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Ethinyl estradiol/ levonorgestrel (seasonale®) a new extended cycle oral contraceptive

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Introduction

Oral contraceptive (OC) agents are highly reliable and effective methods of contraception. Over 100 million women worldwide, and 12 million women in the United States use oral OC agents to prevent unwanted pregnancies.[1] Most of the traditional OC regimens consist of a 28-day cycle with 21 days of active pills followed by either a pill-free week or a week of inactive pill use.[2,3] This cyclic 28-day regimen induces withdrawal bleeding and mimics monthly menstruation.[2,3] However, the belief that a monthly period is normal and healthy for women using contraception is being challenged.

Studies have suggested that extending the use of active hormones continuously over several cycles has offered a number of positive outcomes from personal convenience to health benefits. A survey of Dutch women found that the majority would prefer an OC that eliminated menses completely or reduced the frequency to less than once a month.[5] Menstruation-related problems including menorrhagia, anemia, dysmenorrhea, endometriosis, and menstrual headache may improve with an extended cycle OC regimen as well.[6]

Seasonale® is a 91-day extended cycle regimen OC that can be taken continuously for 84 days followed by 7 days of placebo. Each Seasonale® tablet consists of 30 mg ethinyl estradiol (EE) and 150 mg levonorgestrel (LNG), a synthetic progestogen. Seasonale was evaluated at 47 study sites throughout the United States and has shown to reduce the number of annual menstrual cycles from the current norm of 13 to 14 per year to only four per year.[4] In September 2003, Barr Laboratories received FDA approval to market Seasonale® in the U.S. This article will discuss the efficacy, safety, and tolerability of EE/LNG-84.

Pharmacology and Pharmacokinetics

The primary action of the combination oral contraceptive is to suppress the hypothalamic-pituitary system, decreasing the secretion of gonadotropin-releasing hormone (GnRH)[7] resulting in the inhibition of ovulation. In addition, other modes of action include changes in the cervical mucus, thus preventing penetration of sperm into the uterus and changes in the endometrium, which reduces the likelihood of implantation.[7]

The absolute bioavailability of EE/LNG-84 in humans has not been determined. However, studies have shown that following oral administration in the third cycle of use, levonorgestrel is approximately 100% bioavailable and is not subject to first-pass metabolism. Levonorgestrel is highly protein-bound, primarily to albumin and sex hormone-

INSIDE THIS ISSUE:

Table 1. Reasons for discontinuation of contraceptive therapy[3]

Reason	Extended cycle regimen* N (%)	Conventional regimen† N (%)
Adverse event	68 (14.9)	22 (9.7)
Patient decision	47 (10.3)	7 (3.1)
Lost of follow-up	39 (8.6)	21 (9.3)
Other/unknown‡	31 (6.8)	15 (6.6)
Total	185 (40.6)	65 (28.8)

N=number of patients.
*Total number of patients 456. †Total number of patients 226. ‡Includes noncompliant, pregnant, investigator discretion and other/unknown.

binding globulin (SHBG). Ethinyl estradiol is rapidly and almost completely absorbed from the GI tract, but after first-pass metabolism at the gut mucosa and liver, the bioavailability of EE is approximately 43%. Ethinyl estradiol is highly but nonspecifically bound to albumin. The effect of food on the rate and extent of absorption of LNG and EE following oral administration has not been evaluated.

Ethinyl estradiol is primarily metabolized in the liver via CYP3A4 while sulfation is the major metabolic pathway for LNG. Ethinyl estradiol is excreted in the urine and feces and it undergoes enterohepatic recirculation. The terminal elimination half-life of EE is about 16 hours after a single dose of EE/LNG-84. Whereas about 45% of LNG and its metabolites are excreted in the urine and about 32% are excreted in feces. The terminal elimination half-life of LNG after a single dose of EE/LNG-84 is about 30 hours.[7]

Clinical Trials

Anderson and Hait[3] compared the 91-day extended cycle OC Seasonale® (30 μg EE/150 μg LNG) to the 28-day conventional OC Nordette®-28 (30 μg EE/150 μg LNG). This one-year, parallel, multicenter, open-label trial randomized a total of 682 sexually active women (ages 18–40) of childbearing potential to EE/LNG-84 or Nordette®-28 and was designed to assess the efficacy, safety, and tolerability of EE/LNG-84. Over half of the patients in the study were continuous OC users (60%), 30% had a history of prior OC use, and about 10% had no prior history of OC use.

Bleeding, increased weight, mood swings, and acne were reported as the most common adverse events. Both treatment groups reported high compliance rates (>93%) with 22 (4.8%) EE/LNG-84 patients and nine (4.0%) Nordette®-28 patients discontinuing the study due to noncompliance. After one year of therapy, 59.4% of patients (271/456) in the extended cycle regimen (EE/LNG-84) and 71.2% (161/226) of patients in the conventional regimen (Nordette®-28) completed the study. Adverse events, individual patient decision and "loss to follow-up" were the most common reasons for early discontinuation (Table 1).

The median number of days of withdrawal bleeding was similar in both treatment groups on a per-cycle basis, and the median percent of scheduled withdrawal bleeding and/or spotting and bleeding-only days was similar in both treatment groups as well. Among patients treated with the extended cycle regimen, more than half of the total number of days were attributed to spotting. The median observed total number of days (based on a possible 364 days) of reported bleeding and/or spotting for all patients enrolled in the study was 35 for the extended cycle regimen and 53 for the conventional regimen (Table 2). As expected, extended cycle regimen patients initially experienced more breakthrough bleeding and/or spotting and bleeding-only than did patients treated with the conventional regimen, but the breakthrough bleeding was comparable in the two treatment groups by the last extended cycle (cycle 4).

Dosing and Administration

Patients should receive one active tablet of EE/LNG-84 once daily for 84 days, followed by a period of 7 days of inactive tablets to allow withdrawal bleeding to occur. It must be taken exactly as directed to achieve maximum contraceptive effectiveness and should be initiated on the first Sunday after the onset of menstruation. If it is initiated at any other time during the cycle, the patient must

Table 2. Results of reports of observed days of bleeding and/or spotting versus bleeding alone[3]

Results	Bleeding/Spotting		Bleeding Only	
	Mean (SD)	Median	Mean (SD)	Median
Total observed number of days				
Extended cycle regimen (364 possible days)	48.2 (44.0)	35.0	22.7 (22.8)	16.0
Conventional regimen (364 possible days)	50.8 (27.0)	53.0	37.0 (19.6)	39.5
Scheduled withdrawal bleeding				
Extended cycle regimen (28 possible days)	10.6 (8.2)	10.0	7.9 (6.6)	7.0
Conventional regimen (91 possible days)	32.4 (18.2)	36.0	27.0 (16.3)	29.0
Unscheduled (breakthrough) bleeding				
Extended cycle regimen (336 possible days)	37.6 (38.8)	26.0	14.8 (19.1)	7.0
Conventional regimen (273 possible days)	18.3 (17.2)	13.0	9.9 (11.9)	5.5

SD=standard deviation

use an alternative non-hormonal method to protect herself from getting pregnant until she has taken the active product for 7 consecutive days.

If spotting or breakthrough bleeding occurs, the patient should continue on the same regimen since this event might be transient. If the bleeding is persistent or prolonged, the patient is advised to consult her health care provider. Missing pills can also cause spotting or light bleeding. Any time a patient misses two or more active tablets, she should use another method of non-hormonal back-up contraception until she has taken an active tablet daily for 7 consecutive days. The risk of pregnancy increases with each active tablet that is missed.[7]

Toxicity and Safety

The risks of using EE/LNG-84 are similar to the risks of other conventional oral contraceptives including an increased risk of venous thromboembolism, heart attack, and stroke. Based on the results of SEA 301 trial, the incidence of adverse events is similar across the treatment groups. The most common adverse events reported were those associated with sinus and respiratory tract infection, headache and "unacceptable" bleeding including intermenstrual bleeding and/or spotting (Table 3). The incidence of headache was lower in the extended cycle regimen than in the conventional regimen patients (21% vs. 28%), but higher rates of bleeding-reported events were noted in extended cycle regimen subjects compared to conventional regimen subjects (12% vs. 3%). There were no significant differences with changes in triglycerides and low-density lipoprotein cholesterol between the two treatment groups as well as changes in other laboratory values, body weight, vital signs (systolic and diastolic blood pressure, heart rate or temperature) from baseline to end of study. There were three cases of serious adverse events reported including a pulmonary embolism (PE) event in the extended-cycle regimen and cholecystitis, and an exacerbation of preexisting depression in the conventional regimen.[3]

Cost

The retail costs for one EE/LNG pack (3 month supply) and two EE/LNG packs (6 months supply) are listed in Table 4.

Summary

Seasonale® is the first extended regimen OC agent approved in the U.S and represents a change in the paradigm of OC therapy. It contains a combination of ethinyl estradiol and levonorgestrel and appears to be as safe and effective as conventional OC pills. Seasonale® may help prevent anemia and

Table 4. Cost comparison of EE/LNG-84[9]

Pharmacy	Prices	
	3-month supply (1 pack)	6 months supply (2 packs)
Retail (chain)	$ 111.69	$ 216.69
Internet	$ 142.00	$ 275.00
Mean Price	$ 126.85	$ 245.85

Table 3. Percent of subjects with intermenstrual bleeding and/or spotting[3]

Regimen	Subjects with Intermenstrual Bleeding/Spotting*	
	= 7 days	= 20 days
Seasonale		
Cycle 1 (N=385)	65%	35%
Cycle 4 (N=261)	42%	15%
28-day regimen		
Cycles 1-4 (N=194)	38%	6%
Cycles 10-13 (N=158)	39%	4%

*Based on spotting and/or bleeding on days 1-84 of a 91 day cycle in the Seasonale subjects and days 1-21 of a 28 day cycle over 4 cycles in the 28-day dosing regimen.

endometriosis, a common cause of pelvic pain and infertility, by decreasing the frequency of menstrual cycles. However, Seasonale® users may experience a higher incidence of break-through bleeding than women taking conventional OC agents. Short-term studies have shown that extending the menstrual cycle to 91 days has no negative impact on the quality of life patients. Nevertheless, the long-term effects are still unknown. Seasonale® appears to be a safe and effective OC regimen allowing women the option for fewer menstrual periods.

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Alfuzosin (Uroxatral™) is a selective a_1-antagonist approved for the treatment of benign prostatic hyperplasia (BPH). The recommended dose is one 10-mg extended-release tablet given by mouth once daily. It should be used with caution in patients taking drugs that can inhibit or induce the cytochrome P450 3A4 isozyme and drugs which prolong the QT interval. Common adverse reactions include postural hypotension, dizziness, headache, fatigue, GI upset, and impotence.

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