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Continuous-Use Ethinylestradiol/ Levonorgestrel 20μg/90μg

As an Oral Contraceptive

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Contents

Abstract

▲ The continuous-use combination oral contraceptive ethinylestradiol/levonorgestrel 20μg/90μg suppresses gonadotropins, and subsequently ovulation and endometrial thickening, and suppresses breakthrough bleeding.

▲ Amenorrhoea and absence of breakthrough bleeding increase in incidence with extended administration.

▲ The pregnancy rate attributable to method failure in a large noncomparative trial of healthy, sexually active (aged 18–49 years) women during treatment with ethinylestradiol/levonorgestrel 20μg/90μg for 12 months was 15 per 2134 women (adjusted Pearl Index 1.26 per 100 women-years of use).

▲ There were no differences in pregnancy rates over 12 months between continuous-use ethinylestradiol/levonorgestrel 20μg/90μg and cyclical ethinylestradiol/levonorgestrel 20μg/100μg in a smaller, randomised, nonblind trial.

▲ Adverse menstrual cycle-related symptoms were significantly improved with administration of continuous-use ethinylestradiol/levonorgestrel 20μg/90μg in a noncomparative trial.

▲ In small trials, hormonal and ultrasound changes indicative of reinstated ovulation occurred within a month of discontinuation of the drug, and menstruation began again in most women within 90 days.

▲ The incidence of adverse effects was similar in continuous-use and cyclical regimens of ethinylestradiol/levonorgestrel (20μg/90μg vs 20μg/100μg).

Features and properties of continuous-use ethinylestradiol/levonorgestrel 20μg/90μg (Lybrel™)		
Indication		
Prevention of pregnancy in women who elect to use oral contraceptives as a method of contraception		
Mechanism of action		
Estrogen receptor agonist/progesterone receptor agonist		
Dosage and administration		
Route of administration	Oral	
Dose (ethinylestradiol/ levonorgestrel)	20μg/90μg	
Frequency	Once daily at the same time	
Pharmacokinetic profile (after 28 days of once-daily ethinylestradiol/levonorgestrel 20μg/90μg to 18 healthy fasting women)		
	Ethinylestradiol 20μg	**Levonorgestrel 90μg**
Bioavailability	38–48%	≈100%
Mean maximum plasma concentration (C_{max})	74.4 pg/mL	5.7 ng/mL
Mean area under the plasma concentration-time curve from zero to 24h	717 pg • h/mL	74 ng • h/mL
Mean time to C_{max}	1.4h	1.4h
Mean elimination half-life	21h	36h
Most frequent adverse events (>10%)		
Headache, dysmenorrhoea, upper respiratory tract infection, nausea and pharyngitis		

Traditional monthly oral contraceptive regimens involve 21 days of hormone treatment followed by 7 days of placebo, during which withdrawal bleeding occurs. An oral, continuous, daily hormonal treatment regimen with no hormone-free interval has recently been designed with the aim of reducing or eliminating cyclical menstruation-like periods and decreasing cycle-related adverse effects. This article reviews data relevant to the continuous use of ethinylestradiol/levonorgestrel 20μg/90μg (Lybrel™)[1] as an oral contraceptive.

1. Pharmacodynamic Profile

- The combination of the synthetic estrogen ethinylestradiol 20μg and the synthetic progestogen levonorgestrel 90μg suppresses the gonadotropins luteinising hormone and follicle-stimulating hormone, with subsequent inhibition of ovulation and prevention of endometrial thickening (which helps prevent implantation).[1]
- Histological changes in 93 healthy, sexually active women, in a substudy[2] of the noncomparative trial of daily continuous ethinylestradiol/levonorgestrel 20μg/90μg described in section 3,[3] were indicative of elimination of both menstrual bleeding and cyclical growth of the endometrium. Endometrial biopsy results indicated a weakly proliferative/proliferative endometrium in 60% and 11% of participants at baseline and end of treatment (≥6 months), respectively, and a secretory endometrium in 16% and 2%.[2] No hyperplasia or malignancy was found.
- Ovulation returns quickly after continuous suppression for 3 months. In a noncomparative trial, 37 evaluable healthy women aged 18–35 years received continuous daily ethinylestradiol/levonorgestrel 20μg/90μg for 3 months, followed by 3 months of follow-up to monitor the return of ovulation.[4] Ovulation was inhibited in all women during treatment (figure 1); serum 17β-estradiol and progesterone levels and maximum follicle sizes returned to ovulatory levels within a mean of 16 days of stopping administration (ovulatory levels were reached in everyone within 31 days).
- In a substudy[5] of the noncomparative trial described in section 3,[3] 187 evaluable women with regular baseline menstrual cycles took ethinylestradiol/levonorgestrel 20μg/90μg for >168 (median 364) days before discontinuing the drug. Menstruation (defined as ≥2 days of bleeding requiring sanitary protection, starting ≥13 days after discontinuation) or pregnancy occurred in 39% of the study population within 30 days, 93% within 60 days and 99% within 90 days.
- Twenty-one evaluable women who took ethinylestradiol/levonorgestrel 20μg/90μg for 28–364 (mean 197) days in the same noncomparative trial,[3] and who then planned to become pregnant, were followed for 1 year after their last dose.[6] Twelve (57%) were pregnant at 3 months post-treatment and 17 (81%) at 12 months. One further woman became pregnant 14 months after discontinuing treatment.
- Premenstrual syndrome (n = 78), milder cycle-related (n = 36) and dysmenorrhoea (n = 259) symptoms in healthy women aged 18–49 years were

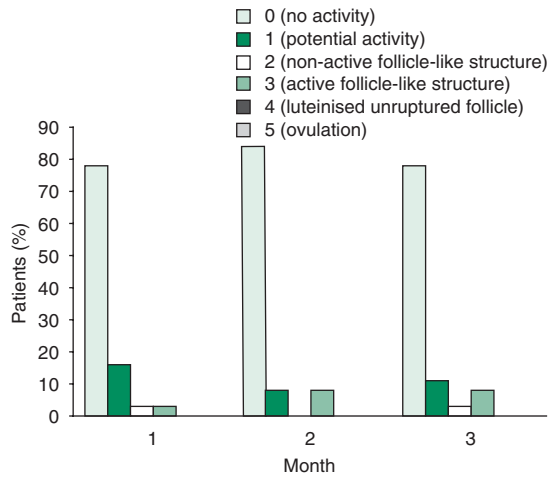

Fig. 1. Suppression of ovulation by continuous oral ethinylestradiol/levonorgestrel 20μg/90μg. The graph shows the percentages of 37 healthy women achieving Hoogland and Skouby ovarian activity grades 0–5 (none reached grade 4 or 5) during 3 months of treatment.[4]

1 The use of trade names is for identification purposes only and does not imply endorsement.

significantly improved from baseline after 3 months of continuous oral ethinylestradiol/levonorgestrel 20μg/90μg (all $p < 0.001$).[7] The Endicott Work Productivity Scale also showed significant improvements from baseline ($p < 0.001$).

2. Pharmacokinetic Profile

There are few published pharmacokinetic data on oral ethinylestradiol/levonorgestrel 20μg/90μg. The data outlined here were obtained from the manufacturer's prescribing information.[1]

- The bioavailability of levonorgestrel after oral administration is approximately 100%; absorption is rapid and the drug is not subject to first-pass metabolism. By contrast, although ethinylestradiol is rapidly absorbed, bioavailability is 38–48% because of first-pass metabolism.[1]
- In 18 women receiving once-daily oral ethinylestradiol/levonorgestrel 20μg/90μg, steady-state concentrations were reached in about 2 weeks. The time to maximum plasma concentrations for both ethinylestradiol and levonorgestrel was approximately 1.4 hours.[1]
- Ethinylestradiol is highly bound to serum albumin and also induces sex hormone-binding globulin, to which levonorgestrel is primarily bound.[1]
- After hydroxylation of ethinylestradiol by cytochrome P450 enzymes in the liver, the 2-hydroxy metabolite is further broken down by methylation, sulphation and glucuronidation before excretion via urine and faeces (terminal elimination half-life [$t_{1/2}\beta$] 21 hours). After reduction, hydroxylation and conjugation of levonorgestrel, circulating metabolites are mainly sulphates while those excreted in urine and faeces are mainly glucuronides ($t_{1/2}\beta$ 36 hours). There are wide intersubject variations in levonorgestrel clearance rates.[1]

3. Contraceptive Efficacy

Two multicentre nonblind trials have investigated the contraceptive efficacy of continuous ethinylestradiol/levonorgestrel 20μg/90μg.[3,8]

In a large noncomparative trial, healthy sexually active women aged 18–49 years took one ethinylestradiol/levonorgestrel 20μg/90μg tablet daily for 12 months (2134 took at least one dose, 921 completed 13 28-day pill packs).[3] Participants had experienced regular menstrual cycles for the previous 3 months. Those >34 years of age who smoked >15 cigarettes per day and those using other hormonal contraceptives in the previous 60 days, depot contraceptive preparations within the previous 10 months or hepatic enzyme-inducing drugs were excluded.

The primary efficacy endpoint in this trial was the number of unplanned pregnancies during treatment, using the adjusted Pearl Index (i.e. the number of pregnancies per 100 women-years of use, obtained by dividing the number of pregnancies by the number of 28-day intervals of observation and multiplying the result by 1300).[3]

Participants in the other trial were randomised to continuous daily ethinylestradiol/levonorgestrel 20μg/90μg (n = 323) or daily ethinylestradiol/levonorgestrel 20μg/100μg for 21 of every 28 days (n = 318) for 12 months (13 cycles).[8] Breakthrough bleeding was defined as bleeding requiring sanitary protection. Spotting was defined as bleeding not requiring sanitary protection. No further design details are available because this trial was reported in abstract form.

- Nineteen pregnancies occurred during treatment over the 12-month noncomparative trial period in participants aged 18–49 years who took at least one dose (adjusted Pearl Index 1.6; 95% CI 0.96, 2.49); four of these were attributed to user failure (pills missed in the 30 days prior to conception) and 15 to method failure (adjusted Pearl Index 1.26; 95% CI 0.71, 2.08).[3]
- In the same trial, 15 pregnancies occurred during treatment or during the 2 weeks after treatment ended in the subgroup of participants aged 18–35 years who took the pills completely as directed (number not reported; adjusted Pearl Index 1.55; 95% CI 0.87, 2.56).[1]
- A subgroup of women from this trial (n = 79) continued to take the drug for a second year; none became pregnant during treatment.[9]

- Zero and three pregnancies occurred during the 12-month continuous and cyclical regimens in the comparative trial (Pearl Indices not reported).[8]
- In both trials, the incidence of amenorrhoea (no breakthrough bleeding or spotting) and absence of breakthrough bleeding (with or without spotting) increased with extended therapy. Among recipients of continuous ethinylestradiol/levonorgestrel 20μg/90μg, amenorrhoea and absence of breakthrough bleeding were reported by 2% and 6%, respectively, during the first 28-day pill pack and by 59% and 79% during pill pack 13 of the noncomparative trial,[3] and by 40% and 50% during pill pack 7 and 53% and 79% during pill pack 13 in the comparative trial.[8]
- In those reporting it in the noncomparative trial, breakthrough bleeding and/or spotting occurred for a mean (median) of 10.1 (8) days during the first pill pack and 10.8 (8) days during the 13th pill pack.[3] The duration of breakthrough bleeding or spotting was lower with the continuous than with the cyclical regimen after the fourth pill pack (data not reported).[8]

4. Tolerability

Data on the tolerability of ethinylestradiol/levonorgestrel 20μg/90μg are available from two large multicentre one-year trials (see section 3 for trial details).[3,8]

- Three hundred and ninety-six (18.6%) of 2134 women who took at least one dose of ethinylestradiol/levonorgestrel 20μg/90μg over a 12-month period discontinued the pill because of uterine bleeding.[3]
- Adverse events that developed or worsened while taking the drug were reported by 87% of recipients.[3] The most common events were headache, dysmenorrhoea, upper respiratory tract infection and nausea (figure 2). The incidence of nausea and breast pain decreased during the second 6 months of use.
- Serious adverse events at least possibly associated with the drug in the noncomparative trial included cholecystitis (two recipients), deep vein thrombosis/pulmonary embolism (one), ectopic pregnancy (one), prolonged uterine bleeding (one) and enlarged uterine fibroids (one).[3]

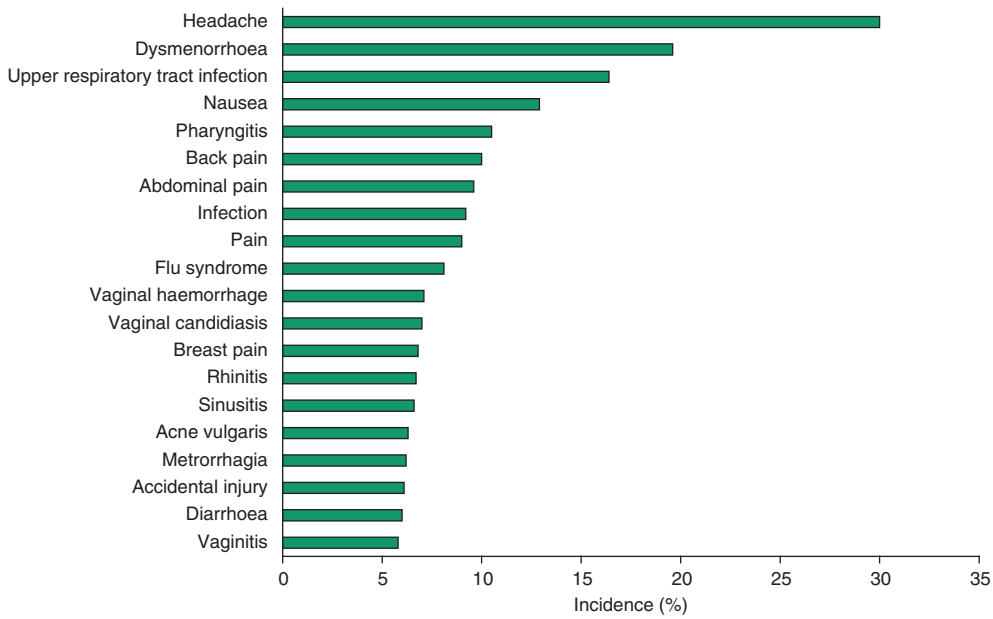

Fig. 2. Tolerability of ethinylestradiol/levonorgestrel 20μg/90μg. Incidence of adverse events that developed or worsened in ≥5% of 2134 recipients during treatment with continuous daily ethinylestradiol/levonorgestrel 20μg/90μg for 12 months.[3]

• Laboratory assessments in the noncomparative trial with 12 months of treatment showed mean increases in fasting glucose (3–4%), fasting total cholesterol, low-density lipoprotein cholesterol and triglyceride levels, haematocrit ($p < 0.001$ vs baseline), blood pressure ($p < 0.05$ vs baseline) and bodyweight (0.76kg; $p < 0.001$ vs baseline). There was a mean 0.7 g/L decrease in haemoglobin levels during the first 7 months of treatment ($p < 0.001$ vs baseline), which had resolved by 12 months.[3]

• Changes in serum chemistry, haematology and haemostasis factors over 2 years' continuous use were deemed not clinically important.[9]

• Adverse effects overall occurred in similar numbers of women receiving continuous or cyclical contraception.[8] Bleeding-related adverse effects occurred to a similar extent after the first 6 months' therapy (comparative rates during the first 6 months were not reported), and nausea and breast pain occurred less often with continuous than with cyclical therapy after the first 6 months.[8]

5. Dosage and Administration

The manufacturer recommends that ethinylestradiol/levonorgestrel 20μg/90μg be taken once daily at the same time every day and at intervals not exceeding 24 hours.[1] Instructions for transition from previous birth-control methods to ethinylestradiol/levonorgestrel 20μg/90μg are provided by the manufacturer.[1] Local prescribing information should be consulted for detailed administration information, including contraindications, warnings, precautions, drug interactions and use in special patient populations.

6. Continuous-Use Ethinylestradiol/Levonorgestrel 20μg/90μg: Current Status as an Oral Contraceptive

The continuous-use oral contraceptive ethinylestradiol/levonorgestrel 20μg/90μg is approved in the US and is preregistration in Europe as an oral contraceptive for the prevention of pregnancy. It has shown clinical efficacy in preventing pregnancy and suppressing breakthrough bleeding in a large noncomparative trial and a randomised nonblind comparison with traditional cyclical administration.

Disclosure

The manuscript was reviewed by: P. Bednarek, Department of Obstetrics and Gynecology, Oregon Health and Science University, Portland, Oregon, USA; C. Davtyan, Iris Cantor UCLA Women's Health Center, UCLA Comprehensive Health Program, Los Angeles, California, USA. During the peer review process, the manufacturer of the agent under review was also offered an opportunity to comment on this article; changes based on any comments received were made on the basis of scientific and editorial merit.

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