DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-697
IND 61,239

WRITTEN REQUEST
Amendment #2

The R.W. Johnson Pharmaceutical Research Institute
Attention: Tracy L. Healy, RN, MBA
Manager, Regulatory Affairs
P.O. Box 300
Raritan, New Jersey 08869-0602

Dear Ms. Healy:

Please refer to the following correspondences (dated January 9, February 10, March 13, and April 14, 2003) to IND 61,239 requesting changes to FDA's January 17, 2003, Amended Written Request for pediatric studies for ORTHO TRI-CYCLEN® (norgestimate/ethinyl estradiol) Tablets:

- January 9, 2003:
  Requests changes to **Entry** criteria.
- February 10, 2003:
  Requests changes to **Age group in which studies will be performed.**
- March 13 and April 14, 2003:
  Request changes in the **Type of studies** (Study 2) and related changes in **Age group in which studies will be performed** (Study 2) and **Study endpoints** (Study 2)

We reviewed your submissions and are amending the Amended Written Request. For convenience, the full text of the Written Request, as amended, follows. This Written Request supercedes the Written Request dated January 17, 2003.

- *Type of studies*:

  Study 1: A randomized, double-blind, placebo-controlled study to examine the efficacy and safety of ORTHO TRI-CYCLEN® in the treatment of adolescent patients with anorexia nervosa (AN).

  Study 2: A pharmacokinetics (PK) study to assess the single-dose and steady-state or alternatively, population PK of ethinyl estradiol (EE), norgestrel (NG), and norelgestromin (NGMN) in pediatric patients with AN.

- *Indications to be studied (i.e., objective of each study)*:

  Study 1: To assess the effect of ORTHO TRI-CYCLEN® on bone mineral density (BMD) of the lumbar spine and hip in patients with anorexia nervosa.

  Study 2: To assess the single-dose and steady-state or, alternatively, population PK of NGMN, NG, and EE in pediatric patients with AN.

- *Study design:*

  Study 1: A one-year (13 cycles), randomized (1:1), double-blind, placebo-controlled study of approximately 120 adolescent women with AN. Enrollment should target patients who have a lumbar spine BMD Z-score, matched for ethnicity, of less than zero at baseline. All patients should receive appropriate care consistent with current clinical practice standards for anorexia nervosa (e.g., medical and psychiatric interventions). The primary efficacy analyses should be performed after cycle 6. Although the Agency will consider submission of the primary efficacy and standard safety data through cycle 6 as satisfying this Written Request, all patients should continue in the study for an additional 6 months of double-blind therapy for a total of 13 cycles.

  Study 2: A randomized, open-label study in pediatric patients with AN, who should be administered 3 consecutive 28-day cycles of 0.18 mg norgestimate (NGM)/ 0.035 mg EE for Days 1 – 7, 0.215 mg NGM/0.035 mg EE for Days 8 – 14, 0.25 mg NGM/0.035 mg EE for Days 15 – 21, and inactive tablets for Days 22 - 28. Serial blood samples should be drawn at specified times upon single-dose administration and during the 3rd cycle of administration for measuring serum NGMN, NG, and EE concentrations.

  - Alternatively, a population PK study with an appropriate sampling approach (per the Guidance for Industry: Population Pharmacokinetics document of Feb. 1999) may be conducted as a substudy of Study 1. This population PK substudy must use an appropriate sampling plan as per the February 1999, Guidance for Industry: Population Pharmacokinetics guidance.

- *Age group in which studies will be performed*:

  Study 1: Pediatric patients 12 through 17 years of age.

  Study 2: Eighteen completed patients who are 12 through 17 years of age for the single-dose and steady-state PK study. Alternatively, at least 40 patients, who are 12 through 17 years of age, for the population PK study.

- *Entry criteria (Studies 1 and 2)*:

- Patients should be 12 through 17 years of age, and have AN as defined by DSM-IV criteria. Patients may not be pregnant or lactating or using any form of hormonal birth control, including parenteral forms of contraception such as levonorgestrel intrauterine system, levonorgestrel implants, and medroxyprogesterone acetate injectable suspension.

  Exclusion criteria should include:

  1. Smoke 15 or more cigarettes per day
  2. History of venous thromboembolic disease
  3. Uncontrolled hypertension
  4. History of liver tumor
  5. History of cholestatic jaundice
  6. Any impairment in liver or kidney function
  7. Diabetes mellitus with vascular involvement
  8. Primary amenorrhea due to a condition other than anorexia nervosa
  9. Current use of bisphosphonates, thiazides, or anti-seizure medication
  10. TSH outside of the normal range

- *Study endpoints*:

  Study 1: The primary endpoint is a comparison of the absolute change in lumber spine BMD from baseline to the end of Cycle 6 between the ORTHO TRI-CYCLEN® and placebo groups. Secondary endpoints should include the mean percent changes in lumbar spine and total hip BMD from baseline to the end of Cycle 6 and the mean percent changes in lumbar spine and total hip BMD from baseline to the end of Cycle 13. The mean percent change in body weight from baseline to the end of Cycles 6 and 13 should also be considered secondary endpoints.

  Study 2: Single-dose and steady-state NGMN, NG, and EE PK parameters such as $AUC_{0-\infty}$, AUC_{0-24h}, CL/F, V_d/F, C_{max}, T_{max}, λ_z, $t_{1/2}$, and their descriptive statistics should be evaluated. The effect of demographic covariates (for example age, race, and body weight) on the PK parameters should also be evaluated. Alternatively, for the population PK study, there should be an estimation of clearance for NGMN, NG, and EE. The effect of demographic covariates (for example age, race, and body weight) on the PK parameters should be evaluated in the population PK approach.

- *Drug information*
  - *dosage form*: Tablet
  - *route of administration*: Oral
  - *regimen*: One tablet per day from a 28-day blistercard for 13 cycles

- Use an age-appropriate formulation in the studies described above. Any unapproved formulation will need to be supported by study of relative bioavailability; these studies may be conducted in adults. A formulation you develop for use in children should meet standards for marketing approval. If you cannot develop a potentially marketable formulation, you will need to document the attempt to do so, and the Agency will consider another formulation that is standardized and palatable. Full study reports of any relative bioavailability studies should be submitted to the Agency.

- *Drug-specific safety concerns*: The primary safety concern with ORTHO TRI-CYCLEN® is vascular disease (i.e., venous thromboembolism, myocardial infarction, cerebrovascular accident. The risk for cardiovascular disease increases with the age of the patient and with heavy smoking (15 or more cigarettes per day). Patients with a history of venous thromboembolic or cardiovascular disease should be excluded from the study, as should girls who smoke 15 or more cigarettes per day.

- *Statistical information, including power of study and statistical assessments*:

  The two treatment groups should be compared on the primary endpoint using analysis of covariance (ANCOVA). The ANCOVA model should include treatment and center as factors and screening total lumbar spine BMD as a covariate. The same analysis technique should also be used for the analysis of hip BMD.

  Sixty patients per group is expected to provide 80% power to detect a 0.050 gm/cm^2 difference in total lumbar spine BMD change from baseline between the two treatment groups at the end Cycle 6 with a common SD = 0.096 gm/cm^2.

  The primary analysis population is the intent-to-treat population consisting of all randomized patients with baseline and on-treatment data.

- *Labeling that may result from the studies*: Appropriate sections of the label may be changed to incorporate the findings of the studies.
- *Format of reports to be submitted*: Full study reports not previously submitted to the Agency addressing the issues outlined in this request with full analysis, assessment, and interpretation. In addition, the reports are to include information on the representation of pediatric patients of ethnic and racial minorities.
- *Timeframe for submitting reports of the studies*: Reports of the above studies must be submitted to the Agency on or before September 26, 2003, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act. The Agency will consider the primary efficacy and standard safety data submitted for the first 6 cycles as fulfilling this Written Request. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that has not expired at the time you submit your reports of the studies in response to this Written Request.
- *Response to Written Request:* As per the Best Pharmaceuticals for Children Act, section 4(A), within 180 days of receipt of this Written Request, you must notify the Agency as to your intention to act on the Written Request. If you agree to the request, then you must indicate when the pediatric studies will be initiated.

Please submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY**" in large font, bolded type at the beginning of the cover letter of the submission. Notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Clearly mark your submission "**PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the studies should be submitted as **a new drug application (NDA)** with the proposed labeling changes you believe would be warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED**" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger, to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission. We will notify you in writing if we agree to any changes to this Written Request.

We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits in the pediatric population.

If you have any questions, call Pat Madara, Regulatory Project Manager, at 301-827-6416.

Sincerely,

{See appended electronic signature page}

Robert J. Meyer, M.D.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

Robert Meyer
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