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Name of finished product: Seasonique®		
Name of active ingredient: Seasonique®: levonorgestrel (150 µg)/ethinyl estradiol (30 µg) x 84 days, ethinyl estradiol 10 µg x 7 days		
Trial Number: PSE-301	Study period (dates): 14 APR 2002 – 8 APR 2004	
Title of Study: A Phase III, Randomized, Multicenter Clinical Trial to Evaluate the Efficacy and Safety of Combination Oral Contraceptive Regimens Utilizing Ethinyl Estradiol During the Pill-Free Interval For Prevention of Pregnancy in Women.		
Investigator: Multiple Investigators		
Study centers: 36 Centers (all in the U.S.)		
Publication (Reference): Anderson FD, Gibbons W, Portman D. Safety and efficacy of an extended-regimen oral contraceptive utilizing continuous low-dose ethinyl estradiol. <i>Contraception</i> . 2006;73(3):229-234.		
Link to Labeling: http://www.seasonique.com/Files/PrescribingInfo.pdf		
Clinical phase: Phase III		
Objectives: <u>Primary Objective:</u> To demonstrate the efficacy and safety of the 91-day extended regimen oral contraceptive, Seasonique®, which include 84 days of combination therapy followed by 7 days of ethinyl estradiol monotherapy, taken for one year in women desiring pregnancy prevention. <u>Secondary Objectives:</u> 1) Observation of the incidence and severity of hormonal-related symptoms during the treatment period and 2) Observation of the number of reported days of scheduled (withdrawal) and unscheduled (breakthrough) bleeding and/or spotting.		
Methodology: Multicenter, randomized, open-label study. Patients were to take the study medication for one year (four 91-day cycles).		
Numbers of patients: Seasonique®: N = 1024 (randomized); 1006 (treated with at least one dose of study medication) DP3 84/30: N= 1025 (randomized); 1013 (treated with at least one dose of study medication)		
Diagnosis and Main Criteria for Inclusion: Prevention of pregnancy in sexually active women aged 18 – 40 years, inclusive, who were of childbearing potential and at risk for pregnancy. Volunteers were required to be fluent in English, capable of giving informed consent and agreed to use the study oral contraceptive therapy as their primary birth control method.		
Test Product Dose, Duration, and Route of Administration: Seasonique®: levonorgestrel (150 µg); ethinyl estradiol (30 µg) 84 days combination drug followed by 7 days ethinyl estradiol (10 µg) monotherapy administered orally for four 91-day cycles. DP3 84/30: levonorgestrel (150 µg); ethinyl estradiol (30 µg) 84 days combination drug followed by 7 days ethinyl estradiol (30 µg) monotherapy administered orally for four 91-day cycles.		
Reference Product Dose, Duration, and Route of Administration: None		
Criteria for Evaluation: <u>Efficacy:</u> Pregnancy rate as calculated by the Pearl Index. Secondly, the “Compliant-Use” Pearl Index was also evaluated. <u>Safety:</u> Assessed by comparison of treatment-emergent adverse events, clinical laboratory test results (blood chemistry, hematology, and urinalysis), vital signs, physical examination between baseline and end of treatment or early termination, and the incidence of bleeding and/or spotting.		
Statistical Methods: <u>Efficacy:</u> Calculation of Pearl Index. <u>Safety:</u> Descriptive statistics and shift tables.		

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Summary: <u>Efficacy Results:</u> The Pearl Index among patients 18-35 years of age with at least one complete cycle of treatment (excluding cycles in which another form of birth control was used) was 1.77 for Seasonique®. When used as directed (i.e., “Compliant-Use”), Seasonique® was >99% effective in preventing pregnancy (Pearl Index = 0.78). <u>Safety Results:</u> A total of 23 (2.3%) of the DP3-84/30 and 22 (2.2%) of the Seasonique® patients reported at least one serious adverse event (SAE) during the course of the study. Only 8 patients (5 for DP3-84/30 and 3 for Seasonique®) discontinued the study due to a serious adverse event. There were 5 reports of cholelithiasis, including 1 with pancreatitis, in patients receiving Seasonique®. Four of these five patients had one or more known risk factors for cholelithiasis, including excessive body weight, weight change, and increased age. Other SAEs judged severe and possibly related to the study drug included one case of uterine fibroids aggravated (DP3 84/30) and one case of migraine (Seasonique®). The most frequently reported adverse events occurring in ≥ 5% of all treated patients were intermenstrual bleeding (11.53% for Seasonique®), menorrhagia (5.77% for Seasonique®), nasopharyngitis (7.16% for Seasonique®), sinusitis (6.46% for Seasonique®), weight increased (5.27% for Seasonique®), acne (5.17% for Seasonique®). <u>Cycle Control:</u> The median total number of observed bleeding and/or spotting days normalized to a 28-day cycle for the last 91-day extended regimen (cycle 4) was 2.0 days for Seasonique®. Unscheduled bleeding and/or spotting for both regimens was highest during the first extended cycle but then dropped at subsequent cycles, reaching the low median at cycle 3 for Seasonique®. The median number of observed unscheduled bleeding and/or spotting days normalized to a 28-day cycle, for the last 91-day extended cycle was 1.0 day for the Seasonique® regimen. The days of scheduled bleeding and/or spotting for the last 91-day extended cycle was 3 days for Seasonique®. Other safety results for Seasonique® are comparable to what has been seen in other studies using conventional OC therapy.		