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CLINICAL DEVELOPMENT OF A NEW GENERATION ETONOGESTREL/ETHINYLESTRADIOL VAGINAL RING: COMPARATIVE BIOAVAILABILITY

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Context: Contraceptive vaginal rings have advantages in efficacy, safety and acceptability.
Objective: To show the comparative bioavailability as part of the clinical development of a recently developed contraceptive vaginal ring, compared to the reference product. Safety, tolerability and acceptability results are presented in separate communication.
Subjects: A randomized, single dose, 2-period, 2 sequence, 2-stage crossover, was conducted in 40 healthy females.
Interventions: All subjects worn each vaginal ring during 28 days in each study period separated by a washout of 28 days: the new generation vaginal ring developed by Laboratorios LeonFarma SA, Spain (Etonogestrel/Ethinylestradiol 120/15Âµg/day) and NuvaringÂ®, MSD, Spain (Etonogestrel/Ethinylestradiol 120/15Âµg/day). For the calculation of pharmacokinetic parameters, blood samples were collected prior to and up to 840h after each ring insertion to quantify plasma concentrations of etonogestrel and ethinylestradiol by means of a validated Ms/Ms HPLC method. To compare bioavailability by bioequivalence, pharmacokinetic parameters were analyzed using an ANOVA model with subject effect, treatment, period and sequence as fixed factors. The confidence interval was adjusted to 94.12% due to the 2-stages design.
Outcome measure: The 94.12% confidence interval for the exponential of the difference in LSmeans between the Test and Reference product was calculated for each of the ln-transformed parameters (Test to Reference ratio of geometric LSmeans).
Results: The bioequivalence was demonstrated in the first stage since the 94.12% Confidence Intervals of the three primary parameters laid within the 80-125% acceptance range for both, etonogestrel (Cmax: 96.81-112.20%; AUC0-504h: 98.71-108.61%; AUC0-t: 100.14-109.10%) and ethynilestradiol. (Cmax after day 1: 105.91-120.62%; AUC0-504h: 105.47-114.59%; AUC0-t: 108.31-117.61%). During the first day of use a burst effect was observed with NuvaringÂ® with higher level of etonogestrel (Cmax 0-24h ratio: 94.39%, 94.12CI: 89.75- 99.27%) that was significant in the case of ethinylestradiol (Cmax 0-24h ratio: 78.34%, 94.12CI: 73.55%- 83.45%).
Conclusion: LeonFarma ring is a new generation contraceptive vaginal ring bioequivalent in efficacy and safety to reference product, with the advantage of a more gradual release during the first day of use.

[1] Chemo Group, [2] Chemo Group, [3] Chemo Group, [4] Exeltis, Chemo Group