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Clinical development of Ornibel® a new generation etonogestrel/Ethinylestradiol vaginal ring: Comparative bioavailability and tolerability vs Nuvaring ®

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Objectives: 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. Methods and Patients: A randomized, single dose, 2-period, 2 sequence, 2-stage crossover, was conducted in 40 healthy females. All subjects worn each vaginal ring during 28 days in each study period separated by a washout of 28 days:. 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. Safety was assessed by means of adverse events (AE) recording and clinical laboratory. Vaginal examination evaluated local tolerability prior and at the end of each period. Acceptability was investigated by a 5-point scale questionnaire after each ring removal. AE were classified and described according to MedDRA dictionary. The questionnaires of local tolerability and acceptability were compared using the Cochran-Armitage Test for Trend.

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 Nuvaring® with higher level of etonogestrel (Cmax 0-24h ratio: 94.39%, 94.12CI: 89.75- 99.27%) that were significant in the case of ethinylestradiol (Cmax 0-24h ratio: 78.34%, 94.12CI: 73.55%- 83.45%). Regarding the tolerability and acceptability evaluation, the majority of the women felt comfortable using Ornibel® and was similar to Nuvaring®.Conclusion: Ornibel® is a new generation of contraceptive vaginal ring, bioequivalent in efficacy and safety to reference product, very well tolerated with the advantage of a more gradual release during the first day of use.

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