CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA:	21-690
Submission Type:	Pediatric
Submission Date(s):	24 September 2003
Sponsor Name:	Johnson & Johnson Pharmaceutical Research & Development, LLC
Brand Name:	ORTHO TRI-CYCLEN®
Generic Name:	Norgestimate / ethinyl estradiol
Indication(s):	Prevention of Pregnancy, Treatment of Moderate Acne Vulgaris, and Preservation of Bone Mineral Density in Pediatric Patients with Anorexia Nervosa
Strength(s):	Norgestimate / Ethinyl Estradiol: 180-mcg / 35-mcg; 215-mcg / 35-mcg; 250-mcg / 35-mcg
Reviewer:	Steven B. Johnson, Pharm.D.
Team Leader:	Hae-Young Ahn, Ph.D.
OCPB Division:	DPE-2 (HFD-870)
OND Division:	DMEDP (HFD-510)

Executive Summary

Johnson & Johnson Pharmaceutical Research and Development is seeking a new indication for their approved ORTHO TRI-CYCLEN® product – preservation of bone mineral density in pediatric patients with anorexia nervosa. To support this indication, the sponsor has submitted the results of a population analysis, gleaning three month pharmacokinetic (PK) data from an ongoing one-year double blind, placebo-controlled clinical study.

Per the Written Request, Amendment #2, dated 15 August 2003, the sponsor was to conduct a population PK study to evaluate ethinyl estradiol (EE), norgestrel (NG), and norelgestromin (NGMN) in a subset of pediatric patients with anorexia nervosa. The study was to use the single-trough sampling design, as recommended in the February 1999 Guidance to Industry: Population Pharmacokinetics, in evaluating at least forty patients between 12 and 17 years of age. The primary endpoint for the PK analyses was apparent clearance (Cl/F). The effects of age, body weight, and body mass index on Cl were also to be evaluated.

Results of this study were confounding. The sampling technique ultimately used by the sponsor was a hybrid method somewhere between a single-trough and full population PK sampling design, but failed to hit either mark. As detailed by the sponsor, "Trough samples, 24-hours post dose, were drawn during Days 4-7 and 18-21 of Cycle 3 for analysis of serum NGMN, NG, and EE concentrations. A composite AUC_{24} was estimated using all concentrations for each analyte. C_{max} was observed from the serum concentration-time curves. Apparent clearance was calculated as dose divided by AUC_{24}. C_{trough} concentrations were defined as between 16 to 26.5 and 16 to 27.5 hours for Days 4-7 and 18-21, respectively…" Only 26 of the proposed 60 patients, and required 40 for this study, had trough concentrations that fell within these time ranges, and very few had true trough concentrations.

The basis for conducting a single-trough sampling design study relies on the following three assumptions: 1) the sample size is large, 2) the assay and sampling errors are small, and 3) the dosing regimen and sampling times are identical for all patients. Failure to comply with any of these three assumptions can result in data that does not accurately reflect the strict PK variability because the data will include other sources of random fluctuation that can significantly contribute to the observed spread.

Since the sponsor was unable to conduct this study in a manner consistent with recognized protocol, the value of the calculated apparent clearance is clearly suspect. This finding is apparently consistent with the sponsor's, as they are not requesting a labeling change to include apparent clearance for this pediatric population at this time.

Recommendation
The Office of Clinical Pharmacology and Biopharmaceutics has reviewed the Clinical Pharmacology section of NDA 21-690 and finds the results to be unacceptable due to the sparsity of the data.

Briefing (1 March 2004)
Attendees: Larry Lesko, Sheiw Mei Huang, John Hunt, Don Stanski, Hae-Young Ahn, He Sun, S.W. Johnny Lau, Sang Chung, and Steven Johnson.

Steven B. Johnson, Pharm.D.
Division of Pharmaceutical Evaluation-II
Office of Clinical Pharmacology and Biopharmaceutics

RD initialed by Hae-Young Ahn, Ph.D., Team Leader:

FT initialed by Hae-Young Ahn, Ph.D., Team Leader:

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

Pediatric Decision Tree

Indication: Preservation of bone mineral density in patients with anorexia nervosa.

1. Is it reasonable to assume that pediatric patients are similar to adults with regard to disease progression?

- Unknown. Bone mineral loss is most often associated with drug-induced osteoporosis or aging. In patients with anorexia nervosa, the bone loss/preservation is multi-factorial. Patients with anorexia nervosa are also known to be estrogen deficient and often lack sufficient dietary intake of calcium.

2. Would you expect a similar response to intervention?

- ORTHO TRI-CYCLEN does not currently have an indication for "preservation of bone mineral density." However, conjugated estrogens are approved for post-menopausal osteoporosis. Its seems plausible that a low dose estrogen, as found in oral contraceptives, could be helpful in preventing bone loss.

3. Is there a pharmacodynamic measurement that can be used to predict efficacy?

- The accepted clinical endpoint for bone mineral density is assessment of bone mass density of the lumbar spine and hipbone using dual energy x-ray absorptiometry scans.

4. Since disease progression and response to pharmaceutical intervention are unknowns, and because the clinical endpoint is a long-term marker, has an efficacy / safety study been initiated this population?

- Yes. The sponsor conducted a randomized, multi-center, double blind, placebo controlled study designed to evaluate bone mineral density in pediatric patients with anorexia nervosa following treatment with either ORTHO TRI-CYCELN or placebo for 13 consecutive 28-day cycles. Approximately 120 female subjects were to be evaluated with equal randomization into each treatment group.

5. Has the sponsor conducted a stand-alone or add-on pharmacokinetic study?

The sponsor used an add-on component to their one-year clinical efficacy study. However, due to the sampling method used for this study, insufficient data was collected to make an adequate assessment of apparent clearance. No additional PK studies are planned.

SYNOPSIS

NAME OF SPONSOR/COMPANY: Johnson & Johnson Pharmaceutical Research & Development, L.L.C. NAME OF FINISHED PRODUCT: ORTHO TRI-CYCLEN 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.: CAPSS-169 **Title of Study: The Effect of ORTHO TRI-CYCLEN on Bone Mineral Density in Pediatric Subjects with Anorexia Nervosa: A Double-Blind, Placebo-Controlled Study**		
Principal Investigator: multicenter study		
Publication (Reference): none		
Studied Period (years): Clinical Conduct: Sample Analysis: 28 March – 01 July 2003		**Phase of development: 1**
Objectives: The objective of the study was to evaluate the efficacy and safety of ORTHO TRI-CYCLEN® on lumbar spine (l1-L4) and total hip bone mineral density (BMD) in pediatric subjects with anorexia nervosa. The objective of this report is to describe the steady-state pharmacokinetics of ORTHO TRI-CYCLEN® during Cycle 3 and to evaluate the effect of age and weight on trough concentrations of norelgestromin (NGMN), norgestrel (NG) and ethinyl estradiol (EE).		
Methodology: This was a randomized, multicenter, double-blind, placebo-controlled study designed to evaluate BMD in pediatric subjects with anorexia nervosa following treatment with either ORTHO TRI-CYCLEN® or placebo for 13 consecutive 28-day cycles. This report includes data collected during Days 4-7 and 18-21 of Cycle 3.		
Criteria for Evaluation: Trough samples (24 hours postdose) were drawn during Days 4-7 and 18-21 of Cycle 3 for analysis of serum NGMN, NG, and EE concentrations. A composite AUC_{24} was estimated using all concentrations for each analyte. C_{max} was observed from the serum concentration-time curves. CL/F was calculated as dose/AUC_{24}. C_{trough} concentrations were defined as between 16 to 26.5 and 16 to 27.5 hours for Days 4-7 and 18-21, respectively. C_{min} was calculated as the mean of the C_{trough} values for each visit. Pharmacokinetic data from this study are compared to data from a previous study of ORTHO TRI-CYCLEN in healthy adult females (NRGTRI-OC-115).		
Statistical Methods: Trough NGMN and NG serum concentrations during Days 4-7 (180 µg norgestimate) were dose normalized to 250 µg norgestimate. Descriptive statistics (mean, standard deviation, minimum and maximum) for the trough NGMN, NG, and EE serum concentration were calculated. Relationships between trough NGMN, NG, and EE serum concentrations and age, race and body weight or BMI were evaluated using regression models.		

SYNOPSIS (CONTINUED)

NAME OF SPONSOR/COMPANY:	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER	(FOR NATIONAL AUTHORITY USE ONLY)
Johnson & Johnson Pharmaceutical Research & Development, L.L.C.		
NAME OF FINISHED PRODUCT: ORTHO TRI-CYCLEN	Volume:	
NAME OF ACTIVE INGREDIENT(S): norgestimate/ethinyl estradiol	Page:	

SUMMARY – CONCLUSIONS

PHARMACOKINETIC RESULTS: Selected pharmacokinetic parameters were compared to data from a previous study of ORTHO TRI-CYCLEN in healthy adult females. Mean (SD) pharmacokinetic parameters from this study and NRGTRI-OC-115 are presented in the table below.

		180 µg NGM/35µg EE		250 µg NGM/35µg EE	
Analyte	Parameter	OC-115	CAPSS-169	OC-115	CAPSS-169
NGMN	C_{min} (ng/mL)	0.30 (0.09) to 0.35 (0.13)[a]	0.23 (0.07)[c]	0.45 (0.13) to 0.59 (0.11)[b]	0.37 (0.20)[d]
	C_{max} (ng/mL)	1.8 (0.46)	1.36	2.66 (0.47)	2.34
	AUC_{24} (ng•h/mL)	15.0 (3.88)	10.2	21.4 (3.46)	14.3[d]
	CL/F (L/h)	12.6 (3.49)	17.6	12.0 (1.79)	17.5
NG	C_{min} (ng/mL)	0.99 (0.47) to 1.33 (0.62)[a]	0.84 (0.44)[c]	2.33 (0.67) to 2.41 (0.96)[b]	2.10 (0.83)[d]
	C_{max} (ng/mL)	1.94 (0.82)	2.55	3.66 (1.15)	1.80
	AUC_{24} (ng•h/mL)	34.8 (16.5)	33.9	69.3 (23.8)	51.8[d]
	CL/F (L/h)	6.54 (3.46)	5.31	4.10 (1.64)	4.83
EE	C_{min} (pg/mL)	22.8 (11.4) to 23.9 (10.2)[a]	23.1 (9.84)[c]	21.3 (9.85) to 31.2 (17.6)[b]	33.2 (15.9)[d]
	C_{max} (pg/mL)	124 (39.5)	186	126 (34.7)	149
	AUC_{24} (pg•h/mL)	1130 (420)	1531	1090 (359)	1223[e]
	CL/F (L/h)	35.0 (12.9)	22.0	36.0 (13.5)	28.6

[a] Mean C_{min} values Days 6-8
[b] Mean C_{min} values Days 20-22
[c] Mean (SD) C_{trough} over 16-26.5 hours
[d] Mean (SD) C_{trough} over 16-27.5 hours
[e] $AUC_{0\text{-(average of 21 and 27.5)}}$

The effects of age and BWT on trough concentrations for NGMN, NG, and EE were found to be not statistically significant at 5% level of significance (p-value > 0.05). The effects of age and BMI on trough concentrations for NGMN, NG, and EE were also found to be not statistically significant at 5% level of significance (p-value > 0.05).

CONCLUSION:

The pharmacokinetic results in post-menarchal pediatric subjects with anorexia nervosa appear to be generally similar to those observed previously in healthy adult females. Age and BWT/BMI had no statistically significant effect on the trough concentration NGMN, NG, and EE

Date of the report: 03 September 2003

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Steve Johnson
3/1/04 04:42:08 PM
BIOPHARMACEUTICS

Hae-Young Ahn
3/8/04 01:39:17 PM
BIOPHARMACEUTICS