HFD-104 /D.MURPHY

NDA 21-130
NDA 21-131
NDA 21-132

Pharmacia & Upjohn Company
Attention: Peter J. DiRoma, Regulatory Manager
7000 Portage Road
Kalamazoo, MI 49001-0199

DEC 22 [illegible]

Dear Mr. DiRoma:

Reference is made to your revised Proposed Pediatric Study Request (PPSR) submitted on July 12, 1999, for linezolid (U-100766) to investigational new drug applications (IND) 49,195 and 55,618. We also refer to your original PPSR submitted March 15, 1999, our comments on the proposed studies provided in the Agency's letter dated May 21, 1999, and the teleconference on June 14, 1999.

To obtain needed pediatric information on linezolid, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), that you submit information from the following studies:

- *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: "A randomized, open-label comparison of IV linezolid/oral linezolid and IV vancomycin/oral cephalosporin in suspected resistant gram positive infections in pediatric patients 17 years of age and younger."
  Study #4: "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."
  Study #6: "A Randomized, Comparative Trial of Linezolid vs. Vancomycin in Combination with a Cephalosporin for the Treatment of Acute Bacterial Meningitis."

- *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 and/or intravenous linezolid vs. oral and/or intravenous cephalosporin in for the treatment of skin and skin structure infections in pediatric patients.
Study #3: 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), penicillin-resistant *Streptococcus pneumoniae* (PRSP), and vancomycin-resistant *Enterococcus* species (VRE), in pediatric patients. A secondary objective is to study population pharmacokinetics in pediatric patients receiving linezolid.
Study #4: Objectives – To provide information on the safety of linezolid and provide experience with use of linezolid for VRE infections in pediatric patients.
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.
Study #6: Objectives – To evaluate the comparative tolerance of linezolid and vancomycin in combination with a cephalosporin for treatment of acute bacterial meningitis due to *Streptococcus pneumoniae* in the pediatric population.

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

  Study #1: Male and female infants less than 3 months of age, stratified by gestational age (≥ 37 weeks, 30-36 weeks, and <30 weeks gestation).
  Study #2: Pediatric patients (male and female) from 3 months through 17 years of age. Enrollment will be stratified into the following age groups: 3 to 23 months, 2 to 11 years, and 12 to17 years. Enrollment will be stopped in the oldest age group if enrollment in that group exceeds 30%.
  Study #3, 4, 5: Pediatric patients (male and female) from birth through 17 years of age.
  Study #6: Pediatric patients (male and female) from 2 months 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 #2-6: 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 8 term infants (≥ 37 weeks gestation), 6 infants between 30 and 36 weeks gestation, and 6 infants <30 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%. Enrollment in the oldest age group (12 to17 years) should not exceed 30% of total enrollment. At least 50 subjects in each treatment arm should receive intravenous therapy.
  Study #3: The study should have a total enrollment of at least 120 patients. At least 20 patients should be 3 months of age or less. This number of patients is selected to provide adequate information on the tolerance of linezolid for gram positive infections.
  Study #4: The study should include at least 40 subjects with Vancomycin-Resistant Enterococcal infections who receive linezolid. At least 10 patients should be 3 months of age or less. This number of patients is selected to provide adequate information on the tolerance of linezolid for VRE infections.
  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.
  Study #6: The study should have a total enrollment of at least 50 patients with meningitis due to *Streptococcus pneumoniae*. This number of patients is selected to provide adequate information on the tolerance and efficacy of linezolid for pneumococcal meningitis.

- *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. 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.

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. Please 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 or as a supplement to an approved 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, please 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. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

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

Sincerely yours,

Sandra L. Kweder, MD
Acting Director
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

cc:

Archival NDA 21-130, 21-131, 21-132
Archival IND 49,195, 55,618
HFD-520/Division file
HFD-520/RPM/B. Duvall-Miller
HFD-520/MO/J. Alexander
HFD-520/MO/D. Ross
HFD-104/ActOffice Director/S. Kweder
HFD-600/Office of Generic Drugs
HFD-2/M.Lumpkin
[redacted]
HFD-002/T.Crescenzi

Concurrence:
HFD-520/[redacted]CPMS/F. LeSane FVL 12-16-99
HFD-520/MO/J. Alexander JA 12/17/99
HFD-520/SMO/J. Soreth
HFD-520/Dir/G. Chikami 12/20/99
HFD-104/ActDir/S. Kweder 12/21/99

Drafted by: bdm/12/6/99/M:\PPSR\21130.DOC
Initialed by:
Final: BDM 12/16/99

PEDIATRIC WRITTEN REQUEST LETTER
INFORMATION REQUEST (IR)