

Rationale:

The last 30 years have seen a dramatic rise in antibiotic resistance by common bacterial pathogens. This increasing microbial drug resistance requires the use of antibiotics with broad spectrum activity that can be relied upon when first line antimicrobials fail.

Imipenem-cilastatin and meropenem are carbapenems with widespread pediatric use. Imipenem-cilastatin has been labeled for use in pediatric patients (including newborns) for many serious infections such as pneumonia, skin and skin structure infections, osteomyelitis and complicated intra-abdominal infections. Meropenem is labeled for pediatric patients from three months of age through adolescence as single agent antimicrobial therapy for meningitis and complicated intra-abdominal infections, and is a recommended option for monotherapy of high severity complicated intra-abdominal infections in adults⁹.

There is significant off-label use of meropenem in newborn and infant patients younger than three months of age. For example, in 2003, the Child Health Corporation of America Pediatric Health Information System dataset (inpatient data from 31 free-standing children's hospitals) mentions 589 uses in this population for serious infections such as necrotizing enterocolitis and peritonitis. This off-label use occurs despite the lack of adequate pharmacokinetic, dosing, tolerability and safety data for this vulnerable age group. Collecting this data through the study of newborns and young infants with complicated intra-abdominal infections will fill this knowledge gap.

Complicated intra-abdominal infections are heterogeneous in etiology. By definition, these infections are characterized by systemic inflammation and an intra-abdominal process extending into the peritoneal space that necessitates a surgical or percutaneous drainage procedure. The post-procedure findings of purulent exudates with inflamed or necrotic tissue confirms the diagnosis⁸. Examples of intra-abdominal processes in the youngest patients that can result in peritonitis include: necrotizing enterocolitis, bowel obstruction with perforation, Hirschsprung's disease with perforation, meconium ileus with perforation, and others.

Though complicated intra-abdominal infections in the youngest pediatric patients are more severe than in older infants and children, the bacterial pathogens that contribute to this disease process are similar. Thus, the efficacy of antimicrobial agents such as meropenem for the treatment of complicated intra-abdominal infections can be extrapolated from older children to the youngest.

Administration of antimicrobials prior to enrollment is a common problem in clinical trials of antibiotics and a concern for the studies requested below. The onset of complicated intra-abdominal infections in the youngest patients may range from an acute and fulminant presentation to a more indolent process that progresses over hours to days. The indolent presentation often begins with a non-specific pattern of signs and symptoms suggestive of an infectious process; only later does the intra-abdominal nature of the infection become apparent. During this period of sub-acute infection, infants with a possible intra-abdominal infection may receive antibiotic treatment. Such early antibiotic treatment complicates the design of clinical trials to evaluate efficacy and safety of specific antimicrobials. As a result, clinical trials of complicated infections routinely require a design strategy that minimizes the influence of early therapy on the later interpretation of safety and efficacy data.

We request the following studies of meropenem for use in complicated intra-abdominal infection in preterm and term newborn and infant patients younger than three months of age.

Indication to be studied:

Meropenem for the treatment of complicated intra-abdominal infections in preterm and term newborn and infant patients younger than 91 days of age.

Types of Studies and Study Objectives:

1. Single Dose Pharmacokinetic (PK), Safety, and Tolerability Study (Study 1):
To characterize single dose meropenem PK, safety, and tolerability in preterm and term newborn and infant patients with complicated intra-abdominal infections.
2. Safety and Multi-dose PK Study (Study 2):
 - a. To characterize the safety profile of meropenem in the treatment of complicated intra-abdominal infections in comparison to an alternative standard antibiotic regimen.
 - b. To characterize meropenem multiple-dose PK in patients with complicated intra-abdominal infections.
 - c. To assess collected efficacy data for meropenem for the treatment of complicated intra-abdominal infections.

Age group in which studies will be performed:

Study 1:

Premature to term gestation male and female newborn and infant patients who are younger than 91 days of age and have a suspected or early complicated intra-abdominal infection. These patients must be subdivided into the following four groups:

- Group 1: Gestational age at birth below 32 weeks and post-natal age younger than 8 days;
- Group 2: Gestational age at birth below 32 weeks and post-natal age of 8 days through 90 days;
- Group 3: Gestational age at birth 32 weeks or older and post-natal age younger than 8 days; and
- Group 4: Gestational age at birth 32 weeks or older and post-natal age of 8 days through 90 days.

Study 2:

Premature and term gestation newborn and infant patients younger than 91 days of age with complicated intra-abdominal infections, including patients from all four groups described above. For the PK substudy, patients in study 2 should be enrolled based on the age groups described above under study 1.

Inclusion Criteria:

Study 1 will include male and female patients with physical, radiological, and/or bacteriological findings of a suspected or early complicated intra-abdominal infection who require antimicrobial therapy and who have no physiological changes that would significantly alter the elimination of meropenem.

Study 2 will include male and female patients with physical, radiological, and/or bacteriological findings of a complicated intra-abdominal infection as defined in the “Rationale” section. The

protocol will specify additional criteria for study inclusion/exclusion, and will specifically address the presence of viral or fungal infections and the method for addressing antibiotic administration prior to enrollment or randomization.

Study Design:

PK studies within Study 1 and Study 2 will utilize sparse sampling and a population PK approach to minimize blood loss for individual patients. Sparse blood samples should be obtained at defined time intervals rather than at fixed times. Bio-analytical methods to determine meropenem concentrations must be capable of evaluating the smallest possible sample volumes (preferably less than 100 microliters). Measurements of renal function are to be done in conjunction with PK determinations. Multiple-dose PK will be assessed in a subset of patients in Study 2. Confirmation of adequate steady-state levels is a primary endpoint of Study 2.

Study 1 will evaluate at least three clinically relevant doses of meropenem in the four subgroups described in the “Age group in which studies will be performed” section above. The doses to be studied will be guided by extrapolation from the data of meropenem use in older infants and will be justified in the protocol. For example, one possible range of single doses is 10 mg/kg, 20 mg/kg, and 40 mg/kg^{1,3}. These studies are most commonly conducted as an add-on dose of study drug among patients who are already receiving antimicrobial therapy.

Study 2 will be a multi-center, prospective, randomized, parallel-arm, preferably blinded, and active controlled safety study of meropenem for the treatment of complicated intra-abdominal infections in comparison to an alternative standard antibiotic regimen. The definition of complicated intra-abdominal infections for this study is provided in the “Rationale” section above and has been derived from the current Infectious Diseases Society of America (IDSA) guidelines⁸ with modifications to adjust the definition for the newborn and infant population in this study. Investigators are strongly encouraged to identify and incorporate methods for blinding to treatment assignment into the design and analysis. Efficacy data will also be collected.

Currently meropenem is approved for single-agent antimicrobial therapy for complicated intra-abdominal infections in pediatric patients older than three months. The protocol will specify a standard antibiotic regimen for both study arms, a rationale for each antibiotic to be used, and whether meropenem will be used alone or in combination with a second antibiotic. If a second antibiotic is used with meropenem, a microbiological justification for its use must be provided and this additional antibiotic must also be included in the comparator regimen. The protocol will also justify the selection of antibiotics for the comparator arm which may consist of two or more antimicrobial agents.

As mentioned in the “Rationale”, antibiotic administration prior to enrollment or randomization may occur and will complicate the interpretation of safety and efficacy data collected for meropenem. Therefore, the protocol must be designed to minimize the influence of prior antibiotic exposure on the evaluation of meropenem safety and efficacy.

The empiric use of vancomycin within 72 hours prior to enrollment is strongly discouraged. Any change in antibiotic therapy while on study drug will be considered a treatment failure except the addition of vancomycin to treat organisms that require it and have been isolated from a non-abdominal source (including coagulase-negative staphylococcus and methicillin resistant *Staphylococcus aureus*). The protocol must specify how all use of vancomycin will be addressed in the design, conduct and analysis of this study.

The protocol must specify and justify the duration of antibiotic therapy. At four to six weeks following the initial dose, all patients must be followed for safety and those patients who completed the full

treatment course of study drug must have an efficacy determination⁸. The protocol will specify and justify other criteria for determining treatment success or failure and their related efficacy endpoints.

Preferably patients will be enrolled and randomized either at the time of surgery or peritoneal drain placement or immediately afterwards. For these patients, fungal, aerobic and anaerobic bacterial cultures of peritoneal fluid and/or intraoperative specimens must be obtained prior to administration of study drug. Patients may be enrolled and randomized pre-operatively if the complicated intra-abdominal infection is confirmed by surgical intervention within 24 hours of study entry and intraoperative specimens are obtained for culture as described above. Investigators must specify criteria for microbiological cure or resolution and are strongly encouraged to obtain repeat peritoneal fluid and other cultures.

The protocol will address how patients with prior seizures will be followed.

The protocols for Study 1 and Study 2 will be submitted to and assessed by the FDA and agreed upon prior to study initiation. Results from the single dose PK studies of meropenem (Study 1) will be used to guide dosing in Study 2 and must be reviewed by the FDA prior to initiating Study 2.

Criteria for withdrawal of individual patients from Study 1 and 2 must be defined in the protocol. An independent Data Monitoring Committee (DMC) must be established for these studies. The study stopping rules used by the DMC must be specified in the protocol.

Number of Patients:

Study 1: A sufficient number of patients to conduct a dose-ranging study and to adequately characterize single-dose PK of meropenem in the four gestational and post-natal age groups described in the section entitled, "Age group in which studies will be performed" must be studied. A minimum of 12 patients per group per dose must be studied. Investigators are strongly encouraged to assure an even distribution of gestational and post-natal age within each PK study group.

Study 2: This study is powered to assess safety as the primary endpoint and will enroll a sufficient number of patients with complicated intra-abdominal infections to detect serious adverse events in the meropenem arm occurring at the frequency of one percent. Efficacy data will be collected, however the study is not powered to be an efficacy trial. Each study arm must enroll a minimum of 300 treated patients who receive 48 hours or more of study drug. Patients who drop out of the trial prior to 48 hours of study treatment should be replaced until the minimum of 300 patients per study arm is achieved. Patients who receive at least one dose of study drug should be followed for safety until the trial is completed. The multi-dose PK study must include at least 12 patients from each of the four age groups described for Study 1. If enrollment of patients within any of these four age groups is unfeasible, then the sponsor/investigator must formally discuss this enrollment problem with the FDA.

Statistical information:

These studies must have a pre-specified detailed statistical analysis plan appropriate for the study design and outcome measures. The plan will be discussed with the FDA and agreed upon prior to initiating studies. Descriptive statistics of the PK data must also be provided and dose-response relationships and relationships between PK parameters and patient characteristics including renal function will also be explored.

Assessment Parameters:

Pharmacokinetics (All studies): The plasma clearance and volume of distribution of meropenem will be calculated and other PK parameters such as the maximum plasma concentration (C_{max}), time of C_{max} (T_{max}), area under the plasma concentration-time curve from zero to the last quantifiable concentration (AUC_{0-t}), the elimination rate constant (K_e), terminal elimination half-life ($t_{1/2}$), and AUC extrapolated to infinity ($AUC_{0-\infty}$), will be determined to the extent possible. The sponsor/investigator is strongly encouraged to study the correlation between pharmacokinetic parameters and pharmacodynamic parameters such as MIC for various doses of meropenem.

Efficacy:

The protocol will specify and justify the method for identifying severity of acute illness to assist in measuring improvement or resolution of infection, clearly delineate criteria and endpoints for treatment success and failure, and provide definitions of evaluable patients and microbial clearance.

Safety (all studies):

Safety assessments will track the occurrence of any adverse events (AEs) including: seizures; the incidence of superinfections (particularly fungal infections); vital signs including heart rate, blood pressure, and respiratory rate; pulse oximetry; apnea monitoring; standard laboratory assessments of hematologic, liver, and renal function; assessments of hearing and growth (weight, length, and head circumference). Criteria for identification and clinical evaluation of suspected seizures will be described in the protocol. AEs will be followed to their resolution or stabilization. Nosocomial infections will be tracked by pathogen.

Drug -Specific Safety Concerns (all studies):

1. In older susceptible patients, treatment with carbapenems (including meropenem) may decrease the seizure threshold^{4,5}. In meningitis treatment studies of patients without CNS abnormalities, the rate of seizures among those patients receiving meropenem was similar to that of patients treated with cefotaxime or ceftriaxone^{2,6,7}. The clinical manifestation of seizures in newborn and young infants can be subtle. The protocol must specify the definition of seizures and the criteria for identification and documentation of possible seizures and must address the role of electroencephalograms and other diagnostic methods in seizure diagnosis. Collection of a serum meropenem level at time of suspected seizure is strongly encouraged.
2. The use of carbapenems and other similar broad spectrum antimicrobials poses a risk of fungal superinfection. The protocol will specify the method of tracking the incidence of superinfections, both bacterial and fungal.
3. In children, the most common adverse events occurring with meropenem treatment are diarrhea, rash, nausea, and emesis. Hemolytic anemia in pediatric patients on meropenem has been reported.

Drug information:

- Dosage form: Powder for injection. Reconstitute with a compatible diluent.
- Route of administration: intravenous.
- Regimen: The pharmacokinetic data from Study 1 will guide dosing in Study 2.

Labeling that may result from these studies:

Appropriate sections of the label may be changed to incorporate the findings of the studies performed in response to this written request.

Format of reports to be submitted:

Full study reports with analysis, assessment, and interpretation, not previously submitted to the Agency addressing the issues outlined in this request, will be submitted. Pharmacokinetic study reports should include analytical method and assay validation, individual drug and/or metabolite concentration-time data and individual pharmacokinetic parameters. In addition, the reports are to include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study (studies) should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity one of the following designations should be used: Hispanic/Latino or Not Hispanic Latino.

Response to Written Request:

As per the Best Pharmaceuticals for Children Act, section 3, if we do not hear from you within 30 days of the date of this Written Request, we will refer this Written Request to the Director of the NIH. If you agree to the request, then you must indicate when the pediatric studies will be initiated.

Please submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission **"PEDIATRIC PROTOCOL SUBMITTED IN RESPONSE TO WRITTEN REQUEST"** in large, bold 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, bold type at the beginning of the cover letter of the submission.

Reports of the studies should be submitted as 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 reports, please clearly mark your submission **"SUBMISSION OF PEDIATRIC STUDY REPORTS -COMPLETE RESPONSE TO WRITTEN REQUEST"** in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter.

In accordance with section 9 of the Best Pharmaceuticals for Children Act, *Dissemination of Pediatric Information*, if a pediatric supplement is submitted in response to a Written Request and filed by FDA, FDA will make public a summary of the medical and clinical pharmacology reviews of pediatric studies conducted. This disclosure, which will occur within 180 days of supplement submission, will apply to all supplements submitted in response to a Written Request and filed by FDA, regardless of the following circumstances:

1. the type of response to the Written Request (complete or partial);
2. the status of the supplement (withdrawn after the supplement has been filed or pending);
3. the action taken (i.e. approval, approvable, not approvable); or
4. the exclusivity determination (i.e. granted or denied).

FDA will post the medical and clinical pharmacology review summaries on the FDA website at <http://www.fda.gov/cder/pediatric/Summaryreview.htm> and publish in the Federal Register a notification of availability.

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, please call Susmita Samanata, MD, Project Manager, at 301-827-2125.

Sincerely,

Reference List

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2. **Klugman, K. P. and R. Dagan.** 1995. Carbapenem treatment of meningitis. *Scand.J Infect.Dis.Suppl.* **96:45-8.**:45-48.
3. **Martinkova, J., R. de Groot, J. Chladek, et al.** 1995. Meropenem pharmacokinetics in pre-term and full-term neonates [Abstract 686]. Program and Abstracts of the 7th European Conference of Clinical Microbiology and Infectious Diseases, Vienna.
4. **Norrby, S. R. and K. M. Gildon.** 1999. Safety profile of meropenem: a review of nearly 5,000 patients treated with meropenem. *Scand.J Infect.Dis.* **31**:3-10.
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6. **Odio, C. M., J. R. Puig, J. M. Feris, W. N. Khan, W. J. Rodriguez, G. H. McCracken, Jr., and J. S. Bradley.** 1999. Prospective, randomized, investigator-blinded study of the efficacy and safety of meropenem vs. cefotaxime therapy in bacterial meningitis in children. Meropenem Meningitis Study Group. *Pediatr Infect Dis J* **18**:581-590.
7. **Schmutzhard, E., K. J. Williams, G. Vukmirovits, V. Chmelik, B. Pfausler, and A. Featherstone.** 1995. A randomised comparison of meropenem with cefotaxime or ceftriaxone for the treatment of bacterial meningitis in adults. Meropenem Meningitis Study Group. *J Antimicrob.Chemother* **36 Suppl A:85-97.**:85-97.
8. **Solomkin, J. S., D. L. Hemsell, R. Sweet, F. Tally, and J. Bartlett.** 1992. Evaluation of new anti-infective drugs for the treatment of intraabdominal infections. Infectious Diseases Society of America and the Food and Drug Administration. *Clin.Infect.Dis.* **15 Suppl 1:S33-42.**:S33-S42.
9. **Solomkin, J. S., J. E. Mazuski, E. J. Baron, R. G. Sawyer, A. B. Nathens, J. T. DiPiro, T. Buchman, E. P. Dellinger, J. Jernigan, S. Gorbach, A. W. Chow, and J. Bartlett.** 2003. Guidelines for the selection of anti-infective agents for complicated intra-abdominal infections. *Clin Infect Dis* **37**:997-1005.