D. Murphy - 104

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

IND 48,485

MAY 15 2000

Merck & Company, Inc.
Attention: Michelle W. Kloss, PhD
Director, Regulatory Affairs
P. O. Box 4, BLA-20
West Point, PA 19486-0004

Dear Dr. Kloss:

Reference is made to your Proposed Pediatric Study Request (PPSR) submitted on February 10, 2000 for MK-0826 to IND 48,485.

To obtain needed pediatric information on MK-0826, 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:***

  Study 1: An open-label, intravenous study to evaluate the plasma concentration profiles of MK-0826 in pediatric patients

  Study 2: An open-label, multicenter study to evaluate the cerebrospinal fluid concentration profile of MK-0826 after intravenous administration in pediatric patients with meningitis

  Study 3: A prospective, multicenter, randomized, comparative study to evaluate the safety, local tolerability and clinical outcome of MK-0826 versus comparator (to be named) in pediatric patients with hospital acquired pneumonia, intra-abdominal infection, or acute pelvic infection

  Study 4: A prospective, multicenter, double-blind, randomized, comparative study to evaluate the safety, local tolerability and clinical outcome of MK-0826 versus ceftriaxone sodium in pediatric patients with community acquired pneumonia, complicated urinary tract infection, or skin infection

  Study 5: A prospective, multicenter, randomized, comparative study to evaluate the safety, local tolerability and efficacy of MK-0826 versus comparator (to be named) in pediatric patients for the treatment of acute bacterial meningitis

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

  Study 1: Objective - To assess the pharmacokinetics, safety, and tolerability of MK-0826 in pediatric patients following a single intravenous dose of 20 mg/kg or 40 mg/kg of MK-0826.

  Study 2: Objective – To assess the pharmacokinetics of MK-0826 in cerebrospinal fluid in pediatric patients following a single intravenous dose of 20 mg/kg or 40 mg/kg of MK-0826.

  Study 3: Objective – To assess the clinical outcome, safety, and tolerance of intravenous MK-0826 to an appropriate unblinded comparator for the treatment of hospital acquired pneumonia, intra-abdominal infection, and acute pelvic infection in pediatric patients.

  Study 4: Objective – To assess the clinical outcome, safety, and tolerance of intravenous MK-0826 to ceftriaxone, in a double-blind study, for the treatment of community acquired pneumonia, complicated urinary tract infection, and skin and soft tissue infections in pediatric patients.

  Study 5: Objective – To assess the efficacy, safety, and tolerance of intravenous MK-0826 to an appropriate comparator in a statistically adequate and well controlled multicenter trial for the treatment of acute bacterial meningitis in pediatric patients

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

  Studies 1, 2, 3, 4, 5: Each study should enroll male and female pediatric patients aged 3 months to 17 years.

  Studies 1, 2, 4, 5: Each study should enroll pediatric patients approximately evenly distributed among the following age strata: 3 to 23 months, 2 to 12 years, and 12 to 17 years.

- ***Study endpoints***

  Study 1: Pharmacokinetic parameters will be determined from assessments of MK-0826 plasma concentrations. Safety and tolerability endpoints will be determined.

  Study 2: Cerebrospinal fluid pharmacokinetic parameters in pediatric patients with meningitis will be determined from assessments of MK-0826 CSF and plasma concentrations. Safety and tolerability endpoints will be determined.

Study 3, and 4: Clinical outcome, microbiological response, and safety will be the endpoints for these studies.

Study 5: Clinical efficacy, microbiological response, and safety will be the endpoints for this study.

- ***Drug information***

  dosage form: Intravenous solution

  route of administration: Intravenous

  regimen: The regimen will be determined based on results from Studies 1 and 2.

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

  Study 1: The study should include at least 48 pediatric patients approximately uniformly distributed within each age strata and gender to determine, at a minimum, the $AUC_{(0-\infty)}$, clearance, and $t_{1/2}$ for MK-0826.

  Study 2: The study should include adequate numbers of pediatric patients to determine the time CSF concentration is > 0.06 ug/mL, AUC_{CSF}, C_{maxCSF}, and $t_{1/2CSF}$ for MK-0826.

  Study 3: The study should include at least 75 pediatric patients with intra-abdominal infection, hospital acquired pneumonia or acute pelvic infection in the MK-0826 arm. The numbers of patients should be approximately evenly distributed among the three types of infections.

  Study 4: The study should include at least 100 patients with community acquired pneumonia, at least 100 patients with complicated urinary tract infection, and at least 100 patients with skin and soft tissue infection in the MK-0826 arm.

  Study 5: The study should be a statistically adequate and well-controlled multicenter trial that establishes equivalence or superiority to an approved product.

- ***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.

- ***Timeframe for submitting reports of the studies***: Reports of the above studies must be submitted to the Agency on or before November 30, 2004. Please keep *in mind that pediatric exclusivity only extends existing patent protection or* exclusivity that has not expired or been previously extended at the time you submit your reports of the 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. Frances LeSane, Regulatory Health Project Manager, at (301) 827-2125.

Sincerely Yours,

5/15/00

Diane Murphy, M.D.
Director
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Archival IND 48,485
HFD-520/Division file
HFD-520/MO/JMulinde
HFD-520/CHEM/JTimper
HFD-520/TLCHEM/DKatague
HFD-520/TLPharm/Toxr/ROsterberg
HFD-520/Pharm/Tox/KSeethaler
HFD-520/TLMicro/ASheldon
HFD-520/Micro/HSilver
HFD-520/TLClinPharm/FPelsor
HFD-520/STAT/GRochester
HFD-520/TLStat/DLin
HFD-520/DepDivDir/LGavrilovich
HFD-600/Office of Generic Drugs
HFD-2/MLumpkin
HFD-104/DMurphy
HFD-104/TCrescenzi
HFD-520/PM/FVLeSane

Drafted by: JM/FVL/4-6-00/4-20-00
Initialed by:
Final: **5-10-00**

IND 48,485 WR.doc

Concurrence Only:
HFD-520/CPMS/FVLeSane
HFD-520/DivDir/GChikami 5/12/2000
HFD-520/TLMO/ARakowsky 5-10-00