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.

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/s/

Steve Johnson
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Jim. Needs to be signed off. Review was previously signed off by Hae-Young. This is just the Exec Summary

Xiao-xiong Wei
3/12/04 11:09:03 AM
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