



NDA 19-697
IND 61,239

**WRITTEN REQUEST
Amendment #1**

The R.W. Johnson Pharmaceutical Research Institute
Attention: Tracy L. Healy, RN
Manager, Regulatory Affairs
920 Route 202
P.O. Box 300
Raritan, New Jersey 08869-0602

Dear Ms. Healy:

Please refer to your correspondence to IND 61,239 dated November 15, 2002, requesting changes to FDA's November 12, 2002, Written Request for pediatric studies for ORTHO TRI-CYCLEN[®] (norgestimate/ethinyl estradiol) Tablets.

We reviewed your submission and are amending "Study 1" of the *Study design* section of the Written Request. All other terms stated in our Written Request issued on November 12, 2002, remain the same.

- *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 PK of ethinyl estradiol (EE), norgestrel (NG), and norelgestromin (NGMN) in post-menarcheal 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 PK of NGMN, NG, and EE in post-menarcheal 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. At baseline, all patients should be ~~no more than 70% of ideal body weight~~ have a lumbar spine BMD Z-score, matched for ethnicity, of less than zero. All patients should receive medical and psychiatric care consistent with current clinical practice standards. 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 post-menarcheal 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.

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

Study 1: Pediatric patients who are post-menarcheal and 12 through 16 years of age.

Study 2: Eighteen completed patients who are 12 through 16 years of age.

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

Patients should be post-menarcheal, 12 through 16 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
9. Current use of bisphosphonates, thiazides, or anti-seizure medication
10. TSH outside of the normal range
11. Resting heart rate below 60 beats per minute

- *Study endpoints:*

Study 1: The primary endpoint is a comparison of the absolute change in lumbar 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.

- *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/cm² difference in total lumbar spine BMD change from baseline between the two treatment groups at the end of Cycle 6 with a common SD = 0.096 gm/cm².

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. 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.

Reports of the studies that meet the terms of the Written Request dated November 12, 2002, as amended by this letter 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.

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. Please 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.

Submit reports of the studies as a **new drug application (NDA)** or as a **supplement to an approved NDA** with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, 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. In addition, 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. Clearly mark submissions of proposed changes to this request **“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 to the pediatric population.

If you have any questions, call Samuel Y. Wu, Pharm.D., 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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