**Pharmacokinetic Profile of an Ascending-Dose, Estradiol/Progesterin Combination Oral Contraceptive**

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**ABSTRACT**

Introduction: The estrogen component of oral contraceptives provides stability to the endometrium. An elevated estradiol level on an ongoing basis leads to the development of endometrial hyperplasia. An estradiol regimen that leads to the increment of a lower estradiol level may be more effective in preventing unwanted breakthrough bleeding or spotting. Over several cycles, this is hypothesized that gradual increases in estradiol levels may be achieved.

Methods: A population pharmacokinetic (PK) model was used to predict estradiol plasma concentrations over time following administration of a 91-day extended regimen (Seasonique) to premenopausal women (N=136). This AGC consists of the following: LNG 20 mcg for days 1-21, EE 30 mcg for days 22-42, EE 25 mcg for days 43-63, and LNG 100 mcg for days 64-91. PK parameters were estimated using a population model approach, were to NONMEM software, version 6, level 2.0 (ICON Development Solutions 2006). The PK model describes the time course of estradiol concentration in the plasma after administration of escalating EE doses. This model was used to predict estradiol plasma levels in the context of the time when breakthrough bleeding.

Conclusions: The increasing dose of EE in DOR changes estrogen exposure to EE by an increase in the oral bioavailability of estrogen, which makes the typical hormon-free interval possible. Since the estrogen exposure in the last cycle is lower than in the first cycle, the risk of unwanted breakthrough bleeding is diminished.

**METHODS**

**Subjects**

Patients in the pooled studies included healthy women of childbearing potential between the ages of 18 to 51 years (Table 1).

**Study Design**

Because of the variability in bleeding when administered as various EE extended regimens, the EE dose was titrated over the initial 84 days of the extended cycle followed by lower concentrations of EE with the 10-mcg daily dose of estrogen. The risk of unwanted breakthrough bleeding are minimized.

EE dose regimen, Seasonique.

**RESULTS**

The increasing dose of EE in DOR changes estrogen exposure to EE by a stepwise increase in the oral bioavailability of estrogen, which makes the typical hormon-free interval possible. Since the estrogen exposure in the last cycle is lower than in the first cycle, the risk of unwanted breakthrough bleeding is diminished.

**Figure 2.** Mean predicted single-dose and steady-state plasma concentration by time profiles of EE at Day 0 (42), Day 21 (63), Day 42 (84), and Day 56 (91).

**REFERENCE LIST**


**CONCLUSIONS**

• Single- and multiple-dose (pharmacodynamic) parameters of EE following administration of 25 mcg ADER were found.

• Systemic exposure to EE following administration of 25 mcg ADER is comparable to Seasonique, which contains the same EE in a different dosing regimen.

• Increases in systemic exposure occur in a stepwise fashion with increasing EE dose in the extended cycle followed by lower concentrations of EE, which replace the traditional 7-day HFI at the end of the cycle.


• Further studies are needed to investigate the incidence of unwanted bleeding with ADER and to substantiate the pharmacodynamic association between estradiol and progesterone and the estrogen-free bleeding period.

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