receptors present in the nucleus. Estrogen receptors are found in the female reproductive tract, breast, pituitary, hypothalamus, bone, liver and other tissues. The receptor interacts with specific nucleotide sequences present in target genes, and this interaction increases, or decreases in some cases, transcription of hormone-regulated genes. The receptor-estrogen complex binds to DNA and stabilises a multiprotein complex that includes RNA polymerase and other proteins necessary for the initiation of RNA synthesis.[6]

• Estradiol is the predominant source of estrogen in premenopausal women; after menopause, estrone is the main source of estrogen and is derived from peripheral conversion of androstenedione.[19] In premenopausal women, serum levels of estradiol range from 0.18 to 1.1 nmol/L during different stages of the menstrual cycle, whereas serum estradiol levels drop to approximately 0.05 nmol/L in postmenopausal women. Furthermore, FSH and LH levels start increasing several years before ovulation ceases because of the loss of feedback inhibition by estrogen and/or inhibin.[20] After oral administration of estradiol valerate 2mg to postmenopausal women, serum/plasma levels of estradiol are restored to those found during the early to mid-follicular phase of the ovulatory cycle in premenopausal women, and FSH levels are reduced.[20,21]

• Estrogens are also associated with the prevention of osteoporosis via a decrease in bone resorption. Therefore, treatment of postmenopausal osteoporosis with estrogens is of primary importance.[6] Although the effects of continuous-combined treatment with estradiol valerate 2mg/dienogest 2mg on bone mass have not yet been evaluated, markers of the extent of bone resorption (alkaline phosphatase, pyridinoline and desoxypyridinoline) were measured in a large, noncomparative, multicentre trial (see section 3 for study details) in which 1501 postmenopausal women received estradiol valerate 2mg/dienogest 2mg for 48 weeks.[22]

• Levels of pyridinoline, desoxypyridinoline (both of which are components of bone collagen) and alkaline phosphatase, were determined from blood samples in a subset of patients (n = 237 to 302) at baseline and at weeks 24 and 48. At week 24, mean levels of alkaline phosphatase had decreased from 11.6 to 7.9 μg/L (32% reduction) and remained constant until endpoint ($p = 0.001$ versus baseline values after 48 weeks). Levels of free pyridinoline and desoxypyridinoline decreased by 18 and 19%, respectively, after 24 weeks and remained constant until endpoint ($p = 0.001$ versus baseline after 48 weeks).[22]

Dienogest

• Dienogest, which contains a unique 17α-cyanomethyl group, is a progestogen that combines the properties of both progesterone and 19-nortestosterone derivatives. Dienogest shows moderate affinity for the progesterone receptor in human uterus tissue, i.e. about 10% of that of progesterone.[23]

• *In vitro* and *in vivo* studies in rats have shown that dienogest has no androgenic activity but has antiandrogenic activity,[24,25] and a study in women with hyperandrogenism demonstrated the antiandrogenic activity of dienogest.[26] Treatment with oral dienogest 2 mg/day plus ethinylestradiol 50 μg/day for ≤2 years improved androgenic signs and symptoms in 18 women with hyperandrogenism. Hair follicle and sebaceous gland volume were significantly decreased during treatment; hirsutism and seborrhoea were also improved.[26] Furthermore, treatment with estradiol valerate 2mg/dienogest 2mg for 12 weeks in 15 healthy postmenopausal volunteers significantly ($p < 0.05$) reduced plasma levels of testosterone.[27]

• Results from *in vitro* studies in human and rabbit uterus tissue showed that dienogest has negligible affinity for estrogen receptors. Although dienogest has shown slight estrogenic and antiestrogenic ef-

fects in animal models,[25,28,29] these effects have not been seen with clinically relevant doses in women.[24,30,31] *In vitro* studies demonstrated that dienogest has negligible affinity for glucocorticoid and mineralocorticoid receptors in rat tissue.[23,32]

• Dienogest showed significant progestational activity in *in vivo* studies in rabbits (50% effective dose was 0.11 mg/kg).[24,33,34] Furthermore, in postmenopausal women receiving oral ethinylestradiol 50 μg/day, an oral dosage of dienogest 0.45 mg/day was required for complete secretory transformation of the endometrium.[35] Dienogest has also demonstrated antiproliferative activity *in vitro* and *in vivo*.[24] Unlike other progestogens, dienogest inhibited estrogen-stimulated tumour growth of human endometrial carcinoma (HEC)-88nu cell lines (which do not express progesterone receptors) in mice. Estrogen-stimulated growth of Ishikawa and MCF-7 cells was also inhibited by dienogest.[36]

• In cyclic women, serum levels of prolactin, cortisol-binding globulin (CBG), SHBG and renin were not significantly affected by treatment with oral dienogest 1 or 2mg/day.[24,30,31]

Estradiol Valerate/Dienogest

• Fifty-two healthy postmenopausal women without cardiovascular disease but complaining of menopausal symptoms were randomised to receive estradiol valerate 2mg/dienogest 2mg (n = 27) or estradiol valerate 2mg (n = 25) once daily for 12 weeks.[14] Urine samples (excreted between the hours of 22:00 and 06:00) were collected from the women before treatment and after 6 and 12 weeks, and were analysed for vasoactive markers, i.e. cyclic guanosine 3′,5′-monophosphate (cGMP) and urodilatin, and the stable metabolites of prostacyclin (2,3-dinor-6-keto-prostaglandin $F_{1\alpha}$), thromboxane (11-dehydro-thromboxane B_2) and serotonin (5-hydroxyindole acetic acid).

• There were no significant between-group differences in the measured vasoactive makers after 6 or 12 weeks of treatment, which suggests that the possible vascular effects of dienogest may not be clinically significant. However, there were significant differences within the groups with respect to changes from baseline (see figure 1). Both estradiol valerate 2mg/dienogest 2 mg/day and estradiol valerate 2 mg/day significantly increased the excretion of cGMP after 6 ($p < 0.05$) and 12 weeks ($p < 0.01$; figure 1). 5-Hydroxyindole acetic acid levels were significantly increased after 6 ($p < 0.01$) and 12 ($p < 0.05$) weeks in patients treated with estradiol valerate, and after 12 weeks ($p < 0.05$) in the estradiol valerate/dienogest group (figure 1).

• The increase in cGMP suggests a vasodilating effect of the administered drugs; the increase in serotonin also suggests a vasodilating effect because the volunteers did not have cardiovascular disease and, therefore, more than likely had intact vascular endothelia. However, unlike the estradiol valerate/dienogest group, patients treated with estradiol valerate alone had a significant increase in levels of serotonin after 6 weeks. Thus, an antagonising effect by dienogest on estradiol-induced serotonin production cannot be ruled out.[14]

• The excretion of prostacyclin metabolites was not significantly different from baseline values in either group after 6 or 12 weeks (figure 1). However, thromboxane metabolites were significantly decreased by 21.9% ($p < 0.05$) after 12 weeks of treatment with estradiol valerate; although thromboxane metabolite levels were decreased in the estradiol valerate/dienogest group, the reduction did not reach statistical significance (figure 1). Consequently, the prostacyclin/thromboxane metabolite ratio was significantly increased ($p < 0.05$) in the estradiol valerate group after 6 and 12 weeks ($p < 0.01$, both comparisons) but the increases were not significant in the group that received the combination (figure 1). Thus, dienogest may antagonise the positive effect of estrogen-induced thromboxane formation. In contrast to treatment with estradiol valerate alone, significant increases in the excretion of urodilatin were observed during treatment with estradiol valerate/dienogest (figure 1), perhaps due to a counter-regulatory reaction of the kidney to a vasoconstrictive effect of dienogest.[14]

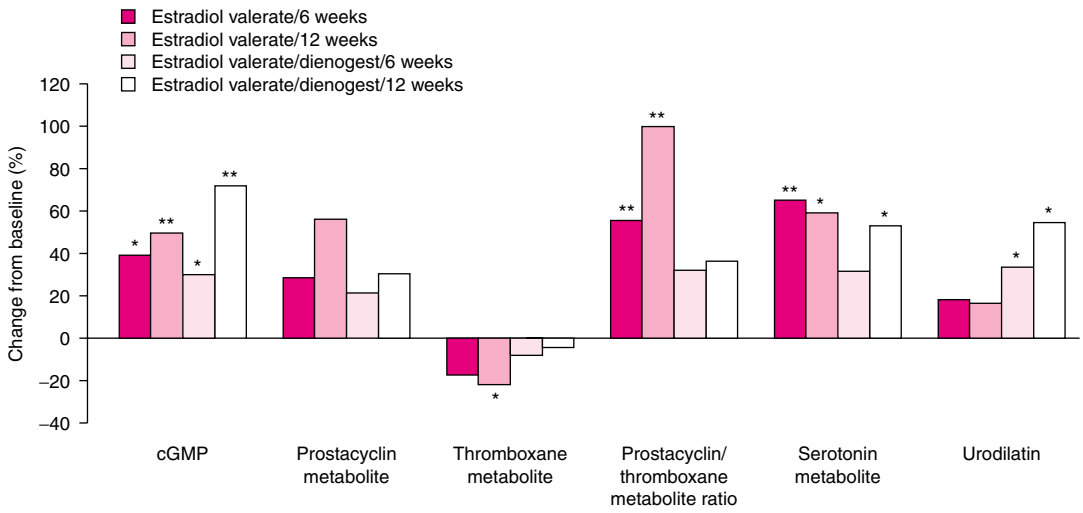


Fig. 1. Effects on vasoactive markers by estradiol valerate or estradiol valerate/dienogest. Fifty-two healthy postmenopausal women received estradiol valerate 2mg (n = 25) or estradiol valerate 2mg/dienogest 2mg (n = 27) once daily for 12 weeks. Urine samples collected before treatment and after 6 and 12 weeks were analysed for cyclic guanosine 3′,5′-monophosphate (cGMP) and urodilatin, and the stable metabolites of prostacyclin (2,3-dinor-6-keto-prostaglandin $F_{1\alpha}$), thromboxane (11-dehydro-thromboxane B_2) and serotonin (5-hydroxyindole acetic acid).[14] * $p < 0.05$, ** $p < 0.01$ *vs* baseline.

• In a randomised, double-blind, multicentre trial in 581 postmenopausal women (see section 3 for details), the effect of estradiol valerate 2mg/dienogest 2mg, estradiol valerate 2mg/dienogest 3mg or estradiol 2mg/estriol 1mg/norethisterone acetate 1mg on serum levels of IGF-I, SHBG and PP14 were also evaluated (in 38.4, 38.4 and 36% of the patients in the three treatment groups, respectively). Serum levels of IGF-I were significantly ($p \leq 0.04$ versus baseline values) decreased, and serum levels of SHBG were significantly ($p = 0.0001$) increased in patients treated with estradiol valerate 2mg/dienogest 2mg (a decrease of 10 and an increase of 69.8%, respectively) or estradiol valerate 2mg/dienogest 3mg (a decrease of 14.5 and an increase of 77.4%), but not in patients treated with estradiol/estriol/norethisterone acetate. Conversely, serum levels of PP14 were significantly ($p = 0.009$) increased from baseline (by 34.5%) in the estradiol/estriol/norethisterone acetate group but not in the other two treatment groups.[15]

• In a further randomised, double-blind, multicentre study,[16] the effects of estradiol valerate 2mg/dienogest 3mg on coagulation, the lipid profile and glucose metabolism were evaluated in 83 postmenopausal women. Patients were randomised to receive estradiol valerate 2mg/dienogest 3mg or placebo once daily for 6 months. The primary parameter measured in the study was the change from baseline in levels of prothrombin fragments 1 and 2 (F1+2), with increased levels reflecting a procoagulatory effect.

• After 6 months, there was a significantly ($p < 0.001$) greater reduction from baseline in median levels of F1+2 during treatment with placebo (a decrease of 57%) compared with treatment with estradiol valerate/dienogest (a decrease of 31%). The between-group difference was also statistically significant ($p < 0.05$). However, the investigators deemed this difference clinically insignificant because the 95% confidence intervals for the difference in changes from baseline were within the equivalence range of 1.47 μmol/L.[16]

• Among recipients of estradiol valerate/dienogest, total cholesterol, high density lipoprotein (HDL) cholesterol and low density lipoprotein (LDL) cholesterol levels were significantly ($p < 0.05$) reduced from baseline values (reductions of 11.2, 13.7 12.1%, respectively); corresponding changes among placebo recipients did not reach statistical significance. The between-group difference was also statistically significant ($p < 0.05$).[16]

• Haemoglobin A_{1C} levels among recipients of estradiol valerate/dienogest or placebo fluctuated only slightly, indicating normal blood sugar levels throughout the treatment period. There were also no significant differences in oral glucose tolerance or average insulin levels in either treatment group.[16]

2. Pharmacokinetic Profile

The pharmacokinetics of estradiol valerate 2mg/ dienogest 2mg administered as single or multiple doses have been evaluated in 15 healthy postmenopausal women.[27] In this study, pharmacokinetic parameters for estradiol, total and free estrone and dienogest were determined. For single-dose evaluation, estradiol valerate 2mg/dienogest 2mg was administered under fasting conditions; blood samples were taken during the day of the last dose in the 12-week multiple-dose study. The bioavailability of estradiol valerate and dienogest after the administration of coated tablet formulations of estradiol valerate/dienogest to healthy postmenopausal women has been compared with that after the administration of a microcrystalline suspension of the two drugs in a randomised, crossover study. Furthermore, the administration of dienogest either alone or in combination with estradiol valerate has been evaluated for bioequivalence in another randomised, crossover study.

Absorption and Distribution

• After administration of single-dose estradiol valerate 2mg/dienogest 2mg, the mean maximum plasma concentration (C_{max}) of estradiol (0.03079 μg/L) was achieved after 8 hours (t_{max}); C_{max} of dienogest (53.68 μg/L) was reached after 1 hour.[27] C_{max} values for total and free estrone were 22.31 and 0.3066 μg/L, respectively, and were achieved after 1 and 6 hours. The area under the plasma concentration-time curve after 24 hours ($AUC_{0\text{-}24h}$) for estradiol and dienogest was 0.4455 and 482.6 μg • h/L, respectively. Corresponding values for total and free estrone were 156.3 and 4.409 μg • h/L.

• After repeated daily administration of estradiol valerate 2mg/dienogest 2mg for 12 weeks, mean C_{max} values for estradiol and dienogest (0.1045 and 66.47 μg/L, respectively) were significantly ($p < 0.001$) higher than those after single-dose administration; t_{max} values for estradiol and dienogest were 6 hours and 1 hour, respectively. The C_{max} of free estrone (0.6999 μg/L) was also significantly ($p < 0.001$) higher after repeated administration than after a single dose of the two drugs. In contrast, the C_{max} of total estrone was similar after multiple (27.10 μg/L) or single (22.31 μg/L) doses. At steady-state, $AUC_{0\text{-}24h}$ values for estradiol, dienogest, total and free estrone (1.475, 627.2, 230.2 and 10.69 μg • h/L, respectively) were all significantly ($p < 0.001$) higher than after a single dose of estradiol valerate 2mg/dienogest 2mg; median t_{max} values for total (1 hour) or free (6 hours) estrone were the same after single or multiple doses.[27]

• The bioavailability of dienogest after administration of estradiol valerate 2mg/dienogest 2mg was shown to be equivalent to that after administration of dienogest 2mg in a randomised, crossover study in 16 healthy postmenopausal women.[37] The volunteers were randomised to receive a single dose of estradiol valerate 2mg/dienogest 2mg or dienogest 2mg after a 10-hour fast before crossing over to the other treatment a week later. Blood samples were taken during the 36 hours after administration of the drugs.

• The mean C_{max} and $AUC_{0\text{-}\infty}$ values for dienogest after administration of dienogest 2mg were 45.2 μg/L and 522.8 μg • h/L, respectively. After administration of estradiol valerate 2mg/dienogest 2mg, the mean C_{max} and $AUC_{0\text{-}\infty}$ values for dienogest were 42.2 μg/L and 503.9 μg • h/L, respec-

tively. There were no significant between-group differences in any of the measured pharmacokinetic parameters. The mean ratios for the $AUC_{0-\infty}$ and C_{max} were 103.7 and 106.9%, respectively; the 90% confidence intervals for the two parameters met the criterion for bioequivalence.[37]

• The bioavailability of estradiol valerate and dienogest after the administration of estradiol valerate/dienogest tablets was shown to be equivalent to that after the administration of a microcrystalline suspension of estradiol valerate/dienogest in a further randomised, crossover study in 18 healthy postmenopausal women.[38] Volunteers were randomised to receive two tablets containing estradiol valerate 2mg/dienogest 2mg or estradiol valerate 2mg/dienogest 3mg or a microcrystalline suspension containing estradiol valerate 4mg plus dienogest 6mg after a 10-hour fast. Crossover to a different treatment regimen took place after a 1-week washout period. Blood samples were collected during the 48 hours after administration of the drugs.

• The mean C_{max} and $AUC_{0-\infty}$ values for estradiol after administration of two tablets containing estradiol valerate 2mg/dienogest 2mg were 0.075 μg/L and 2.05 μg • h/L, respectively; corresponding values for dienogest were 87.1 μg/L and 1067.2 μg • h/L. After the administration of two tablets containing estradiol valerate 2mg/dienogest 3mg, mean C_{max} and $AUC_{0-\infty}$ values for estradiol were 0.072 μg/L and 2.22 μg • h/L, respectively; corresponding values for dienogest were 128.8 μg/L and 1640.4 μg • h/L. After administration of a microcrystalline suspension containing estradiol valerate 4mg plus dienogest 6mg, mean C_{max} and $AUC_{0-\infty}$ values for estradiol were 0.073 μg/L and 1.944 μg • h/L, respectively; the corresponding values for dienogest were 145.7 μg/L and 1599.4 μg • h/L.[38]

• The relative bioavailabilities of estradiol and dienogest after administration of two doses of estradiol valerate 2mg/dienogest 2mg, compared with those after administration of the microcrystalline suspension (after accounting for the different administered dosage of dienogest) were 101.6 and 101.4%, respectively. Similarly, the relative bioavailabilities of estradiol and dienogest after administration of two doses of estradiol valerate 2mg/dienogest 3mg, compared with that after administration of the microcrystalline suspension were 101.4 and 101.9%, respectively.[38]

• Estrogens are widely distributed throughout the body, and the distribution of exogenous estradiol is similar to that of endogenous estradiol.[39] Estradiol is extensively bound to serum proteins, in particular to albumin (61%) and to SHBG (37%).[7] Dienogest is highly bound to albumin (approximately 90%), but is not bound to SHBG or CBG.[11]

Metabolism and Elimination

• After oral administration, estradiol valerate is rapidly hydrolysed to estradiol in the intestinal mucosa. Estradiol, like endogenous estrogens, is metabolised in the liver and the predominant metabolites in postmenopausal women are estrone, estrone sulphate and estradiol sulphate.[7] Circulating estrogens, including exogenous estradiol, are reversibly converted to estrone and exist in a dynamic equilibrium; estrone and estradiol are converted to estriol, the main urinary metabolite.[39] Estrogens undergo enterohepatic recirculation via sulphate and glucuronide conjugation; the sulphates are mainly hydrolysed and reabsorbed, whereas the glucuronides are excreted in the bile or urine within 48 hours of administration.[7,9] Terminal elimination half-life ($t_{½\beta}$) values for estradiol after single and multiple oral doses of estradiol valerate 2mg/dienogest 2mg were 17.2 and 16.5 hours, respectively; total apparent clearance (CL/F) values were 2084.2 and 1356.3 L/h, respectively.[27]

• After oral administration of dienogest as a single agent, dienogest initially exists predominantly unchanged in the plasma. However, it is subsequently converted to a number of metabolites, the majority of which remain unidentified, via hydroxylation, hydrogenation, aromatisation and conjugation reactions.[10,11] Because these metabolites are rapidly cleared from plasma, dienogest

remains the dominating fraction.[40] The $t_{½\beta}$ of dienogest after single or multiple oral doses of estradiol valerate 2mg/dienogest 2mg was 10.8 and 11.1 hours, respectively; the CL/F was 3.2 L/h after single or multiple doses.[27] The metabolites of dienogest are eliminated in the urine mostly during the 24 hours after administration of the drug.[10]

• Both exogenous and endogenous estrogens undergo extensive oxidative metabolism via low specificity cytochrome P450 (CYP) enzymes. The majority of CYP enzymes involved in estradiol metabolism belong to the CYP1A, 3A, 1B, 2C and 2E families.[41-43] Hydroxylation of estradiol at the 2-, 4- and 16α-positions is mainly mediated by CYP1A2 and CYP3A4 enzymes.[41]

• *In vitro* and *in vivo* studies have demonstrated that dienogest has no effect on the activity of CYP enzymes in humans.[44-46]

3. Therapeutic Efficacy

The efficacy of estradiol valerate/dienogest in the treatment of climacteric symptoms in postmenopausal women has been evaluated in a large randomised, double-blind, multicentre trial,[15] a large multicentre, noncomparative trial,[22] as well as in a small randomised, nonblind, dose-finding study.[47] Efficacy analysis in the two large studies[15,22] involved the change from baseline in Kupperman index scores, whereas in the dose-finding study,[47] endometrial biopsy results were used for the primary efficacy analysis. In the larger trials,[15,22] endometrial biopsy results were used to evaluate the tolerability of estradiol valerate/dienogest (see section 4). The two comparative studies included the incidence of uterine bleeding as an efficacy parameter, whereas the noncomparative study included bleeding as a tolerability parameter.

• Estradiol valerate 2mg/dienogest 2mg and estradiol valerate 2mg/dienogest 3mg were shown to be the optimal doses for continuous-combined HRT in a randomised, nonblind, multicentre, dose-finding study in 120 postmenopausal women.[47] Patients included in the study were aged 42 to 68 years, had been amenorrhoeic for ≥2 years and were experiencing postmenopausal symptoms.

• Patients were excluded if they had confirmed or suspected endometrial hyperplasia, were status posthysterectomy or had been previously treated with a continuous-combined estrogen/progestogen combination. Patients were also excluded if they required hormonal or nonhormonal treatment for disturbances of lipid, carbohydrate or thyroid metabolism, were undergoing treatment for these disorders or were being treated with drugs known to influence these processes, or if they had severe systemic diseases, past or present hormone-dependent tumours or a contraindication for HRT.[47]

• Patients who had previously received HRT underwent a washout period: 2 weeks for transdermal estradiol, oral progestin or estrogen with ≥10 days sequential progestogen, or 4 weeks for intramuscular injection of estradiol; 41% of patients had previously undergone HRT.[47]

• Patients were randomised to receive estradiol valerate 2mg plus dienogest 0.5 (n = 25), 1 (n = 26), 2 (n = 24), 3 (n = 22) or 4mg (n = 23) once daily for 6 months (six 28-day treatment cycles) and were assessed at baseline and during weeks 5 to 8 (second cycle), 13 to 16 (fourth cycle) and 21 to 24 (sixth cycle). Patients previously treated with estrogen alone were required to have an initial endometrial biopsy, and all patients still enrolled had an endometrial biopsy during the sixth treatment cycle. Primary efficacy analysis was based on endometrial histology (the presence of atrophic material was a marker for efficacy) and uterine bleeding (frequency, intensity and duration of bleeding). Secondary efficacy analysis involved patient assessment of menopausal symptoms (hot flushes, vasomotor and psychonervous symptoms, vaginal and urological complaints) using a 4-point scale (0 to 3, increasing in severity).[47]

• Endometrial biopsies were available from 91 of 120 patients (76%). Although 33% of the biopsies were either not assessable or not available, they were still included in the analysis. Figure 2 illustrates the incidence of atrophic or proliferative ma-

terial in the biopsies. The ratio of atrophic to proliferative material was 0.7 and 1.0 in the dienogest 0.5 and 1 mg/day groups, indicating a lack of efficacy. However, in the dienogest 2, 3 and 4 mg/day groups, the corresponding ratios were 2.0, 5.0 and 6.0.[47]

• Although the differences did not reach statistical significance because of the small sample sizes, the frequency of uterine bleeding was lowest in the dienogest 0.5 mg/day group and highest in the 4 mg/day group; among the dienogest 0.5, 1, 2, 3 and 4 mg/day groups, 23.5, 35.0, 38.0, 27.5 and 56.5% of patients, respectively, reported bleeding (data interpreted from a graph). The number of bleeding episodes was lowest in the dienogest 3 mg/day group and highest in the 4 mg/day group; there were 22, 36, 33, 16 and 41 episodes of uterine bleeding in the dienogest 0.5, 1, 2, 3 and 4 mg/day groups, respectively. Furthermore, the frequency of bleeding events during the fourth cycle was significantly ($p \leq 0.05$) lower among recipients of dienogest 3 mg/day compared with the other treatment groups.[47]

• After 4 to 8 weeks, there were no reports of hot flushes among recipients of the three lower dosages of dienogest; however, in the dienogest 3 and 4 mg/day groups, hot flushes were absent after 12 to 16 weeks of treatment. Compared with baseline, the overall incidence of hot flushes was significantly ($p < 0.001$) reduced in all treatment groups during the sixth cycle. The severity of vasomotor and psychonervous symptoms was significantly ($p < 0.05$) reduced in all groups over the course of treatment except for loss of libido which was not significantly improved in the dienogest 2 mg/day group.[47]

• Vaginal discharge, burning and dryness improved significantly ($p < 0.05$) in all but the dienogest 2 mg/day groups; vaginal redness and dyspareunia were significantly ($p < 0.05$) improved in all treatment groups. Dysuria and urological burning improved significantly ($p < 0.05$) in all but the dienogest 1 mg/day group; urinary frequency improved significantly ($p < 0.01$) only in recipients of dienogest 0.5 mg/day. Recipients of dienogest 0.5 and 3 mg/day had a significant ($p < 0.05$) improvement in urinary incontinence.[47]

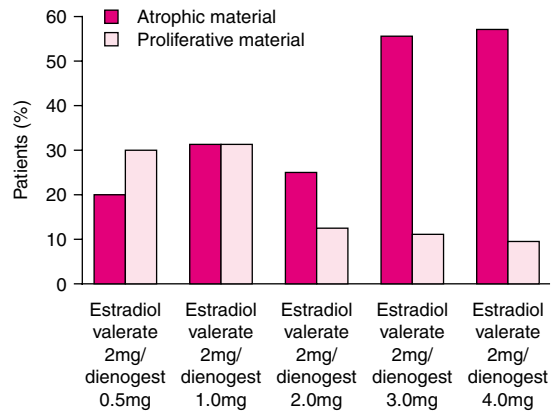


Fig. 2. The presence of atrophic or proliferative material in endometrial biopsies from postmenopausal women; a comparison of the efficacy of estradiol valerate 2 mg/day plus five different doses of dienogest. Results from endometrial biopsies taken from 91 patients who received estradiol valerate 2.0 mg/day plus dienogest 0.5 (n = 20), 1.0 (n = 16), 2.0 (n = 16), 3.0 (n = 18) or 4.0 (n = 21) mg/day for 1 year in a randomised, nonblind, multicentre, dose-finding study. [47]

• Estradiol valerate 2mg/dienogest 2mg and estradiol valerate 2mg/dienogest 3mg were then further evaluated, in comparison with estradiol 2mg/estriol 1mg/norethisterone acetate 1mg, in a randomised, double-blind, multicentre trial involving 581 postmenopausal women experiencing climacteric symptoms.[15] Patients were included in the study if they were aged ≤65 years and were experiencing postmenopausal symptoms. The patients had to have been amenorrhoeic for ≥2 years and have FSH levels >30 mIU/ml.

• Patients were excluded if they had an intolerance to HRT, had received continuous-combined HRT in the previous 6 months, sequential HRT in the previous 4 weeks or any other therapy for climacteric symptoms. Further exclusion criteria included previous or existing thromboembolic disease, insufficiently controlled hypertension, endo-

metrial hyperplasia, hormone-dependent tumours, liver or fat metabolism disorders, sickle cell anaemia, otosclerosis that deteriorated during pregnancy, severe diabetes mellitus, Dubin-Johnson syndrome, Rotor syndrome and a history of herpes gestationes.[15]

• Five hundred and eighty one patients were randomised to receive estradiol valerate 2mg/dienogest 2mg (n = 199), estradiol valerate 2mg/dienogest 3mg (n = 186) or estradiol 2mg/estriol 1mg/norethisterone acetate 1mg (n = 196) once daily for 1 year. Patients were scheduled to visit at study entry (visit 1) and at months 1, 3, 6 and 12 (visits 2 to 5). A physical examination took place at visits 1 and 5, and included endometrial biopsy, endovaginal sonography and cytology. Blood pressure and heart rate were monitored at each visit.

• The primary efficacy analysis was based on changes in the Kupperman index which were calculated at each visit. Patients rated hot flushes, paraesthesias, insomnia, nervousness, melancholia, vertigo, fatigue, arthralgias/myalgias, headache, palpitations and itching on a 4-point scale (0 to 3, increasing in severity). Each symptom was weighted, with the total highest score possible being 51; baseline scores were 25.6, 25.5 and 24.4 in the estradiol valerate 2mg/dienogest 2mg, estradiol valerate 2mg/dienogest 3mg and estradiol/estriol/norethisterone acetate groups, respectively. Secondary efficacy analysis was based on the incidence of uterine bleeding, the severity of hot flushes, vaginal cytology results and on an overall subjective assessment of efficacy by the patients and the investigator (conducted during visits 2 to 5).[15]

• Estradiol valerate 2mg/dienogest 2mg, estradiol valerate 2mg/dienogest 3mg and estradiol 2mg/estriol 1mg/norethisterone acetate 1mg showed equivalent efficacy in reducing climacteric symptoms throughout the 12-month treatment period. There were no significant between-group differences in the reduction in mean Kupperman index scores at any of the visits, including at endpoint. Mean reductions at endpoint in Kupperman index scores were 78.5, 74.5 and 75.0% in the estradiol valerate 2mg/dienogest 2mg, estradiol valerate 2mg/dienogest 3mg and estradiol/estriol/norethisterone acetate groups, respectively (Kupperman index scores in the three groups at endpoint were 5.5, 6.5 and 6.1, respectively). Although quantitative data were not reported, there were no between-group differences in the severity of hot flushes or any other climacteric symptoms during the treatment period, or in the subjective efficacy assessments made by the patients and the investigator at endpoint.[15]

• The number of days with any type of bleeding was significantly lower among patients treated with estradiol valerate 2mg/dienogest 2mg (8.7 days) than in recipients of estradiol/estriol/norethisterone acetate (9.3 days, $p = 0.001$).[15] Estradiol valerate 2mg/dienogest 3mg, however, was associated with the highest number of days with bleeding (12.1 days, $p < 0.001$ versus estradiol/estriol/norethisterone acetate).

• There were no significant between-group differences in the incidence of bleeding episodes.[15] Throughout the trial there were 590, 698 and 610 bleeding episodes in the estradiol valerate 2mg/dienogest 2mg, estradiol valerate 2mg/dienogest 3mg and estradiol/estriol/norethisterone acetate groups, respectively; the mean number of bleeding episodes per patient in the three groups was 6.2, 8.6 and 6.5, respectively. However, the mean total duration of any type of bleeding was significantly ($p < 0.05$) higher in the estradiol valerate 2mg/dienogest 3mg group than in patients treated with estradiol/estriol/norethisterone acetate. The incidence of bleeding among patients treated with estradiol valerate 2mg/dienogest 2mg decreased over the course of treatment; during month six, 24.6% of patients reported bleeding, compared with 14.5% during month twelve. Data were not reported for the other treatment groups.

• Although quantitative data were not reported, there were no significant between-group differences in vaginal cytology results at the start of treatment or at endpoint. However, Schmitt scores

of <3 were markedly reduced versus baseline in all three groups at the end of the study.[15]

• Estradiol valerate 2mg/dienogest 2mg was subsequently further evaluated in a large noncomparative, multicentre study in 1501 postmenopausal women, and was shown to be effective at reducing climacteric symptoms, as measured by the Kupperman index.[22] Patients included in the study were aged between 52 and 65 years and had been amenorrhoeic for ≥12 months or had undergone surgically induced menopause, with bilateral ovariectomy having been carried out ≥6 months before enrolment. Patients had to have estradiol levels <40 pg/ml and FSH levels ≥25 mIU/ml. Patients previously treated with sequential-combined HRT (28%) had their menopausal state confirmed by determination of their estradiol and FSH levels after a 4-week washout period. Patients previously treated with continuous-combined HRT (22%) did not have to undergo a washout period as long they did not have endometrial hyperplasia, which was determined by sonography, biopsy or hysteroscopy.

• Patients were excluded if they were status posthysterectomy, had endometrial hyperplasia, were undergoing concomitant treatment for climacteric symptoms, had a Papanicolaou smear class III to V, had an endometrial thickness >12mm or had conspicuous intrauterine structures. Further exclusion criteria included a history of acute thromboembolic events or thrombophlebitis, cerebral disorders, otosclerosis, acute or chronic liver disease, insufficiently controlled hypertension or other concomitant diseases.[22]

• 1501 patients received estradiol valerate 2mg/dienogest 2mg once daily for 48 weeks. Patients were scheduled to visit at study entry and at weeks 8, 24 and 48, during which assessments of efficacy, based on changes in the Kupperman index, and tolerability (see section 4) were undertaken. Physical examinations took place at baseline and at weeks 24 and 48. Patients also recorded bleeding episodes and the incidence and severity of hot flushes in diaries; bleeding events were included in the tolerability assessment (section 4).[22]

• At baseline, the mean Kupperman index score was 17.9. Among patients with no previous HRT, the mean baseline score was 20.7, and in patients who had previously been treated with sequential- or continuous-combined HRT, mean baseline scores were 19.0 and 10.3, respectively. The mean reduction at endpoint in the Kupperman index scores among all patients was 78.8%. Figure 3 illustrates Kupperman index scores at baseline and after 8, 24 and 48 weeks of treatment. At endpoint, the mean reduction in the Kupperman index score among previously untreated patients was 79.2%; among patients previously treated with sequential- or continuous-combined HRT, mean reductions in Kupperman index scores were 81.6 and 68.0%, respectively.[22]

• At study entry, 85% of all patients were experiencing a mean 4.8 hot flushes per day, although the frequency was lower in patients who had been

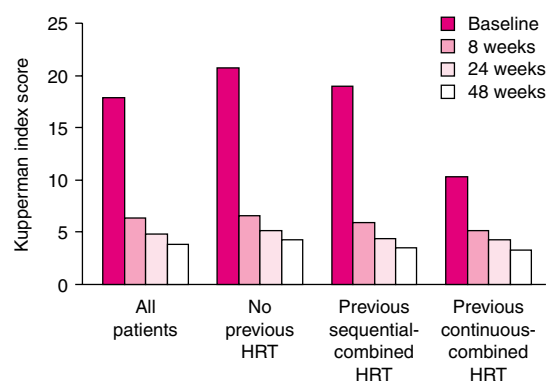


Fig. 3. Efficacy of estradiol valerate 2mg/dienogest 2mg; results from a large noncomparative, multicentre study. Mean Kupperman index scores at baseline and after 8, 24 and 48 weeks of treatment in 1501 postmenopausal women who received estradiol valerate 2mg/dienogest 2mg for 48 weeks. Patients previously treated with sequential-combined HRT (n = 419) underwent a 4-week washout period before enrolment; patients previously treated with continuous-combined HRT (n = 330) did not have to undergo a washout period as long they did not present with endometrial hyperplasia. Statistical analysis was not reported. **HRT** = hormone replacement therapy.[22]

previously treated with continuous-combined HRT (1.9/day) than in previously untreated patients (5.3/day) or patients previously treated with sequential-combined HRT (6.0/day). The mean frequency of hot flushes decreased by 87.5% (to 0.6/day) after 8 weeks of treatment with estradiol valerate 2mg/dienogest 2mg. This improvement was maintained throughout the duration of the study. At endpoint, 13% of all patients were still experiencing hot flushes.[22]

4. Tolerability

• In the double-blind trial,[15] the incidence of adverse events was similar among patients treated with estradiol valerate 2mg/dienogest 2mg, estradiol valerate 2mg/dienogest 3mg or estradiol 2mg/estriol 1mg/norethisterone acetate 1mg once daily for one year; 29.6, 32.3 and 31.6% of patients, respectively, reported adverse events. Adverse events, excluding uterine bleeding, reported among all patients included breast problems, vaginal bleeding/dysmenorrhoea and events relating to the gastrointestinal, respiratory, cardiovascular and genitourinary systems. Figure 4 illustrates the incidence of these events in the three treatment groups; there were no significant between-group differences. Specific adverse events were not reported.

• Endometrial biopsy results, recorded at endpoint in 396 patients, were similar among all treatment groups; atrophic material was found in 90.8, 87.4 and 87.5% of the biopsies from patients who were treated with estradiol valerate 2mg/dienogest 2mg (n = 141), estradiol valerate 2mg/dienogest 3mg (n = 119) or estradiol/estriol/norethisterone acetate (n = 136), respectively. Proliferative material was found in 4.2, 2.5 and 4.4% of the respective biopsies; there was no incidence of hyperplasia in any of the treatment groups.[15]

• In the dose-finding study,[47] 34 patients (28.3%) reported adverse events. The most frequent treatment-related adverse events, excluding uterine bleeding, among the five groups that received estradiol valerate 2mg plus dienogest 0.5, 1, 2, 3 or 4 mg once daily for six months were headache/migraine (9.2%) and prolonged bleeding (5.8%). Data concerning the incidence of other adverse events were not reported. Five percent of patients (6 of 120) discontinued treatment prematurely because of adverse events.

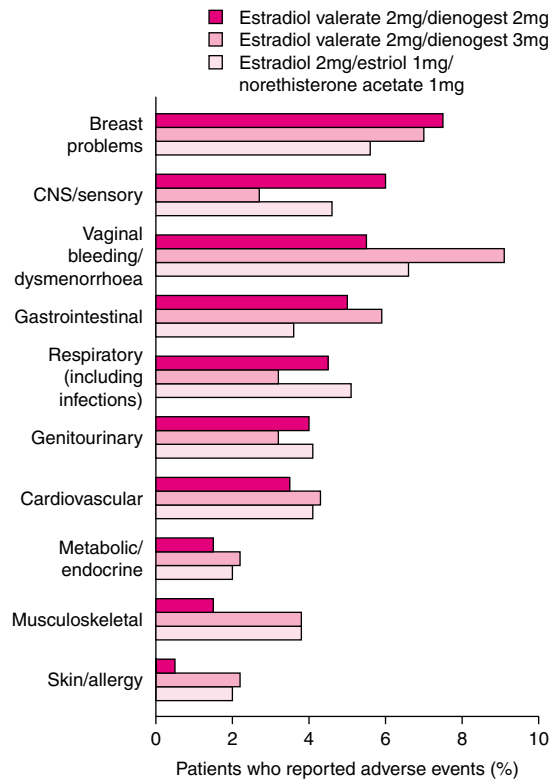


Fig. 4. Tolerability of estradiol valerate/dienogest hormone replacement therapy in postmenopausal women. Incidence of adverse events (whether related to treatment or not), excluding uterine bleeding, in 581 patients with climacteric symptoms who received estradiol valerate 2mg/dienogest 2mg (n = 199), estradiol valerate 2mg/dienogest 3mg (n = 186) or estradiol 2mg/estriol 1mg/norethisterone acetate 1mg (n = 196) once daily for one year. There were no statistically significant between-group differences.[15]

• Treatment with estradiol valerate 2mg/dienogest 2mg for 48 weeks was well tolerated in a large noncomparative trial in 1501 postmenopausal women. Adverse events occurring in >2% of pa-

tients included breakthrough bleeding (25% of patients), mastalgia (15%), headache (6%), abdominal pain (3.7%), hypertension (3.5%), thrush (2.8%), migraine (2.7%), weight gain (2.5%), increase in endometrial thickness (2.5%) and metrorrhagia (2.3%).[22]

- At baseline, 8% of all patients reported irregular bleeding during the previous 6 months. During the first treatment cycle, 28.2% of patients experienced at least one bleeding event. By week 48, 13.8% of all patients still experienced any bleeding.[22]

5. Estradiol Valerate/Dienogest: Current Status

Estradiol valerate 2mg/dienogest 2mg is an oral estrogen/progestogen formulation that has been approved throughout the European Union for the treatment of climacteric symptoms in postmenopausal women. Estradiol valerate 2mg/dienogest 2mg was as effective as estradiol 2mg/estriol 1mg/norethisterone acetate 1mg in a randomised, double-blind, multicentre trial in 581 postmenopausal women. The combination is well tolerated and estradiol valerate 2mg/dienogest 2mg was associated with a more favourable bleeding profile than estradiol 2mg/estriol 1mg/norethisterone acetate 1mg.

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