SYNOPSIS

Johnson & Johnson Pharmaceutical Research & Development, L.L.C. REFERENSG TO PART OF THE DOSSIER AUTHORITY USE ONLY: ORTHO-CYCLEN®+ Folic Acid Volume: Image: Construction of the second of the secon	NAME OF SPONSOR/COMPANY:	INDIVIDUAL STUDY TABLE	(FOR NATIONAL		
ORTHO-CYCLEN® + Folic Acid NAME OF ACTIVE INGREDIENT(S): Norgestimate-Ethinyl Estradiol + Folic Acid Page: Page: Page: Page: Protocol No:: NRGMON-CON-1001 CR002206 Title of Study: An Open-Label Pharmacokinetic Drug Interaction Study of Folic Acid and 250 µg Norgestimate-35 µg Ethinyl Estradiol (ORTHO-CYCLEN®) in Healthy Women Principal Investigator: Daniel Freeland, D.O CEDRA Clinical Research, L.L.C., Austin, Texas; USA Publication (Reference): None Studied Period (years): Clinical Conduct: 20 Jan 2005 to 24 Feb 2005 Sample Analysis: Not performed. Phase of development: 1 Sample Analysis: Not performed. Methodology: This was an open-label, randomized, single-center, pharmacokinetic interaction between folic acid and 250 µg norgestimate (NGM), the active metabolites norelgestromin (NGMN) and norgestrel (NG), and 35 µg ethinyl estradiol (EE). Safety was also assessed. Methodology: This was an open-label, randomized, single-center, pharmacokinetic interaction study. Healthy adult female subjects who met the prestudy eligibility criteria were randomized to 1 of 2 treatment groups. The randomized was balanced using permuted blocks. Subjects in Group 1 were to receive a single oral dose of 250 µg NGM35 µg EE (1 tablet of ORTHO-CYCLEN) on Days 1 and 17, and 1 ng of folic acid on Days 1 and 17. Subjects were to receive a single, oral 1 mg dose of folic acid on Days 1 and 17, and Days 2 and 18. Subjects in Group 2 were to receive a single, oral 1 mg dose of folic acid son pays 1 and 17. Subjects were to be confliced overight at the study unit until the 24-hour blood samples were dosing on Days 1 and 17. Subjects were to advance versus, and on changes in clinical laboratory values (hematology, chemistry, and urinalysis), vital signs, electrocardiograms (ECGs), and physical and gynecological examination findings. The Sponsor prematurely terminated this study on 14 February 2005 because of errors made at the study site in subject randomization, the timing of blood draws, and handling of laboratory samples. As a result			AUTHORITY USE ONLY)		
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Reference Therapy, Dose and Mode of Administration, Batch No.: None			.m. Subjects were required to fast		
	Reference Therapy, Dose and Mode of Adminis	tration, Batch No.: None			

SYNOPSIS (CONTINUED)

<u>NAME OF SPONSOR/COMPANY:</u> Johnson & Johnson Pharmaceutical Research & Development, L.L.C.	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER	(FOR NATIONAL AUTHORITY USE ONLY)
NAME OF FINISHED PRODUCT: ORTHO-CYCLEN [®] + Folic Acid	Volume:	
<u>NAME OF ACTIVE INGREDIENT(S):</u> Norgestimate-Ethinyl Estradiol + Folic Acid	Page:	
Duration of Treatment: 18 days Group 1; 17 days Group 2		

Criteria for Evaluation:

<u>Pharmacokinetics</u>: Mean concentrations of NGMN, NG, EE, and folic acid were to be determined from blood samples collected predose and up to 72 hours postdose. The pharmacokinetic parameters to be determined included C_{max} , t_{max} , AUC₂₄, AUC₇₂, AUC_{1ast}, AUC_{∞}, C_{last} , λ_{z} and $t_{/2}$.

<u>Safety</u>: Safety was evaluated by monitoring adverse events and changes in clinical laboratory values (hematology, serum chemistry, and urinalysis), vital sign measurements, ECGs, and physical and gynecological examination findings.

Statistical Methods:

<u>Pharmacokinetics:</u> Concentration vs. time profiles for NGMN, NG, EE, and folic acid were to be plotted for each subject and by treatment group (i.e., Group 1: ORTHO-CYCLEN alone, ORTHO-CYCLEN + folic acid; Group 2: folic acid alone, folic acid + ORTHO-CYCLEN). Descriptive statistics (mean, median, geometric mean, SD, CV, and range) were to be summarized by treatment group.

<u>Safety:</u> The incidence of adverse events was summarized for each treatment group using a standard adverse event dictionary (Medical Dictionary for Regulatory Activities [MedDRA]). Laboratory, vital signs, and physical and gynecological examination results were listed.

SUMMARY – CONCLUSIONS

PHARMACOKINETIC RESULTS: The pharmacokinetic analyses were not performed.

<u>SAFETY RESULTS</u>: ORTHO-CYCLEN (250 μ g NGM/35 μ g EE) in combination with folic acid (1 mg) was well tolerated in healthy adult females 19 to 45 years of age. Of the 48 subjects enrolled, 20 (41.7%) reported 1 or more adverse event. The most common events, dysmenorrhea and metrorrhagia, were each reported in 3 (6.3%) subjects. All adverse events were mild to moderate in severity except for 1 case of severe dysmenorrhea, and the majority of events were considered by the investigator to be possibly related to study medication. There were no deaths, serious adverse events, or adverse events leading to premature treatment discontinuation. There were no treatment-related trends or clinically relevant changes in laboratory values (serum chemistry, hematology, and urinalysis), vital signs, ECG assessments, physical examination, or gynecological examination findings. Two subjects became pregnant during the conduct of this study. One of these subjects chose to terminate her pregnancy. The other subject chose to continue the pregnancy. Her expected date of delivery is October 28, 2005.

<u>CONCLUSION</u>: Concomitant administration of folic acid with ORTHO-CYCLEN was well tolerated in healthy adult women. There were no significant safety findings.

Date of the report: 16 August 2005

Disclaimer

Information in this posting shall not be considered to be a claim for any marketed product. Some information in this posting may differ from, or not be included in, the approved labeling for the product. Please refer to the full prescribing information for indications and proper use of the product.