SYNOPSIS

NAME OF SPONSOR/COMPANY: Johnson & Johnson Pharmaceutical Research & Development, L.L.C. NAME OF FINISHED PRODUCT: Norgestimate-Ethinyl Estradiol/Folic Acid NAME OF ACTIVE INGREDIENT(S): Norgestimate-Ethinyl Estradiol	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)
Protocol No.: NRGMON-CON-1006 CR002380 **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: 26 April to 23 June 2005 Sample Analysis: 1 June to 24 July 2005		**Phase of development:** 1
Objectives: The primary objective of this study was to evaluate the pharmacokinetic drug interaction between folic acid and ORTHO-CYCLEN (250 μg norgestimate [NGM] and 35 μg ethinyl estradiol [EE]) as measured by the pharmacokinetics of the active metabolite of NGM, norelgestromin [NGMN], and EE. The secondary objective was to evaluate the pharmacokinetic drug interaction between folic acid and ORTHO-CYCLEN as measured by the pharmacokinetics of the active metabolite of NGM, norgestrel [NG]. Additionally, the effect of ORTHO-CYCLEN on the pharmacokinetics of folic acid was evaluated. Safety also was also assessed.		
Methodology: This was a single-center, open-label, pharmacokinetic drug interaction study between folic acid (1 mg) and ORTHO-CYCLEN (250 μg NGM/35 μg EE) in 2 groups of at least 20 healthy women each. In Group 1, a single oral dose of 250 μg NGM/35 μg EE (ORTHO-CYCLEN) was administered to the subjects at the study site on Days 1 and 17 and folic acid 1 mg was administered orally on Days 4 to 18; in Group 2, folic acid 1 mg was administered orally on Days 1 and 17 at the study site and 1 tablet of ORTHO-CYCLEN was administered on Days 2 to 17. Serial blood samples were collected at specified times for 72 hours postdose on Days 1 and 17 for subjects in Group 1 for determination of plasma concentrations of NGMN and NG (the active metabolites of NGM), and EE. For subjects in Group 2, serial blood samples were collected for 24 hours after the folic acid dose on Days 1 and 17 for determination of plasma concentrations of total folates. Pharmacokinetic parameters for NGMN, NG, EE concentrations and folate concentration were determined for each subject using non-compartmental analysis.		
Number of Subjects (planned and analyzed): A total of 48 subjects were planned for enrollment, 47 subjects were enrolled, and 41 subjects (21 in Group 1; 20 in Group 2) completed the study. Data from the 41 subjects who completed the study were included in the statistical analysis of the pharmacokinetic data, and 47 subjects were included in the safety analysis.		
Diagnosis and Main Criteria for Inclusion: Healthy, nonpregnant, nonlactating, nonsmoking women, aged 18 to 45 years, weighing at least 110 pounds, with regular menstrual cycles, a body mass index between 16 and 29.9 kg/m^2, and a hematocrit of at least 36% were enrolled in the study.		
Test Product, Dose and Mode of Administration, Batch No.: 250 μg NGM/35 μg EE was administered as a single tablet corresponding to cycle Day 16 in the commercial dialpak of ORTHO-CYCLEN (package lot number: R13202). Folic acid was supplied in a commercially-available 1-mg United States Pharmacopeia (USP) tablet (package lot number: R13201).		
Reference Therapy, Dose and Mode of Administration, Batch No.: None		
Duration of Treatment: Approximately 20 days plus the screening period (up to 21 days)		

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Criteria for Evaluation:

Pharmacokinetics: The following pharmacokinetic parameters were estimated by non-compartmental methods for serum NGMN, NG, and EE and plasma folate for each subject: C_{max}, t_{max}, AUC_{12} (folate only), AUC_{24} (NGMN, NG, and EE only), AUC_{72} (NGMN, NG, and EE only), AUC_{last}, AUC_{last*} (folate only), AUC_{∞} (NGMN and EE only), λ_z, and $t_{½}$. The pharmacokinetic parameters of contraceptive steroids (NGMN, NG, EE) with and without coadministration of folic acid were determined to evaluate the effect of folic acid on the pharmacokinetics of ORTHO-CYCLEN. Additionally, folate pharmacokinetic parameters with and without coadministration of ORTHO-CYCLEN were determined to evaluate the effect of ORTHO-CYCLEN on the pharmacokinetics of folate.

Safety: Safety was assessed through the monitoring of adverse events, vital sign and electrocardiogram (ECG) measurements, physical examinations, and clinical laboratory tests (hematology, chemistry, and urinalysis). Pregnancy tests were done at screening, before each dose, and at poststudy.

Statistical Methods:

Pharmacokinetics: The statistical analysis was carried out for each group and analyte separately. For both Groups 1 and 2, all estimated pharmacokinetic parameters were summarized with mean, median, minimum, maximum, standard deviation, and coefficient of variation for each treatment.

To evaluate the interaction of folic acid and NGMN, NG and EE, the primary parameters of interest for the statistical analysis, were AUCs (AUC_{last} and $AUC_{\infty)}$ and C_{max} of contraceptive steroids in Group 1, and AUC_{last} and C_{max} of plasma folate in Group 2. The analysis was performed on log-transformed estimated pharmacokinetic parameters. Only the data from subjects who completed the study were included in the statistical analysis. Mixed-effects models were fit to the data with 1 of the estimated pharmacokinetic parameters of interest as the dependent variable, treatment as a fixed effect, and subject as a random effect. The estimated least square means and intra-subject variability from the mixed effects model were used to construct 90% confidence intervals for the difference in means on the log scale between the 2 treatments. The limits of the confidence intervals were re-transformed using anti-logarithms to obtain 90% confidence intervals for the ratio of the mean pharmacokinetic parameters of NGMN, EE, and NG with and without co-administration of folic acid and of folate with and without ORTHO-CYCLEN.

Safety: Safety evaluations were based upon the type, incidence, and severity of treatment-emergent adverse events reported throughout the study, and on prestudy to poststudy changes in vital sign measurements, clinical laboratory test results, ECGs, and physical examinations.

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SUMMARY – CONCLUSIONS

PHARMACOKINETIC RESULTS: Arithmetic mean (SD) of serum pharmacokinetic parameters of NGMN, EE, and NG following a single oral dose of ORTHO-CYCLEN with and without folic acid are summarized below:

	NGMN		EE[a]		NG	
Parameters	ORTHO-CYCLEN Alone (n=23)	ORTHO-CYCLEN With Folic Acid (n=21)	ORTHO-CYCLEN Alone (n=23)	ORTHO-CYCLEN With Folic Acid (n=21)	ORTHO-CYCLEN Alone (n=23)	ORTHO-CYCLEN With Folic Acid (n=20)
C_{max} (ng/mL)	1.40 (0.413)	1.34 (0.374)	93.1 (26.1)	91.4 (27.1)	0.415 (0.164)	0.435 (0.130)
t_{max}[b] (h)	1.22 (1.00-5.00)	1.50 (1.00-5.00)	1.05 (1.00-2.00)	1.50 (1.00-3.00)	2.00 (1.00-5.00)	2.00 (1.00-5.00)
AUC_{24} (ng.h/mL)	8.91 (2.38)	9.13 (2.26)	640 (173)	637 (119)	6.33 (2.46)[g]	6.09 (2.77)[k]
AUC_{72} (ng.h/mL)	13.7 (2.68)[c]	13.9 (3.13)[d]	1023 (481)[e]	926 (246)[f]	16.6 (5.62)[h]	20.7 (6.94)[l]
AUC_{last} (ng.h/mL)	12.6 (3.25)	13.4 (3.31)	773 (260)	784 (190)	9.14 (6.89)[i]	10.4 (8.28)
AUC_{∞} (ng.h/mL)	14.3 (3.61)	15.7 (4.08)	848 (274)	864 (208)	NAs	NAs
$t_{1/2}$ (h)	24.1 (8.14)	28.3 (14.6)	15.8 (8.30)	16.9 (8.79)	34.9 (20.7)[j]	46.3 (37.2)[m]

NAs= not accessible
[a] Mass units for EE are pg
[b] Represented by median (range)
[c] n=15; [d] n=19; [e] n=4; [f] n=6; [g] n=15; [h] n=7; [i] n=22; [j] n=12; [k] n=18; [l] n=6; [m] n=9

Mean C_{max}, AUC_{last}, and AUC_{∞} for NGMN and EE were similar for ORTHO-CYCLEN when dosed with and without folic acid. Mean NGMN $t_{1/2}$ was 24.1 hours and 28.3 hours, for ORTHO-CYCLEN and ORTHO-CYCLEN dosed with folic acid, respectively. Mean EE terminal half-life ($t_{1/2}$) was also similar when dosed with and without folic acid (16.9 hours and 15.8 hours, respectively). The differences for other exposure parameters such as AUC_{24} and AUC_{72} between the 2 treatments for both NGMN and EE (ORTHO-CYCLEN alone and with folic acid) were <10%.

Mean C_{max} for NG was similar when dosed with and without folic acid. Mean AUC_{last} was approximately 14% higher when dosed with folic acid compared to ORTHO-CYCLEN alone. AUC_{∞} could not be determined because the terminal log-linear phase could not be reliably characterized within the sampling period for these subjects. Mean terminal half-life was approximately 33% higher when dosed with folic acid compared to ORTHO-CYCLEN alone. Other exposure parameters such as AUC_{24} and AUC_{72} were determined. AUC_{72} increased by approximately 24% when dosed with folic acid compared to ORTHO-CYCLEN alone. This approximate 25% increase for NG AUC_{72} may be an artifact due, in part, to limited data (n=7 without folic acid and n=6 with folic acid). The differences for AUC_{24} between the 2 treatments (ORTHO-CYCLEN alone and ORTHO-CYCLEN with folic acid) for NG was <10%.

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The statistical results for evaluating the effect of folic acid on the pharmacokinetics of ORTHO-CYCLEN (EE, NGMN, and NG) are summarized below:

Analyte	Parameter	Intra-Subject CV (%)	ORTHO-CYCLEN With Folic Acid (Test)[a]	ORTHO-CYCLEN Alone (Reference)[a]	Ratio (%) Test/Reference	90% CI for Ratio (%)
EE	AUC_{∞} [b]	11.25	841.77	809.55	103.98	97.94 – 110.40
	AUC_{last} [b]	10.49	763.80	737.80	103.52	97.90 – 109.47
	C_{max} [b]	13.67	87.80	89.95	97.62	90.77 – 104.98
NGMN	AUC_{∞} [b]	11.27	15.16	13.49	112.33	105.79 – 119.27
	AUC_{last} [b]	10.10	13.03	11.96	108.93	103.23 – 114.95
	C_{max} [b]	19.04	1.29	1.27	101.09	91.35 – 111.88
NG	AUC_{last} [c]	23.47	8.29	6.25	132.55	116.16 – 151.26
	C_{max} [d]	14.97	0.42	0.38	109.38	100.78 – 118.71

[a] Geometric mean [b] n=21; [c] n=19; [d] n=20

The 90% confidence intervals for the ratio of geometric means of ORTHO-CYCLEN with and without folic acid with respect to the primary pharmacokinetic parameters (C_{max}, AUC_{last}, and AUC_{∞} of NGMN and EE) were contained within the equivalence range of 80% to 125%. The 90% confidence intervals for the ratios of geometric means of the secondary analyte, NG, with and without folic acid were contained within the equivalence range of 80% to 125% for C_{max}, while the ratio of AUC_{last} for NG was outside the range (116.16% to 151.26%). Based on the primary analytes, no effect of folic acid on the pharmacokinetics of the hormonal components of ORTHO-CYCLEN was observed.

Arithmetic mean (SD) of plasma folate pharmacokinetic parameters for observed and baseline corrected plasma folate concentrations are summarized below:

	Observed		Corrected For Baseline	
Parameters	Folic Acid Alone (n=24)	Folic Acid With ORTHO-CYCLEN (n=20)	Folic Acid Alone (n=24)	Folic Acid With ORTHO-CYCLEN (n=20)
C_{max} (ng/mL)	62.8 (11.5)	63.1 (9.22)	42.2 (9.62)	44.1 (7.08)
t_{max} [a] (h)	1.50 (1.00-3.00)	1.75 (1.00-3.00)	1.50 (1.00-3.00)	1.75 (1.00-3.00)
AUC_{12} (ng.h/mL)	367 (82.3)	382 (69.7)	158 (21.4)[b]	167 (22.6)[c]
AUC_{last} (ng.h/mL)	574 (147)	606 (136)	131 (39.0)	170 (45.1)
AUC_{last*} [d] (ng.h/mL)	277 (93.7)	390 (182)	129 (38.5)	162 (46.9)
$t_{1/2}$ (h)	4.62 (1.54)[e]	24.1 (28.5)[f]	1.51 (0.485)[e]	3.65 (3.35)[g]

[a] Represented with median (range)
[b] n=6; [c] n=15
[d] Parameter equal to AUC of the interval: 0 to the time point at which the subsequent folate concentration drop below baseline folate level for the first time
[e] n=13; [f] n=9; [g] n=10

For observed and baseline corrected plasma folate data, mean C_{max} and AUC_{12} were similar when dosed with and without ORTHO-CYCLEN. For observed data, mean AUC_{last} was also similar between the 2 treatments, while mean AUC_{last} for baseline corrected data increased by approximately 30% when folic acid was dosed with ORTHO-CYCLEN compared to folic acid alone. Mean AUC_{last*} calculated using the baseline corrected, as well as uncorrected, method was higher when folic acid was dosed with ORTHO-CYCLEN compared to folic acid alone. Mean $t_{1/2}$ increased substantially for both observed and baseline corrected data when folic acid was dosed with ORTHO-CYCLEN compared to folic acid alone. This increase may be due, in part, to the plasma folate levels approaching the endogenous folate concentrations near the last few collection times of the observed data. The $t_{1/2}$ of 24.1 hours reported for the observed total folate in the folic acid with ORTHO-CYCLEN treatment may not reflect the true elimination half-life and thus reinforces the above point about interference of endogenous folate at the terminal phase.

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The statistical results for evaluating the effect of ORTHO-CYCLEN on folate pharmacokinetics (baseline corrected and uncorrected) are summarized below:

Folate	Parameter	Intra-subject CV (%)	Folic Acid With ORTHO-CYCLEN (Test)[a]	Folic Acid Alone (Reference)[a]	Ratio (%) Test/Reference	90% CI for Ratio (%)
Corrected for Baseline	AUC_{last}	28.77	164.00	130.50	125.67	107.37 – 147.08
	AUC_{last*}[b]	29.22	156.09	128.49	121.48	103.54 – 142.52
	C_{max}	14.08	43.52	40.96	106.24	98.37 – 114.74
Observed (uncorrected)	AUC_{12}	9.40	376.12	354.03	106.24	100.91 – 111.84
	AUC_{last}	9.34	590.50	551.51	107.07	101.74 – 112.68
	AUC_{last*}[b]	39.20	355.03	275.53	128.86	104.00 – 159.66
	C_{max}	10.73	62.40	60.81	102.62	96.77 – 108.82

N=20

[a] Geometric mean

[b] Parameter equal to AUC of the interval: 0 to the time point at which the subsequent folate concentration drop below baseline folate level for the first time

All of the 90% confidence intervals for the ratio of geometric means of folate pharmacokinetic parameters with and without coadministration of ORTHO-CYCLEN were contained within the equivalence range of 80% to 125%, except AUC_{last} for baseline corrected folate and AUC_{last*} for both methods. Therefore, pharmacokinetic parameter values of total folates (baseline corrected and baseline uncorrected) were generally not affected by multiple-dose coadministration of ORTHO-CYCLEN.

SAFETY RESULTS: In general, both treatments were safe and well tolerated. No deaths or serious adverse events occurred during the study, and no subject discontinued treatment because of an adverse event. Nausea and headache were the most common adverse events, and there was a higher incidence of headache and vasovagal syncope in Group 2 compared with Group 1. None of the clinical laboratory values that were outside the normal ranges at the final visit were twofold outside the ranges, and none was considered clinically significant. Similarly, changes in vital signs, ECGs, and physical examination results from screening to final visit were not of clinical significance.

CONCLUSION: For the primary analytes, EE and NGMN, C_{max}, AUC_{∞}, and AUC_{last} values were similar between ORTHO-CYCLEN administered alone and ORTHO-CYCLEN coadministered with folic acid. Overall, no clinically significant pharmacokinetic interaction between folic acid and ORTHO-CYCLEN was observed at the dose level used in this study. Both treatments administered during this study were safe and well tolerated.

Date of the report: 14 March 2006

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