DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-130; 21-131; 21-132
IND 49,195; 55,618

Pharmacia & Upjohn Company
Attention: Robert S. Gremban
Regulatory Affairs Manager
7000 Portage Road
Kalamazoo, MI 49001

Dear Mr. Gremban:

Please refer to your correspondence dated August 24, 2001, requesting changes to the December 22, 1999, Written Request for pediatric studies for linezolid. We also refer to the amended Written Request for pediatric studies dated February 28, 2002.

We reviewed your proposed changes and are amending the Written Request. For convenience, the full text of the Written Request, as amended, follows. This Written Request supercedes the Written Request dated December 22, 1999 and the amended Written Request dated February 28, 2002.

- *Type of studies (e.g., double-blind, randomized, parallel group, safety, and/or pk):*

  Study #1: "Assessment of Linezolid Pharmacokinetics in Full Term and Pre-Term Neonates."
  Study #2: "A randomized, blinded comparison of the safety and efficacy of oral linezolid vs. a cephalosporin for treatment of skin and skin structure infections in pediatric patients aged 3 months to 18 years."
  Study #3/4: "A randomized, open-label comparison of IV linezolid/oral linezolid and IV vancomycin (with other IV/oral antibiotic switch, if appropriate) in suspected resistant gram positive infections in pediatric patients." and "A Prospective Study of Vancomycin-Resistant Enterococcal Infections in Pediatric Patients."
  Study #5: "A Randomized, Comparative Trial of Linezolid vs. Vancomycin in Pediatric Patients with CSF Shunt Infections."

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

  Study #1: Objective – To assess the pharmacokinetics of linezolid in full-term and pre-term neonates following a single 10 mg/kg intravenous dose of linezolid.
  Study #2: Objectives – To assess the comparative efficacy, safety and tolerance of oral linezolid vs. oral cephalosporin for the treatment of skin and skin structure infections in pediatric patients.
  Study #3/4: Objectives – To evaluate the comparative tolerance of linezolid and vancomycin in the empiric treatment of suspected resistant gram-positive bacterial infections, including methicillin-resistant Staphylococcus aureus (MRSA), other methicillin-resistant Staphylococcus species (MRSS), and penicillin-resistant Streptococcus pneumoniae (PRSP), in pediatric patients. Information on the safety of linezolid and experience with the use of linezolid for VRE infections in pediatric patients will also be gathered in a separate, non-comparative portion of the study. A

secondary objective is to study population pharmacokinetics in pediatric patients receiving linezolid.
Study #5: Objectives – To evaluate the comparative tolerance of linezolid and vancomycin in the treatment of CSF shunt infections due to gram-positive bacteria in the pediatric population. The study may primarily enroll patients with CSF shunt infections due to coagulase-negative staphylococci.

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

  Study #1: Male and female infants less than 3 months of age, stratified by post-conceptional age (< 34 weeks and ≥ 34 weeks). Further stratification based on other factors (e.g., post-natal age) may also be performed.
  Study #2: Pediatric patients (male and female) from 5 through 17 years of age.
  Study #3/4: Pediatric patients (male and female) from birth through 11 years of age.
  Study #5: Pediatric patients (male and female) from birth through 17 years of age.

- *Study endpoints*

  Study #1: Pharmacokinetic parameters will be determined from assessments of linezolid plasma concentrations. Tolerance of a single dose of linezolid in neonates.
  Study #2-5: Clinical efficacy, microbiological response, and safety are the endpoints of interest for these studies.

- *Drug information*

  dosage form: Intravenous Solution, Oral Tablets, and Oral Suspension

  route of administration: Intravenous and/or Oral

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

  Study #1: A comparison between Term and Pre-term groups will be made for pharmacokinetic parameters. The study should include at least 12 subjects with post-conceptional age < 34 weeks and 12 subjects > 34 weeks gestation.
  Study #2: The study should include at least 240 subjects in each treatment arm. Assuming a 90% success rate and 60% clinical evaluability rate and using a 2-sided test with α=5% and power=80%, this target enrollment will provide a sufficient number of clinically evaluable patients to demonstrate equivalence between the two treatment groups to within 10%. All patients may be treated with oral linezolid or comparator.
  Study #3/4: The total enrollment should include at least 160 patients. At least 40 subjects should have vancomycin-resistant enterococcal infections treated with linezolid. At least 30 patients should be 3 months of age or less and at least 10 of these young infants should have vancomycin-resistant enterococcal infections treated with linezolid.
  Study #5: The study should have a total enrollment of at least 50 patients with CSF shunt infections. This number of patients is selected to provide preliminary information on the tolerance and efficacy of linezolid for CSF shunt infections.

- *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 addressing the issues outlined in this request with full analysis, assessment, and interpretation should be provided for all requested studies. INCLUDE OTHER INFORMATION AS APPROPRIATE.

- *Timeframe for submitting reports of the studies:* Reports of the above studies must be submitted to the Agency on or before September 30, 2004, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act. Please remember that pediatric exclusivity extends only to existing patent protection or exclusivity that has not expired or been previously extended at the time you submit your reports of studies in response to this Written Request.

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 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 Ms. Beth Duvall-Miller, Regulatory Project Manager, at (301) 827-2125.

Sincerely,

{See appended electronic signature page}

Mark Goldberger, M.D.
Acting Director
Office of Drug Evaluation IV
Center for Drug Evaluation and Research