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Estradiol Valerate/Dienogest

In Oral Contraception

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Contents

Abstract

▲ Estradiol valerate/dienogest is an oral contraceptive for women that combines the natural estrogen estradiol with the 19-nortestosterone derivative dienogest in a four-phasic formulation.

▲ Estradiol valerate/dienogest demonstrated contraceptive efficacy in a large (n = 1377), noncomparative, multicentre study in women aged 18–50 years, with 13 pregnancies over 1797.5 women-years of exposure generating an unadjusted Pearl Index (PI) of 0.73 (upper limit of 95% CI 1.24) [primary endpoint]. Six of the pregnancies were attributed to method failure, resulting in an adjusted PI, based on 1786.5 women-years of exposure, of 0.34 (upper limit of 95% CI 0.73).

▲ In a double-blind study in 798 women aged 18–50 years, estradiol valerate/dienogest and ethinylestradiol/levonorgestrel demonstrated an acceptable bleeding pattern and level of cycle control, according to several co-primary endpoints.

▲ As reported in the UK manufacturer's summary of product characteristics, the unadjusted PI for women aged 18–35 years or 18–50 years in a pooled analysis of clinical studies was 1.01 (upper limit of 95% CI 1.59) and 0.79 (upper limit of 95% CI 1.23). This pooled analysis of three studies excluded those pregnancies occurring within 14 days of the cessation of therapy.

▲ Estradiol valerate/dienogest was generally well tolerated in this population, with the nature of adverse events generally similar across the studies and between estradiol valerate/dienogest and ethinylestradiol/levonorgestrel.

Features and properties of estradiol valerate/dienogest (Qlaira®)	
Indication	
Oral contraception	
Mechanism of action	
Estrogen/progestogen	
Dosage and administration	
Dosage	Estradiol valerate 3 mg for 2 days followed by estradiol valerate/dienogest 2 mg/2 mg for 5 days, estradiol valerate/dienogest 2 mg/3 mg for 17 days, estradiol valerate 1 mg for 2 days and placebo for 2 days
Route of administration	Oral
Frequency of administration	Once daily
Pharmacokinetic profile of estradiol valerate/dienogest (at steady state) in women aged 18–50 years; geometric mean values unless stated otherwise (serum values)	
Maximum concentration (C_{max})	Estradiol: 0.0660 ng/mL Dienogest: 82.9 ng/mL
Median time to C_{max}	Estradiol: 3 h Dienogest: 1.5 h
Average concentration	Estradiol: 0.0516 ng/mL Dienogest: 33.7 ng/mL
Area under the concentration-time curve from zero to 24 h	Estradiol: 1.239 ng • h/mL Dienogest: 809 ng • h/mL
Most frequent treatment-related adverse events (incidence ≥2%)	
Acne, breast pain	

Since the inception of combined oral contraceptives (COCs), both the nature and the quantities of the hormonal components have been substantially modified; discovery of the dose-dependent risks of adverse hormonal events induced the development of low-dose ethinylestradiol and/or novel progestin combinations.[1,2] Until recently, the primary estrogen utilized in COCs was ethinylestradiol.[3] Utilization of the natural estrogen estradiol in COCs was investigated as estradiol was postulated to induce fewer thrombogenic effects.[3] However, it was associated with poor cycle control,[3] particularly when administered as part of a monophasic or biphasic regimen.[2] In order to combat the poor cycle control observed with earlier estradiol-containing COCs, estradiol has been combined with a novel 19-nortestosterone derivative, dienogest, in a four-phasic formulation (with an estrogen step-down and progestogen step-up sequence).[2]

This article reviews the pharmacological properties of estradiol valerate/dienogest (Qlaira®), focusing on its efficacy and tolerability as a contraceptive in women. Medical literature on the use of estradiol valerate/dienogest was identified using MEDLINE and EMBASE, supplemented by AdisBase (a proprietary database of Wolters Kluwer Health | Adis). Additional references were identified from the reference lists of published articles.

1. Pharmacodynamic Profile

The pharmacodynamic properties of estradiol valerate and dienogest have been briefly reviewed in *Drugs*[4] and discussed in detail elsewhere.[5-7]

Estrogens exert their effects via estrogen receptors, which are located throughout the female reproductive tract, particularly the ovaries, uterus and vagina, and in bone, brain, endothelial cells, hypothalamus, lungs, mammary glands and vascular smooth muscle.[5] Estrogens passively diffuse through cell membranes, binding to estrogen receptors present in the nucleus; this binding increases the affinity and rate to which the estrogen-receptor complex binds to DNA.[5] The estrogen-receptor-DNA complex then interacts with various co-activator proteins located in the target genes, affecting the transcription of messenger RNA and hormone-regulated genes.[4,5]

Dienogest is a 19-nortestosterone derivative, with the 17α-ethinyl group indicative of 19-nortestosterones (e.g. levonorgestrel) replaced with a 17α-cyanomethyl group.[6,7] It has demonstrated limited binding affinity (approximately 10% relative to progesterone) to the progesterone receptor in human uterine tissue;[6,7] however, despite this, dienogest has exhibited a strong progestogenic effect *in vivo*.[8] Dienogest has negligible binding affinities for the estrogen, glucocorticoid and mineralocorticoid receptors and a low binding affinity for the androgen receptor *in vitro*; it has exhibited antiandrogenic activity *in vitro* and *in vivo*.[6,7]

This section focuses on data specifically related to the oral contraceptive formulation of oral estradiol valerate/dienogest derived from randomized, nonblind,[9,10] crossover[9] studies in women aged 18–50 years (available as abstract plus poster[10] or oral[9] presentations). Participants in these studies received oral estradiol valerate/dienogest (estradiol valerate 3 mg for 2 days followed by estradiol valerate/dienogest 2 mg/2 mg for 5 days, estradiol valerate/dienogest 2 mg/3 mg for 17 days, estradiol valerate 1 mg for 2 days and placebo for 2 days)[9,10] or oral ethinylestradiol/levonorgestrel (ethinylestradiol/levonorgestrel 0.03 mg/0.15 mg for 21 days and placebo for 7 days[9] or ethinylestradiol/levonorgestrel 0.03 mg/0.05 mg for 6 days followed by ethinylestradiol/levonorgestrel 0.04 mg/0.075 mg for 5 days, ethinylestradiol/levonorgestrel 0.03 mg/0.125 mg for 10 days and placebo for 7 days[10]) for three[9] or seven[10] cycles. Treatments in the crossover study were separated by a two-cycle washout period.[9]

- Estradiol valerate/dienogest and ethinylestradiol/levonorgestrel appear to exert no clinically relevant effects on the majority of haemostatic parameters, with values predominately remaining within the normal reference ranges.[9,10] For instance, in the crossover study in 29 women (full analysis set), no significant between-group difference in the mean intraindividual absolute change from baseline (0.00 vs +0.03 nmol/L) in prothrombin fragment

1+2 levels (indicative of thrombin turnover) [co-primary endpoint] was observed with estradiol valerate/dienogest (mean absolute level after three cycles 0.18 nmol/L) and ethinylestradiol/levonorgestrel (mean absolute level after three cycles 0.22 nmol/L); mean values after three cycles remained within the normal range.[9]

- Furthermore, where stated, the mean of the absolute values for the other haemostatic parameters measured, including factors VII (VIIc)[9,10] and VIII (VIIIc),[9,10] anti-thrombin III,[9,10] proteins C[9,10] and S,[9,10] and plasminogen activator inhibitor (PAI)-1[10] activity, and activated protein C resistance,[10] remained within the normal range following therapy with estradiol valerate/dienogest or ethinylestradiol/levonorgestrel, with the exception of prothrombin (factor II) [higher than the normal range][9] and PAI-1 antigen (lower than the normal range)[10] levels. Fibrinogen levels were within the normal range following estradiol valerate/dienogest or ethinylestradiol/levonorgestrel therapy in one study[10] but were higher than the normal range in another.[9]

- After three[9] or seven[10] cycles, mean absolute D-dimer levels (indicative of fibrin turnover) remained within the normal range in the estradiol valerate/dienogest and ethinylestradiol/levonorgestrel groups in two nonblind studies; however, the mean intraindividual change from baseline in D-dimer levels was significantly greater in the ethinylestradiol/levonorgestrel group than in the estradiol valerate/dienogest group in one study[9] (no statistical analysis reported for the other study[10]). For instance, in the crossover study, a significant ($p = 0.01$) between-group difference in the mean intraindividual absolute change from baseline (increased by 39 vs 158 ng/mL) in D-dimer levels (co-primary endpoint) was observed after three cycles with estradiol valerate/dienogest (mean absolute level after three cycles 237 ng/mL) versus ethinylestradiol/levonorgestrel (mean absolute level after three cycles 353 ng/mL).[9]

- For the most part, estradiol valerate/dienogest was associated with minimal effects on lipid parameters after seven cycles, with all lipid parameter levels remaining within the normal range apart from high-density lipoprotein-2 cholesterol (HDL_2-C) levels.[10] At study end, no significant between-group differences were observed in the mean intraindividual relative changes from baseline in plasma HDL-C (co-primary endpoint) [+7.9% vs −2.3%] and low-density lipoprotein cholesterol (co-primary endpoint) [−6.5% vs −3.0%] levels in estradiol valerate/dienogest and ethinylestradiol/levonorgestrel recipients. Respective changes in HDL_2-C levels were +6.4% and −0.1%, with absolute mean levels of 10.0 and 9.21 mg/dL (normal range 11–25 mg/dL). Women in both treatment groups had increases from baseline in triglyceride (31.4% in the estradiol valerate/dienogest group vs 32.0% in the ethinylestradiol/levonorgestrel group) and very low-density lipoprotein cholesterol (27.3% vs 48.5%) levels.[10]

- Sex hormone binding globulin (SHBG) levels were elevated from baseline by 63% and 112% following estradiol valerate/dienogest and ethinylestradiol/levonorgestrel therapy, with the mean levels following ethinylestradiol/levonorgestrel therapy exceeding the normal range.[10] Cortisol-binding globulin levels were elevated from baseline by 28% and 146% following estradiol valerate/dienogest and ethinylestradiol/levonorgestrel therapy; mean values for both treatment groups were within the normal range.[10]

2. Pharmacokinetic Profile

The pharmacokinetics of oral estradiol valerate/dienogest have been evaluated in one fully published, noncomparative study in women aged 18–50 years.[11] Data from the UK summary of product characteristics[8] are also discussed. Data are reported as geometric mean or coefficient of variation (CV) values unless otherwise stated.

Participants in the noncomparative study were nonsmokers with a body mass index (BMI) of 18–26 kg/m^2 and follicle-stimulating hormone levels ≤10 mIU/mL who underwent a screening period of up to 3 weeks before receiving estradiol valerate 3 mg for 2 days followed by estradiol valerate/dienogest 2 mg/2 mg for 5 days, estradiol

valerate/dienogest 2 mg/3 mg for 17 days, estradiol valerate 1 mg for 2 days and placebo for 2 days for one cycle.[11] Each 1 mg of estradiol valerate corresponds to 0.76 mg of 17β-estradiol.[11] Treatment commenced on the second day of each women's menstrual cycle, with the tablets taken once daily before breakfast.[11] Where data for certain pharmacokinetic properties are not available for this formulation of estradiol valerate/dienogest, those for other formulations are discussed.

Estradiol Valerate

- Estradiol valerate is completely absorbed by the intestinal mucosa following oral administration, with cleavage to estradiol and valeric acid occurring during absorption or first-past metabolism.[8] Approximately 3% of the oral estradiol valerate dose is directly bioavailable as estradiol.[8]
- Maximum serum estradiol concentrations (C_{max}) of 0.0706 ng/mL (CV 27.8%) on day 1 and 0.0660 ng/mL (CV 39.9%) on day 24 were achieved in a median time of 6 (range 1.5–12 hours) and 3 (range 1.5–12 hours) hours.[11]
- Serum estrone and estrone sulfate C_{max} values of 0.416 (CV 54.1%) and 16.384 (CV 53.5%) ng/mL on day 1 and 0.444 (CV 44.9%) and 13.478 (CV 54.3%) ng/mL on day 24 were achieved in a median time of 4 (range 3–12 hours) and 3 (range 1.5–10.0 hours) hours on day 1, respectively, and 4 (range 3–12 hours) and 3 (range 1.5–12 hours) hours on day 24, respectively.[11]
- Mean trough serum estradiol concentrations remained stable during the 28-day treatment period (range 0.0336–0.0647 ng/mL).[11] On day 1, average serum estradiol, estrone and estrone sulfate concentrations were 0.0519 (CV 29.2%), 0.240 (CV 52.9%) and 7.395 (CV 56.5%) ng/mL, respectively. On day 24, the corresponding values were 0.0516 (CV 39.9%), 0.284 (CV 52.1%) and 6.826 (CV 56.0%) ng/mL, with steady state estradiol concentrations achieved on days 3–24.[11]
- Exposure to estradiol and estrone on day 1 was generally similar to that on day 24.[11] Area under the serum concentration-time curve from time 0 to 24 hours (AUC_{24}) values for estradiol of 1.246 (CV 29.2%) and 1.239 (CV 39.9%) ng • h/mL were achieved on days 1 and 24.[11] AUC_{24} values for estrone and estrone sulfate were 5.750 (CV 52.9%) and 177.489 (CV 56.5) ng • h/mL on day 1 and 6.814 (CV 52.1%) and 163.820 (CV 56.0%) ng • h/mL on day 24. Overall, the serum estrone : estradiol ratio was ≈5 : 1.[11]
- In serum, approximately 98% of estradiol is bound to proteins (SHBG: 38%; albumin: 60%).[8] Although estradiol may induce dose-dependent changes in serum SHBG levels, no statistically significant elevations from baseline in arithmetic mean serum SHBG levels were observed at study end (day 1: 57.9 nmol/L [CV 42.9%]; day 29: 81.5 nmol/L [CV 38.1%]) in a noncomparative study.[11] SHBG levels remained within the normal range of 26–120 nmol/L, apart from those in one participant that reached 181.7 nmol/L. Arithmetic mean serum cortisol-binding globulin (CBG) levels were relatively unchanged throughout the study (day 1: 45.5 nmol/L [CV 55.4%]; day 29: 49.2 nmol/L [CV 24.8%]).[11]
- Following intravenous estradiol valerate administration, the apparent volume of distribution is ≈1.2 L/kg.[8]
- Estradiol valerate undergoes extensive first-pass metabolism, giving rise to estradiol and its metabolites (estrone, estrone sulfate and estrone glucuronide).[8] Estradiol metabolism also occurs in the gastrointestinal mucosa, and this, coupled with the first-past effect, results in the metabolism of approximately 95% of the oral estradiol valerate dose prior to its entry into the systemic circulation.[8]
- The plasma half-life of estradiol is ≈1.5 hours.[8] The terminal elimination half-life of estradiol following oral administration is ≈13–20 hours and is dependent upon enterohepatic recirculation and circulating estrogen sulfate and glucuronide levels.[8]
- Estradiol and its metabolites are predominately excreted in the urine.[8] Minimal (≈10%) excretion occurs via the faces.[8]
- The pharmacokinetic profile of estradiol in women with hepatic or renal impairment has not yet been investigated.[8]

Dienogest

- Following oral administration, dienogest shows dose-proportional pharmacokinetics across a dose range of 1 to 8 mg and is rapidly and almost completely absorbed, with an oral bioavailability of ≈91%.[8] No clinically relevant effect on the rate and extent of dienogest absorption is observed with concomitant food administration.[8]
- On day 24, a serum dienogest C_{max} of 82.9 ng/mL (CV 25.7%) was reached in a median time of 1.5 hours (range 1–2 hours).[11] Mean minimum serum dienogest concentrations were 6.8–15.1 ng/mL, with only slight elevations observed following each dose adjustment of dienogest.[11]
- Minimum dienogest concentrations exhibited only minor accumulation following each dose adjustment, with an average dienogest concentration at steady state (day 24) of 33.7 ng/mL (CV 22.5%).[11] The dienogest AUC_{24} value on day 24 was 809 ng • h/mL (CV 22.5%);[11] the mean accumulation ratio for AUC_{24} was 1.24.[8]
- Approximately 90% of dienogest is nonspecifically bound to albumin; dienogest does not bind to SHBG or CBG and the pharmacokinetics of dienogest are not influenced by SHBG levels.[8] The volume of distribution at steady state following intravenous ^{3}H-dienogest (85 μg) administration is 46 L.[8]
- Dienogest is almost completely metabolized via the cytochrome P450 (CYP) 3A4 isoenzyme to form pharmacologically inactive metabolites, with the unchanged drug constituting ≈50% of the circulating dienogest compounds in the plasma.[8]
- The plasma half-life of dienogest is ≈11 hours.[8] Total dienogest clearance following intravenous ^{3}H-dienogest (85 μg) administration is 5.1 L/h.[8]
- Only 1% of the unchanged drug is excreted; following the administration of oral dienogest 0.1 mg/kg, there is a urinary to faecal excretion ratio of 3 : 1, with 42% and 63% of an oral dose excreted renally within the first 24 hours and the first 6 days.[8] Approximately 86% of a dienogest dose is excreted via the urine or faeces in 6 days.[8]
- The pharmacologically inactive metabolites of dienogest are rapidly excreted.[8]
- Concomitant administration of dienogest and CYP3A4 inducers (e.g. barbiturates, carbamazepine, phenytoin, primidone, rifampicin [rifampin] and potentially felbamate, griseofulvin, HIV medications such as ritonavir and/or nevirapine, hypericum, oxcarbazepine, topiramate) may result in elevated dienogest clearance rates.[8] Thus, the utilization of a barrier contraceptive method is recommended with the administration of concomitant dienogest and CYP3A4 inducer therapy.[8]
- Concurrent treatment with CYP3A4 inhibitors (e.g. antidepressants, azole antifungals, cimetidine, grapefruit juice, diltiazem, macrolides, verapamil) may elevate plasma dienogest concentrations.[8]

3. Therapeutic Efficacy

The therapeutic efficacy of oral estradiol valerate/dienogest as a contraceptive has been assessed in two short-term, randomized, nonblind, phase II, dose-finding studies[2] and two longer-term multicentre studies (one randomized, double-blind, double-dummy study[12] and one noncomparative study[13]) conducted in Europe. Three of the studies are fully published,[2,12] with the other study currently available as an abstract plus poster presentation.[13] Pooled longer-term data from two[12,13] of these studies and a noncomparative, multicentre study (n = 490) conducted in North America[14] are also discussed (available as an abstract plus poster presentation); these data are supplemented by data from the UK manufacturer's prescribing information.[8]

Where stated, eligible women were aged 18–35[2] or 18–50[12-14] years. Women were excluded if they had, among other criteria, any contraindications (not specified) to combined[2] oral contraceptive use,[12,14] specified coexisting disease, including endocrine or metabolic diseases,[2] suspected malignant or premalignant disease,[12] undiagnosed genital bleeding,[2,13] a history of hepatic or vascular disease,[2] or a BMI of >30 kg/m^2.[12,14] Smokers aged >30 years[2,12-14] or those aged ≤30 years who smoked >10 cigarettes/day[12] and women receiving

'sex steroids' or drugs known to induce or inhibit liver enzymes were also excluded.[2]

The studies were conducted in women with a mean age of 25.4–33.4 years and a mean BMI of 22.2–23.2 kg/m^2.[2,12,13] At screening, 5.8% and 7.3% of women randomized to receive estradiol valerate/dienogest and ethinylestradiol/levonorgestrel had haemoglobin levels below the reference range (12–16 g/dL).[12] At baseline, 12.3–36.5% of participants were smokers,[2,12,13] 40.6–91.7% were using oral contraceptives prior to the start of the study[2,12] and 75.0–89.0% were nullipara.[2] The incidence of dysmenorrhoea over the previous 6 months was 9.5% and 6.8% of women randomized to receive estradiol valerate/dienogest and ethinylestradiol/levonorgestrel.[12]

The full-analysis set was defined as those women who took at least one dose of the study medication and who had at least one study observation following dosing.[2,13]

Short-Term Dose-Finding Studies

The two dose-finding studies were performed in sequence, with the first (study 1) determining the length of application of estradiol valerate/dienogest and the second (study 2) ascertaining the most effective dose of dienogest for effective ovulation inhibition.[2] Therapy was administered for up to three cycles.[2]

In study 1,[2] women were randomized to receive:

- regimen 1A (estradiol valerate 3 mg for 3 days followed by estradiol valerate/dienogest 2 mg/1 mg for 4 days, estradiol valerate/dienogest 2 mg/2 mg for 16 days, estradiol valerate 1 mg for 2 days and placebo for 3 days);
- regimen 2A (estradiol valerate 3 mg for 2 days followed by estradiol valerate/dienogest 2 mg/1 mg for 5 days, estradiol valerate/dienogest 2 mg/2 mg for 17 days, estradiol valerate 1 mg for 2 days and placebo for 2 days).

In study 2,[2] women were randomized to receive:

- regimen 2B (estradiol valerate 3 mg for 2 days followed by estradiol valerate/dienogest 2 mg/2 mg for 5 days, estradiol valerate/dienogest 2 mg/3 mg for 17 days, estradiol valerate 1 mg for 2 days and placebo for 2 days);
- regimen 2C (estradiol valerate 3 mg for 2 days followed by estradiol valerate/dienogest 2 mg/3 mg for 5 days, estradiol valerate/dienogest 2 mg/4 mg for 17 days, estradiol valerate 1 mg for 2 days and placebo for 2 days).

Treatment commenced on the first day of menstrual bleeding, with the tablets taken at approximately the same time each day.[2]

Participants underwent a pretreatment cycle commencing on the first menstruation day following screening; those ovulating or with a follicular diameter ≥15 mm (as assessed by transvaginal ultrasound) on or prior to day 23 of the pretreatment cycle were randomized to therapy.[2]

In study 1, only those women with a non-persisting follicular-like structure of >13 mm (Hoogland score of 4) at the end of the second cycle were included in the third cycle to monitor follicular growth.[2] In study 2, data from the second and third cycles rather than the first and second cycles were analyzed.[2]

The primary efficacy endpoint was the proportion of women with a Hoogland score of 5 (luteinized unruptured follicle >13 mm as assessed by transvaginal ultrasound with a serum progesterone level of >5 nmol/L and a 17β-estradiol level of >0.1 nmol/L[15]) or 6 (ovulation; ruptured follicle-like structure >13 mm as assessed by transvaginal ultrasound with a serum progesterone level of >5 nmol/L and a 17β-estradiol level of >0.1 nmol/L) at the second cycle.[2]

A total of 196 (study 1) and 210 (study 2) women were randomized to treatment, with 192 and 203 women comprising the full-analysis sets, respectively.[2] The primary efficacy outcome was based on data from 186 (study 1) and 193 (study 2) women.[2]

- Based on the primary endpoint analysis, the optimal regimen of estradiol valerate/dienogest (with the lowest effective dose of dienogest for ovulation inhibition) in women was estradiol valerate 3 mg for 2 days followed by estradiol valerate/dienogest 2 mg/2 mg for 5 days, estradiol valerate/dienogest

2 mg/3 mg for 17 days, estradiol valerate 1 mg for 2 days and placebo for 2 days (i.e. regimen 2B).[2]

- In the second cycle, documented Hoogland scores of 5 or 6 occurred in 10.87% and 6.38% of the women treated with regimen 1A (n = 92) and regimen 2A (n = 94) in study 1 and in 3.13% and 1.03% of the women treated with regimen 2B (n = 96) and regimen 2C (n = 97) in study 2 (primary endpoint).[2] Only one woman (receiving regimen 2A) with a Hoogland score of 5 or 6 had a luteinized unruptured follicle in the second cycle; the remaining women ovulated.[2]
- Third cycle ovulations occurred in 53.3% (8 of 15) and 31.3% (5 of 16) of those women treated with regimens 1A and 2A in study 1 who were permitted to continue therapy for a third cycle and in 2.2% (2 of 91) and 1.1% (1 of 95) of those treated with regimens 2B and 2C in study 2.[2]
- More than 80% of those women assessed during the post-treatment cycle (n = 158) resumed ovulation.[2]

Longer Term Studies

Where stated, participants received the optimal dosage regimen of estradiol valerate/dienogest,[12-14] as determined by the dose-finding studies,[2] or ethinylestradiol/levonorgestrel 0.02 mg/0.10 mg for 21 days followed by placebo for 7 days[12] for 7–28 cycles.[12-14] Compliance, assessed by daily diary cards, was 97.1% in estradiol valerate/dienogest and 96.8% in ethinylestradiol/levonorgestrel recipients in the double-blind study.[12]

The primary efficacy endpoints were the number of unintended pregnancies (calculated utilizing the Pearl Index [PI; defined as number of pregnancies per 100 woman-years of exposure]),[13] the number of days and episodes of bleeding/spotting per 90-day period,[12] the length of the bleeding/spotting episodes,[12] and the incidence and characteristics of scheduled (withdrawal) and unscheduled (intracyclic) bleeding per cycle.[12]

Scheduled (withdrawal) bleeding was defined as an episode of bleeding/spotting that commenced during the hormone-free period or less than or equal to 4 days prior to the withdrawal of the progestin[14] (i.e. day 21 of estradiol valerate/dienogest therapy or day 18 of ethinylestradiol/levonorgestrel therapy)[12] and continued into the progestin-free period. Those bleeding episodes not considered to be scheduled were classified as unscheduled (intracyclic) bleeding.[12] Bleeding intensity was defined on a scale from one to five (higher scores indicating heavier bleeding).[12]

In the double-blind study, 798 women comprised the full analysis set (399 in each treatment group).[12] In the noncomparative, multicentre study, 1391 women were enrolled, 1377 comprised the full analysis set and 1074 completed treatment.[13]

- Estradiol valerate/dienogest demonstrated contraceptive efficacy in the noncomparative study.[13] In the full-analysis set, 13 pregnancies occurred over 1797.5 women-years of exposure, generating an unadjusted PI of 0.73 (upper limit of 95% CI 1.24) [primary endpoint].[13] Six of the pregnancies were attributed to method failure, resulting in an adjusted PI, based on 1786.5 women-years of exposure, of 0.34 (upper limit of 95% CI 0.73).[13] Based on a Kaplan-Meier estimate, there was a 0.0109 (95% CI 0.0063, 0.0188) cumulative pregnancy rate during an estradiol valerate/dienogest exposure period of 20 cycles.[13]
- In a subset of women aged 18–35 years participating in this study, 12 pregnancies occurred, five of which were attributed to method failure; the unadjusted PI, based on 1277.5 women-years of exposure, was 0.94 (upper limit of 95% CI 1.65), while the adjusted PI, based on 1268.5 women-years of exposure, was 0.40 (upper limit of 95% CI 0.92).[13] The Kaplan-Meier estimate of the cumulative pregnancy rate for this subset of women was 0.0142 (95% CI 0.0080, 0.0251).[13]
- In the double-blind study, estradiol valerate/dienogest and ethinylestradiol/levonorgestrel demonstrated an acceptable bleeding pattern and level of cycle control, according to several co-primary endpoints.[12] Statistically significant between-group differences were observed for a number of endpoints, including the number of days and episodes of bleeding/spotting per 90-day period (figure 1).[12]

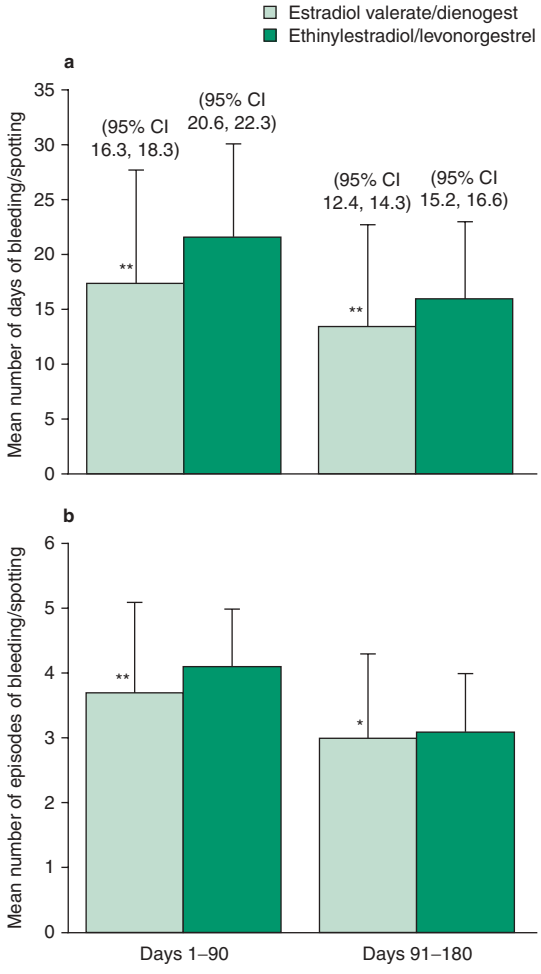

Fig. 1. Efficacy of estradiol valerate/dienogest in women aged 18–50 years. Mean (plus standard deviation) number of (**a**) days and (**b**) episodes of bleeding/spotting per 90-day period (co-primary endpoints) in a randomized, double-blind study.[12] Women received estradiol valerate/dienogest (estradiol valerate 3 mg for 2 days followed by estradiol valerate/dienogest 2 mg/2 mg for 5 days, estradiol valerate/dienogest 2 mg/3 mg for 17 days, estradiol valerate 1 mg for 2 days and placebo for 2 days) [n = 399] or ethinylestradiol/levonorgestrel (ethinylestradiol/levonorgestrel 0.02 mg/0.10 mg for 21 days followed by placebo for 7 days) [n = 399] for seven cycles.[12] Data reported are for the full analysis set. * $p < 0.05$, ** $p < 0.0001$ vs ethinylestradiol/levonorgestrel.

- Withdrawal bleeding was experienced by significantly ($p < 0.0001$ for each cycle) fewer estradiol valerate/dienogest recipients (77.7–83.2%) than ethinylestradiol/levonorgestrel recipients (89.5–93.8%) over seven cycles, with a mean absence of withdrawal bleeding in 19.4% (range 16.8–22.3%) versus 7.7% (range 6.2–10.5%) of women.[12] The absence of withdrawal bleeding was experienced at least once over the seven cycles by 56.9% and 37.8% of women receiving estradiol valerate/dienogest and ethinylestradiol/levonorgestrel, with 21.2% and 22.2% experiencing the absence of withdrawal bleeding once and 12.2% and 7.1% experiencing the absence of withdrawal bleeding twice.[12] An absence of all withdrawal and intracyclic bleeding occurred in 15.4% and 4.5% of cycles with estradiol valerate/dienogest and ethinylestradiol/levonorgestrel.[12]

- The mean length of withdrawal bleeding was significantly ($p < 0.05$) shorter in estradiol valerate/dienogest recipients (4.1–4.7 days) than ethinylestradiol/levonorgestrel recipients (5.0–5.2 days).[12] In a descriptive analysis, 56.3–62.5% and 37.5–43.8% of women in the respective treatment groups experienced 'spotting' and/or 'light bleeding' (data derived from a graph).[12]

- A significant (p-value not reported) difference in the maximum intensity of withdrawal bleeding was observed between estradiol valerate/dienogest and ethinylestradiol/levonorgestrel therapy; mean maximum intensity withdrawal bleeding scores were 3.2–3.3 per cycle with estradiol valerate/dienogest and 3.6 per cycle with ethinylestradiol/levonorgestrel.[12] From the end of the exposure to the progestogen component, the median onset of withdrawal bleeding was days 2 to 3 with estradiol valerate/dienogest and day 3 with ethinylestradiol/levonorgestrel.[12]

- Withdrawal bleeding was generally stable throughout the noncomparative, multicentre study, with 76.8–81.6% of women experiencing withdrawal bleeding during cycles 1–19 of estradiol valerate/dienogest therapy, although the intensity and length of withdrawal bleeding lessened as therapy progressed (no data or statistical analysis reported).[13]

- A minority of women experienced intracyclic bleeding in the double-blind[12] and noncomparative[13] studies. For instance, no significant difference in the incidence of intracyclic bleeding over

seven cycles was observed between the estradiol valerate/dienogest (10.5–18.6% of women) and ethinylestradiol/levonorgestrel (9.9–17.1%) groups in the double-blind study, with a heavier intensity observed less often with estradiol valerate/dienogest than with ethinylestradiol/levonorgestrel (mean 2.4% vs 4.0% of women).[12]

- One unintended pregnancy (with ethinylestradiol/levonorgestrel therapy), attributed to method failure, was observed in the double-blind study.[12]
- Approximately 79.5% of estradiol valerate/dienogest recipients[12,13] and 79.9% of ethinylestradiol/levonorgestrel recipients[12] rated themselves as 'very satisfied' or 'satisfied' with treatment. Emotional and physical well-being during estradiol valerate/dienogest therapy was maintained or improved in 89.7% and 86.4% of women in the noncomparative study, with acceptability (i.e. a future contraceptive method of choice) achieved in 67.5%.[13]

Pooled Analysis

- As reported in the UK manufacturer's summary of product characteristics,[8] the unadjusted PI for women aged 18–35 years or 18–50 years in a pooled analysis of clinical studies was 1.01 (upper limit of 95% CI 1.59) and 0.79 (upper limit of 95% CI 1.23).[8] This pooled analysis of three studies excluded those pregnancies occurring within 14 days of the cessation of therapy.[16]
- The contraceptive efficacy of estradiol valerate/dienogest in preventing pregnancy was confirmed in another pooled analysis of these three studies (n = 2266) that included pregnancies occurring during cycles 1–13 or within 14 days of the cessation of therapy.[14] Sixteen pregnancies occurred over 1267 women-years of exposure in a subset of women aged 18–35 years (n = 1687) who were treated with estradiol valerate/dienogest, generating an unadjusted PI of 1.27 (upper limit of 95% CI 2.06).[14] Nine and seven pregnancies were attributed to method and subject failure, resulting in an adjusted PI, based on 1247 women-years of exposure, of 0.72 (95% CI 1.37).[14] Based on a Kaplan-Meier estimate over a period of 1 year, there was a 0.0122 (95% CI 0.0075, 0.0200) cumulative pregnancy rate in women aged 18–35 years.[14]
- Seventeen pregnancies occurred, ten of which were attributed to method failure, in women aged 18–50 years; the unadjusted PI was 0.99 (upper limit of 95% CI 1.59), while the adjusted PI was 0.59 (upper limit of 95% CI 1.09) [no data on the number of women-years of exposure were reported].[14]
- The mean length of scheduled withdrawal bleeding over cycles 1–13 was 4.3 days (range 4.0–4.6 days) in women aged 18–50 years, with an absence of scheduled withdrawal bleeding occurring in a mean of 20.9% of estradiol valerate/dienogest recipients per cycle.[14] The maximum intensity of scheduled withdrawal bleeding was rated as 'spotting' or 'light' by the majority of women (no data reported).[14]
- Unscheduled intracyclic bleeding over cycles 2–13 of estradiol valerate/dienogest therapy occurred in a mean of 16.8% of women per cycle, with the maximum intensity most often rated as 'spotting' or 'light'.[14] A numerical reduction in the incidence of unscheduled intracyclic bleeding was observed (from 23.3% of women in the second cycle to 14.5% in the thirteenth cycle) [no statistical analysis reported].[14]

4. Tolerability

- Oral estradiol valerate/dienogest was generally well tolerated as a contraceptive in women aged 18–50 years participating in the clinical studies reviewed in section 3,[2,12-14] with discussion focusing on the longer-term studies.[12-14]
- Adverse events led to treatment discontinuation in 3.3% of women in the randomized, double-blind study; however, none of the discontinuations were because of bleeding disorders.[12] In the noncomparative, multicentre study (n = 1377), 10.2% of women discontinued therapy because of adverse events.[13]
- In the double-blind study, 176 and 162 treatment-emergent adverse events were reported in 108 (27.1% of women) and 102 (25.6%) women receiving estradiol valerate/dienogest and ethinylestradiol/levonorgestrel.[12] The most frequently reported treatment-emergent adverse events affecting ≥5% of women in the noncomparative study were

nasopharyngitis (17.9% of women), headache (9.4%), diarrhoea (6.6%) and vaginal candidiasis (5.4%); the majority of adverse events were of mild intensity.[13]

- Treatment-related adverse events occurred in 272 women (19.8%) in the noncomparative study.[13] figure 2 presents the incidence of treatment-related adverse events affecting ≥1% of women in the double-blind study[12] and the noncomparative study.[13] The nature of treatment-related adverse events was generally similar across these two studies (figure 2).[12,13]

- The frequency (10.0% vs 8.5%) and nature (figure 2) of treatment-related adverse events was generally similar between the estradiol valerate/dienogest and ethinylestradiol/levonorgestrel treatment groups.[12]

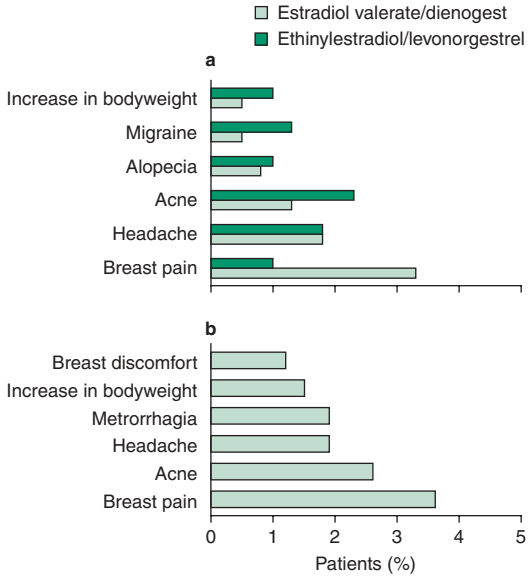

Fig. 2. Tolerability profile of oral estradiol valerate/dienogest as a contraceptive in women aged 18–50 years. Incidence of treatment-related adverse events affecting ≥1% of women in (**a**) a fully published randomized, double-blind study[12] and (**b**) a noncomparative, multicentre study (available as an abstract plus poster presentation).[13] Participants received estradiol valerate/dienogest (estradiol valerate 3 mg for 2 days followed by estradiol valerate/dienogest 2 mg/2 mg for 5 days, estradiol valerate/dienogest 2 mg/3 mg for 17 days, estradiol valerate 1 mg for 2 days and placebo for 2 days) [n = 399[12] and 1377[13]] or ethinylestradiol/levonorgestrel (ethinylestradiol/levonorgestrel 0.02 mg/0.10 mg for 21 days followed by placebo for 7 days) [n = 399][12] for 7[12] or 20[13] cycles. Data reported are for the full analysis set.

- Serious adverse events occurred in four estradiol valerate/dienogest recipients and three ethinylestradiol/levonorgestrel recipients in the double-blind study.[12] None of the serious adverse events reported were deemed related to the study medication, apart from the ruptured ovarian cyst and autonomic nervous system imbalance (one estradiol valerate/dienogest recipient) and breast cancer (one ethinylestradiol/levonorgestrel recipient).[12] No deaths were reported.[12]

- At the end of the double-blind study, 5.5% and 4.3% of women receiving estradiol valerate/dienogest and ethinylestradiol/levonorgestrel had haemoglobin levels below the reference range (12–16 g/dL); 0.5% and 0.5% of women had dysmenorrhoea during the study.[12]

- The most frequently reported treatment-emergent adverse events in women aged 18–50 years in the pooled analysis (n = 2266) were breast discomfort (4.9% of women), metrorrhagia (4.9%) and headache (3.1%).[14] Other treatment-emergent adverse events occurring in ≥1% of women included acne (2.8% of women), increase in bodyweight (1.5%), amenorrhoea (1.7%), dysmenorrhoea (1.7%) and abdominal pain (1.7%).[14]

5. Dosage and Administration

Oral estradiol valerate/dienogest (estradiol valerate 3 mg for 2 days followed by estradiol valerate/dienogest 2 mg/2 mg for 5 days, estradiol valerate/dienogest 2 mg/3 mg for 17 days, estradiol valerate 1 mg for 2 days and placebo for 2 days) is indicated as a contraceptive in women.[8]

Treatment should commence on the first day of menstrual bleeding, with the estradiol valerate/dienogest tablets administered (with liquid as required) daily for 28 consecutive days in the order directed and at approximately the same time each day.[8] Contraceptive efficacy is not reduced if a delay of less than 12 hours in administering a tablet occurs; however, contraceptive efficacy may be reduced if a delay of more than 12 hours in administering a tablet occurs.[8] Absorption may be impaired by the

presence of severe gastrointestinal disturbances (e.g. diarrhoea, vomiting).[8]

Estradiol valerate/dienogest is contraindicated in women with an acquired or hereditary predisposition for arterial or venous thrombosis; a history of or current arterial thrombosis, cerebrovascular accident, liver cancer, pancreatitis (if associated with severe hypertriglyceridaemia), severe hepatic disease or venous thrombosis; a history of migraine with focal neurological symptoms; hypersensitivity to the active substances or to any of the excipients; known or suspected sex-steroid influenced cancer; the presence of severe or multiple arterial or venous thrombosis risk factors, including diabetes mellitus with vascular symptoms, severe dislipoproteinaemia and severe hypertension; or undiagnosed vaginal bleeding.[8]

No data are currently available on the efficacy and tolerability of estradiol valerate/dienogest in adolescents aged <18 years.[8]

Local prescribing information should be consulted for detailed information, including contraindications, drug interactions, precautions and use in special patient populations.

6. Estradiol Valerate/Dienogest: Current Status

Oral estradiol valerate/dienogest has been approved in Europe under the decentralized procedure, with the Netherlands as the reference member state, as a contraceptive in women.[17,18] An application for the approval of oral estradiol valerate/dienogest as a contraceptive has also been filed with the US FDA.[19]

Estradiol valerate/dienogest demonstrated contraceptive efficacy in women aged 18–50 years in a pooled analysis of three large, longer-term, multicentre studies (up to 28 cycles), including two noncomparative studies and a double-blind study. It also exhibited an acceptable bleeding pattern and level of cycle control in a double-blind study in women aged 18–50 years. Estradiol valerate/dienogest was generally well tolerated, with the nature of adverse events generally similar across the studies and between estradiol valerate/dienogest and ethinylestradiol/levonorgestrel.

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