CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-679/S-007

MEDICAL REVIEW

HFD-5[illegible]

MEDICAL OFFICER REVIEW OF PEDIATRIC USE SUPPLEMENT
NDA 50-679/SLR-007

Date of Submission: Dec. 23, 1996
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DRUG PRODUCT INFORMATION
Generic Name: Cefepime Hydrochloride
Dosage Form: Maxipime®
Pharmacologic Category: Cephalosporin
Dosage Form: Parenteral
Route of Administration: Intramuscular or Intravenous

MATERIALS SUBMITTED

43 volumes were submitted on Dec. 23, 1996, including pediatric [redacted] Two volumes were submitted on May 16, 1997 and Dec. 4, 1997 including data on compassionate use subjects and subjects with febrile neutropenia, respectively. One volume containing proposed labeling changes was submitted on Nov. 25, 1998.

RESUME

Maxipime® is a parenteral cephalosporin antibiotic that was approved on January 18, 1996. This efficacy supplement included clinical information for two purposes. [redacted] This submission also includes the results of several studies of serious bacterial infections in pediatric patients. The purpose of this submission is to revise the Pediatric Use subsection in support of the use of cefepime in the treatment of infants and children based on indications approved in adults.

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INTRODUCTION

As stated by the sponsor, "this submission is being made in support of the use of MAXIPIME® in the treatment of infections in infants and children". The sponsor cites the final rule issued in the Federal Register on Dec. 13, 1994 in proposing revision of the pediatric use subsection of the label. The current indications for this antibiotic, based on clinical trials in adult patients, include:

- pneumonia(moderate to severe),
- empiric therapy for febrile neutropenic patients,
- uncomplicated and complicated urinary tract infections (including pyelonephritis),
- uncomplicated skin and skin structure infections, and
- complicated intra-abdominal infections.

The indication for complicated intra-abdominal infections was approved subsequent to the original pediatric submission. The sponsor's current proposal for Pediatric Use labeling includes only the first four of these adult indications.

The studies providing supportive information for the pediatric use of cefepime are outlined in the Pediatric Clinical Studies section of this review. In addition, the sponsor has provided a document titled, "Background Document on Cefepime for Pediatric Indications" by Jeffrey Blumer, Ph.D., M.D. to give the rationale for extrapolating efficacy data for adults to pediatric patients for these indications.

PROPOSED LABELING

The following revisions to the label were provided by the sponsor in a submission dated Nov. 25, 1998.

1. Currently the Pediatric Use subsection of the **PRECAUTIONS** section states, "The safety and efficacy of MAXIPIME(cefepime hydrochloride) in pediatric patients below the age of 12 years have not been established. This product is intended for use in patients 12 years of age and older." The sponsor proposes the following change:

"The safety and effectiveness of cefepime in the treatment of uncomplicated and complicated urinary tract infections (including

pyelonephritis), uncomplicated skin and skin structure infections, pneumonia, and as empiric therapy [redacted] febrile neutropenic patients have been established in the age groups [redacted] Use of MAXIPIME in these age groups is supported by evidence from adequate and well-controlled studies of cefepime in adults with additional pharmacokinetic and safety data from pediatric trials (see **CLINICAL PHARMACOLOGY**[redacted]

[redacted]

Safety and effectiveness in pediatric patients below the age of [redacted] have not been established. [redacted]

2. The following section is added to the Special Populations subsection of the **CLINICAL PHARMACOLOGY** section of the label:

"*Pediatric patients:* Cefepime pharmacokinetics have been evaluated in pediatric patients following single and multiple [redacted] doses on q8h (n=29) and q12h (n=13) schedules. [redacted] Following a single IV dose, total body clearance and the steady volume of distribution averaged 3.3 (±1.0)mL/min/kg and 0.3 (±0.1) L/kg, respectively. [redacted] The urinary recovery of unchanged cefepime was 60.4 (±30.4)% of the administered dose, and renal clearance was [redacted] 2.0 (±1.1)mL/min/kg. [redacted]

The absolute bioavailability of cefepime after an IM dose of 50 mg/kg was 82.3 (±15.6)% in eight patients. The exposure to cefepime, [redacted] following a 50 mg/kg IV dose in a pediatric patient is comparable to that in adults treated with a 2 g IV dose.

[redacted]

4. The following is added to the end of the Clinical Trials subsection of the **ADVERSE REACTIONS** section of the label.

"A similar safety profile

see **PRECAUTIONS: Pediatric Use**

5. A table of recommended dosage schedule in the **DOSAGE AND ADMINISTRATION** section is also modified to include the following statement:

up to **years)**

The maximum dose for should not exceed the recommended adult dose. The usual recommended daily dosage in up to 40 kg in weight for uncomplicated and complicated urinary tract infections (including pyelonephritis), uncomplicated skin and skin structure infections, pneumonia, and as empiric therapy febrile neutropenic patients is 50 mg/kg administered q12h (q8h for febrile neutropenic patients), for durations as given above."

Other minor editorial changes are included in the labeling revisions provided, but they are not included here.

PEDIATRIC CLINICAL STUDIES

[redacted] the sponsor has submitted the following pediatric studies in support of the proposed labeling changes:

- AI411-131: A Comparative Study of Cefepime versus Ceftazidime in the Treatment of Pediatric Cancer Patients with Fever and Neutropenia

- AI411-129: A Non-Comparative Study of the Safety, Efficacy, and Pharmacokinetics of Cefepime in Pediatric Patients with Serious Bacterial Infections

- AI411-123: A Multi-Investigator Comparative Study of Cefepime and Cefuroxime in the Treatment of Serious Bacterial Infections in Pediatric Subjects

- AI411-157: A Multi-Investigator Comparative Study of Cefepime and Cefotaxime in the Treatment of Serious Bacterial Infections in Pediatric Subjects

- AI411-999-007: Compassionate Use of Cefepime for Treatment of Pediatric Patients with Multi-Resistant Salmonella Type B Infection

This study was performed at a single site in Costa Rica where nineteen infants (aged 2 days to 8 months) with varying clinical presentations of Salmonellosis were treated with cefepime under a compassionate use protocol. Eleven satisfactory, 3 unsatisfactory, and 5 non-evaluable responses were reported. Among the nineteen infants there were four deaths. A premature infant with hydrocephalus died of Salmonella meningitis after having received a single dose cefepime. Death followed rapid deterioration with seizures, apnea, and cardiac arrest. Two premature infants with symptoms consistent with necrotizing enterocolitis with septic shock received several days of treatment with cefepime. Only one of these two infants had *Salmonella* group B isolated from stool. This infant was also noted with coagulase negative *Staphylococci* on blood culture. Both subjects displayed brief improvement followed by rapid clinical deterioration, shock, and arrest. The remaining death occurred in a neonate with myelomeningocele treated for severe gastroenteritis due to

resistant *Salmonella*. Again, a brief improvement followed by increasing symptoms was noted. Cefepime was stopped due to suspected *C. difficile* infection, although this was not demonstrated. The infant developed a nosocomial varicella infection with interstitial pneumonia and severe respiratory distress, leading to hypoxia and death. Adverse events were noted in sixteen of the nineteen subjects. Only one report of rash on the twelfth day of therapy was considered related to study drug. Other adverse events including vomiting, diarrhea, hypotension, apnea, abdominal pain, melena, and wheezing were likely related to the *Salmonella* infection or other underlying disease. One non-evaluable subject was switched to other therapy after developing symptoms and signs consistent with tibial osteomyelitis on the fourth day of cefepime therapy. **(M.O. Comment: Little valuable information is obtained from this case series of infants with severe infections complicated by underlying prematurity or congenital disease. Adverse events that may be related to the study drug are difficult to distinguish from symptoms of infection. This study will not be addressed further in this review.)**

- AI411-900: Open Label Study of Cefepime for Patients with Serious or Life-Threatening Infections Including Those Due to Organisms with Multiple Antibiotic Resistance

This last study is a compassionate use protocol. [redacted] A subsequent submission(SLR-007 Submission date: May 16,1997) included brief narratives of three other pediatric patients treated under this protocol. The first was a fifteen year old female with leukemia following a bone marrow transplant who was treated for a right knee septic arthritis and thigh abscess due to Enterobacter *cloacae*. Eight months after completing cefepime and tobramycin, she developed a right femur chronic osteomyelitis with the same organism. Continued symptoms and renal and liver dysfunction were noted, and she had an amputation above the right knee. She completed 2 weeks of cefepime and tobramycin after her AKA and was discharged. No further follow-up was reported.

[redacted]

Limited information was provided about a fifteen year old male with severe burns. He had several blood cultures positive for *Pseudomonas aeruginosa, Enterococcus faecalis, Acinetobacter calcoaceticus,* and MRSA. He received 15 days of cefepime therapy in combination with several other antibiotics. The patients died "of several complications secondary to his burns, including bacteremia and renal failure". The renal failure was not considered to be related to cefepime.

(M.O. Comment: The safety information from all four patients was included in the integrated summary of safety in the original pediatric submission. Poor outcomes for burn patients, and bone marrow transplant patients are not unusual. This study will not be discussed further in this review.)

RATIONALE FOR PEDIATRIC USE LABELING

As part of this submission, the sponsor provided a document titled, "Background Document on Cefepime for Pediatric Indications" by Jeffrey L. Blumer, Ph.D., M.D., to provide the rationale for applying the 1994 pediatric final rule to the adult indications in the Maxipime® label. The 1994 rule states that a pediatric use statement may be based on adult indications provided that "the course of the disease and the drug's effects are sufficiently similar in the pediatric and adult populations to permit extrapolation from the adult efficacy to pediatric patients. This section will discuss the similarities and differences between adult and pediatric manifestations of the infections for which pediatric use labeling is being sought.

EMPIRIC THERAPY FOR FEBRILE NEUTROPENIC PATIENTS

In evaluating the similarities between adult and pediatric patients with fever and neutropenia, the purpose of empiric antibiotic therapy must first be determined. Empiric therapy for febrile neutropenic patients developed in the 1960's.[1] It was recognized that initiating therapy when neutropenic patients first developed fever led to a reduction of mortality and morbidity, especially seen with gram-negative infections. Broad spectrum antibacterial therapy with the use of two or more antimicrobial agents was used to provide coverage against both gram-positive and gram-negative agents. When empiric therapy became more widely used, *Pseudomonas aeruginosa* and other gram-negative organisms were the predominant pathogens. More recently, concern about gram-positive infections has increased. However, the objective of empiric therapy in reducing morbidity and mortality from systemic infections in an immunocompromised patient appears to be the same. It also is apparent that this objective is the same for both adults and pediatric patients who receive empiric antibiotic treatment.

Given that the objective of treatment is the same, how similar is the course of the disease? The etiology of neutropenia for adults and children is the same. Most often, neutropenia results from the use of chemotherapy used for the treatment of cancer. While the types of

[1] Hathorn JW, Rubin M, Pizzo PA "Empirical Antibiotic Therapy in the Febrile Neutropenic Cancer Patient: Clinical Efficacy and Impact of Monotherapy" Antimicrob Agents Chemother 31(7):971-977 July 1987.

cancer may differ, with ALL and other leukemias seen more often in children, the increased susceptibility to infection that results from neutropenia is similar in both groups. The etiologic agents and outcome from febrile neutropenic patients are also similar.[2] Hann et al. found that children developed more streptococcal infections and fewer staphylococcal bacteremias than adults. They also found that children had a better overall success rate and lower mortality than adults. Mortality was 1% in children versus 4% in adults.

Overall, the disease process and clinical course for fever and neutropenia appear to be similar in adults and children. The outcome may be better in children than adults for mortality, and the drug's anti-bacterial effects are expected to be similar. There appears to be sufficient evidence that empiric therapy for febrile neutropenic patients is sufficiently similar in adults and children to consider extrapolation of adult data to children.

SKIN AND SKIN STRUCTURE INFECTIONS

Uncomplicated skin and skin structure infections are most often caused by either *Staphylococcus aureus* or *Streptococcus pyogenes*. This is true irrespective of age. The clinical presentation with erythema, swelling, and contiguous spread of infection are also similar for both adults and children. The pathogenesis of infection is usually from direct inoculation of bacteria under the skin, whether from surgical wounds, trauma, or other source of skin breakdown. Antibiotic penetration into soft tissues, which are well vascularized, should not be different in children and adults if the drug serum levels achieved are equivalent. Other less common skin infections, such as bite wounds, tennis shoe puncture wounds infected by *P. aeruginosa*, and fresh water wounds with *Aeromonas* spp., are also similar in presentation and pathogenesis.

There are some skin infections that are different entities based on age. An example is facial cellulitis caused by *Hemophilus influenzae* type b in infants. There is also the group B Streptococcal cellulitis that may occur in neonates. These entities are different in that they are

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[2] Hann I, Viscoli C, Paesmans M, Gaya H, Glauser M, and the International Antimicrobial Therapy Working Group of the European Organization for Research and Treatment of Cancer "A Comparison of Outcome from Febrile Neutropenic Episodes in Children Compared with Adults: Results from Four EORTC Studies" British Journal of Haematology 99:580-588 1997

frequently associated with bacteremia and systemic spread of infection. There are also different entities that occur in adults, such as the diabetic foot ulcer. However, these entities are easily distinguished based on clinical presentation from typical uncomplicated skin and skin structure infections.

The conclusion to be drawn from this information is that uncomplicated skin and skin structure infection caused by *Staphylococcus aureus* and *Streptococcus pyogenes* are sufficiently similar in adults and children to allow for extrapolation of data from adults to children. The limitations to this extrapolation are for those unusual clinical entities that occur almost exclusively in infants, or complicated skin and skin structure infections.

URINARY TRACT INFECTIONS

First, it should be noted that cefepime is indicated for uncomplicated and complicated urinary tract infections due to *E. coli* or *K. pneumoniae*. The two organisms are the most common causes of urinary tract infections (UTI) in both children and adults. Cefepime is also indicated for infections caused by *Proteus mirabilis*, "when the infection is mild to moderate". This organism, *P. aeruginosa*, and enterococci are other less common causes of UTI. The pathogenesis of UTI is also similar in adults and children. The ascending route of infection is most common, though hematogenous spread to the kidney also occurs. Voiding through an unobstructed urinary tract helps to prevent infection. The clinical presentation of urinary tract infections can be limited to the bacterial growth in the bladder, or spread with infection of the renal parenchyma, and development of bacteremia or renal abscess. As with skin, the kidney is well vascularized and cephalosporins are concentrated in the urine, since they are renally excreted. Thus, the antibacterial activity of the drug should be the same in children and adults with equivalent serum drug levels.

There are important differences between adults and children with UTI that must be considered. While adolescents and older children are able to localize infection and communicate symptoms of dysuria, this is not the case for infants and toddlers. Clinical presentation of UTI in pre-verbal children can be non-specific, with fever, vomiting, diarrhea, or poor food intake. For these children, pyelonephritis, bacteriuria, and/or renal abscess are more likely to be seen at presentation or develop as a

consequence of inadequate treatment. Also, congenital anomalies that contribute to urinary stasis may be identified after UTI is diagnosed. In adults, such anomalies would have been identified and treated surgically or medically. The majority of urinary tract infections identified in childhood occur in these pre-verbal children who may have congenital anomalies or upper tract infection.

The differences identified between children and adults with UTI would limit the ability to extrapolate efficacy data from adults with uncomplicated UTI to children. As described above, there are significant differences between the presentation and outcome of UTI in children and the typical subjects in clinical trials of uncomplicated UTI. Since cefepime is labeled for complicated UTI including pyelonephritis, the extrapolation of adult clinical trial data to children is acceptable. The urinary tract infections typically seen in childhood appear to be sufficiently similar to the complicated UTI in adults to allow this extrapolation. Congenital anomalies and the higher likelihood of upper tract infection in children do not require more extensive treatment than is needed for adults with complicated UTI (though infants will typically receive conservative treatment with at least 5 days of intravenous therapy for pyelonephritis).

PNEUMONIA

Cefepime is indicated for "pneumonia (moderate to severe) caused by *Streptococcus pneumoniae*, including cases with concurrent bacteremia, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and *Enterobacter* species". The organisms listed in this indication include pathogens involved in community- and hospital-acquired pneumonia.

The clinical presentation of adults and children with pneumonia are similar. Cough, fever, and varying degrees of respiratory difficulty are the main presenting symptoms. Rales, rhonchi and/or egophony on chest exam and infiltrate on chest X-ray are also seen in both adults and children. Although the presence of these symptoms and signs may vary by age (e.g., rales are difficult to detect in infants) the disease entity is still similar in the different age groups. The etiologic agents causing community-acquired pneumonia (CAP) are thought to vary with age with *Mycoplasma pneumoniae* recognized more often in older children and adults and some viral agents (e.g., RSV) are seen more in infants. The viral and bacterial pneumonias can not be distinguished clinically in most patients.

However, the treatment of CAP is empiric in the majority of cases, and the purpose of antibiotic treatment is the elimination of bacterial pathogens. Thus the objectives of antibiotic use and disease process is sufficiently similar in adults and children when considering treatment of CAP due to bacterial pathogens. Likewise, the disease process for hospital-acquired pneumonia (HAP) is similar in adults and children. Gram-negative organisms are the predominant pathogens. Predisposing factors, such as mechanical ventilation, are seen in both children and adults. The clinical symptoms for HAP are similar to CAP. Finally, the penetration of antibiotic into alveoli and the drug effect at that site should be the same for adults and children.

For the purposes of applying the 1994 pediatric rule to bacterial pneumonia, the course of the disease and drug effect should be sufficiently similar in adults and children to allow extrapolation of adult efficacy data. Some caution will need to be taken when considering agents for mycoplasma, since there is still some controversy regarding the existence of mycoplasma pneumonia in children under age 5. For cefepime, *Streptococcus pneumoniae* and the gram-negative organisms in the product label are known etiologic agents of pneumonia in children of all ages.

This page of the document contains confidential information that will not be included in the redacted portion of the document for the public to obtain.

FEVER AND NEUTROPENIA

AI411-131: A Comparative Study of Cefepime versus Ceftazidime in the Treatment of Pediatric Cancer Patients with Fever and Neutropenia

Principal Investigator

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Objectives

The primary objective of this study was: "To evaluate the safety and efficacy of cefepime and ceftazidime in the treatment of cancer patients with fever and neutropenia."

STUDY DESCRIPTION

This study was an open-label, randomized (1:1) clinical trial at a single site designed to evaluate and compare the clinical efficacy and safety of cefepime with ceftazidime for the treatment of febrile episodes in neutropenic pediatric cancer patients. The addition of vancomycin as concomitant treatment in either arm of the study was also permitted. Pediatric cancer patients who were neutropenic and became febrile were eligible for this trial. The original protocol was written for an open label study of fever and neutropenia in adult subjects at another center. The protocol was modified by three amendments for use by this investigator. The first modification added Dr. McCracken as an investigator. It allowed enrollment of children aged 2-18 years, and changed other aspects of the protocol for pediatrics. The second modification increased maximum treatment duration from 28 days to 8 weeks. The third modification allowed children as young as 2 months of age to be enrolled. This study represents data collected at Children's Medical Center of Dallas. The first patient was enrolled on June 10,1991 and the last patient completed participation on June 24, 1993. A total of 150 subjects were projected for this site.

(M.O. Comment: This protocol has been reviewed previously by David Ross, M.D., Ph.D., in his review of NDA 50,679 SE1-002. The data for other sites where adult patients

were treated under this protocol were included in that submission, but the information from Dr. McCracken's site was not included. A brief review of the protocol is provided below, but the main body of this section will concentrate on the study results for this site, in particular the safety results.)

Inclusion Criteria:
Patients must meet all of the following criteria:

- have provided a signed informed consent;
- be 2 months to 18 years of age; Note: Female patients who are of childbearing potential must have a negative pregnancy test result prior to enrollment.

(M.O. Comment: As noted above, the original protocol was designed for an adult study. When Dr. McCracken was enlisted as an investigator, the age range was 2 years to 18 years at his study site. An amendment in November of 1992 changed the lower age limit to 2 months at this site.)

- cancer patients with fever >38°C or 100.4°F occurring at least twice in a 24-hour period, or a single temperature of >38.5°C
- afebrile (<38°C or 100.4°F) for at least 72 hours prior to the present febrile episode requiring antimicrobial therapy;
- absolute neutrophil count(ANC) of less than or equal to 1000 granulocytes per mm^3;

(M.O. Comment: A threshold of 500 granulocytes per mm^3 is most often used. Only three subjects were reported to have baseline ANC of >500.)

- and life expectancy at least 3 months.

Exclusion Criteria:
Patients meeting any of the following criteria will be excluded from the study:

- patients with aplastic anemia;
- patients who have received parenteral antibiotics in the previous 72 hours;
- patients previously treated on this study protocol for a febrile episode occurring during the current hospital admission or within the two weeks prior to the current febrile episode;
- history of a serious hypersensitivity reaction to a cephalosporin or penicillin antibiotic;
- pregnant and/or lactating women;
- patients who are hypotensive;

(M.O. Comment: This exclusion would eliminate the most seriously ill subjects from study.)

- patients with CML who are in blast crisis;
- patients with renal failure (creatinine ≥ 2.0);
- treatment regimen likely to include other antimicrobial drugs during therapy with the study medication or during a period approaching 2 weeks post treatment, with the exception of antifungal or antiviral medications;
- in the opinion of the investigator, the patient would require long-term (greater than 8 weeks) antimicrobial therapy for treatment of clinical symptoms or eradication of the causative pathogen(s) (e.g. osteomyelitis, empyema, lung abscess);

(M.O. Comment: The original protocol specified maximum treatment duration of 28 days. This was modified by amendment prior to the first patient enrollment at this study site.)

- drug therapy constitutes empiric management of a contaminated body site (e.g. immediate treatment of post-traumatic injury);
- patients with signs and symptoms of CNS infection;
- presence of a medically significant disease or disorder except cancer which may have a bearing on the outcome of the study (e.g. a HIV infected patient with a possible infection - MAI, pneumocystis, CMV which would not be treatable with a cephalosporin);
- or patients who have been placed on "do not resuscitate (DNR)" or "No Code" status (includes patients for whom ventilator support will not be administered).

The following exclusions were applied in the event that the patient had a known or suspected infection at a particular site:

Suspected Bacteremia

- patients with endocarditis or a suspected *Bacteroides fragilis* infection (e.g. certain intra-abdominal infections);

Lower Respiratory Tract Infection

- patients with [redacted] empyema, lung abscess or pneumonia distal to obstructive carcinoma (excluded because of the need for long-term therapy);

Skin/Soft Tissue Infection

- patients with infections of severe burns (i.e. 20% or more full thickness), facial burns with respiratory complications, patients with infected prostheses, or

patients who are likely to receive major surgical intervention on-therapy (e.g. amputation of infected limb).

Treatment Assignment

Subjects were randomly assigned (in a 1:1 ratio) to receive either cefepime or ceftazidime. Cefepime or ceftazidime were administered at 150 mg/kg/day divided every eight hours (maximum 6 grams per day). Vancomycin was administered at 40 mg/kg/day divided every 6 hours (maximum 2 grams per day). No other systemic antibacterial therapy is allowed. Recommended treatment duration is 10 days. For patients with clinically or bacteriologically documented infection, treatment was required until ANC recovery and a minimum of 7 days of therapy was completed.

Indications for the addition of vancomycin were:

- fever persistent for more than 96 hours after beginning cefepime or ceftazidime therapy;
- *in vitro* susceptibility testing indicates the pre-therapy causative pathogen is resistant to cefepime or ceftazidime and susceptible to vancomycin (i.e. [redacted] resistant staphylococci)

Study Procedures

Subjects were screened and those who successfully passed the inclusion and exclusion criteria were enrolled. Informed consent was obtained for each patient.

Pre-treatment procedures included history and physical examination, evaluation of signs and symptoms, culture, chest X-ray, and laboratory studies. The procedures were to be obtained within 48 hours prior to initiation of treatment. Chest X-ray is performed in those subjects with suspected lower respiratory tract infection. Two blood culture specimens from separate body sites or separated by time (at least one hour) were to be obtained. A sputum specimen obtained by sterile suctioning or expectoration was included in the protocol for subjects with lower respiratory tract infection. A sterile syringe or swab to obtain purulent material from skin structure infections was also included in the protocol.

During therapy, subjects were evaluated "as frequently as clinically required". An abbreviated physical exam, evaluation of signs and symptoms, cultures from blood or infected site, and laboratory studies were scheduled for a visit at days 3-5 and weekly thereafter.

End of treatment evaluation procedures were scheduled between the last day of therapy and 4 days after completion of therapy. This visit included physical exam, clinical evaluation, and laboratory studies for all subjects. X-ray could be obtained at this visit or at follow-up. Culture was to be obtained if source material was present for culture. Otherwise the investigator documented "no source to culture". Blood culture could be obtained at this visit, but was not necessary if the subject was afebrile and the during therapy blood culture was negative.

The following is a list of indications for which early withdrawal from the study with termination of the study drug was allowed:

- resistance of the causative pathogen to the antibiotics and vancomycin by *in vitro* susceptibility testing;
- in the investigator's opinion, a poor clinical response occurs after 72 hours of combined cefepime/vancomycin or ceftazidime/vancomycin therapy (the patient will be considered a therapeutic failure if all eligibility criteria are met up to that point);
- serious or alarming adverse reaction(s) (follow-up of adverse events for resolution or complications was still required);
- intercurrent illness;
- subject's decision to withdraw from the study;
- in the investigator's opinion, it is in the subject's best interest;
- or administrative reasons

The post-therapy evaluation was scheduled 10-14 days after completion of therapy (5-9 days for subjects with UTI). It included a clinical evaluation of signs and symptoms and culture when indicated. Children with UTI will have culture obtained at this visit. Children with complicated UTI will also have a culture repeated at 4-6 weeks after therapy.

Non-comparative Study Arm

The study included a non-comparative arm to treat subjects whose isolates were resistant to ceftazidime but sensitive to cefepime. Subjects receiving ceftazidime could be switched to cefepime after a repeat clinical evaluation.

(M.O. Comment: None of the subjects enrolled in the study were shifted into the non-comparative arm. It will not be discussed further.)

Evaluation of Patient Safety

Patients were observed during administration of the study medication for any evidence of local or systemic reaction. The investigator was required to record on the case report form "relevant and complete information on all adverse experiences or other on-therapy conditions occurring during the course of the study, whether or not associated with study medication. The investigator was required to report promptly all significant adverse events, whether drug related or not. Requirements for reporting serious events to the study monitor were included in the protocol.

Laboratory Tests

The laboratory tests specified for pediatric patients are listed below. Alkaline phosphatase, total bilirubin, and AST could be omitted where limited amounts of blood were obtained.

Hematology

Hemoglobin	Platelet Count
Hematocrit	Direct Coombs Test
WBC Count and Differential	

Serum Chemistries

ALT	Calcium
Creatinine	Sodium
AST	Potassium
Total Bilirubin	Glucose
Alkaline Phosphatase	

These studies were outlined specifically for pediatric patients in the first protocol amendment. Adults had a more extensive list of studies required.

CRITERIA FOR EVALUATION OF SAFETY AND EFFICACY

All patients who received study medication were considered eligible for evaluation of safety. To be eligible for evaluation for efficacy the following were required:

Pre-therapy Requirements

- documented fever following an afebrile period;
- ANC $\leq 1000/cm^3$;

(M.O. Comment: In the sponsor's analysis, an ANC ≤ 500/cm^3 was used as the eligibility requirement. This is acceptable.)

- pre-treatment blood cultures must be obtained (two positive cultures are required for bacteremias caused by coagulase negative staphylococci or other possible contaminants);
- for suspected infections of the lower respiratory tract, urinary tract, or skin and skin structure a pre-treatment culture must be obtained from the suspected site of infection and the presence of one or more of the known clinical signs and symptoms associated with the diagnosis will be documented;
- for pneumonia, a chest x-ray with a radiologic interpretation consistent with pneumonia;
- for urinary tract infection, a pre-therapy urine culture with at least 10^5 CFU/mL;
- susceptibility testing must be performed with cefepime, ceftazidime against all pathogens isolated;
- gram-positive pathogens must have susceptibility testing against vancomycin if this antibiotic is used for therapy;
- the pre-treatment identified pathogen(s) must be susceptible to cefepime and ceftazidime and/or vancomycin if vancomycin is used for therapy.

(M.O. Comment: The first three of these are reasonable requirements. The x-ray and urine culture requirements are also acceptable. Obtaining culture material for suspected clinical infections is useful but is not required for evaluation. Requirements for susceptibility testing, especially in this study of empiric therapy, should not be required for evaluation of efficacy.)

During/Post-therapy Requirements

- for all infections except UTI, a post-therapy clinical follow-up at 10-14 days (for UTI, 5-9 day follow-up);
- for bacteremia, at least one blood culture during, near the end, or post-treatment;
- for pneumonia, a second chest x-ray should be obtained toward the end of therapy;
- for UTI, a during-therapy and a post-therapy (must be 5-9 days post-therapy) culture;
- for LRI and S/ST infections, a post-therapy culture (≥ 3 days post-therapy) of sputum or material from skin site, or documentation of "no source to culture" at 10-14 days;

- the study drug must be administered at the dose, frequency, and duration specified by the protocol;
- the patient will not have received any other systemic antimicrobial agent between the time of pre-treatment and post-treatment clinical follow-up or culture whichever occurs later. The exceptions are:
    1. addition of vancomycin as specified in the protocol;
    2. anti-fungal or anti-viral therapy;
    3. Patients who fail to respond to the study drug, or who develop signs and symptoms of infection after completion of therapy and before the time of post-treatment culture.

(M.O. Comment: A follow-up visit should not be required for failures. Timing of follow-up urine culture or chest x-ray is not critical, nor are attempts at post-therapy culture for LRI or S/ST infections. For the last criteria, some of these subjects may be considered failures rather than ineligible.)

Subjects were grouped into three categories:

- Microbiologically Documented Infection (MDI)- Signs and symptoms of infection are present and pathogen(s) is(are) isolated from the local site of infection or blood.
- Clinically Documented Infection(CDI) - Signs and symptoms of a local infection are present but no pathogen is isolated for blood or a local site of infection
- Unexplained Fever(FUO) - Neither of the above definitions are met.

Clinical Response

- Satisfactory - Fever and/or all clinical signs and symptoms relevant to the infection are resolved or improved after 96 hours and no new clinical signs or symptoms, relevant to an infection, occur at the time of the post-therapy follow-up evaluation. For pneumonia patients, if the chest X-ray shows evidence of an increase or worsening of the infiltrate, but signs and symptoms have improved, the investigator will determine the response based on the clinical setting.
- Unsatisfactory - Persistence or increase in severity of fever and/or clinical signs or symptoms relevant to the original infection for 96 hours or more after the start of therapy with the study drug resulting in a clinical decision being made to change antimicrobial agents, or death resulting from a microbiologically or clinically

documented infection for which the patient was entered into the study.

-OR-

Following initial improvement, recurrence or worsening of any fever or clinical signs or symptoms relevant to the original site of infection by the time of post-therapy follow-up (10-14 days);

(Note: This classification will be used unless specific criteria for a new infection are met.)

- New Infection - A new infection is defined as the presence of new, persistent, or worsening symptoms and/or signs of infection associated with the isolation of a new pathogen from the original site(s) of infection or any pathogen from a new site of infection.
- Unable to Determine - No follow-up evaluation of clinical signs and symptoms or other reason for which the response cannot be classified according to the response categories above.

(M.O. Comment: A "new infection" that is due to fungal or viral infections are acceptable. Isolation of bacteria in subjects classified as FUO patients should be considered an unsatisfactory response. The development of a new bacterial infection while on therapy should be considered unsatisfactory.)

Bacteriologic Response

- Eradicated - For bacteremia, pre-therapy causative pathogens are not isolated in blood cultures taken during or post-therapy. For UTI, urine colony count is reduced to $<10^4$ CFU/mL in during and post-therapy cultures. For, lower respiratory tract or skin and skin structure infection, response is eradicated if the pre-therapy causative pathogen is not present in post-therapy culture or there is no source to culture at the post therapy visit.
- Persisted - Pre-therapy causative pathogen is present in the post-therapy culture. If the patient has been removed from the study and the during or post-therapy culture obtained was positive, then the response will be considered persisted. For UTI, if the pre-therapy causative pathogen is found at $\geq 10^4$ CFU/mL in the 5-9 day post-therapy culture then the response is persisted. If the patient is removed from the study and the last culture obtained showed $\geq 10^4$ CFU/mL then the response is persisted.

- Undetermined - Unable to evaluate the response (e.g. lost to follow-up, inappropriate cultures obtained, etc.)

(M.O. Comment: The eradicated category includes elements that would be considered part of a presumptive eradication category in other studies.)

EFFICACY RESULTS

Demographics: A total of 104 patients were treated for 149 febrile episodes. The sponsor based the primary analysis on the first episode of fever that was treated, but a separate analysis of all febrile episodes was also performed. The safety review focuses on the analysis of all febrile episodes. Unless otherwise specified, the demographics and efficacy analysis are based on the first episode of study enrollment.

Patient Demographics for First Episode of Fever

Demographic Factors	Cefepime (N=49)	Ceftazidime (N=55)	Total (N=104)
Male	28 (57)	35 (64)	63 (61)
Female	21 (43)	20 (36)	41 (39)
White	28 (57)	30 (55)	58 (56)
Black	6 (12)	7 (13)	13 (13)
Hispanic	13 (27)	16 (29)	29 (28)
Other	2 (4)	2 (4)	4 (4)
Age:			
Median (years)	7	6	6
Range	5 months-19 years	1-15 years	5 months-19 years
Age Groups:			
5-23 months	4 (8)	1 (2)	5 (5)
2-11 years	29 (59)	46 (84)	75 (72)
12-15 years	12 (24)	8 (15)	20 (19)
16-19 years	4 (8)	0 (0)	4 (4)

The table on the prior page shows the demographic data for patients who participated in this trial. The majority of participants were between 2 and 11 years of age. Few children less than 2 years of age participated in this trial. This is due, in part, to the fact that the original protocol excluded children under 2 years of age. Children under 2 were included as part of the protocol for the last 7 months of the trial.

The cancer diagnosis for the 104 subjects included in the trial are shown in the table below. Solid tumors were more frequent in the ceftazidime group, but the number of patients with leukemia was similar in both groups.

Cancer Diagnosis by Treatment Arm

Cancer Diagnosis	Cefepime (N=49)	Ceftazidime (N=55)	Total (N=104)
Leukemia	31 (63)	33 (60)	64 (62)
ALL	23 (47)	29 (53)	52 (50)
ANLL	8 (16)	4 (7)	12 (12)
Lymphoma	7 (14)	3 (5)	10 (10)
Non-Hodgkin's	5 (10)	3 (5)	8 (8)
Hodgkin's	2 (4)	- - -	2 (2)
Urologic Cancer	1 (2)	1 (2)	2 (2)
Solid Tumors	7 (14)	16 (29)	23 (22)
Sarcoma	3 (6)	9 (16)	12 (12)
Bone	2 (4)	7 (13)	9 (9)
CNS	2 (4)	- - -	2 (2)
Neuroblastoma	3 (6)	1 (2)	4 (4)
Yolk Sac Tumor	- - -	1 (2)	1 (1)

The table on the following page shows the number of patients in each arm of the trial by the sponsor's diagnostic categories: Microbiologically Documented Infection (MDI), Clinically Documented Infection (CDI), and Fever of Unknown Origin (FUO). The majority of patients in both treatment arms had fever without a known source. The majority of CDI were pharyngitis, otitis media, and "mucositis". Two patients in each treatment arm were diagnosed with viral infections (1 MDI and 1 CDI in each arm). Two MDI in the ceftazidime arm were reclassified by the medical officer as FUO. Coagulase negative Staphylococci were identified on only one blood culture in these two patients. By the protocol definitions, these patients should not be included in the MDI category. **(M.O. Comment: Three CPM and 5 CTZ patients had MDI. One ceftazidime patient had streptococcal pharyngitis. The remainder had bacteremia. Given the low numbers, this review will discuss MDI for all episodes of fever and neutropenia in a later part of this section.)**

Diagnosis Categories by Sponsor

Category	CPM	CTZ	Total
MDI	4 (8)	8 (15)	12 (12)
CDI	15 (31)	11 (20)	26 (25)
FUO	30 (61)	36 (65)	66 (63)

The sponsor also looked at type of cancer therapy and use of antimicrobial prophylaxis. More frequent use of prophylaxis was noted in ceftazidime patients, 21/49(43%) of CPM subjects and 33/55(60%) of CTZ subjects. Part of this represents more frequent use of trimethoprim-sulfamethoxazole, and part is due to more frequent use of pentamidine. Other reported pretreatment variables were similar across the two arms of the trial.

Evaluability: Patient evaluability, as determined by the sponsor, is shown in the table that follows. Overall, there were a high number of non-evaluable patients in each arm of the trial. The most common reason is due to the addition of concomitant antimicrobial agents. While the protocol allowed use of vancomycin in specific cases, it was common for patients to have other antibiotics added by the subject's physician. This is also the reason that 77% of subjects with FUO were evaluable while for MDI and CDI only 42-46% were evaluable. Physicians were more likely to add therapy where clinical or microbiologic confirmation of infection was present.

Sponsor's Determination of Subject Evaluability

	Evaluable/All Patients (%)		
Category	**CPM**	**CTZ**	**Total**
All Subjects	35/49 (71)	33/55 (60)	68/104 (65)
MDI	2/4 (50)	3/8 (38)	5/12 (42)
CDI	9/15 (60)	3/11 (27)	12/26 (46)
FUO	24/30 (80)	27/36 (75)	51/66 (63)

There were 36 subjects(35%) who were non-evaluable for response per the sponsor. Fewer cefepime patients were non-evaluable. Eighteen of these subjects (50%) were non-evaluable due to the use of other antibiotics just prior to or during therapy with the study drug. Five subjects discontinued therapy early. Most of these subjects were less than 2 years of age at the time when the protocol did excluded them. Five subjects were non-evaluable due to an

identified viral infection. Seven patients either did not have fever or weren't neutropenic (ANC<500) at study entry. **(M.O. Comment: The use of other antibiotics or early use of vancomycin is problematic for determining the efficacy of cefepime. This will be discussed further in the section that discusses subjects with microbiologically documented infections. Patients with non-bacterial infections are considered evaluable by the medical officer. In addition, the medical officer has determined that some non-evaluable subjects should be categorized as clinical failures based on the protocol's criteria. While a clinical success may be due to the concomitant use of another antibiotic, a subject whose fever persists is a failure regardless of co-administration of another antibiotic. Those subjects without fever or neutropenia are non-evaluable for clinical response. Those subjects withdrawn from the study were usually switched to other antibiotic therapy. They were also considered non-evaluable by the medical officer, except in cases of failure.)**

Medical Officer's Determination of Subject Evaluability

	Evaluable/All Patients (%)		
Category	**CPM**	**CTZ**	**Total**
All Subjects	39/49 (80%)	39/54 (72%)	78/104 (75%)
MDI	2/3 (67%)	2/5 (40%)	4/8 (50%)
CDI	13/19 (68%)	10/16 (63%)	23/35 (66%)
FUO	24/27 (89%)	27/33 (82%)	51/60 (85%)

One subject was randomized to ceftazidime but did not receive study drug or participate in the study. The medical officer removed this subject from the list of all patients, since he is not evaluable for safety or efficacy. This accounts for the medical officer having 54 ceftazidime subjects while the sponsor lists 55. Again, fewer patients in the MDI and CDI categories are evaluable compared to FUO subjects due to concomitant antibiotic use.

Clinical Outcome: The clinical response rates for patients in each treatment are provided in the following table. The response rate by category of infection is also provided. The majority of failures are due to the persistence of fever for 5 days or more. Subjects with MDI will be discussed in more detail in another section of this review. Equal numbers of subjects in each treatment arm are

failures due to persistent infection or relapse of fever after treatment.
(M.O. Comment: The validity of defining patients with persistent fever as failures is questionable, since most of these patients go on to have resolution of fever later on. However, continued fever is commonly a part of clinical failure in patients with fever and neutropenia.)

Sponsor's Clinical Outcome for Evaluable Patients

	No. Success/All Evaluable Patients (%)		
Category	**CPM**	**CTZ**	**Total**
All Subjects	26/35 (74%)	23/33 (70%)	49/68 (72%)
MDI	1/2 (50%)	0/3 (0%)	1/5 (20%)
CDI	8/9 (89%)	2/3 (67%)	10/12 (83%)
FUO	17/24 (71%)	21/27 (78%)	38/51 (75%)

The following table shows the medical officer's determination for clinical response. Overall the results are similar to those reported by the sponsor. Similar results are also seen for clinical response rates for all treated episodes. For all episodes, the clinical response determined by the medical officer was 36/56 (64%) for cefepime subjects and 37/54 (68%) for ceftazidime subjects.

Medical Officer's Clinical Outcome for Evaluable Patients

	No. Success/All Evaluable Patients (%)		
Category	**CPM**	**CTZ**	**Total**
All Subjects	27/39* (69%)	26/39* (67%)	53/78 (68%)
MDI	1/2 (50%)	1/2 (50%)	2/4 (50%)
CDI	8/13 (62%)	5/10 (50%)	13/23 (56%)
FUO	18/24 (75%)	20/27 (74%)	38/51 (74%)

*Confidence interval for comparison(-20.7%,25.8%)

Among the subjects who are scored as failures, the majority are failures for fever that persists five or more days. One subject in each treatment arm was readmitted for fever and neutropenia within seven days of the end of study

drug treatment. They were both started on antibiotics again. Two subjects, one per treatment arm, had persistent bacteremia on blood culture. (They are discussed in the following section.) Two ceftazidime subjects were reported as new infections after growth of *Streptococcal* spp. on blood cultures during therapy.

Microbiologically Documented Infections: The following section discusses the cases of fever and neutropenia where a bacterial pathogen was identified at baseline. The following chart shows the bacterial pathogens by patient identified in each treatment arm and the clinical response. The ceftazidime patient who was treated for pharyngitis was non-evaluable because of a high ANC (=600) at baseline. The patient completed treatment with penicillin after two days of ceftazidime. In both failures, the pathogen was present on repeat blood culture on therapy. Vancomycin and tobramycin were added to the study drug for treatment of the α-hemolytic *Streptococci* and *E. coli*, respectively. Susceptibility testing for the *Streptococci* was not reported. *In vitro* resistance to ceftazidime was reported for the *E. coli*. Both subjects survived with successful resolution of infection. Only the cefepime subject with two pathogens identified completed treatment without additional antimicrobials. The ceftazidime subject with *Pseudomonas* received concomitant treatment with clindamycin for a suspected cellulitis. Ceftazidime was still considered successful in eradication of the *Pseudomonas* by the medical officer. All of the non-evaluable subjects had resolution of fever and bacteremia. They were non-evaluable because of concomitant antibiotics active against the identified pathogen. (Tobramycin for *E. coli* and vancomycin for coagulase negative *Staphylococci*)

Microbiologically Documented Infections (Medical Officer)

Organism	Source	Clinical Response
Cefepime Subjects		
Streptococci (α-hemolytic)	Blood	Failure
Escherichia coli	Blood	Non-evaluable
Streptococcus pneumoniae & *E. coli*	Blood	Success
Ceftazidime Subjects		
Escherichia coli	Blood	Failure
Pseudomonas aeruginosa	Blood	Success
Coagulase Negative *Staphylococci*	Blood	Non-evaluable
Coagulase Negative *Staphylococci*	Blood	Non-evaluable
Streptococci (β-hemolytic)	Throat	Non-evaluable

Mortality: As part of the safety assessment, the sponsor provided information on the deaths that occurred during the study period. None of the subjects died while on therapy. Thirty day all-cause mortality following treatment of a first febrile episode included 2/49 (4%) of CPM patients and 0/54 ceftazidime patients. For all febrile episodes, there were 3 deaths in CPM subjects (in 74 episodes–4%) and 1 death in a CTZ subject (in 75 episodes–1%). In patients treated for their first febrile episodes, one subject was brought to the hospital comatose from a severe intracranial bleed on the day after discharge. The second subject was a 7 month old who received 4 doses of cefepime but was discontinued from the study due to his age. He received other antibiotics for treatment of fever and neutropenia. He developed *C. difficile* colitis and was noted with an RSV infection. Over the next week his respiratory condition deteriorated further (possible ARDS vs. pneumonia). The patient died 11 days after cefepime therapy was stopped. Blood cultures grew *Pseudomonas aeruginosa, Enterococci,* and coagulase negative *Staphylococci*. Autopsy showed evidence of RSV pneumonia, ARDS, and fungal colitis.

In deaths from subsequent episodes, the CTZ subject died from hyponatremia and seizure during a hospitalization for chemotherapy 29 days after completion of CTZ therapy. The CPM subject was an 11 year old male who completed therapy with cefepime for fever and neutropenia during induction therapy. His fever resolved with 5 days of CPM, but neutropenia was expected to continue due to induction chemotherapy. He returned 4 days after discharge with "a rapidly fatal gram positive septicemia". The organism was *Stomatococcus mucilaginosus*.

SAFETY RESULTS

Duration of Study Therapy: Subjects were treated for a median of four days in each treatment arm. Patients in the MDI category were treated for a longer duration than other subjects (median = 8 days). Drug exposure for cefepime was as short as one day for some subjects who were discontinued for protocol violations up to 17 days. Treatment duration was similar in both treatment arms, but was highly variable.

Adverse Events: Roughly two-thirds of all subjects reported at least one adverse event(AE) during the first febrile episode(33/49 for CPM, 37/54 for CTZ). For all episodes, at least one AE was reported in 48/74 (65%) CPM episodes and 51/75 (68%) CTZ episodes. The remainder of

this section will focus on all febrile episodes, unless otherwise specified. The following chart includes all adverse events that occurred in more than twice for either drug.

Most Frequent Adverse Events Per Sponsor–All Fever Episodes

Adverse Event	**CPM (n=74)**	**CTZ (n=75)**
Vomiting	21(28)	7(9)
Diarrhea	11(15)	6(8)
Nausea	10(14)	2(3)
Coughing	8(11)	4(5)
Headache	8(11)	2(3)
Rash	8(11)	4(5)
Epistaxis	7(10)	2(3)
Pain	6(8)	10(13)
Abdominal Pain	6(8)	9(12)
Fever	5(7)	7(9)
Chills	4(5)	5(7)
Lung Rales	4(5)	2(3)
Dyspnea	4(5)	2(3)
Pruritis	4(5)	3(4)
Urinary Incontinence	4(5)	0

Adverse Event	**CPM (n=74)**	**CTZ (n=75)**
Ecchymosis	3(4)	7(9)
Gum Bleeding	3(4)	1(1)
Rhinitis	3(4)	6(8)
Somnolence	3(4)	2(3)
Urticaria	3(4)	1(1)
Asthma	2(3)	3(4)
Constipation	2(3)	3(4)
Erythema	2(3)	4(5)
Chest Pain	2(3)	3(4)
Stomatitis	2(3)	3(4)
Urine Retention	2(3)	3(4)
Anorexia	1(1)	6(8)
Lesion	1(1)	3(4)
Tachycardia	1(1)	3(4)
Sweating	0	5(7)

The most common events seen in cefepime patients are similar to those reported in the **ADVERSE REACTIONS** section of the label for adult clinical trials; vomiting, diarrhea, and nausea. Many of the gastrointestinal complaints that are common AE seen with antibiotics are reported here in higher frequency than is common for treatment in other indications. Part of this is due to the presence of these AE as part of the underlying disease process. Vomiting, nausea, epistaxis, bruising, gum bleeding, and stomatitis are commonly seen in cancer patients. The greater frequency of epistaxis in CPM subjects compared to CTZ subjects may be related to drug effect on hemostasis, but episodes of ecchymosis are more frequent in CTZ subjects. Bleeding as a result of thrombocytopenia from chemotherapy is expected in this study population. The contribution of the drug to epistaxis is uncertain. Similarly, headache and coughing is seen more frequently in CPM vs. CTZ subjects. More coughing may be related to the greater frequency of clinically documented infections in the CPM

group. (These were frequently upper respiratory infections.) The fact that this was an open label trial adds to the uncertainty. Are more adverse reactions being reported by patients (or parents) who know they are receiving an experimental agent? Safety data from the treatment of pediatric patients with other types of infection may aid in distinguishing unusual adverse events in children.

Local Intolerance: Local intolerance of study drug administration was also reported by the sponsor. The majority of subjects in both treatment arms tolerated IV administration well. Problems with IV infiltrate, swelling, erythema, etc. were reported in 5/74 (7%) for CPM and 14/75 (19%) for CTZ subjects. Infiltration of the IV was reported more often in CTZ subjects (7/75) than CPM subjects (2/75). Other reports of local intolerance were similar.

Serious Adverse Events: Deaths that occurred during the study were discussed in a prior section of this review. Serious AE other than deaths are provided in the chart below. None of these adverse events were felt to be related to the study drug by the investigator.

Serious/Life-Threatening Adverse Events

Subject/ Study Drug	Adverse Events	Relation to Study Drug
16-CPM	Death-Intracranial Bleeding	None
20-CTZ	Death-Seizure	None
53-CPM	Colitis-*C. difficile* Death-ARDS	None None
56-CPM	Epistaxis	None
57-CPM	Cyanosis Dyspnea Death-Cardiac Arrest	None None None
79-CTZ	Chills	None
108-CTZ	Chills Rectal Hemorrhoids Hypotension Hypoxia Shock	None Unknown Unknown Unknown Unknown
111-CTZ	Dyspnea	None

The subject with colitis received 4 doses of cefepime followed by more than a week of other broad spectrum antibiotics, leading the investigator to report no relation to cefepime use. Doubtless, administration of cefepime alone could result in *C. difficile* colitis.

Laboratory Abnormalities: Laboratory abnormalities were reported by the sponsor. Specific line listings for laboratory studies other than white blood cell counts and ANC were not provided. The following chart provides "clinically relevant" laboratory changes. Information about hematologic or urinalysis changes was not provided by the sponsor. No clinically relevant changes in creatinine were noted during the study. BUN wasn't measured. Similar laboratory value changes were seen in CPM and CTZ subjects for these clinically relevant changes.

Clinically Relevant Laboratory values (Class) During or After Study Drug Treatment

Subject #	Test	Baseline	Worst Value
Cefepime			
100	ALT/SGPT	33 (I)	117 (CR)
78	ALT/SGPT	72 (III)	192 (CR)
142	ALT/SGPT	54 (II)	361 (CR)
4	ALT/SGPT	175 (CR)	236 (CR)
66	ALT/SGPT	177 (CR)	332 (CR)
53	Total Bilirubin	0.8 (I)	3.1 (CR)
53	Calcium	8.2 (II)	6.7 (CR)
Ceftazidime			
61	ALT/SGPT	101 (III)	114 (CR)
140	ALT/SGPT	42 (II)	517 (CR)
141	ALT/SGPT	69 (II)	167 (CR)
35	ALT/SGPT	159 (CR)	188 (CR)
43	ALT/SGPT	153 (CR)	325 (CR)
55	ALT/SGPT	148 (CR)	593 (CR)
38	Total Bilirubin	1.1 (I)	3.2 (CR)

CONCLUSIONS

These results show significant deviation from the protocol in this open-label trial. The subjects frequently received concomitant antibiotics in the first 2-3 days of therapy if a clinically documented infection was present or a pathogen was isolated (MDI). This is similar to the results of adult trials for empiric therapy of fever and neutropenia, except that oral therapy was frequently used for adults. Despite the deviation from the protocol, the study does provide sufficient information for a pediatric use statement regarding empiric therapy for febrile neutropenic patients. Specific labeling recommendations are provided by the reviewer at the end of this document.

SERIOUS BACTERIAL INFECTIONS

In contrast to the study for empiric therapy for fever and neutropenia in pediatric patients, subjects with other bacterial infections were studied as a group. Three studies of pediatric patients with serious bacterial infections were performed. These studies grouped together subjects with lower respiratory tract infections, skin and skin structure infections, and urinary tract infections. This section of the supplement review will summarize the safety information provided by the sponsor from these pediatric studies. Efficacy information will not be reviewed in detail, since pediatric patients with disparate types of infections are put together in these trials. A short summary of the individual trials precedes the safety information.

AI411-129: A Non-Comparative Study of the Safety, Efficacy, and Pharmacokinetics of Cefepime in Pediatric Patients with Serious Bacterial Infections

Study Summary: This is a phase II non-comparative study of pediatric patients with serious bacterial infections. The objective of this trial was to "make an initial assessment of the safety, tolerance, pharmacokinetics, and efficacy of intravenously or intramuscularly administered cefepime in hospitalized pediatric patients with suspected bacteremia (with or without a documented site of local infection), [redacted] erious infections of the lower respiratory tract, urinary tract, or skin and skin structure". This was the first pediatric multiple dose study performed by the sponsor for cefepime (study dates: Jan 29, 1990-Jan 6, 1994). It was also the largest of the studies of serious bacterial infections. A total of 214 patients were enrolled at 11 study sites. The majority of patients were enrolled at two centers, and most participants in the pharmacokinetic portion of the study were from a single center. The study enrolled hospitalized pediatric patients from 2 months (by amendment on March 5, 1991) to 18 years. [redacted] Exclusions were for pregnancy, nursing, elevated creatinine, renal impairment, hepatic impairment, neutropenia, need for long-term therapy or concomitant antibiotics, HIV, shock, organ failure, suspected meningitis, "no code" status, endocarditis, suspected anaerobic infection, burn infections, prosthetic

infections, or likelihood of major surgery. Subjects were examined at a screening within 48 hours prior to initiating cefepime, on day 3-5 of therapy and weekly thereafter on therapy. An end-of-treatment evaluation was made on day 0-4 after therapy, and post-treatment evaluation occurred on day 10-14 after therapy. Post-treatment evaluation was on day 5-9 for UTI. Safety evaluations were performed on all subjects who received at least one dose of cefepime. Adverse clinical events were classified by relationship to the study drug and severity. The following chart shows the laboratory studies that were performed at screening, end of therapy, and during therapy for subjects receiving more than one week of therapy.

Hematology:
- Hemoglobin
- Hematocrit
- Total WBC & Differential
- Plat Ct or Smear Estimate
- Direct Coombs' Test

Urinalysis:
- Specific Gravity
- pH
- Albumin
- Glucose
- Microscopic Examination

Serum Chemistry:
- AST
- ALT
- Total Bilirubin
- Alkaline Phosphatase
- Creatinine
- Glucose
- Potassium
- Calcium
- Phosphorus
- Sodium

Cefepime administration was altered during the course of the study. The original protocol specified a dose of 50 mg/kg every 12 hours. This was changed to 50 mg/kg every 8 hours [redacted] then this dose was used for all subjects. The maximum dose was 2 grams/dose, or 6 grams/day. Maximum duration was 14 days initially, then changed to 28 days.

Study Results: There were 214 patients enrolled by 11 investigators in this study. The largest study center (83 subjects) was in Costa Rica. Pharmacokinetic studies were not performed at this site. All other sites were within the U.S. The second large site enrolled 62 subjects, and also enrolled the majority of patients in the pk study. **(M.O. Comment: For further information regarding the pharmacokinetic analysis, please see the biopharmaceutics review by He Sun, Ph.D. The remainder of this review will focus on the safety results.)**

Patient Demographics: The following table shows the demography for all subjects enrolled in the study. There are more males in the study, and a higher proportion of Hispanic subjects. The latter is most likely due to the heavy involvement of the Costa Rican site.

As they represent only 5% of the total study population, they were not excluded from this analysis of pediatric adverse events.

Patient Demographics

Demographic Factors	Cefepime (N=214)
Gender: N(%)	
Male	117 (55)
Female	97 (45)
Race: N(%)	
White	67 (31)
Black	51 (24)
Hispanic	96 (45)
Age:	
Median	5 years
Range	2 mo. - 47 yr.
Age Groups: N(%)	
2-23 months	45 (21)
2-11 years	131 (61)
12-15 years	23 (11)
>15 years	15 (7)

Infection Type: The diagnosis for which subjects received cefepime are shown in the following table. The other category included 7 subjects who received cefepime as surgical prophylaxis, three *Salmonella* enteritis, two suspected septic arthritis, two epiglottitis, two sinusitis, and one otitis media.

Diagnosis	N(%) of Subjects
SSTI	90 (42)
LRTI	65 (30)
UTI	19 (9)
Other	16 (7)

Treatment Duration: The following table shows the treatment duration for all subjects. The table separates subjects who received cefepime on BID or TID dosage schedules. The majority of subjects received 6 or more days of cefepime therapy. For the purposes of this safety review, this chart of treatment duration from the sponsor is sufficient. The increase in median duration of treatment for TID patients is most likely due to the protocol revision that allowed longer treatment duration towards the end of the study.

Duration of Treatment by Dose Schedule

Duration of Treatment (Days)	BID (N=80)	TID (N=134)	Total (N=214)
<3	20 (25)	5 (4)	25 (12)
3	7 (9)	14 (10)	21 (10)
4	7 (9)	12 (9)	19 (9)
5	10 (13)	14 (10)	24 (11)
>5	36 (45)	89 (66)	125 (58)
Median	5	7	6.5
Range			

Deaths: There were four patient deaths reported by the sponsor. All deaths were considered unrelated to cefepime.

[redacted]

A five year old girl with [redacted] developed respiratory distress and cardiovascular(CV) instability after Broviac catheter insertion. Over the week that followed, she could not be weaned from the ventilator, and required tracheostomy. The next day she developed fever, dyspnea, sputum production from the tracheostomy, and right upper lobe atelectasis. Sputum cultures grew *Pseudomonas aeruginosa* and *Escherichia coli*. After 3-4 days of cefepime, no clinical improvement was noted. Cefepime was withdrawn, and she was treated with vancomycin, amphotericin B, and gentamicin. She died two days later due to worsened CV instability. Autopsy showed multiple patchy foci of pneumonia. *Pseudomonas aeruginosa* grew from the lung and ascitic fluid; *E. coli* grew from the

lung and heart blood; and enterococci grew from heart blood alone. Death was considered "to be due to diffuse alveolar damage with infection as a contributory cause".

An 11 year old male from Costa Rica with mental retardation and left hydronephrosis had cystorrhaphy and Foley catheter placement. He developed a UTI 2-3 weeks later. His *Pseudomonas* UTI responded to cefepime therapy. He was still on cefepime (day 17) when he developed disseminated varicella infection with shock and DIC. He died despite efforts to control the shock and DIC. **(M.O. Comment: Death due to disseminated, hemorrhagic varicella is a rare, but known event. The patient was on steroids for 11 days following UTI diagnosis. Laboratory results were not reported in the narrative or provided elsewhere. This subject was also noted with hematuria throughout his hospitalization. Cefepime could have contributed to a bleeding tendency, but there is no specific evidence for that. Varicella, in a subject possibly immunocompromised by steroid use, can result in this hospital course.)**

A four month old male with broncho-pulmonary dysplasia(BPD) was hospitalized for respiratory distress and intubated. Five days later, he was started on cefepime for LRTI. *E. coli* and *Hemophilus influenzae* were isolated from sputum. His condition deteriorated, and he died on the 5th day of therapy due to BPD, RSV, and pneumonia.

Adverse Events: The following table shows a list of adverse events reported by more than two subjects. The most frequent events were rash, vomiting, fever, nausea, and diarrhea. Epistaxis and cough were each noted in 4 subjects (2%).

Adverse Events Reported by More than Two Subjects

Adverse Event	Number (%) of Subjects N=214	Adverse Event	Number (%) of Subjects N=214
Patients with at least one AE	92 (43)	Coughing	4 (2)
Rash	22 (10)	Epistaxis	4 (2)
Fever	21 (10)	Pruritis	4 (2)
Nausea	11 (5)	Somnolence	4 (2)
Diarrhea	9 (4)	Dizziness	3 (1)
Abdominal pain	7 (3)	Hypertension	3 (1)
Dyspnea	6 (3)	Hyperventilation	3 (1)
Headache	5 (2)	Nervousness	3 (1)
Malaise	5 (2)	Tachycardia	3 (1)

Drug-Related Adverse Events: For adverse events that were drug-related, rash was the most common. In two cases the rash was considered severe. The majority of drug-related adverse events were mild. One subject being treated for cellulitis developed wheezing and bronchospasm. The following table provides a list of AE which were considered probably drug-related.

Adverse Events Reported as Probably Drug-Related

Adverse Event	Number (%) of Subjects N=214	Adverse Event	Number (%) of Subjects N=214
Patients with at least one drug-related AE	15 (7)	Wheezing/ Bronchospasm	1 (<1)
Rash	9 (4)	Diarrhea	1 (<1)
Dizziness	3 (1)	Headache	1 (<1)
Fever	2 (1)	Moniliasis Oral	1 (<1)
Nausea	2 (1)	Pruritis	1 (<1)
Agitation	1 (<1)	Vasodilation	1 (<1)

Serious Adverse Events: Seven subjects experienced serious adverse events during or within 30 days after cefepime therapy. There were three hospitalizations, two deaths, one prolonged hospitalization due to rash, and one life-threatening event (pleural effusion with dyspnea). The last two subjects withdrew from the study and are discussed below. None of these adverse events were considered drug-related other than the rash. (one for sinusitis, one for shortness of breath), and one subject with spinal muscular atrophy and LRTI was admitted to an occupational therapy unit for treatment of skin breakdown.
(M.O. Comment: It is unclear why only two of the four deaths reported during the study are considered serious adverse events.)

Withdrawals due to Adverse Events: Four subjects were withdrawn from the study due to adverse events. withdrew on day 2 of cefepime due to symptoms of dizziness, nausea, pruritis, and mild rash. a 7 year old boy, also withdrew due to a pruritic rash after 5 doses of cefepime. The rash was considered a serious AE that prolonged hospitalization. An 11 year old boy was treated for cellulitis of the right eye and developed wheezing, bronchospasm, and rash on the third

day of therapy. The last was an 11 month old girl who was withdrawn from therapy for LRTI on the second day of cefepime due to dyspnea and pleural effusion. The infant was started on nafcillin, ceftriaxone, and erythromycin. **(M.O. Comment: Three subjects were withdrawn for allergic drug reactions. Two of these subjects were [redacted] 5 of 9 cases of drug-related rash occurred [redacted] This is consistent with a report in the literature which suggests a higher incidence of allergic reactions to beta-lactam antibiotics.[4] The disease course in the infant is typical for severe pneumonic processes in infants.)**

Local Tolerance: Fifteen patients (7%) suffered IV site infiltration, and two (1%) had phlebitis. Infusions were well tolerated in 194 (91%) subjects.

Laboratory Test Abnormalities: The following chart presents the laboratory test abnormalities that were reported in subjects with normal pre-treatment test results. The most striking of these abnormalities is the abnormal hemoglobin values reported in a third of these patients. This may simply be related to the definition used for abnormality. A class II abnormality is defined as a value from 9.0 to <LNL. The lower normal limit was not defined, but is usually derived from age specific indices. Children who are hospitalized due to illness and who have blood drawn for laboratory studies commonly have mild anemia. However, mild anemia as a result of microscopic bleeding can not be ruled out as a cause. Changes in PT and PTT were not measured in any of the pediatric trials, though clinically relevant changes in these values were noted in 1.5% and 1.6% of subjects in the original NDA, respectively. The number of subjects with clinically relevant changes in hemoglobin was low 2/111 (2%), but for subjects with an abnormal pretreatment result, 8/64 (14%) showed clinically relevant changes in hemoglobin.

A high proportion of clinically relevant (CR) changes were reported for hyperphosphatemia and hyperkalemia. For phosphorus, the issue of defining appropriate pediatric laboratory parameters is important. The sponsor defines a clinically relevant increase in phosphorus as >6.0 mg/dL. However, the normal range of phosphorus for children 0-15

years is 3.2 to 6.3 mg/dL.[5] Thus, the CR abnormal range includes part of the range of normal pediatric values for phosphorus. Phosphorus was not studied in the trial of empiric therapy of fever and neutropenia in order to compare with this study. For hyperkalemia, fewer clinically relevant changes were noted. These clinically relevant changes were not seen in the fever and neutropenia trial. The frequency of hyperkalemia in this trial may be related to the difficulty of phlebotomy in children resulting in hemolysis. This would not be seen in the fever and neutropenia trial, since the vast majority of these children would have central venous catheters. Class II/III changes in AST and ALT are seen.

Laboratory Test	Number (%) of Patients		
	All Tested Patients	Abnormal	Clinically Relevant
Hematologic Tests:			
Hemoglobin	111	37(33)	2(2)
Platelet Count	132	3(2)	1(1)
Leukocytes	170	11(6)	0
Neutrophil Count	163	17(10)	0
Liver Function Tests:			
Alkaline Phosphatase	138	1(1)	0
AST/SGOT	112	28(25)	2(2)
ALT/SGPT	151	22(15)	1(1)
Total Bilirubin	154	3(2)	0
Renal Function Tests:			
BUN	12	1(8)	0
Creatinine	174	8(5)	1(1)
Electrolytes:			
Sodium	116		
Hyponatremia		29(25)	0
Hypernatremia		7(6)	0
Potassium	141		
Hypokalemia		18(13)	1(1)
Hyperkalemia		25(18)	4(3)
Calcium	148		
Hypocalcemia		27(18)	2(1)
Hypercalcemia		6(4)	0
Phosphorus	114		
Hypophosphatemia		10(9)	0
Hyperphosphatemia		28(25)	11(10)

[5] Barone MA, Editor "Blood Chemistries/Body Fluids" Chapter 6 in The Harriet Lane Handbook 14th Edition Mosby-Year Book Inc. ©1996

AI411-123: A Multi-Investigator Comparative Study of Cefepime and Cefuroxime in the Treatment of Serious Bacterial Infections in Pediatric Subjects

Study Summary: This is a phase III, open-label, multi-center, randomized (2:1,cefepime:cefuroxime) study of pediatric patients with serious bacterial infections. The objectives of this trial were "1) To evaluate the clinical efficacy and safety of cefepime in the treatment of pediatric patients with suspected bacteremia (with or without a documented site of infection), or serious infections of the lower respiratory tract, urinary tract, or skin and skin structure; 2) To compare the clinical efficacy and safety of cefepime with cefuroxime for these indications". The inclusion and exclusion criteria were similar to study AI411-129 with two exceptions. The cefepime subjects received 50 mg/kg BID for up to 21 days. Cefuroxime was given at a dose of 100 mg/kg/day in three divided doses. The remainder of the study procedures were similar to AI 411-129. Four U.S. centers (Florida, New Jersey, Georgia, and Puerto Rico) participated. The study ran from March 27, 1990 to May 7, 1991. The sponsor planned to enroll up to 200 patients at ten centers. A total of 28 subjects were enrolled (20 cefepime, 8 cefuroxime). The study was closed due to slow patient accrual. A brief review of the safety results is provided below. All subjects were considered clinical successes except for 1 failure in the cefepime group (thyroid abscess) and 3 non-evaluable subjects.

Safety Results: Detailed review of demography and treatment duration are provided by the sponsor, but are not repeated here since the number of patients and adverse events are few. The cefepime subjects ranged from 2-15 years (Median=5.5 years). These subjects received cefepime BID, and duration ranged from 2-9 days (median =5 days). There were no deaths, serious AE, or withdrawals due to AE in the study. There were six adverse events reported in four cefepime patients. No AE were reported in cefuroxime subjects. There were three reports of vomiting, two reports of nausea, and one report of fever. All adverse events were considered unrelated to cefepime. Two cefepime patients reported problems with local tolerance of infusion (1 infiltration,1 phlebitis). Others tolerated infusions well. Two cefepime subjects were reported with clinically relevant abnormalities(hyperkalemia, hyperphosphatemia).

AI411-157: A Multi-Investigator Comparative Study of Cefepime and Cefotaxime in the Treatment of Serious Bacterial Infections in Pediatric Subjects

(M.O. Comment: This study was identical to AI411-123 with the exception that cefotaxime is the comparator, rather than cefuroxime. The same issue of low participation is seen in this trial. Again, only a brief safety review is provided.)

Study Summary: This is a phase III, open-label, multi-center, randomized (2:1,cefepime:cefotaxime) study of pediatric patients with serious bacterial infections. The objectives of this trial were "1) To evaluate the clinical efficacy and safety of cefepime in the treatment of pediatric patients with suspected bacteremia with or without a documented site of infection, or serious infections of the lower respiratory tract, urinary tract, or skin and skin structure; 2) To compare the clinical efficacy and safety of cefepime with cefuroxime for these indications". The inclusion and exclusion criteria were similar to study AI411-123 with the exception that one center enrolled children as young as 2 months of age. (This was by amendment for the one center in December 1991. The original protocol's age range was 2 years to 18 years.) The cefepime subjects received 50 mg/kg BID for up to 21 days. Cefotaxime was given at a dose of 120 mg/kg/day in four divided doses. The remainder of the study procedures were similar to AI 411-129. Three U.S. centers (Ohio, West Virginia, and Michigan) participated. The study ran from January 4, 1991 to February 8, 1993. The sponsor planned to enroll up to 100 patients at ten centers. A total of 34 subjects were enrolled (22 cefepime, 12 cefotaxime). The study was closed due to slow patient accrual. The sponsor reported unsatisfactory response in one cefepime patient with a knee abscess. Two cefepime subjects with LRTI were reported with indeterminate response. All other subjects were reported as clinical successes.

Safety Results: Detailed review of demography and treatment duration are provided by the sponsor, but are not repeated here since the number of patients and adverse events are few. The cefepime subjects ranged from 2 months to 13 years (Median=6 years). These subjects received cefepime BID, and duration ranged from 2-11 days (median=4 days). There were no deaths or withdrawals due to AE in

the study. Two serious adverse events were reported in the trial(1 cefepime, 1 cefotaxime). Both serious AE were related to re-hospitalization for LRTI 17 and 12 days after the end of treatment, respectively. Three cefepime patients reported four adverse events. Two cefotaxime subjects reported five AE. Adverse events reported in cefepime patients were fever, facial swelling, anorexia, and stridor. All adverse events were considered unrelated to cefepime. One cefepime patient reported problems with local tolerance of infusion(IV infiltration). All other subjects tolerated infusions well. For laboratory studies, "clinically relevant" abnormalities included 3 subjects with hyperkalemia and 1 with hyperphosphatemia for cefepime patients. Two reports of clinically relevant abnormalities (hyperkalemia and hyperphosphatemia) were reported in cefotaxime subjects.

[M.O. Comment: As described in the review of AI411-129, increased phosphate and increased potassium are most likely related to inappropriate, age-related ranges or difficulty with phlebotomy, respectively. The anemia seen in AI 411-129 was not seen in AI 411-123 or this trial.

The adverse events in cefepime patients are either included in the label (fever, anorexia, vomiting, and nausea) or are not unexpected in pediatric patients receiving IV fluids (facial swelling) or with LRTI (stridor). These two comparative studies of serious bacterial infections do not provide evidence of an AE profile different from adults.]

REVIEW CONCLUSIONS

The labeling changes proposed by the sponsor to include a Pediatric Use statement on pneumonias, urinary tract infections, skin and skin structure infections, and empiric therapy for febrile neutropenic patients are approvable. The safety information provided in the pediatric studies and the rationale for extrapolation of adult efficacy data to pediatric patients reviewed here provide adequate evidence to allow for some of the proposed labeling changes under the 1994 pediatric final rule. (59 FR 64240, Dec. 13,1994)

Appendix I provides the medical officer's proposed revisions for the Maxipime® label. Appendix II provides the final revisions to the Maxipime® label, as agreed between the sponsor and the division in a telephone conference on January 21, 1999 and by facsimile correspondences on Jan. 21, 22, and 25.

/S/

John Alexander, M.D.

CC:
NDA 50-679
HFD-340
HFD-520
HFD-520/MO/Alexander
HFD-520/DEPDIR/Gavrilovich
HFD-520/CSO/Duvall-Miller
HFD-880/Biopharm/Sun

Concurrence Only:
HFD-520/DIVDIR/Chikami
HFD-520/SMO/Soreth

/S/

1/26/99

1/26/99

6 pages of revised draft labeling have been redacted from this portion of the document.