DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

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

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

Dear Mr. Gremban:

Reference is made to your correspondence dated November 2, 2001, requesting changes to FDA's December 22, 1999 Written Request for pediatric studies for Linezolid (PNU-100766).

We have reviewed your proposed changes and are amending the below listed sections of the Written Request (WR). All other terms stated in our Written Request issued on December 22, 1999 remain the same.

- *All Sections:*

  The request for Study #6 is deleted from all sections of the WR.

  Instead of separate Studies #3 and #4, the sponsor may perform a single study that includes the elements of and meets the combined enrollment for these studies, as provided below.

- *Types of Studies:*
  The comparator for Studies #3 and #4 (or a single study combining these two studies) is amended as follows. For patients with vancomycin-resistant enterococcal infections, no comparator group is required. For other resistant Gram-positive infections, IV vancomycin may be used as a comparator with switch to other IV and/or oral antibiotics, if appropriate. A specific comparator agent is not required to meet the terms of the WR.

- *Indications to be studied*:
  The objectives for Study #2 are amended as follows. This study may be performed with oral dosing only for linezolid and the comparator. Intravenous treatment is not required to meet the terms of the WR.

  The objectives of Study #5 are amended as follows. The study may primarily enroll patients with CSF shunt infections due to coagulase-negative staphylococci.

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

  Stratification for Study #1 is changed to post-conceptional age groups of <34 weeks and ≥ 34 weeks, rather than gestational age (≥ 37 weeks, 30-36 weeks, and <30 weeks gestation). Further stratification based on other factors (e.g., post-natal age) may also be performed.

  Study #2 may enroll patients aged 5-17 years. Stratification of patients and limited enrollment in the oldest age group are not required to meet the terms of the WR.

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

  For Study #1, the specific enrollment criteria are modified. The study should include at least 12 subjects with post-conceptional age <34 weeks and 12 subjects ≥ 34 weeks.

  For Study #2, enrollment in the oldest age group (12 to 17 years) is not limited to <30% of total enrollment. Intravenous therapy is no longer required for a subset of patients. All patients may be treated with oral linezolid or comparator.

  For a single study that combines Studies #3 and #4, the total enrollment should include at least 160 patients. At least 40 of these patients should have vancomycin-resistant enterococcal infections treated with linezolid. At least 30 patients in this study 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.

Reports of the studies that meet the terms of the Written Request dated December 22, 1999, as amended by this letter must be submitted to the Agency on or before September 30, 2004, in order to possibly qualify for pediatric extension under Section 505A of the Act.

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. 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.

Reports of the studies should be submitted to **a new drug application (NDA) 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 final 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 to the pediatric population.

If you have any questions, contact LTJG Raquel Peat, Regulatory Health Project Manager, at (301) 827-2125.

Sincerely yours,

{See appended electronic signature page}

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